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STUDIES IN THE PREPARATION AND PROPERTIES OF SOME 3-KETO-3,4-DIHYDRO-2H-1,5-BENZODIOXEPINS AND RELATED COMPOUNDS

by

DAVID FRANK HAYMAN

A Thesis submitted for the degree of Doctor of Philosophy of the City University, London.

September, 1975.

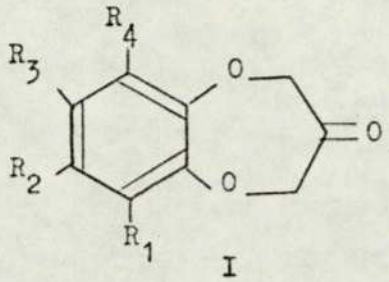
ACKNOWLEDGEMENTS

The author wishes to express his sincere gratitude to Dr. P. A. Claret, B.Sc., F.R.I.C., for his supervision, advice and encouragement during this work.

I should also like to thank the Science Research Council and the Physico-chemical Measurements Unit, Harwell, for the mass spectrographic measurements and the 100 and 220 MHz nuclear magnetic resonance spectra.

ABSTRACT

Efficient methods for the preparation of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (I, $R_1=R_2=R_3=R_4=H$) have been developed.

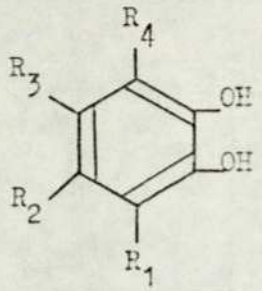


I

This compound was then used as an intermediate for the synthesis of a series of derivatives of potential pharmacological interest. These were submitted to biological screening [redacted] and preliminary results revealed that one of these compounds possessed weak tranquillising and antidepressant activity. However, this aspect of the work was abandoned at an early stage owing to the publication of patents[1a,2a] claiming biological activity for a variety of dihydro-1,5-benzodioxepins.

Attention was then focussed on the preparation of a series of ketones of the general formula (I) having from one to four t-butyl, methyl or phenyl substituents in the aromatic ring in order to study their chemical and physical properties and if possible to correlate these with the conformations of the heterocyclic rings.

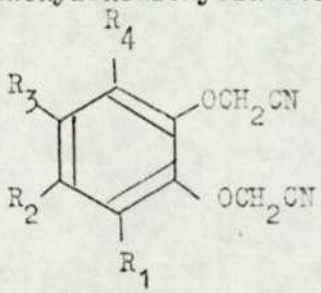
Most of the substituted pyrocatechols (II) required as starting



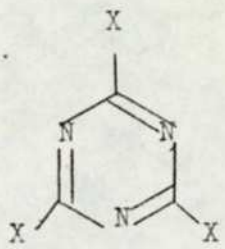
II

materials in this investigation were prepared by established procedures; marked improvements were made in the preparations of 3-t-butyl, 3,4,5- and 3,4,6-trimethylpyrocatechols.

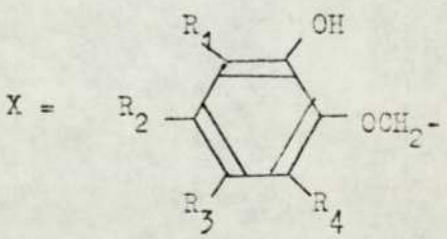
The conversion of the pyrocatechols (II) into the substituted o-phenylenedioxydiacetonitriles (III)



III

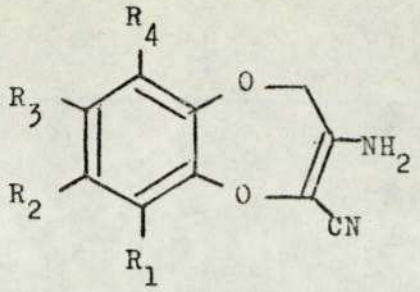


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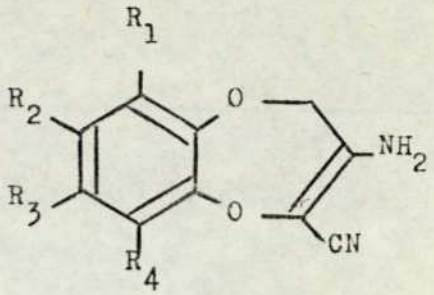


was accompanied in a number of cases by the formation of the symmetrical triazines (IV).

Intramolecular cyclisation of the dinitriles (III) gave high yields of the enaminonitriles of the general formulae (V) and (VI).



V

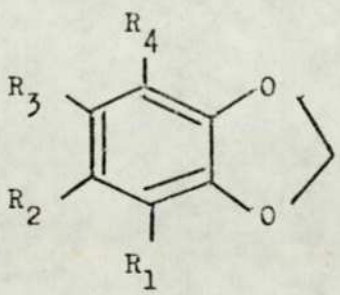


VI

Those derived from unsymmetrically substituted dinitriles were shown by nuclear magnetic resonance spectroscopy to be approximately 1:1 mixtures of the two possible isomers (V and VI). From a mixture containing the 6- and 9-methyl compounds (V, R_1= Me, R_2= R_3= R_4= H and R_1= R_2= H, R_3= Me, R_4= H) one pure isomer was separated and identified on the basis of its nuclear magnetic resonance spectrum.

Acid hydrolysis of the enaminonitriles (V) gave the corresponding ketones (I) which were characterised by chemical and physical methods.

Attempts were made to determine the conformation of the heterocyclic ring of the substituted ketones (I) and their derivatives from the extent of their ultra-violet absorption in the 260-270nm band compared with those of the correspondingly substituted planar



VII

1,3-benzodioxoles (VII), as described by Archer and Claret[3].

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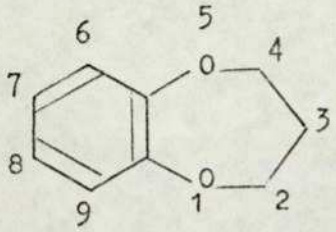
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CHAPTER 1. INTRODUCTION

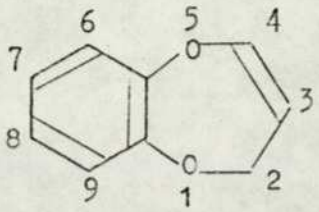
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1.1 Nomenclature

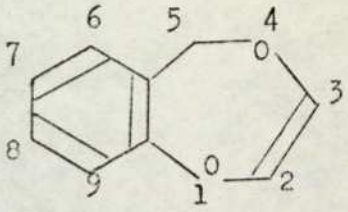
The compounds described in this thesis are derivatives of the benzoheterocyclic compound (VIII) originally described as



VIII



IX



X

pyrocatechol trimethylene ether and later as 3,7-dioxa-1,2-benzocycloheptene; it is now named systematically as 3,4-dihydro-2H-1,5-benzo[b]dioxepin, a derivative of the parent compound (IX), 2H-1,5-benzodioxepin. The symbol [b] may be omitted[4] without ambiguity, as the alternative structure (X) would be 5H-1,4-benzodioxepin.

The Ring Index nomenclature and numbering, as shown above, are used with derivatives named in accordance with the IUPAC 1957 Rules (Sections A and B)[5] and the IUPAC Rules (Section C)[6], as modified by the Chemical Society, London.[7]

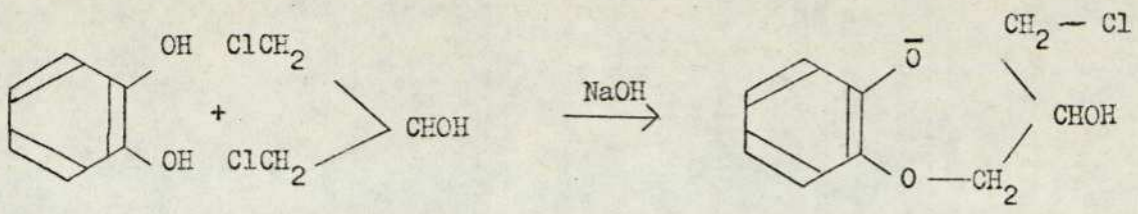
To avoid repetition of the full systematic name, the terms "benzodioxepin" or "dihydrobenzodioxepin" are used to denote a 2H-1,5-benzodioxepin or a 3,4-dihydro-2H-1,5-benzodioxepin respectively, but also where no ambiguity can occur, the general term "benzodioxepin" is used for either structure as required by the context.

1.2 Literature survey of preparative routes to 3-keto-3,4-dihydro-2H-1,5-benzodioxepin.

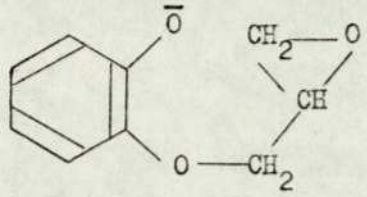
1.2.1 Condensations of pyrocatechol with 1,3-bifunctional reagents.

In 1962, Rosnati and De Marchi[8] isolated a small quantity of a reactive crystalline compound, $C_9H_8O_3$, from the neutral fraction formed during the preparation of 1,4-benzodioxan-2-carboxylic acid (XIV) by the oxidation of 2-hydroxymethyl-1,4-benzodioxan (XIII) with alkaline potassium permanganate. They showed that this was the previously unreported 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (Ia) and not the expected isomeric 2-formyl-1,4-benzodioxan (XVII) which they synthesised unambiguously by oxidation of the diol (XVI) with periodic acid.

It appeared that the 2-hydroxymethyl-1,4-benzodioxan (XIII), which they had prepared by the condensation of pyrocatechol with 1,3-dichloro-2-propanol, contained approximately 5% of the isomeric secondary alcohol 3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (XVa). This idea was supported by the observation that when pure 2-hydroxymethyl-1,4-benzodioxan (XIII), prepared[9] by the reduction of ethyl 1,4-benzodioxan-2-carboxylate (XVIII) with lithium aluminium hydride, was similarly oxidised, none of the ketone (I) was obtained[8]. The Italian workers[8] suggested that the simultaneous formation of the alcohols (XIII) and (XV), could have occurred from the same intermediate anion (XI), the primary alcohol (XIII) being formed through an intermediate epoxide (XII) by intramolecular nucleophilic attack at the secondary carbon atom (path 'a') as proposed by



XI

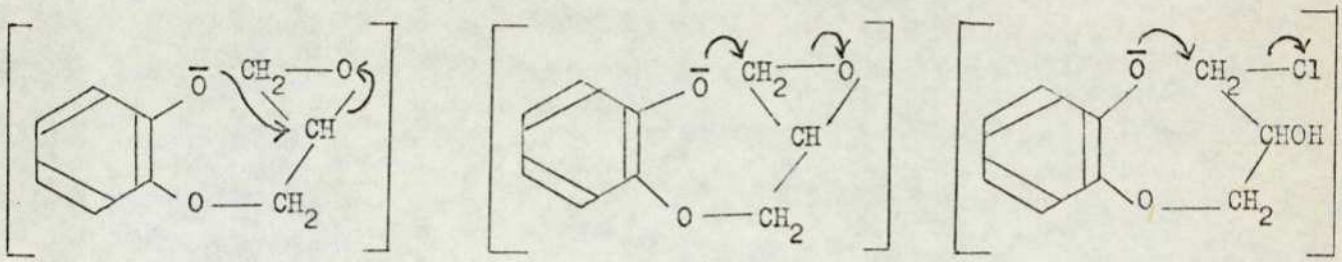


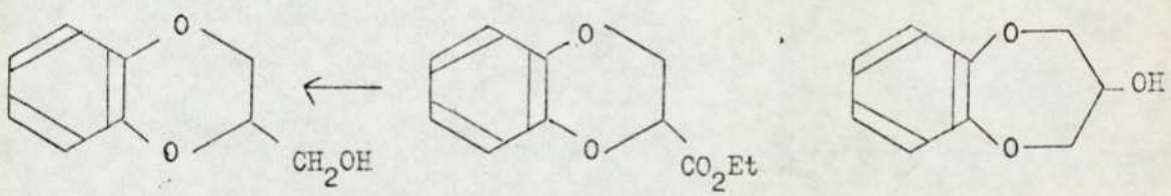
XII

path 'a'

path 'b'

path 'c'

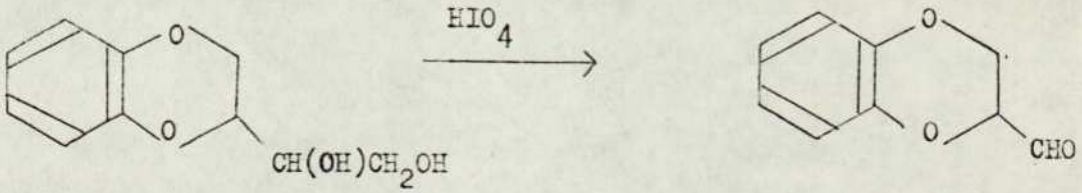




XIII XVIII XVa



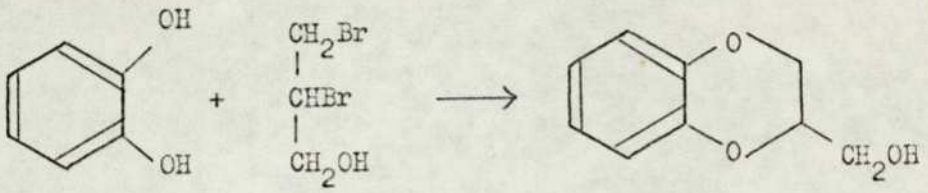
XIV Ia



XVI XVII

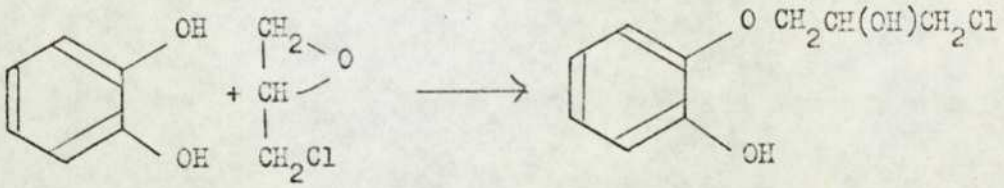
Stephenson[10]; the secondary alcohol (XVa) resulting directly by seven membered ring closure, with displacement of the chloride anion (path 'c').

Strong support for the participation of an intermediate epoxide (XII) stems from the investigations of other workers. Thus Moureu[11] has prepared the benzodioxan (XIII) from 2,3-dibromo-1-propanol and pyrocatechol and Stephenson[10] showed that pyrocatechol

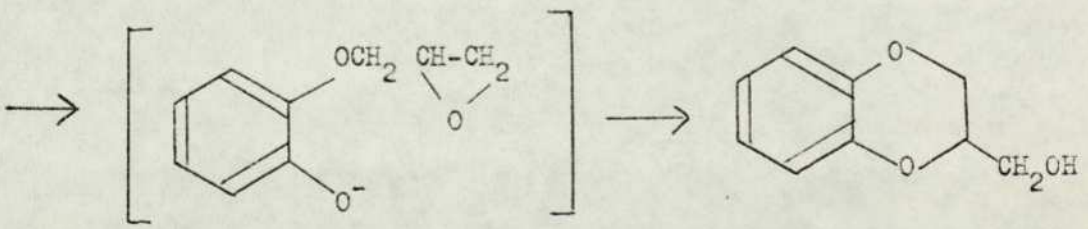


XIII

and epichlorohydrin in pyridine gave 3-chloro-1-(o-hydroxyphenoxy)-2-propanol (XIX) which with aqueous potassium carbonate gave the alcohol (XIII).

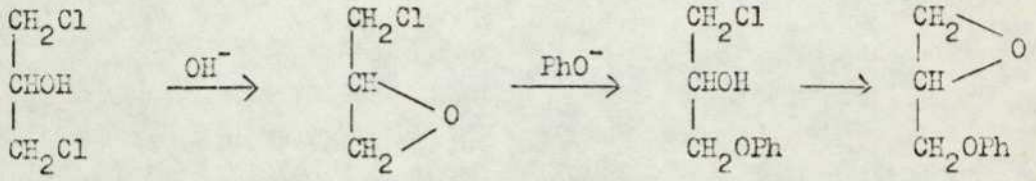


XIX



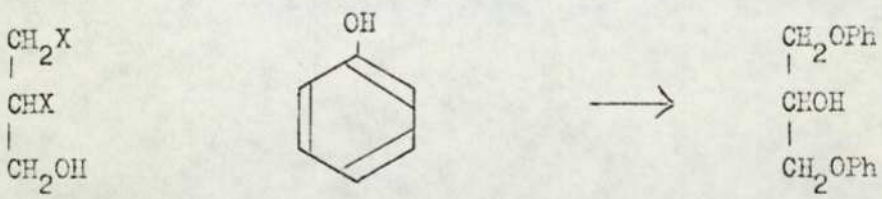
XII XIII

Additional evidence to support the formation of an intermediate epoxide (XII) was obtained by Fairbourne and co-workers[12] who showed that 1,3-dichloro-2-propanol with aqueous alkali readily gave 1-chloro-2-hydroxy-3-phenoxypropane (XX) and finally 1,2-epoxy-3-phenoxypropane (XXI).



XX XXI

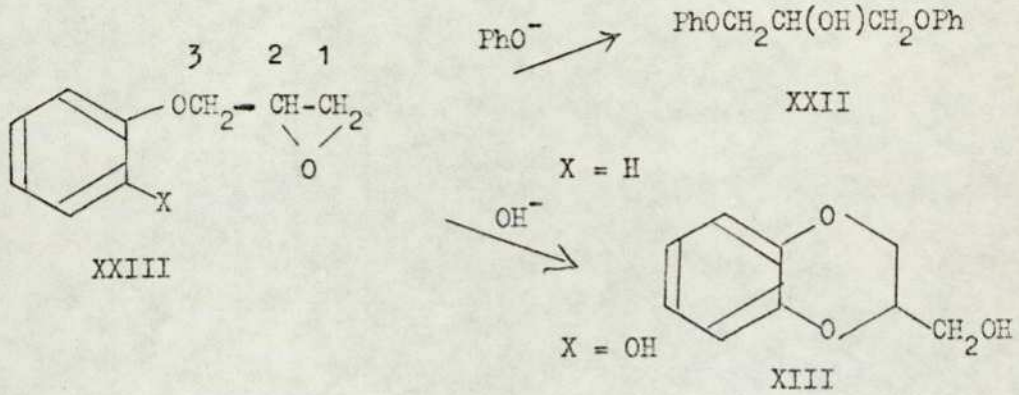
The latter compound has also been suggested by Boyd[13] and Delaby and Dubois[14] as the reaction intermediate in the formation of 1,3-diphenoxy-2-propanol (XXII) from phenol and 1,3-dichloro-2-propanol[12,15] or epichlorohydrin[16] probably proceeds through the intermediate epoxide (XXI) in an analogous manner.



X = Cl and Br XXII

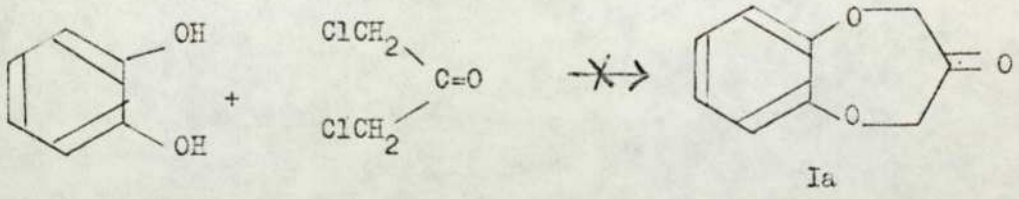
From these results and the extensive studies that have been made on the mode of reaction of mono-substituted epoxides with phenols etc.[17], it is quite conceivable that the epoxide (XII) could also suffer intramolecular nucleophilic attack at the primary carbon atom (path 'b') to produce the secondary alcohol (XVa).

In the case of the phenoxy derivative (XXIII, X = H) intramolecular nucleophilic attack by a second phenoxide now occurs, as expected, at the less sterically hindered C_1 affording the 1,3-diphenoxy derivative (XXII).



However, with the o-hydroxyphenoxy derivative (XXIII, X = OH) intramolecular nucleophilic attack on C_2 to give the benzodioxan derivative (XIII), would be easier than reaction at C_1 to give the benzodioxepin (XVa).

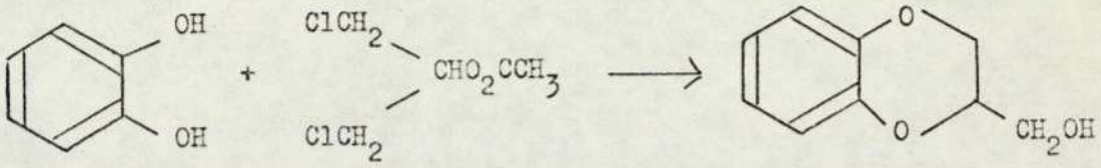
Attempts by Rosnati and De Marchi[8] to synthesise the ketone (Ia) by the reaction of pyrocatechol with 1,3-dichloroacetone (or its ketal) were unsuccessful but experimental conditions were not stated.



In 1967 studies on the preparation and properties of some 3,4-dihydro-2H-1,5-benzodioxepins were undertaken in this laboratory by Archer[18]. Included in his investigations were attempts to synthesise the ketone (Ia) and related compounds by the following methods

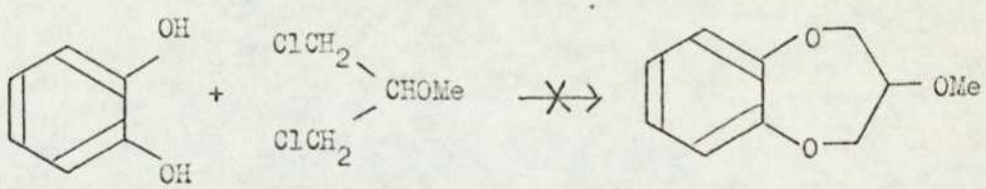
(i) The reaction between pyrocatechol and 2-acetoxy-1,3-dichloropropane in the presence of excess alkali yielded 75% of 2-hydroxy-

methyl-1,4-benzodioxan (XIII); a similar reaction in which exactly two equivalents of base were used gave only unchanged 2-acetoxy-1,3-dichloropropane as the alkali insoluble product.



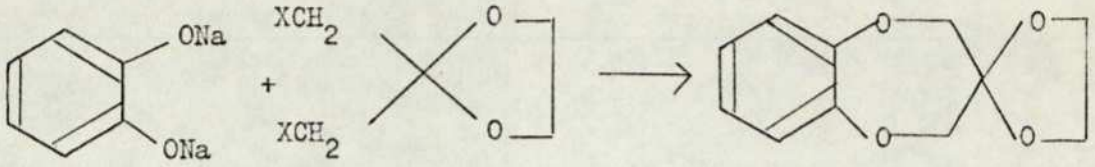
XIII

(ii) A small yield of an unidentified non-cyclic compound resulted from the reaction of pyrocatechol and 1,3-dichloro-2-methoxypropane in aqueous sodium hydroxide.



(iii) The reactions between pyrocatechol and 1,3-dichloroacetone under varying conditions were examined but only ether insoluble brown oils were obtained; results that agreed with the findings of Rosnati and De Marchi[8].

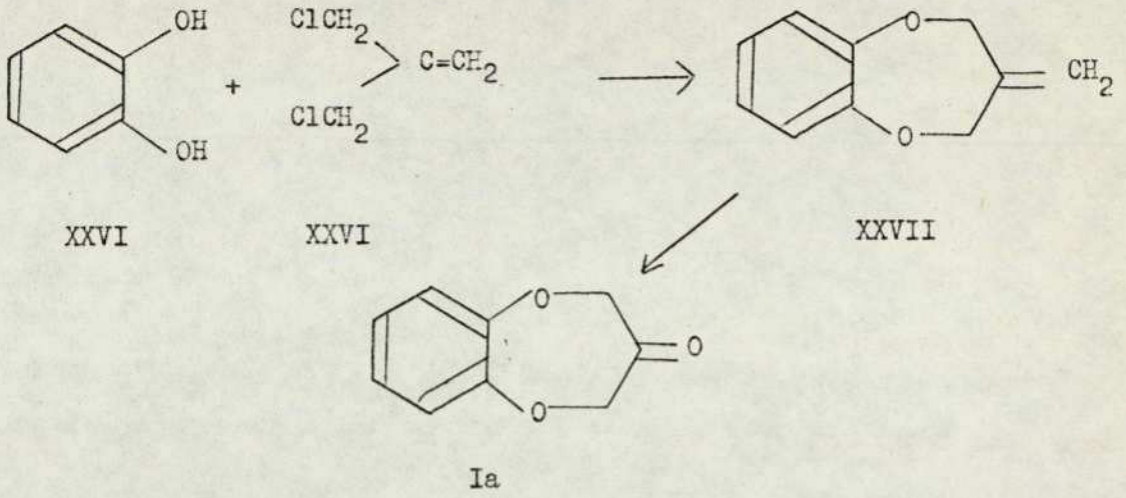
(iv) An attempt to prepare the spiroketal (XXV) from the reaction between 2,2-bis-(chloromethyl)-1,3-dioxolan (XXIV, X = Cl) and the sodium salt of pyrocatechol in dimethylsulphoxide at 100° for 7 hr. gave only unchanged dioxolan (XXIV, X = Cl).



XXIV XXV

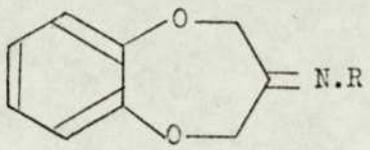
This method was also used unsuccessfully by Rosnati and De Marchi[8] but no reaction conditions were recorded. However, a communication by Schroth and Werner[19] in 1970 described the successful preparation of the spiro-ketal (XXV) in 40% yield by the reaction of pyrocatechol with 2,2-bis-(bromomethyl)-1,3-dioxolan (XXIV, X = Br) in dimethyl sulphoxide in the presence of sodium hydride, but their attempts to hydrolyse it to the ketone (Ia) with 15% sulphuric acid for 5 hr. or with a boiling mixture of 50% sulphuric acid in acetic acid for the same time failed.

Whilst Archer's work[18] was in progress, Richter and co-workers[20] in 1968, described the reaction of 3-chloro-2-chloromethyl-propen-1 (XXVI) and pyrocatechol to give 3-methylene-3,4-dihydro-2H-1,5-benzodioxepin (XXVII) which on ozonolysis afforded the 3-keto compound (Ia). Few details other than the melting points of the semicarbazone (XXVIII, R = $-NHCONH_2$) and 2,4-dinitrophenyl-hydrazone (XXIX, R = $-NO_2$) were given.

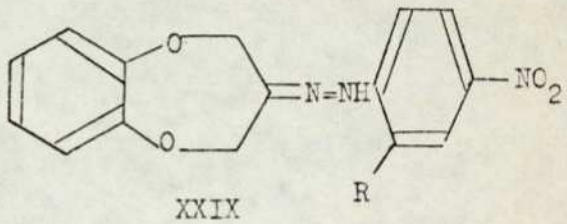


XXVI XXVI XXVII

Ia



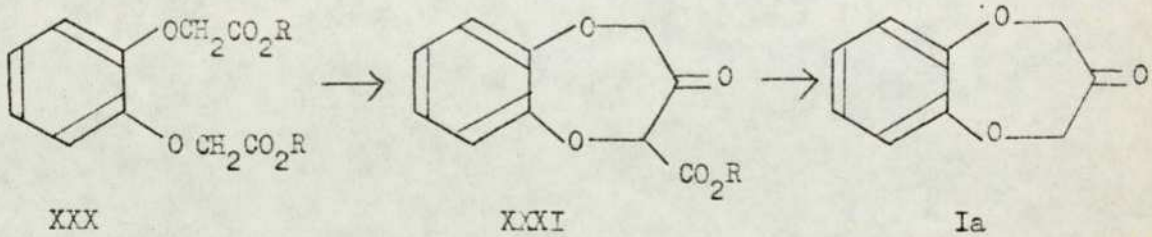
XXVIII



XXIX

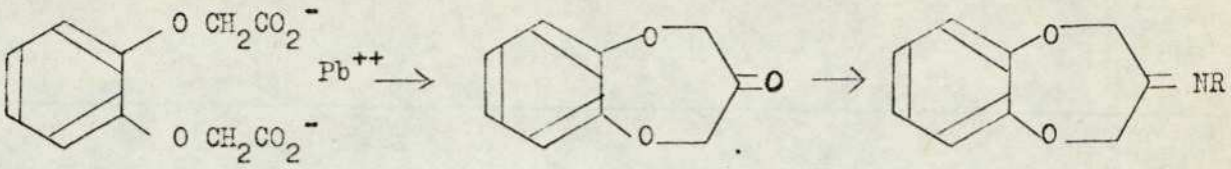
1.2.2 Ring closure of derivatives of pyrocatechol.

The Dieckmann cyclisation of diethyl o-phenylenedioxydiacetate (XXX, R = Et) to give the β-keto-ester (XXXI, R = Et), and thence



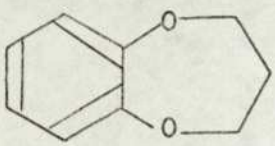
XXX XXXI Ia

the ketone (I), was also reported by Rosnati and De Marchi[8] to be unrewarding but again no details were given. However, a very low yield of the ketone (Ia), isolated as its semicarbazone (XXVIII, R = $-NHCONH_2$), was obtained[8] by the thermal decomposition of the

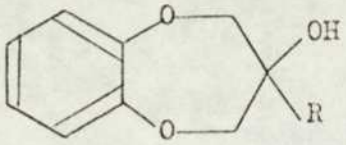


XXXII Ia XXVIII

lead salt of o-phenylenedioxydiacetic acid (XXXII). Wolff-Kischner reduction of the semicarbazone (XXVIII, R = -NHCONH$_2$) yielded the known[21] 3,4-dihydro-2H-1,5-benzodioxepin (VIII) and reaction of



VIII



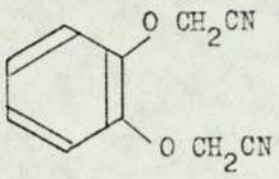
XXXIII

the ketone with methyl magnesium iodide afforded the carbinol (XXXIII, R = Me). In addition the 4-nitrophenyl- (XXIX, R = H) and 2,4-dinitrophenylhydrazone (XXIX, R = -NO$_2$) derivatives were described[8].

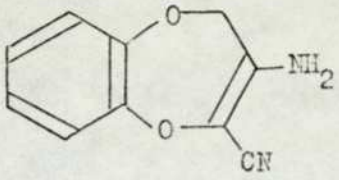
Although the Dieckmann cyclisation of diethyl o-phenylenedioxydiacetate (XXX, R = Et) failed in the hands of the Italian workers[8], Archer[18,3] found that the dimethyl ester (XXX, R = Me) could be cyclised to the β-keto-ester (XXXI, R = Me) in 45% yield with sodium hydride in toluene containing a catalytic amount of methanol. A stepwise hydrolysis of the β-keto-ester (XXXI, R = Me) to the corresponding β-keto-acid (XXXI, R = H) with alkali followed by

decarboxylation with mineral acid gave o-phenylenedioxydiacetic acid (XXX, R = H) in 35% yield together with a negligible quantity of a pale yellow oil which afforded a 2,4-dinitrophenylhydrazone (XXIX, R = $-NO_2$) identical with that reported[8] for the ketone (Ia).

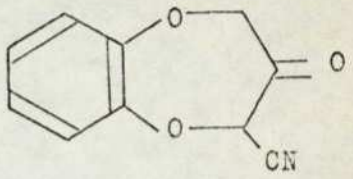
Another potential route to the ketone (Ia) involved the Thorpe cyclisation of o-phenylenedioxydiacetonitrile (IIIa) to the enaminonitrile (Va).



IIIa

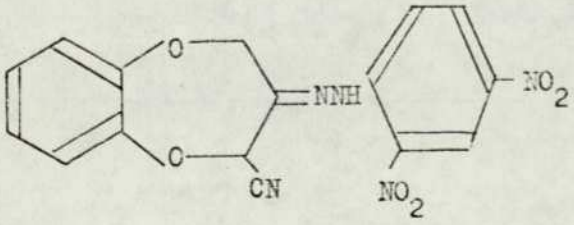


Va



XXXIV

Sodium methoxide in methanol failed to effect ring closure and lithium N-ethylanilide yielded only 2.7% of the enaminonitrile (Va), but a 77% yield of the latter compound was obtained [18,3] when the reaction was carried out with sodium hydride in dimethyl sulphoxide at 65-70°. Hydrolysis of the enaminonitrile (Va) with 2.5N hydrochloric acid for 2 hr. afforded the cyano-ketone (XXXIV) in 66% yield whereas after 7 hr. both ketone (Ia) and cyano-ketone (XXXIV) were detected, the former as the oxime (XXVIII, R = OH), the latter as its 2,4-dinitrophenyl-hydrazone (XXXV). When the cyano-ketone (XXXIV)



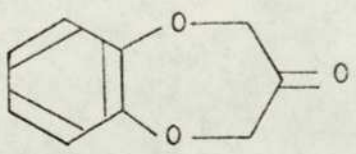
XXXV

was hydrolysed for a short time with aqueous alkali and acidified, a 66% yield of the di-acetic acid (XXX, R = H) was isolated. A small sample of the crude ketone (Ia) having an infra-red spectrum identical with that published[8] was obtained in about 45% yield by hydrolysis of the cyano-ketone (XXXIV) with orthophosphoric acid in aqueous acetic acid for 20 hr. but further investigations were not pursued.

1.3 Aims of the present work.

1.3.1 Syntheses of some novel derivatives of 3,4-dihydro-2H-1,5-benzodioxepin of potential pharmacological interest.

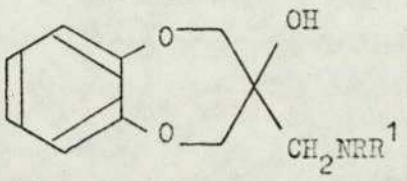
One of the original objectives of the present work was to develop syntheses for derivatives of 3,4-dihydro-2H-1,5-benzodioxepin likely to possess valuable pharmacological activity. The development of an efficient synthesis of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (Ia) as the precursor was considered to be the most promising approach to this problem.



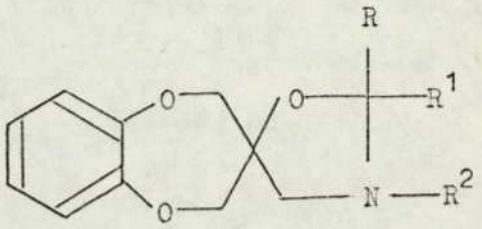
Ia

Subsequently a German patent[1a] and its abstract[1b] by Charles E. Frosst and Company was published (1970) describing a series of

N-substituted-3-hydroxy-3-aminomethyl-2H-1,5-benzodioxepins (XXXVI) and spiro [3,4-dihydro-2H-1,5-benzodioxepin-3,5'-imidazolidines] (XXXVII) which were claimed to possess β-adrenergic stimulant and bronchodilatory activity.



XXXVI



XXXVII

In the patent itself[1a] two processes were disclosed for the preparation of the ketone (Ia) which were similar to those already developed independently in this laboratory by Archer and Claret[18,3,22] and the present author[3] and are described later (Chapter 2.1 and 2.2).

1.3.2 Synthesis of substituted 3-keto-3,4-dihydro-2H-1,5-benzodioxepins for structural studies.

After the investigations outlined above (see 1.3.1) had been started the publication of patents by Charles E. Frosst and Co.[1a,2a] and Charles Pfizer and Co.[23] resulted in the loss of the facilities for biological screening of the derivatives and the subsequent abandonment of this aspect of the programme.

It was then proposed to utilise the capability of synthesising the 3-keto-3,4-dihydro-2H-1,5-benzodioxepins (I) to prepare a series of these compounds with substituents in the benzene ring in order to compare their absorptions in the 270 nm region of their ultra-violet spectra with those of the correspondingly substituted planar 1,3-benzodioxoles (VII) and thus obtain information

concerning the conformation of the heterocyclic dioxepin ring as described by Archer and Claret[3]. This project involved the synthesis of most of the pyrocatechols (II) which were required as intermediates for the preparation of both the 1,3-benzodioxoles (VII) and the 3-keto-3,4-dihydro-2H-1,5-benzodioxepins (I).

CHAPTER 2. SYNTHESES OF 3-KETO-3,4-DIHYDRO-2H-1,5-BENZODIOXEPIN

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2. Syntheses of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin

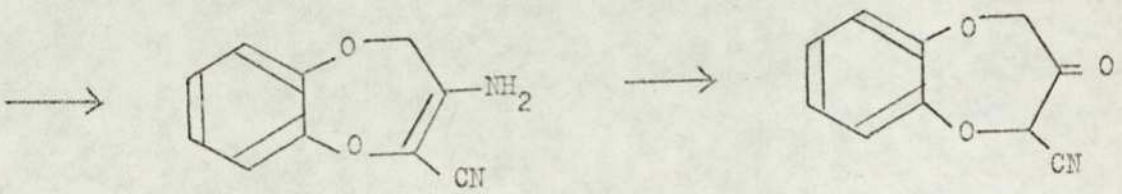
During the course of an earlier investigation in this laboratory on dihydro-2H-1,5-benzodioxepins, Archer[18] studied a number of possible methods for the preparation of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (Ia). (See Chapter 1.2.1 - 1.2.2 for a survey of methods attempted). Of the routes which he examined only two closely related syntheses were found to yield any of the desired products but unfortunately yields were disappointing. As this ketone (Ia) was required in quantity for the proposed syntheses of some novel compounds of pharmaceutical interest (Chapter 3) it was decided to reinvestigate both methods in more detail in an effort to remedy this. For convenience the more promising of the two approaches is discussed first.

2.1 The Thorpe-Ziegler condensation

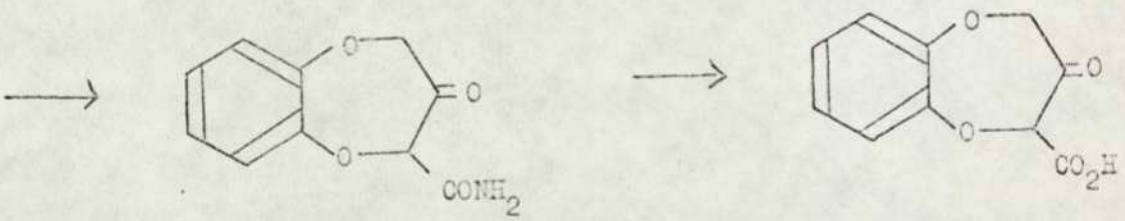
Archer[18] prepared o-phenylenedioxydiacetonitrile (IIIa) in 73% yield from pyrocatechol and chloroacetonitrile and successfully



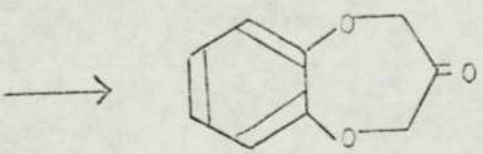
IIIa



Va XXXIV

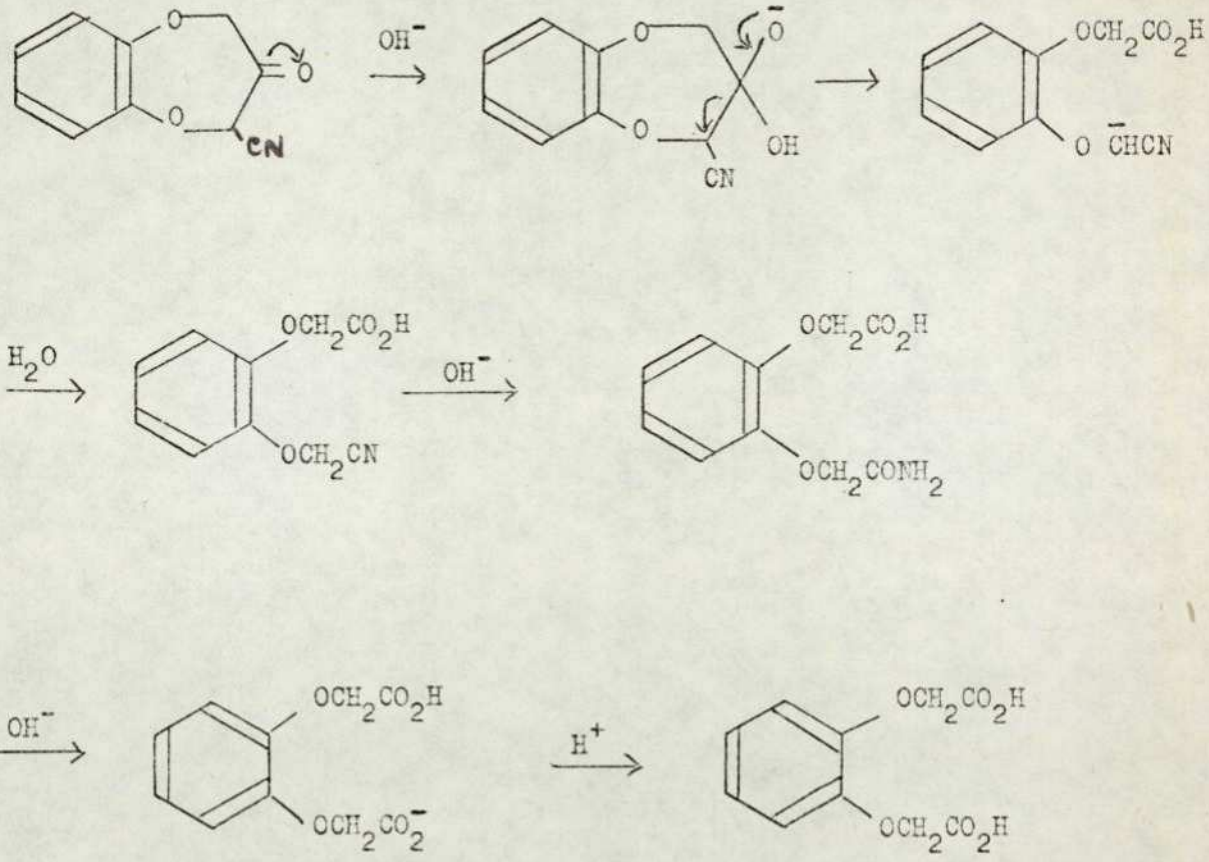


XXXVIII XXXIX



Ia

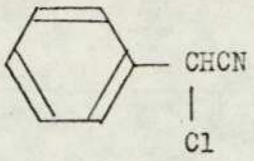
cyclised it to the enaminonitrile (Va) in 77% yield using sodium hydride in dimethyl sulphoxide at 65-70°. Attempts to hydrolyse this compound to the ketone (Ia) for 2 hr. with 2.5N hydrochloric acid afforded 66% of the cyano-ketone (XXXIV) but on extending the reaction time to 7 hr. both cyano-ketone (XXXIV) and ketone (Ia) were detected. Basic hydrolysis of the cyano-ketone (XXXIV) caused cleavage of the heterocyclic ring with formation of 66% o-phenylenedioxydiacetic acid[18] (XXX, R = H) and can be represented in the following way:-



However, a 45% yield of ketone (Ia) resulted[18] when hydrolysis of the cyanoketone (XXXIV) was effected with boiling orthophosphoric acid in acetic acid for 20 hr., a method recommended by Baldwin[24] for the hydrolysis of enaminonitriles to ketones.

The starting material for this work, o-phenylenedioxydiacetonitrile (IIIa), was prepared in essentially the same way as described earlier by Archer and Claret[22]. It involved reacting pyrocatechol (1 mole) with chloracetonitrile (2.4 moles) in refluxing acetone in the presence of a catalytic amount of potassium iodide (0.12 mole) with anhydrous potassium carbonate (1.2 moles) as the acid abstractor. In this investigation the reaction time was increased from 7 to 16 hr. and after filtration and evaporation of the acetone the crude product was recrystallised from 50% aqueous ethanol instead of ethanol alone. The yields of recrystallised dinitrile (IIIa) from four similar experiments were 88 ± 1% and further purification was unnecessary.

It seems pertinent at this stage to mention that unless rubber gloves are worn throughout the preparation and purification of the dinitrile (IIIa) described above and numerous analogues prepared later (Chapter 4.4) there is a serious risk of severe skin irritation which can persist for up to a month. At first this was attributed to the chloracetonitrile but it was noticed that the symptoms only appeared during, or some time after, the actual isolation of the dinitrile (IIIa). No mention of skin irritant properties for chloracetonitrile was found in the literature but the α-phenyl analogue (XL) was reported to be both a skin irritant and a strong



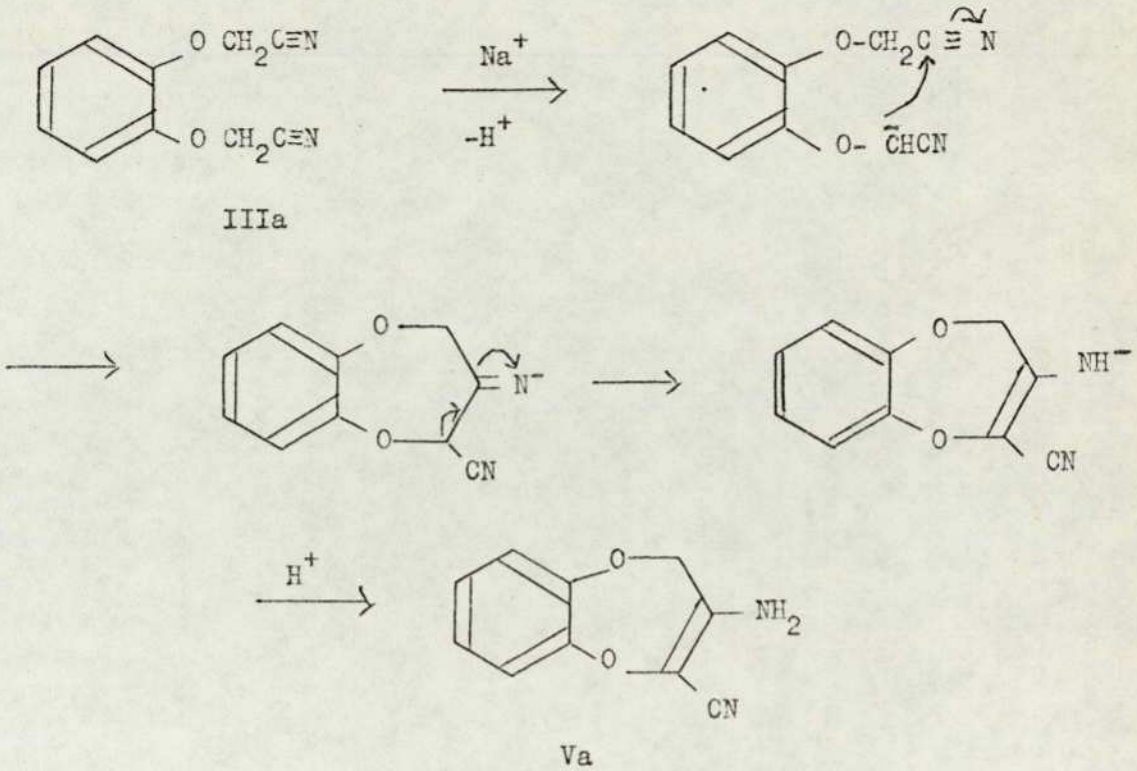
XL

lachrymator. However, the causative agent was eventually identified as iodoacetonitrile formed in the reaction by halogen exchange between chloracetonitrile and the potassium iodide catalyst.

$$ClCH_2CN + KI \longrightarrow ICH_2CN + KCl$$

Scholl[26] observed that even a short contact time with iodoacetonitrile vapour would cause swelling and inflammation of the fingers. These symptoms are accompanied by intense irritation which gradually subsides after about a week when the affected skin begins to peel. Application of a corticosteroid anti-inflammatory cream such as Betnovate[27] was the most successful treatment.

The original Thorpe cyclisation conditions used by Archer[18] involved the controlled addition of a solution of o-phenylenedioxydiacetonitrile (IIIa) (1 mole) in dimethyl sulphoxide (7.5 volumes) to sodium hydride (1 mole) in dimethyl sulphoxide (15 volumes) between 65-70° followed by precipitation of the enaminonitrile (IIIa) with water.

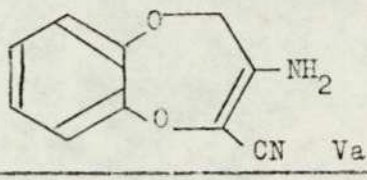


IIIa

Va

Although the method was basically satisfactory several minor but beneficial changes have been introduced during this work. These involved reducing by half both the volume of dimethyl sulphoxide and the reaction time that were originally employed[18]. The crude enaminonitrile (Va) was obtained in excellent yield adopting these modifications and was readily freed from any mineral oil, present in the sodium hydride dispersant, by digestion with warm light petroleum. Removal of the mineral oil at this stage was advisable since it could contaminate the ketone (Ia) later and prove difficult to remove. Table 1 shows the yields of oil-free enaminonitrile (Va) obtained from six identical experiments.

TABLE 1

Experiment Number	Scale (moles)	% yield of oil-free  Va	m.p.*
1	0.1	91	158-160°
2	"	92	157-161°
3	"	90.5	158-161°
4	"	93	156-159°
5	"	96	157-161°
6	"	90	159-162°
Average yield 92%			

* an analytical sample had m.p. 163-164.5°

The material from these six experiments was combined and recrystallised from 66% aqueous ethanol (15 volumes) to give 69% of the pure enaminonitrile (Va), m.p. 163-165°. In an attempt to recover more material, the filtrate was concentrated at reduced pressure yielding a sticky brown solid (19.5 g.) from which an additional 5% of pure enaminonitrile (Va), m.p. 161-164°, was obtained after several recrystallisations from methanol. In an effort to reduce the loss of enaminonitrile (Va) during the purification, the crude oven-dried material from another series of six 0.1 mole runs (116g; 101.5%; m.p. 157-160°) was dissolved in boiling ethyl acetate, filtered to

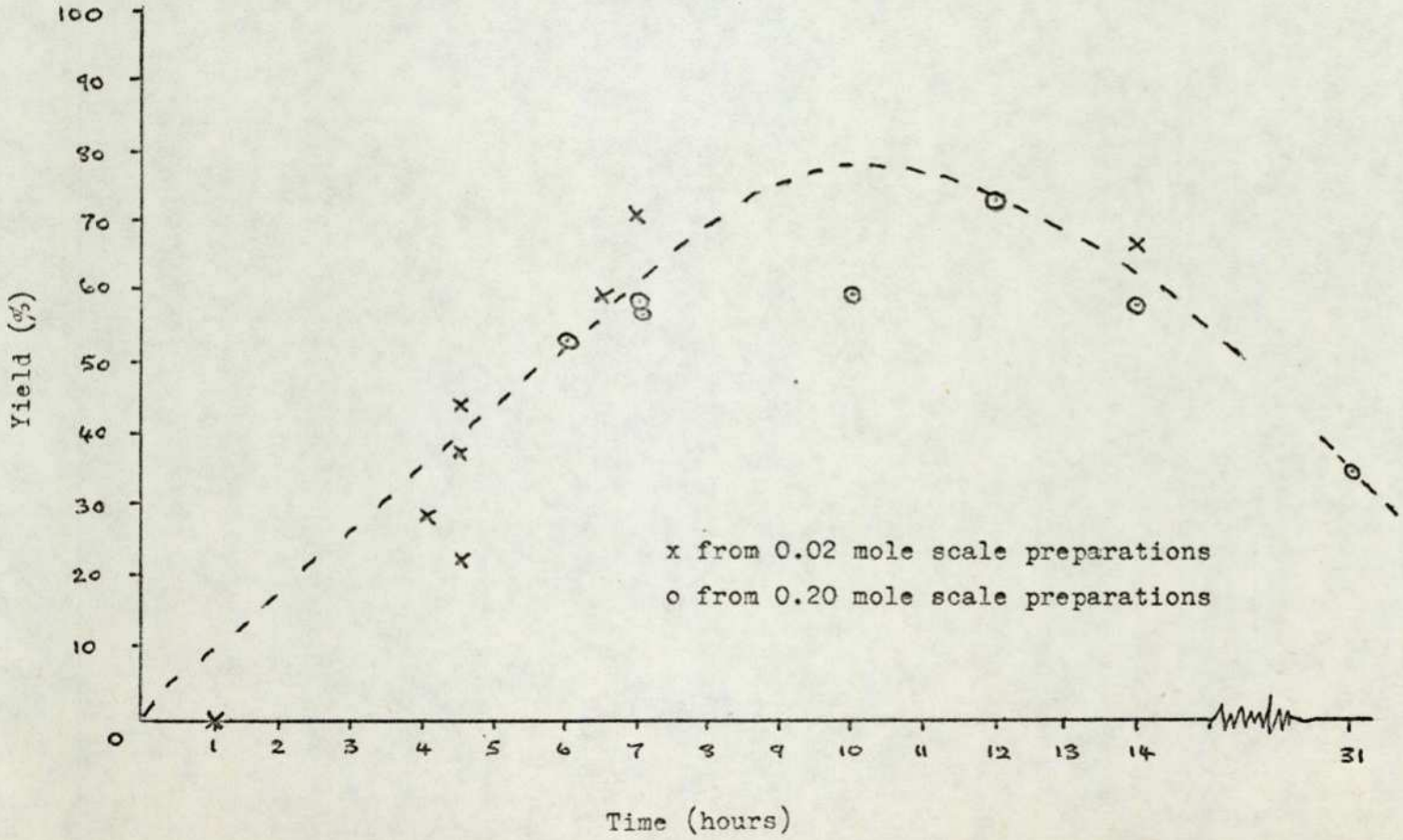
remove a small amount of slimy black material and evaporated at reduced pressure. The residual pale cream solid was then triturated with warm petroleum ether and filtered to give 89% of oil-free enaminonitrile (Va), m.p. 159-162°. When the crude product from another six 0.1 mole runs (113g. >100%; m.p. 153-155°) was similarly purified an 89% yield of pale cream enaminonitrile (Va) m.p. 156-159°, was also realised. The enaminonitrile (Va) obtained by this alternative purification technique was sufficiently pure for the next stage. It was subsequently found that providing the crude material was freed from mineral oil no further purification was in fact necessary.

Previous work[18] had shown that the enaminonitrile (Va) could be hydrolysed with dilute hydrochloric acid to the cyanoketone (XXXIV) which could then be converted into the ketone (Ia) with 85% orthophosphoric acid in aqueous acetic acid (see Chapter 1.2.2). Consequently there appeared to be no reason why the latter conditions could not be successfully applied to effect hydrolysis of the enaminonitrile (Va) directly to the ketone (Ia). The reaction sequence Va ⟶ XXXIV ⟶ XXXVIII ⟶ XXXIX ⟶ Ia (see page 25) depicts the discrete steps that must occur whilst the hydrolysis progresses. A series of small scale (0.02 mole) experiments was therefore conducted in which the enaminonitrile (Va) was hydrolysed for different times with 85% orthophosphoric acid in aqueous acetic acid. Any ketone (Ia) present was isolated by dilution of the reaction mixture with water and extracting it into chloroform (dichloromethane was subsequently used). Evaporation of the solvent and distillation

of the residue then yielded the ketone (Ia). The yields of distilled product are recorded in the experimental section (2.1.4, experiments 1-8) and are also presented graphically (Fig. 1). The graph shows clearly that optimum yields were realised after about 8-10 hr. and that prolonging the hydrolysis tended to decrease the yield. These findings were supported by the results obtained later from some 0.2 mole preparations (see Fig. 1, experiments 1-8; 2.1.4). It was also found that coloured and polar impurities were readily removed by passing a benzene or toluene solution of the crude ketone (Ia) through a short column of neutral alumina. This procedure greatly improved the quality of the ketone (Ia) obtained before and after its distillation. The pure ketone (Ia) was obtained initially as a colourless liquid, b.p. 78-84°/0.05 mm, which readily crystallised but even after repeated chromatography and sublimation the m.p. could not be raised above 37-38° although the reported[8] m.p. was 40-42°. The ketone (Ia) possessed a penetrating odour reminiscent of water-melons, a property that was later reported in a patent[23]. Its infra-red spectrum (in $CHBr_3$) agreed with that reported[8,18] (Fig. 2). The nuclear magnetic resonance spectrum (in CCl_4) (Fig. 3) revealed two singlets with identical areas at 3.08 and 5.38 τ corresponding to the aromatic and heterocyclic protons respectively whereas the spectrum published by Rosnati and De Marchi[8] recorded 3.04 and 5.75 τ but the solvent was not specified. It is possible that the latter value is a typographical error since on assuming their spectrum was a scale reproduction, remeasurement gave values of 3.06 and 5.30 τ which agreed closely with our findings.

Figure 1.

Variation in yield of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (Ia) with hydrolysis time.



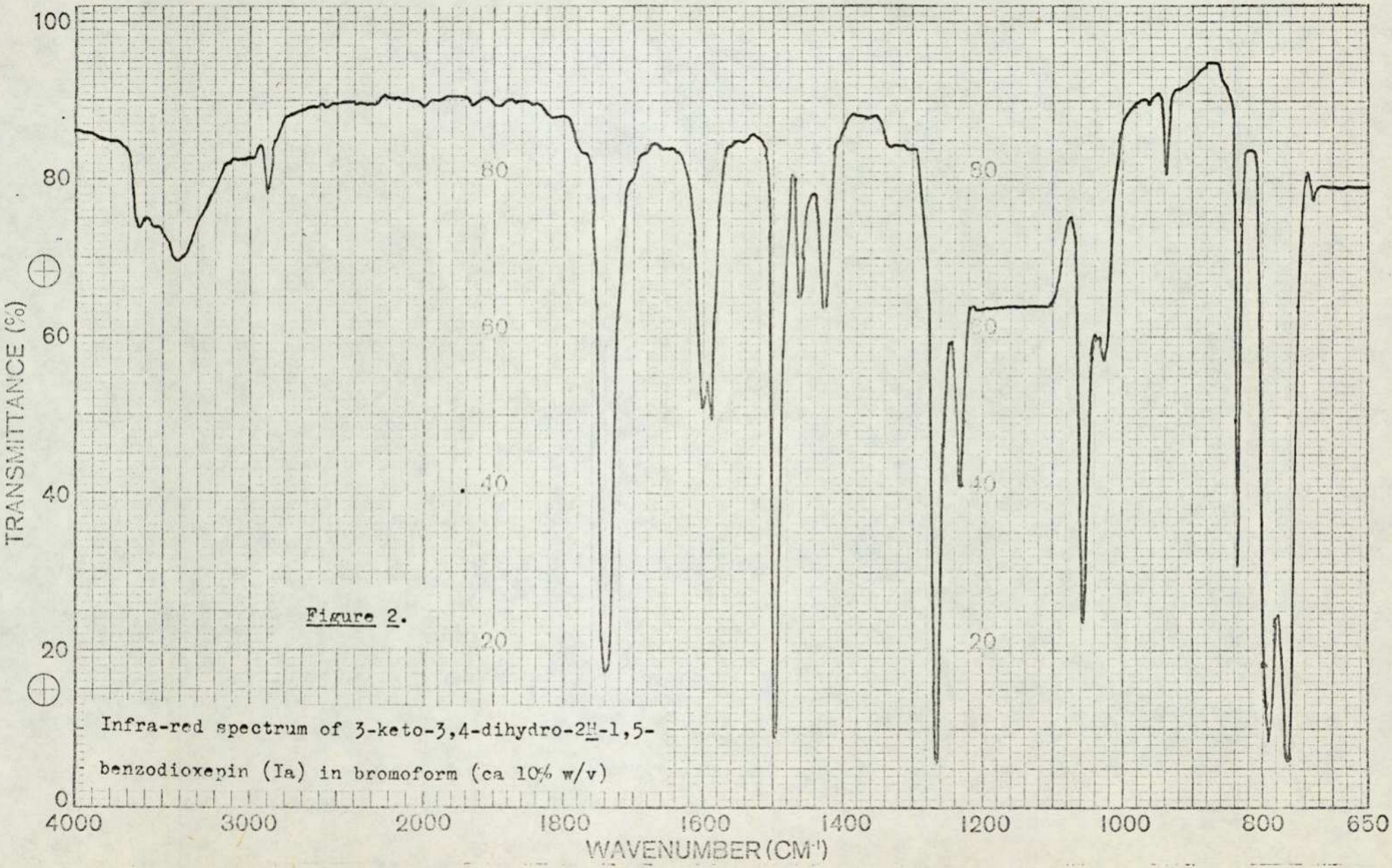


Figure 2.

Infra-red spectrum of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (Ia) in bromoform (ca 10% w/v)

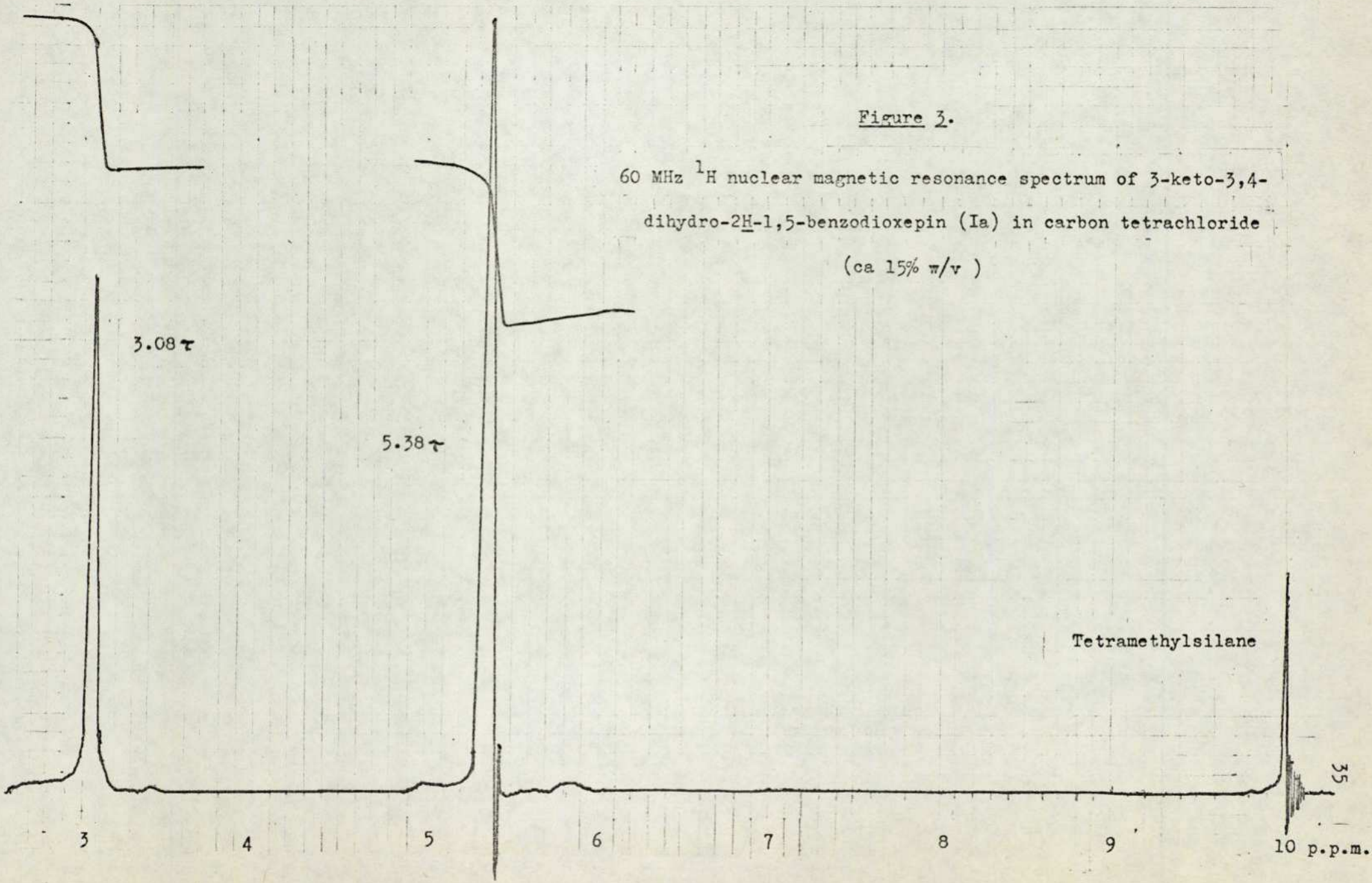
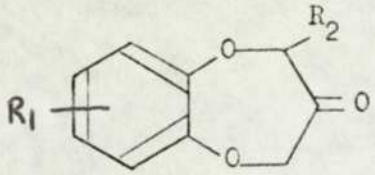


Figure 3.

60 MHz ^{1}H nuclear magnetic resonance spectrum of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (Ia) in carbon tetrachloride (ca 15% w/v)

The ketone (Ia) was characterised as the known[8] 2,4-dinitrophenylhydrazone (XXIX, R = $-NO_2$) and the hitherto unreported oxime (XXVIII, R = OH) (see Chapter 3.5.1).

Subsequent to these developments there appeared a patent[1a] by Charles E. Frosst and Co. (1970) which claimed the preparation of the ketone (Ia) by an almost identical synthesis. Cyclisation of the dinitrile (IIIa) to the enaminonitrile (Va) was achieved with sodamide or potassium t-butoxide in dimethyl sulphoxide at room temperature in 64 and 62% yields respectively. It is interesting to note that the hydrolysis of the enaminonitrile (Va) to the ketone (Ia) was effected in 62% yield with 85% orthophosphoric acid in acetic acid. Some months later a second patent application by Charles E. Frosst and Company claimed[2a] the preparation of the ketone (Ia) and a number of other substituted ketones (XLI).



XLI

R_1 = 7-Cl, R_2 = H

R_1 = 7-Cl, R_2 = Me

R_1 = 6-OMe, R_2 = H

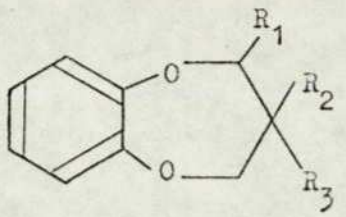
R_1 = 6-OCH_2Ph, R_2 = H

R_1 = H, R_2 = Ph

R_1 = H, R_2 = 2-pyridyl

R_1 = H, R_2 = 2-pyridylmethyl

from which some amines (XLII) possessing bronchodilatory activity



XLII

R_1 = H, R_2 = OH, R_3 = $-CH_2NH_2$

R_1 = H, R_2 = OH, R_3 = $-CH_2NCH(Me)_2$

R_1 = 2-pyridyl, R_2 = OH, R_3 = $-CH_2NHCH(Me)_2$

were prepared.

Potter[28] (1970) has also described the cyclisation of the dinitrile (IIIa) with lithium N-methylanilide under high dilution conditions but no yields were recorded for this or for the hydrolysis of the enaminonitrile (Va) to the ketone (Ia) which was effected with dilute hydrochloric acid.

2.1.1 Experimental and Instrumentation

All reactions using lithium aluminium hydride and sodium hydride were performed under dry nitrogen.

Melting points were determined in capillary tubes and have been corrected.

Gas-liquid chromatography was performed on a Perkin-Elmer PE 800 gas chromatograph fitted with a flame ionisation detector using columns A and B. For column C a Perkin-Elmer model PE-801 was used.

Column A: The stationary phase was silicone gum rubber SE30, 5% w/w on Chromosorb W, 60-80 mesh, packed in a stainless steel tube, 6ft. x $\frac{1}{4}$in. Nitrogen flow rate 80 ml/min.

Column B: Trifluoromethylpolysiloxane (FS 1265), $1\frac{1}{2}$% on Chromosorb W, 80-100 mesh, packed in a stainless steel tube, 6ft. x $\frac{1}{4}$in. Nitrogen flow rate 75 ml/min.

Column C: OV-1, $2\frac{1}{2}$% w/w on Chromosorb G(AW-DCMS), 80-100 mesh packed in a 2m x 2mm glass column. Nitrogen flow rate 75 ml/min

Compositions of mixtures are approximate and were calculated from peak areas on the chart.

For thin-layer chromatography commercial Silica-Gel F_{254} precoated (0.25mm) plates purchased from E. Merck, Darmstadt, Germany, were used. The solvent system was toluene/ethylacetate (3:1) (solvent A) and the plates were examined under ultra-violet light.

Infra-red spectra were recorded for liquid films or Nujol mulls between rock-salt plates with a Perkin-Elmer model 157 spectrophotometer and for potassium bromide discs on a model 137B "Infracord" instrument.

Ultra-violet absorption spectra were recorded for solutions in methanol (BDH spectroscopic grade, refluxed with zinc dust and potassium hydroxide and redistilled) either with a Hitachi-Perkin-Elmer EPS-3T recording spectrophotometer[29a] or a Unicam SP800 instrument[29b] in 10mm matched silica cells. The wavelength calibration for each instrument was checked against a holmium glass and the wavelength resolution with benzene vapour, as described in the manufacturers' handbooks. The optical density scale was checked against standard alkaline potassium dichromate solution[30].

Wavelengths are quoted in nano-metres (nm) (1nm = 1mμ) and extinction coefficients are quoted in litre. mole^{-1}. cm^{-1}.

The nuclear magnetic resonance spectra were recorded for ca 10-20% solutions in deuterochloroform or carbon tetrachloride on a Perkin-Elmer R10 instrument operating at 60 MHz. Chemical shifts are quoted in τ values relative to tetramethylsilane as an internal standard taken as 10.00 τ.

The 100 and 220 MHz nuclear magnetic resonance spectra were recorded on Varian HA-100D and HR-220 instruments respectively by the Physico-chemical Measurements Units, Harwell, who also determined the high resolution mass spectra with an AEI MS-902 spectrometer. The energy source was 70 e/v. Elemental analyses were determined with an F and M CHN analyser, model 185.

2.1.2 o-Phenylenedioxydiacetonitrile (IIIa)

This reaction was carried out in a fume cupboard. Rubber gloves were worn, particularly during the work-up, to avoid contact with any iodoacetonitrile vapour which causes severe and persistent skin inflammation[26].

A mixture of pyrocatechol (73.3g, 0.666 mole), chloracetonitrile (119g, 1.57 moles), anhydrous potassium carbonate (110.7g, 0.8 mole) and potassium iodide (13.3g, 0.08 mole) in acetone (530 ml) was refluxed with stirring for 16 hr. and cooled. The inorganic salts were collected, washed with acetone and the combined filtrates were evaporated. Recrystallisation of the residue from 50% ethanol gave 111.8g (89%) of o-phenylenedioxydiacetonitrile as fawn needles, m.p. 86-88° (lit.,[22] m.p. 85-86°). (Found: C, 63.8; H, 4.2; N, 15.0. Calc. for $C_{10}H_8N_2O_2$ C, 63.8; H, 4.3; N, 14.9%). λ max 269 and 273.5 (ε 1440 and 1380)[29b]. τ ($CDCl_3$) 3.0 (4H, s, aromatic) and 5.32 (4H, s, CH_2).

The yields obtained from three later experiments performed on the same scale were 87%, m.p. 86-88°; 88%, m.p. 84-86° and 87% m.p. 83-85°.

2.1.3 3-Amino-2H-1,5-benzodioxepin-4-carbonitrile (Va)

Sodium hydride (50% w/w dispersion in mineral oil; 4.8g, 0.1 mole) was added to stirred dimethyl sulphoxide (75 ml.) under dry nitrogen and heated at 65-70° for 15 min. A solution of o-phenylenedioxydiacetonitrile (18.8g, 0.1 mole) in dimethyl sulphoxide (50 ml) was then added during 10-15 min., keeping the reaction mixture at 65-70° and for a further 15 min. after the addition. The dark reddish-brown solution was poured into water (1 litre) and the fawn precipitate was collected, washed well with water and dried. After trituration with several portions of boiling light petroleum (b.p. 60-80°) the oil-free product was collected and dried. The crude enaminonitrile from six such experiments was: 17.2g (91%), m.p. 158-160°; 17.3g (92%), m.p. 157-161°; 17.0g (90.5%), m.p. 158-161°; 17.5g (93%), m.p. 156-159°; 18.0g (96%), m.p. 157-161° and 16.9g (90%), m.p. 159-162°. These were combined and recrystallised from 66% aqueous ethanol (15 volumes) to give 74.3g (69%) of 3-amino-2H-1,5-benzodioxepin-4-carbonitrile, m.p. 163-165°. T.l.c., solvent A, showed a single spot, Rf 0.52. Evaporation of the filtrate at reduced pressure yielded a sticky brown solid (19.5g) which required two recrystallisations before satisfactory material (5.4g, 5%), m.p. 161-164°, was obtained. An analytical sample (colourless needles from aqueous ethanol) had m.p. 163-164° (lit., m.p. 163-164°[3], m.p. 168-169° [1b]). (Found: C, 63.6; H, 4.2; N, 14.9. Calc. for $C_{10}H_8N_2O_2$ C, 63.8; H, 4.3; N, 14.9%). ν max (Nujol) 3450, 3350 (NH_2) 3230 (C=C?), 2200 (C≡N), 1650 (NH), 1630 (>C=C<) cm^{-1}. τ ($CDCl_3$) 3.05 (4H, s, aromatic), 5.16 (2H, s, OCH_2) and 5.87 (2H, broad s, NH_2).

The crude product from six similar experiments amounted to 116g (> 100% due to the presence of mineral oil) and had m.p. 157-160°. It was dissolved in boiling ethyl acetate (500 ml), filtered and evaporated *in vacuo*. The pale cream solid was then digested with boiling light petroleum (b.p. 60-80°) (2 x 250 ml), collected and dried to give 96g (89%) of material, m.p. 159-162°, which was sufficiently pure for subsequent reactions.

The crude product (113g, > 100%, m.p. 153-155°) from another six experiments was similarly purified and also yielded 89% of material, m.p. 156-159°.

2.1.4 3-Keto-3,4-dihydro-2H-1,5-benzodioxepin (Ia)

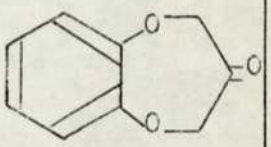
A mixture of 3-amino-2H-1,5-benzodioxepin-4-carbonitrile (37.6g, 0.2 mole), acetic acid (750 ml), 85-88% orthophosphoric acid (300 ml) and water (45 ml) was refluxed for 12 hr., cooled, poured into water (2l.) and exhaustively extracted with chloroform (8 x 100 ml) (in subsequent reactions dichloromethane was used). After removal of the chloroform and some acetic acid at reduced pressure the residual brown oil was digested with several portions of boiling light petroleum (b.p. 60-80°) to remove the ketone from an insoluble brown resin (3.4g). Evaporation of the petroleum gave a pale yellow oil which was dissolved in toluene and then passed through a column of neutral alumina (200g). Removal of the toluene and distillation of the residual oil gave 23.8g (72.5%) of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin, b.p. 78-84°/0.05 mm., m.p. 34-38°. G.l.c., column A at 120°, gave

a single peak. A sample, after recrystallisation from light petroleum (b.p. 40-60°), afforded colourless prisms, m.p. 37-38° which was not raised by sublimation at 0.01 mm (bath temperature 30-35°). (Lit.,[8] m.p. 40-42°). (Found: C, 65.6; H, 4.8. Calc. for $C_9H_8O_3$ C, 65.8; H, 4.9%). ν max ($CHBr_3$) 1750 (C=O), 1600, 1585, 1495 (>C=C<), 1260 (-C=C-OR)cm^{-1}. (See Fig. 2). λ max 273.5 nm (ε 1550)[29b]. τ (CCl_4) 3.08 (4H, s, aromatic) and 5.28 (4H, s, $-OCH_2$). (See Fig. 3). Table 2 shows the yields of ketone obtained after different reaction times.

The ketone gave a 2,4-dinitrophenylhydrazone, (yellow needles from methanol), m.p. 167-168° which did not, as was reported[8], decompose (lit.,[8] m.p. 164° decomp.). (Found: C, 52.4; H, 3.4; N, 16.2. Calc. for $C_{15}H_{12}N_4O_6$ C, 52.5; H, 3.5; N, 16.3%).

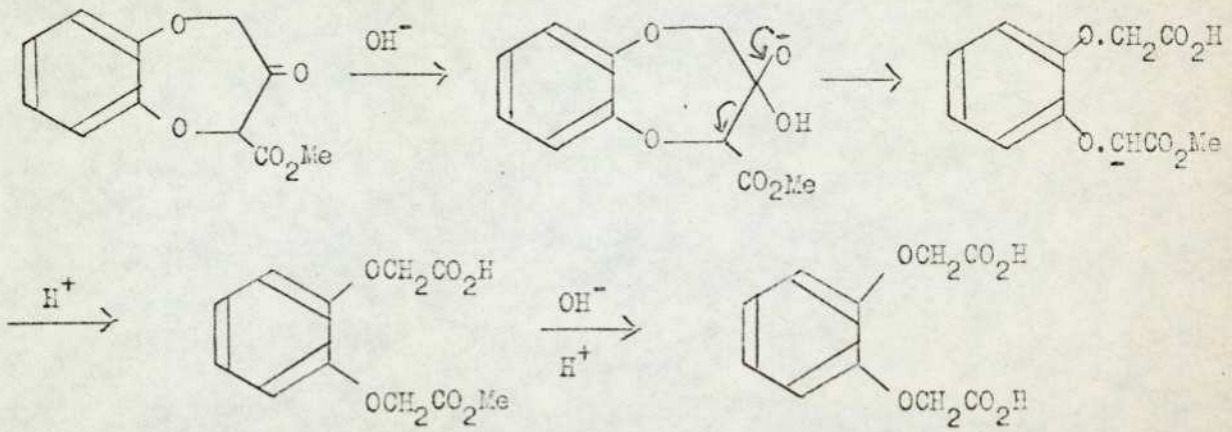
The full preparation and properties of the oxime derivative are given in Chapter 3.5.1.

TABLE 2

Experiment Number	Scale (Moles)	Hydrolysis time	% yield of distilled 
1	0.02	1¼ hr	nil
2	"	4 hr	28.6
3	"	4½ hr	23
4	"	4½ hr	37
5	"	4½ hr	44
6	"	6½ hr	59.5
7	"	7 hr	71
8	"	14 hr	67
9	0.2	6 hr	53.6
10	"	7 hr	58.5
11	"	7 hr	57.6
12	"	10 hr	60.0
13	"	12 hr	72.5
14	"	14 hr	58.5
15	"	31 hr	35.4

2.2 The Dieckmann Cyclisation

In an earlier investigation Archer[18] successfully reacted pyrocatechol with methyl chloroacetate to give a 35% yield of dimethyl o-phenylenedioxydiacetate (XXX, R=Me) and cyclised it to the β-keto-ester (XXXI, R=Me) in 45% yield. His attempt to perform the ketonic hydrolysis on this compound in a stepwise fashion by heating it for a short time with base followed by acid induced decarboxylation gave only a trace of the ketone (Ia); the major product obtained (35%) was o-phenylenedioxydiacetic acid (XXX, R=H) arising from basic cleavage of the heterocyclic ring. This can be expressed as follows:-

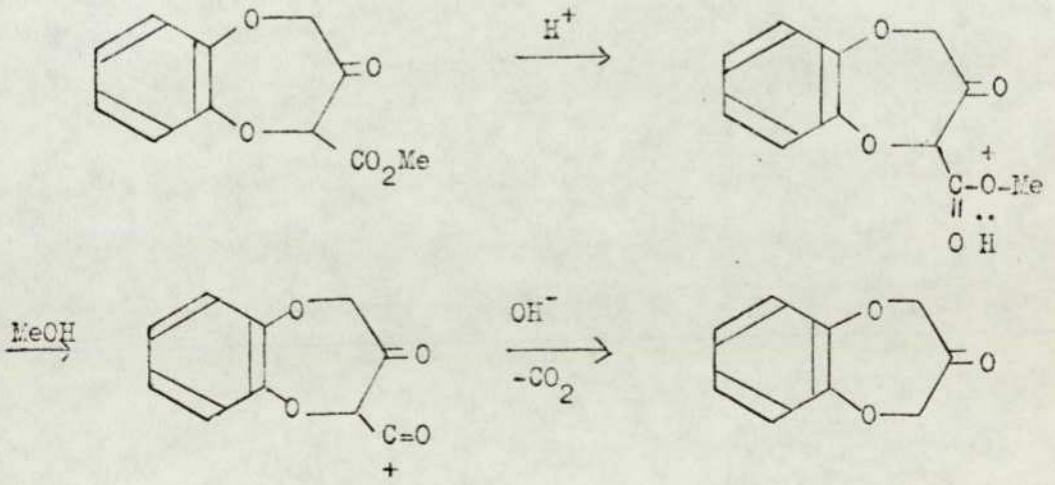


As ketonic hydrolysis of β-keto-esters is usually accomplished with acid[31] we decided to subject the β-keto-ester (XXXI, R=Me) to the same conditions which we had used earlier for hydrolysis of the enaminonitrile (Va). The required dimethyl o-phenylenedioxydiacetate (XXX, R=Me) was prepared by the reaction of pyrocatechol (1 mole) with methyl chloroacetate (1.25 moles) in acetone

containing anhydrous potassium carbonate (1.5 moles) and a catalytic amount of potassium iodide. However, the 35% yield previously obtained after 7 hr.[18] was increased to 63% after 21 hr. (a later experiment gave a 59% yield after 24 hr.) The only minor alteration made during the Dieckmann cyclisation of the dimethyl ester (XXX, R = Me) to the β-keto-ester (XXXI, R = Me) was to reduce the molar ratio of oil-free sodium hydride to ester from 2.2 : 1 (45% yield of β-keto-ester[18]) to 2:1 (57% yield).

Ketonic hydrolysis of the β-keto-ester (XXXI, R = Me) was performed with 85% orthophosphoric acid in aqueous acetic acid for 5 hr. and yielded 84.5% of chromatographically (g.l.c.) pure ketone (Ia) which was identical (infra-red and nuclear magnetic resonance spectra and mixed m.p. of 2,4-dinitrophenylhydrazone) with the ketone (Ia) similarly obtained from the enaminonitrile (Va). The pure (g.l.c.) ketone (Ia) was also obtained in 84% yield by refluxing the β-keto-ester (XXXI, R = Me) in aqueous ethanolic hydrochloric acid (1:1) for 12 hr.

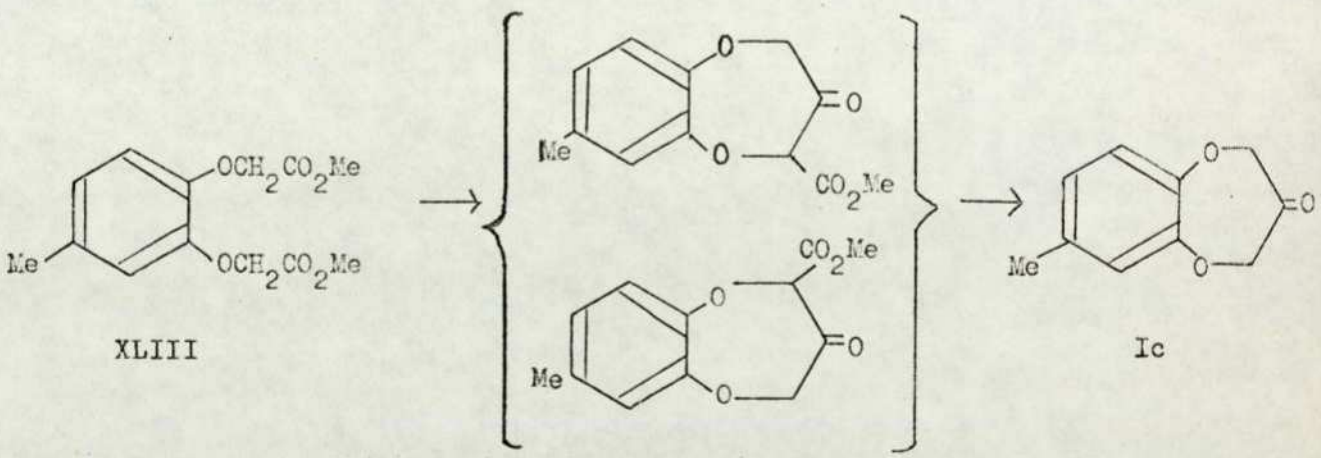
The successful formation of the ketone (Ia) from the β-keto-ester (XXXI, R = Me) in acid media can be explained as follows:-



Whereas basic hydrolysis of the β-keto-ester involves initial attack on the ketonic carbonyl group with consequent cleavage of the heterocyclic ring, an acid medium supresses this and only the ester group suffers hydrolysis with concomitant decarboxylation to the ketone.

Soon after completing this aspect of the work the patent by Charles E. Frosst appeared[1a] in which the cyclisation of dimethyl o-phenylenedioxydiacetate (XXX, R=Me) with potassium t-butoxide in dimethyl sulphoxide to the β-keto-ester (XXXI, R=Me) was claimed together with its hydrolysis to the ketone (Ia) but no yields were recorded for either stage.

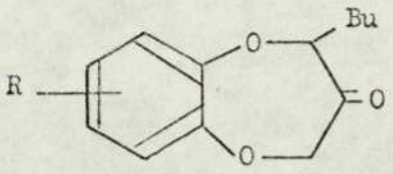
Within the space of a few months two more reports[23, 19a] appeared concerning the preparation of 3-keto-3,4-dihydro-2H-1,5-benzodioxepins. The first was a patent by Charles Pfizer and Company Incorporated[23] which described the Dieckmann cyclisation of the dimethyl ester (XLIII) with sodium hydride in dimethoxyethane



XLIII XLIV Ic

to yield 94.5% of a mixture of the 7- and 8-methyl β-keto-esters (XLIV). Ketonic hydrolysis of this with 2.5% hydrogen chloride

in 50% aqueous ethanol then gave the ketone (Ic) in 92.5% yield. The preparations of the unsubstituted ketone (Ia) and the 2-n-butyl ketone (XLV), R = 7- and/or 8-Me) were also mentioned. These



XLV

compounds were claimed to be useful as perfume constituents and to impart a watermelon flavour and odour to foods.

The second communication by Schroth and Werner[19a] in 1970 described the preparation of the ketone (Ia) in unspecified yield by the ketonic hydrolysis of the β-keto-ester (XXXI, R=Me) with 10% sulphuric acid. However, it appeared that the work was actually carried out in 1965/1966 by Werner[32] who prepared the β-keto-ester (XXXI, R=Me) in 60% yield by a Dieckmann cyclisation of dimethyl o-phenylenedioxydiacetate (XXX, R=Me) with sodium methoxide in toluene without resorting to the high dilution technique generally required in this type of reaction[31]. It is interesting to note that under the same conditions cyclisation of the diethyl ester (XXX, R=Et) yielded only 8% of the β-keto-ester (XXXI, R=Et),[19b] (cf. results of Rosnati and De Marchi[8], Chapter 1.2.2).

2.2.1 Dimethyl o-phenylenedioxydiacetate (XXX, R=Me)

A mechanically stirred mixture of pyrocatechol (66g, 0.6 mole), methyl chloroacetate (69.5g, 0.75 mole), anhydrous potassium carbonate (124.5g, 0.9 mole) and potassium iodide (12g, 0.072 mole) in acetone (675 ml) was refluxed for 21 hr, cooled and filtered. Evaporation of the filtrate at reduced pressure afforded a solid which was dissolved in chloroform (500 ml), washed with ice-cold 5% sodium hydroxide solution (2 x 100ml), water (100 ml) and dried (Na_2SO_4). After removal of the solvent the residue was distilled to give the product, 96g (63%), b.p. 160-170°/0.3mm, m.p. 53-56°. A sample (colourless needles from ether) had m.p. 57-58° (lit.,[18] m.p. 56-57°). (Found: C, 56.9; H, 5.6. Calc. for $C_{12}H_{14}O_6$ C, 56.7; H, 5.55%). ν_{max} (Nujol) 1660 (C=O) cm^{-1}. In a later experiment a 57% yield was obtained after 24 hr.

2.2.2 2-Methoxycarbonyl-3-keto-3,4-dihydro-2H-1,5-benzodioxepin (XXXI, R=Me)

A solution of dimethyl o-phenylenedioxydiacetate (101.6g, 0.4 mole) in dry toluene (400 ml) was added dropwise over 3 hr. to a vigorously stirred suspension of sodium hydride (oil-free ex Koch-Light; 19.2g, 0.8 mole) in dry toluene (500 ml), containing dry methanol (1 ml), under a dry nitrogen atmosphere. After completing the addition the mixture was refluxed for 2 hr., cooled in ice and treated dropwise with acetic acid (80 ml) and water (20 ml). The mixture was stirred for an additional 0.5 hr. when the contents

were decanted from some tarry material and the layers were separated. After washing the organic phase with saturated sodium hydrogen carbonate solution it was dried (Na_2SO_4) and evaporated *in vacuo*. The residue, which gave a purple colouration with aqueous ethanolic ferric chloride solution, was extracted into boiling light petroleum (b.p. 80-100°) (2 x 250 ml) leaving a sticky residue. Evaporation of the petroleum extracts and distillation of the pale yellow residue gave 50.6g (57%) of the keto-ester as a colourless oil, b.p. 125-130°/0.01 mm, n_D^{25} 1.5357 (lit.,[18] b.p. 107-110°/0.02 mm, n_D^{21} 1.5380). It afforded a 2,4-dinitrophenylhydrazone (yellow needles from ethanol), m.p. 192-193° (lit.,[18] m.p. 192-194°).

2.2.3 3-Keto-3,4-dihydro-2*H*-1,5-benzodioxepin (Ia) (with orthophosphoric acid).

When 2-methoxycarbonyl-3-keto-3,4-dihydro-2*H*-1,5-benzodioxepin (8.9, 0.04 mole) was refluxed for 5 hr. in a mixture of glacial acetic acid (200 ml), 85-88% orthophosphoric acid (60 ml) and water (9 ml) and worked up as described previously (2.1.4) there was obtained 5.6g (84.5%) of ketone, b.p. 80-84°/0.4 mm, m.p. 34-36° which was shown by g.l.c., column A at 120° to be almost pure. This material was identical (infra-red spectrum and mixed m.p. of 2,4-dinitrophenylhydrazone) with ketone prepared by hydrolysis of the enaminonitrile (2.1.4).

2.2.4 3-Keto-3,4-dihydro-2H-1,5-benzodioxepin (Ia)

(with hydrochloric acid)

2-Methoxycarbonyl-3-keto-3,4-dihydro-2H-1,5-benzodioxepin (5.55g, 0.025 mole) was refluxed for 12 hr. in a 1:1 mixture of hydrochloric acid (d = 1.18) and ethanol (20 ml), diluted with water (50 ml) and extracted with ether (4 x 20 ml). Evaporation of the dried (Na_2SO_4) ether solution and distillation of the residue gave 3.45g (84%) of ketone, b.p. 82-86°/0.5 mm, m.p. 30-33° which was essentially pure by g.l.c. (column A at 120°). It was identical (infra-red spectrum and mixed m.p. of 2,4-dinitrophenylhydrazone) with ketone prepared by the hydrolysis of the enaminonitrile (2.1.4).

CHAPTER 3. SYNTHESES OF NOVEL DERIVATIVES OF 3,4-DIHYDRO-2H-1,5-BENZODIOXEPIN OF POTENTIAL PHARMACOLOGICAL INTEREST

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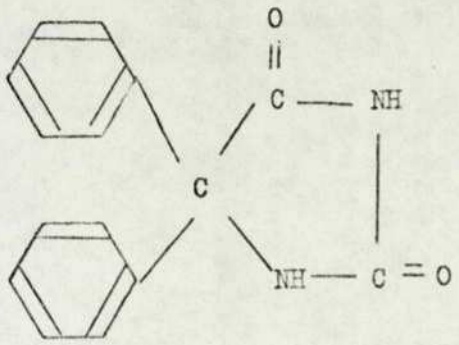
3. Syntheses of novel derivatives of 3,4-dihydro-2H-1,5-benzodioxepin of potential pharmacological interest.

With the ketone (Ia) now available in quantity for the first time it was decided to undertake the synthesis of various derivatives and submit them for biological testing. Emphasis was placed on the preparation of compounds which, by virtue of their chemical structure, might exhibit central nervous system (CNS) depressant activity.

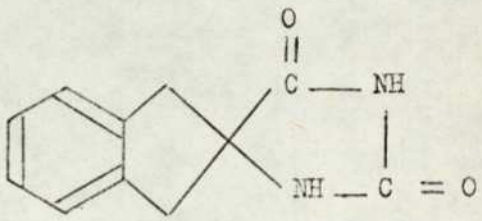
Unfortunately biological screening of these compounds had to be suspended after only one compound had been tested because of the publication in 1970 of a patent by Charles E. Frosst and Co.[1a] which claimed the preparation of a large variety of dihydro-1,5-benzodioxepins possessing β-adrenergic stimulant and bronchodilatory activity.

3.1 The preparation of 3,4-dihydro-spiro [1,5-benzodioxepin-(2H)-3,4'-imidazolidine] -2',5'-dione.

Among the many classes of organic compounds which affect the central nervous system are the hydantoins[33a,34]. One of the most valuable of these is the anticonvulsant drug phenytoin (XLVI), 5,5-diphenylhydantoin, which is widely used in the treatment of

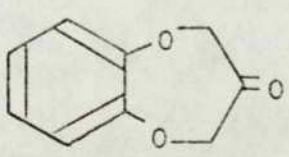


XLVI

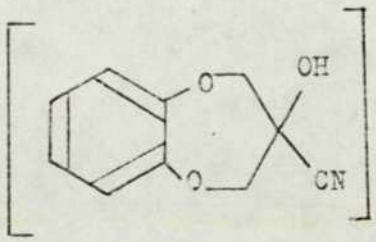


XLVII

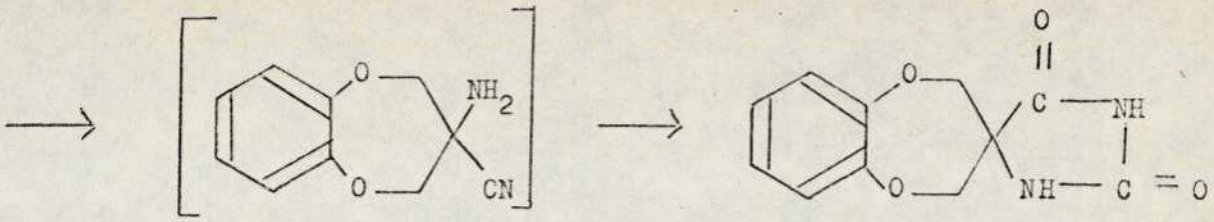
epilepsy and resulted from a systematic study of substituted hydantoins by Putnam and Merritt[35] in 1937. Recently Pinder and co-workers[36] described the preparation of the spirohydantoin (XLVII) which was claimed to possess sedative activity, a result which prompted us to prepare the spirohydantoin (XLIX). It was obtained in 75% yield by heating the ketone (Ia) with a mixture



Ia



XLVIII



XLIX

of ammonium carbonate and potassium cyanide in 50% ethanol at 60-65° for 6 hr. The reaction proceeds via the intermediate cyanohydrin (XLVIII) which though not isolated in this work was subsequently described in a patent[1a]. The presence of a tautomeric hydantoin ring system was confirmed by its solubility in aqueous sodium hydroxide and insolubility in mineral acids. In Nujol its infra-red spectrum showed a band in the NH stretching region with two intense carbonyl absorptions at 1775 and 1725 cm^{-1}. These have been reported to be characteristic of hydantoins; the higher frequency band being allocated to the 5'-carbonyl and the lower to the 2'-carbonyl group[37]. In addition peaks due to the aromatic $>C=C<$ stretching frequencies[38a] at 1650, 1585 and 1495 cm^{-1} and a strong band at 1245 cm^{-1} associated with the $-C=C-O-R$ grouping of an aryl ether[38b] were consistent with the dihydrobenzodioxepin ring system[8].

A preliminary biological assay of the hydantoin (XLIX) revealed only weak anticonvulsant and tranquilliser activity that did not warrant further testing[39]. The results have been summarised in Table 3.

TABLE 3

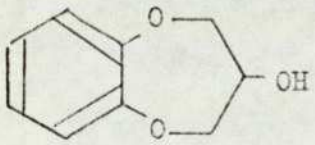
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3.1.1 3,4-Dihydro-spiro-[1,5-benzodioxepin-(2H)-3,4'-imidazolidine]-2',5'-dione (XLIX)

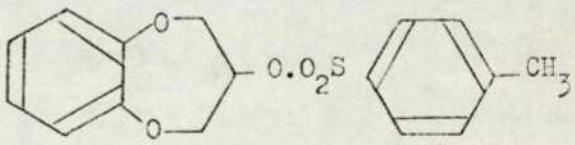
A mixture of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (1.64g, 0.01 mole), ammonium carbonate (7.85g, 0.05 mole), and potassium cyanide (1.3g, 0.02 mole) in 50% ethanol (20 ml) was heated under reflux conditions, at 60-65° for 6 hr. and set aside at 25° overnight. The pale yellow solution was poured into water (100 ml) and neutralised with acetic acid to precipitate the product which was collected and dried. It, 1.75g (75%), had m.p. 249-251°. Recrystallisation from 70% ethanol gave the pure hydantoin as cream prisms, m.p. 252-253°. (Found: C, 56.2; H, 4.2; N, 11.7. $C_{11}H_{10}N_2O_4$ requires C, 56.4; H, 4.3; N, 12.0%). ν max (KBr), 3150 (NH), 1775 (5'-C=O), 1725 (2'-C=O), 1610, 1585 and 1695 (>C=C<), 1245 (-C=C-OR)cm^{-1}. λ max 272 nm (ε 1490)[29a].

3.2 Preparation of 3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin and its carbamate ester

Since many monohydric alcohols possess hypnotic[40] and anticonvulsant[33b] properties we decided to prepare the secondary alcohol (XVa). This compound had not been isolated prior to

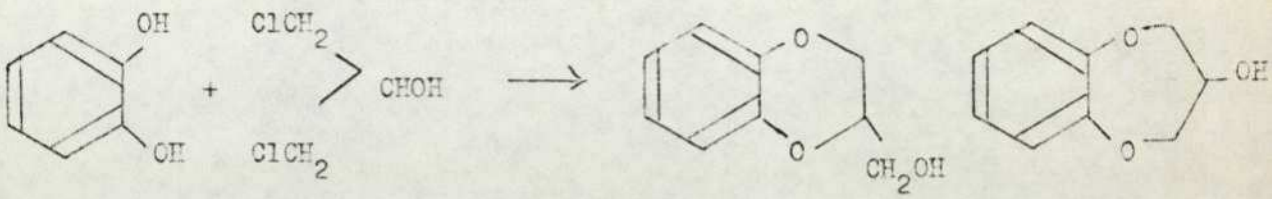


XVa



L

starting this work although its presence as a contaminant in 2-hydroxymethyl-1,4-benzodioxan (XIII) prepared from pyrocatechol and 1,3-dichlor-2-propanol had been firmly established by Rosnati

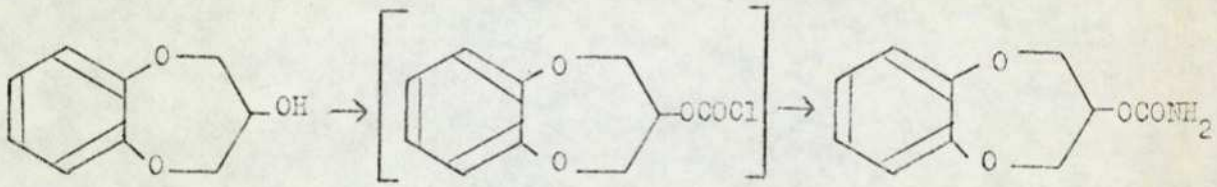


XIII XVa

and De Marchi[8] in 1962 (for the possible modes of formation see Chapter 1.2.1). The alcohol (XVa) was obtained in almost

quantitative yield by reduction of the ketone (Ia) with lithium aluminium hydride in ether using the conditions of Nystrom and and Brown[41]. A strong peak at 3300 cm^{-1} confirmed the presence of a hydroxyl group[38c] and bands at 1600, 1585 and 1500 cm^{-1} ($>C=C<$)[38a] and at 1265 cm^{-1} (-C-C-O-R) were characteristic of the benzodioxepin ring system. The alcohol (XVa) was subsequently prepared using the same procedure by Schroth and Werner[19a] and appeared to be identical with the material described here. A crystalline toluene-p-sulphonate derivative (L) was prepared in 92% yield for characterisation purposes.

With the knowledge that carbamate esters are often more pharmacologically active than their parent alcohols[40] the carbinol (XVa) was converted into its carbamate ester (LII).



XVa LI LII

This was achieved in an overall yield of 91.5% by reaction of the alcohol (XVa) firstly with phosgene in an inert solvent, and preferably in the presence of phenazone[42], to give the chloroformate (LI) by treatment with ammonia. In Nujol, its infrared spectrum showed four distinct peaks in the NH stretching

region (3150-3400 cm^{-1}) as well as a strong carbonyl band at 1690 cm^{-1}. Maxima at 1625 (-NH), 1590 and 1500 (>C=C<) and at 1260 cm^{-1} (-C=C-OR) were consistent with the benzodioxepin ring system[8].

3.2.1 3-Hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (XVa)

A solution of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (16.4g, 0.1 mole) in dry ether (100 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (2.3g, 0.06 mole) in dry ether (150 ml). After the addition the mixture was refluxed for 1 hr, cooled and treated under nitrogen with water (10 ml) and 6N hydrochloric acid. The ether was separated, combined with additional ether extractions (3 x 50 ml) and dried (Na_2SO_4). Evaporation of the ether afforded the title compound as a white crystalline solid, 16.4g, (99%), m.p. 75-78°. An analytical sample [colourless needles from light petroleum (b.p. 60-80°)] had m.p. 82-83° (lit.,[19a] m.p. 79°). (Found: C, 65.1; H, 6.2. $C_9H_{10}O_3$ requires C, 65.05; H, 6.1%). ν max (Nujol) 3300 (OH), 1600, 1585 and 1500 (>C=C<) and 1265 (-C=C-O-R) cm^{-1}. λ max 273.5 nm (ε 1475)[29b]. τ ($CDCl_3$). 3.03 (4H, s, aromatic), 5.3 (5H, t, $-CH_2-CH-CH_2-$) and 6.79 (1H, s, OH).

3.2.2 3-(Toluene-p-sulphonyloxy)-3,4-dihydro-2H-1,5-benzodioxepin (L)

A stirred mixture 3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (3.32g, 0.02 mole) in dry pyridine (7 ml) was cooled to $<5^{\circ}$ and treated with toluene-p-sulphonyl chloride (4.19g, 0.022 mole). The solution was stored for 46 hr. at $<5^{\circ}$ and poured into ice-cold 2N hydrochloric acid when the white crystalline product was collected, washed well with water and dried. It, 5.9g (92%), had m.p. 101-103° which was raised to m.p. 103.5 - 104.5° after recrystallisation from light petroleum (b.p. 80-100°). (Found: C, 60.2; H, 5.0; S, 10.1. $C_{16}H_{16}O_5S$ requires C, 60.0; H, 5.0; S, 10.0%).

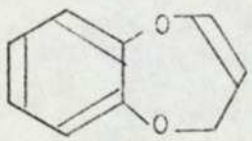
3.2.3 3-Carbamoyloxy-3,4-dihydro-2H-1,5-benzodioxepin (LII)

A solution of 3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (0.83g, 0.05 mole) and phenazone (1.34g, 0.0055 mole) in chloroform (5 ml) was added dropwise to an ice-cold solution of phosgene (0.55g, 0.0055 mole) in toluene (5 ml). The mixture was set aside at 20-25° for 2 days and shaken with ice-cold 2N hydrochloric acid (10 ml). The organic layer was separated and added dropwise to stirred, ice-cold ammonia solution (d = 0.880, 25 ml). After stirring the mixture for 1 hr. chloroform was added to dissolve the solid which had separated. The organic phase was separated, washed with 2N hydrochloric acid (10 ml), dried (Na_2SO_4) and evaporated in vacuo to give an off-white solid. This was triturated with light petroleum (b.p. 60-80°) (20 ml) and collected.

The yield of dry carbamate was 0.96g (91.5%), m.p. 140-142°. After recrystallisation from dilute ethanol the pure product, 0.87g (83%) was obtained as colourless blades, m.p. 142-143°. (Found: C, 57.3; H, 5.2; N, 6.5. $C_{10}H_{11}NO_4$ requires C, 57.4; H, 5.3; N, 6.7%). ✓max. 3150-3400 (four peaks NH_2), 1690 (C=O), 1625 (NH), 1505, 1590, 1500 (>C=C<) and 1260 (-C=C-OR) cm^{-1}. λ max 273 nm (ε 1570)[29a].

3.3 Some attempts to prepare 2H-1,5-benzodioxepin.

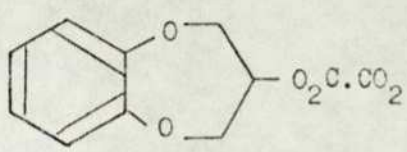
Now that the secondary alcohol (XVa) was available in quantity it appeared of interest to attempt its dehydration to the unreported parent compound, 2H-1,5-benzodioxepin (IX).



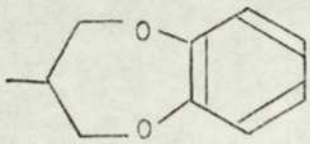
IX

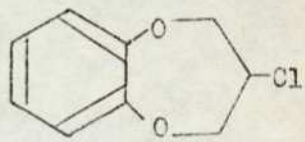
When the alcohol (XVa) was refluxed with toluene-p-sulphonic acid either in toluene or xylene under Dean-Stark conditions for 5 hr. over 90% unchanged starting material was recovered. An alternative approach which has been used successfully for the introduction of a double bond[43] involved heating the toluene-p-sulphonate ester (L) in dimethyl sulphoxide at 100° overnight but again only unchanged starting material (80%) was isolated from the reaction.

It is interesting to note that in a subsequent communication Schroth and Werner[19a] also failed to obtain any 2H-1,5-benzodioxepin (IX). Their attempts to dehydrate the alcohol (XVa) with either potassium hydrogen sulphate at 150-160° or polyphosphoric acid for 2 hr. at 140-160° yielded unchanged starting material. When the alcohol (XVa) was heated with anhydrous oxalic acid for 1 hr. at 140° they obtained the diester (LIII) and reaction of the alcohol (XVa) with a boiling mixture of thionyl chloride in pyridine (1:5) for 5 hr. produced the stable 3-chloro derivative (LIV).



LIII





LIV

3.3.1 Attempted dehydration of 3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin

A mixture of 3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (0.332g, 0.002 mole) and toluene-p-sulphonic acid (0.01g) in toluene (25 ml) was refluxed under a Dean-Stark trap for 5 hr. The solution was cooled, washed with dilute sodium hydrogen carbonate, dried (Na_2SO_4) and evaporated *in vacuo* to give an oil which solidified. It, (0.31g (93.5% recovery) had m.p. 76-80° and proved to be identical (infra-red spectrum) with the starting material.

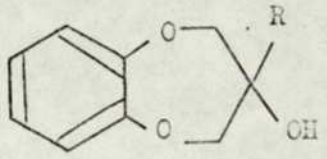
When the reaction was repeated using xylene as solvent a 91% recovery of unchanged alcohol was isolated.

3.3.2 Attempted elimination from 3-(toluene-p-sulphonyloxy)-3,4-dihydro-2H-1,5-benzodioxepin.

The tosylate (0.32g, 0.001 mole) in dimethyl sulphoxide (2 ml) was heated overnight in a steam bath, and diluted with water (10 ml) to give 0.254g (79.4% recovery) of material whose infra-red spectrum was identical with the starting tosylate.

3.4 Preparation of 3-hydroxy-3-methyl- and 3-hydroxy-3-phenyl-3,4-dihydro-2H-1,5-benzodioxepin

Because hypnotic and anticonvulsant activity of alcohols often increases in the order tertiary > secondary > primary[40,33b] we also prepared the two tertiary alcohols (LVa,b). Excellent yields of these two compounds were obtained by reaction of the ketone (Ia) with methyl magnesium iodide and phenyl magnesium bromide respectively. The infra-red spectra of the resultant



LV

(a) R = Me

(b) R = Ph

carbinols (LVa,b) both revealed strong hydroxyl absorptions near 3500 cm^{-1} together with the characteristic[8] bands of the 1,5-benzodioxepin ring system. Moreover the carbinol (LVa) was identical with that prepared similarly by Italian workers[8]. Physical constants of the 3-phenyl analogue (LVb) agreed with those subsequently reported for the compound by Schroth and Werner[19a].

3.4.1 3-Hydroxy-3-methyl-3,4-dihydro-2H-1,5-benzodioxepin (LVa)

A solution of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (0.82g, 0.05 mole) in dry ether (15 ml) was added dropwise over 15 min. to a solution of methyl magnesium iodide [prepared from methyl iodide

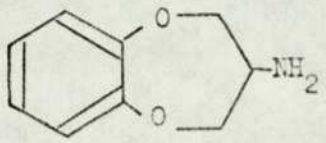
(1.42g, 0.01 mole) in dry ether (10 ml) and magnesium turnings (0.243g, 0.01g. atom)]. The mixture was refluxed for 2 hr., cooled and treated with saturated ammonium chloride solution (20 ml). The ether was separated, combined with additional ether washings (2 x 10 ml) and dried (Na_2SO_4). Evaporation of the ether afforded a colourless oil which solidified on cooling. Crystallisation from light petroleum (b.p. 60-80°) afforded the product, 0.84g (93%), as colourless prisms, m.p. 76-77.5°. An analytical sample had m.p. 77-78° (lit.,[8] m.p. 77-79°). Found: C, 66.8; H, 6.82. Calc. for $C_{10}H_{12}O_3$ C, 66.65; H, 6.7%). ν max (KBr) 3450 (OH), 1610, 1590, 1495 (>C=C<) and 1245 (-C=C-OR) cm^{-1}. λ max 274nm (ε 1585)[29a].

3.4.2 3-Hydroxy-3-phenyl-3,4-dihydro-2H-1,5-benzodioxepin (IVb)

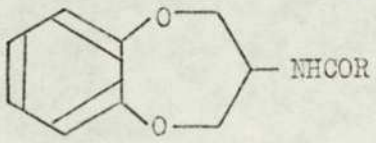
The reaction of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (0.82g, 0.005 mole) in dry ether (15 ml) with phenyl magnesium bromide [prepared from bromobenzene (1.57g, 0.01 mole), magnesium turnings (0.243g, 0.01 g. atom) and ether (15 ml)], as described for the 3-methyl analogue above, afforded a quantitative yield (1.2g) of crude alcohol. Crystallisation from light petroleum (b.p. 60-80°) gave the pure title compound as colourless needles, m.p. 86-87° (lit.,[19a] m.p. 86-87°). Found: C, 74.4; H, 5.8. $C_{15}H_4O_3$ requires C, 74.4; H, 5.8%). ν max (KBr) 3500 (OH), 1605, 1590, 1485 (>C=C<) and 1250 (-C=C-OR) cm^{-1}. λ max 273.5 nm (ε 1900)[29a].

3.5 Preparation of 3-amino-3,4-dihydro-2H-1,5-benzodioxepin hydrochloride and some derivatives

Many amines exert valuable physiological action upon the central nervous system of animals and humans. Consequently it was of interest to synthesise the unknown amine (LVI) for biological study.



LVI



LVII

(a) R = NH_2

(b) R = Me

(c) R = Ph

To achieve this the oxime (XXVIII, R = OH) prepared in 98% yield by the oximation of the ketone (Ia), was reduced with ethereal lithium aluminium hydride[44] to give the amine (LVI) which was isolated in 40% yield as its hydrochloride salt. Reaction of this with potassium cyanate afforded the unreported urea (LVIIa) in 53% yield. The amine (LVI) was also characterised as its N-acetyl- (LVIIb) and N-benzoyl- (LVIIc) derivatives which were prepared in 87% and 93% yields respectively under standard Schotten-Baumann conditions. Both compounds showed infra-red absorption bands at 3300 and 1640 cm^{-1} characteristic of the NH[38d] and C=O[38e] functions respectively.

3.5.1 3-Oximino-3,4-dihydro-2H-1,5-benzodioxepin (XXVIII, R = OH)

A mixture of hydroxylamine hydrochloride (2.5g., 0.036 mole) and sodium acetate trihydrate (4.9g, 0.036 mole) was dissolved in water (10 ml) treated with 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (4.1g, 0.025 mole) and warmed on a steam bath for ½ hr. After refrigeration the product was collected and dried. It, 4.4g, (98%) had m.p. 114-116°, a sample of which was raised to m.p. 118-119° after recrystallisation from dilute ethanol. (Found: C, 60.3; H, 5.0; N, 7.8. $C_9H_9NO_3$ requires C, 60.3; H, 5.1; N, 7.8%). ν max (Nujol) 3250 (OH), 1610, 1590, 1500 (>C=C<) and 1260 (-C=C-OR) cm^{-1}. λ max 274 and 280 nm (ξ 1855 and 1670)[29b].

3.5.2 3-Amino-3,4-dihydro-2H-1,5-benzodioxepin-hydrochloride (LVI)

A solution of the foregoing oxime (3.6g, 0.02 mole) in dry ether (60 ml) was added dropwise over 1 hr. to a stirred suspension of lithium aluminium hydride (3.52g, 0.093 mole) in ether (60 ml) under dry nitrogen. The mixture was refluxed for 8 hr., cooled to 0° and treated dropwise with water (3.5 ml), 15% sodium hydroxide solution (3.5 ml) and water (10.5 ml). The granular precipitate was filtered off and digested with boiling ether (2 x 50 ml). The combined ethereal solutions were dried (Na_2SO_4), filtered and treated with dry hydrogen chloride gas to give the product, 1.6g (39.5%), m.p. 258-260° decomp. (with prior darkening from 160°). An analytical sample from ethanol-ether gave colourless, micro-crystalline needles, m.p. 268-270° decomp. (with darkening from 220°).

(Found: C, 53.5; H, 6.0; Cl, 17.8; N, 6.7. $C_9H_{12}ClNO_2$ requires C, 53.6; H, 6.0; Cl, 17.6; N, 6.95%). ν max (KBr) 3400 ($-NH_2$), 1600 (NH), 1500 ($>C=C<$) and 1260 ($-C-O-R$) cm^{-1}. λ max 272 nm (ε 1490)[29a].

3.5.3 3,4-Dihydro-2H-1,5-benzodioxepin-3-yl urea (LVIIa)

Potassium cyanate (0.3g, 0.0037 mole) was added to a solution of 3-amino-3,4-dihydro-2H-1,5-benzodioxepin hydrochloride (0.404g, 0.002 mole) in water (5 ml). After several minutes crystals separated. The mixture was refrigerated at 0° for 1 hr., acidified with concentrated hydrochloric acid (1 ml) and the product, 0.22g (53%), m.p. 195-197° decomp. was collected. Recrystallisation from dilute ethanol gave the pure title compound, as colourless plates, m.p. 199-201° decomp. (Found: C, 57.5; H, 5.8; N, 13.5. $C_{10}H_{12}N_2O_3$ requires C, 57.7; H, 5.8; N, 13.5%). ν max. (Nujol) 3350 (NH_2), 3200 (NH) cm^{-1}. λ max 273 nm (ε 1370)[29a].

3.5.4 3-Acetamido-3,4-dihydro-2H-1,5-benzodioxepin (LVIIb)

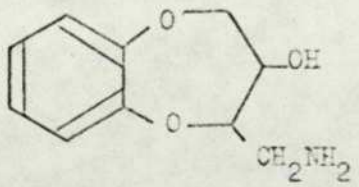
Acetylation of 3-amino-3,4-dihydro-2H-1,5-benzodioxepin hydrochloride under Schotten-Baumann conditions afforded this compound (87%), m.p. 116-117° (colourless needles from water). (Found: C, 63.8; H, 6.3; N, 6.7. $C_{11}H_{13}NO_3$ requires C, 63.75; H, 6.3; N, 6.8%). ν max. (Nujol) 3300 (NH) and 1640 (C=O) cm^{-1} λ max 273.5 nm (ε 1470)[29a].

3.5.5 3-Benzamido-3,4-dihydro-2H-1,5-benzodioxepin (LVIIc)

This compound was similarly prepared (93%), m.p. 152-154° (colourless plates from dilute ethanol). (Found: C, 71.7; H, 5.7; N, 5.2. $C_{16}H_{15}NO_3$ requires C, 71.4; H, 5.6; N, 5.2%). ν max (Nujol) 3300 (NH) and 1640 (C=O) cm^{-1}.

3.6 Preparation of trans-2-aminomethyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin.

All the compounds prepared so far possessed one or two substituents (other than hydrogen) in the 3-position of the heterocyclic ring. Consequently it was considered of interest to convert the cyano-ketone (XXXIV), prepared in an earlier investigation by Archer[18], into the hydroxy-amine (LVIII) as this would also introduce a functional group at the 2-position



LVIII

of the molecule and provide a structure of potential biological interest. The cyano-ketone (XXXIV) was prepared in 95% yield by the controlled hydrolysis of the enaminonitrile (Va) with 2.5N hydrochloric acid[18]. Reduction of the cyano-ketone (XXXIV) with lithium aluminium hydride for 5 hr. gave the free base (LVIII) as an oil in 76% yield. As this was probably a mixture of cis

and trans isomers it was converted into its hydrochloride salt, which, even after repeated recrystallisations had an indefinite melting point. It was assumed to have the trans configuration in view of analogous reductions that have been reported for 2-cyanocyclohexanone by French workers[45].

3.6.1 3-Keto-3,4-dihydro-2H-1,5-benzodioxepin-2-carbonitrile (XXXIV)

3-Amino-2H-1,5-benzodioxepin-4-carbonitrile (9.4g, 0.05 mole) was refluxed in 2.5N hydrochloric acid (60 ml) for 2 hr, cooled and extracted with ether (4 x 50 ml). After evaporating the ether the residue was dissolved in benzene (100 ml) filtered to remove some tar and evaporated to dryness in vacuo. The cream residue, 9g (95%), m.p. 123-127° was recrystallised from a mixture of carbon tetrachloride and benzene to give the cyano-ketone, 6.7g (71.5%), m.p. 130-132°. (lit.,[18] m.p. 132-134°). ν_{max} (Nujol) 1760 (C=O) cm^{-1}.

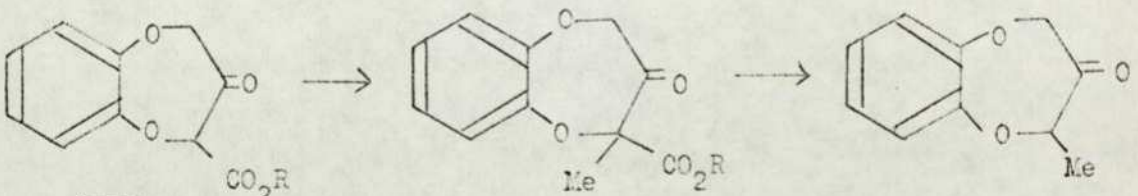
3.6.2 trans-2-Aminomethyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin hydrochloride (LVIII)

A solution of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin-2-carbonitrile (1.89g, 0.01 mole) in dry ether (20 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.2g, 0.03 mole) in dry ether (25 ml) at such a rate that gentle refluxing occurred and for 5 hr. after the addition. The mixture was then cooled and treated sequentially[46] with water (1.2 ml), 15% sodium hydroxide solution (1.2 ml), and water (3.6 ml).

After filtration the granular precipitate was washed with ether (3 x 10 ml). The combined ethereal solutions were dried (KOH) and evaporated to give the free base as an oil (1.48g, 76%). This was redissolved in dry ether (50 ml) and treated with dry HCl gas to give the hydrochloride, 1.48g (62%), which did not melt but just slowly darkened above 200°. Recrystallisation from methanol/ether gave a 60% recovery of a white crystalline material which shrank and darkened above 200°. (Found: C, 51.7; H, 6.1; Cl, 15.2; N, 5.8. $C_{10}H_{14}ClNO_3$ requires C, 51.8; H, 6.1; Cl, 15.3; N, 6.05%). λ max 272 nm (ε 1290)[29a].

3.7 Preparation and reduction of 3-keto-2-methyl-3,4-dihydro-2H-1,5-benzodioxepin

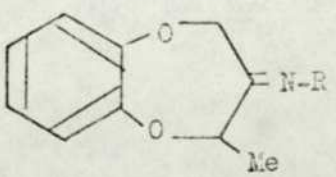
Having established satisfactory conditions for the ketonic hydrolysis of the β-keto-ester (XXXI, R = Me) its methylation was undertaken in order to prepare the unreported 2-methyl-ketone (LX).



XXXI LIX LX

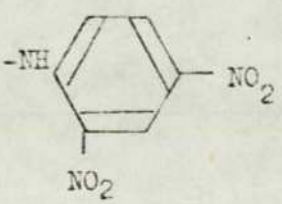
Alkylation of the β-keto-ester (XXXI, R = Me) with sodium ethoxide and methyl iodide[47] was accomplished in about 57% yield. Any unreacted starting material was readily removed by washing with aqueous potassium hydroxide until the crude product no longer

produced a violet colouration with ethanolic ferric chloride solution. However, after distillation the oil was shown by chromatography (g.l.c.) to contain two components in the ratio 3:2. These were attributed to the methyl (LIX, R = Me) and ethyl esters (LIX, R = Et) respectively. The latter compound was believed to have resulted from the transesterification of either the β-keto-ester (XXXI, R = Me) and/or of (LIX, R = Me) during the reaction. This was not an unreasonable assumption since ketonic hydrolysis with ethanolic hydrochloric acid (1:1) for 12 hr. yielded 73% of the chromatographically pure (g.l.c.) 2-methyl-ketone (LX). A strong infra-red absorption at 1750 cm^{-1} confirmed the presence of the ketone function[38f]. The nuclear magnetic resonance spectrum revealed a quartet centred at 5.0 τ (1H, J ~ 6 Hz) and a doublet centred at 8.54 τ (3H, J ~ 6 Hz) which were consistent with the presence of the $>CH-CH_3$ grouping. The ketone (LX) was characterised as the crystalline oxime (LXIa) and 2,4-dinitrophenylhydrazone (LXIb).

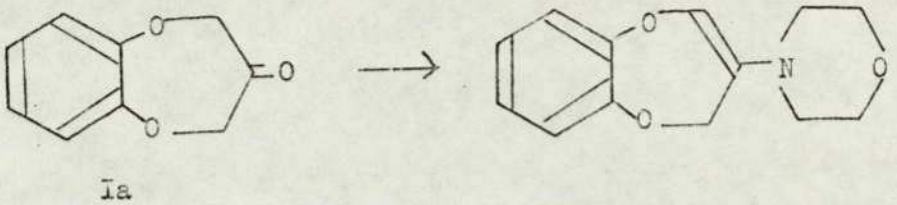


LXI

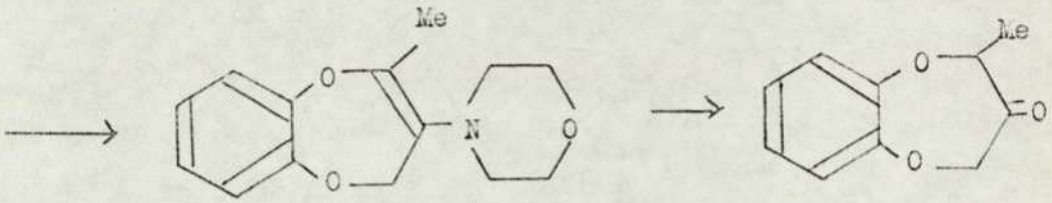
(a) R = OH

(b) R = 

The preparation of this ketone (LIX) was subsequently claimed in a patent[1a] as outlined below, but no yield or physical constants

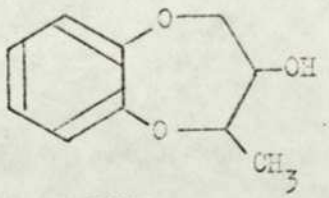


Ia



LX

were recorded for the compound. Reduction of the 2-methyl ketone (LX) with ethereal lithium aluminium hydride yielded 95% of the secondary alcohol (LXII) which was shown by chromatography (g.l.c.) to contain two components in the ratio of 3:7. After three



LXII

recrystallisations the major component was isolated chromatographically pure in 55% yield. It showed a strong infra-red hydroxyl absorption at 3250 cm^{-1} and a 3 proton doublet of a methyl group centred at 8.56 τ (J ~8Hz) in its nuclear magnetic resonance spectrum.

Ultra-violet spectroscopic measurements (see Chapter 5) suggested that the 2-methyl ketone (LX) exists in the chair conformation as does 2-methylcyclohexanone. In view of their similar conformations it was not unreasonable to expect their reduction with lithium aluminium hydride to give comparable epimer ratios for their carbinols. The small steric requirements of lithium aluminium hydride[48] enables it to approach 2-methylcyclohexanone from the same side as the methyl group to give a predominance of the more stable trans epimer (3:1)[49,50] whereas bulky reducing agents such as dicyclohexylborane and diisopinocamphenylborane approach from the opposite side to produce the less stable epimer almost exclusively[50]. On the basis of these considerations the predominant alcohol (LXII) isolated from the reduction of 3-keto-2-methyl-3,4-dihydro-2H-1,5-benzodioxepin (LX) has been tentatively assigned the trans configuration.

3.7.1 Methylation of 2-methoxycarbonyl-3-keto-3,4-dihydro-2H-1,5-benzodioxepin (XXXI, R = Me)

Sodium metal (1.27g, 0.055g. atom) was dissolved in absolute ethanol (25 ml), cooled to -10° and treated with 2-methoxycarbonyl-3-keto-3,4-dihydro-2H-1,5-benzodioxepin (11.1g, 0.05 mole). Methyl iodide (12.7g, 0.1 mole) was then added in one portion whilst the temperature of the brown liquid was kept at -15 to -10°. After 15 min. the mixture became almost solid and an additional portion of methyl iodide (12.7g, 0.1 mole) was added. The brown mobile liquid was stored overnight at room temperature when the ethanol and excess methyl iodide were removed *in vacuo*. The residual gum was dissolved in ether (50 ml), washed with ice-cold 10% potassium hydroxide solution (4 x 5 ml) until the ethereal phase no longer gave a violet colouration with ethanolic ferric chloride solution. Evaporation of the dried (Na_2SO_4) ether solution followed by distillation afforded a colourless oil, b.p. 110-120°/0.05 mm. which was shown by g.l.c. (column B at 175°) to be a mixture of 2-ethoxycarbonyl- and 2-methoxycarbonyl-3-keto-2-methyl-3,4-dihydro-2H-1,5-benzodioxepin in the ratio of 2:3. The yield was 6.9g (57%; corrected for mixture). (Found: C, 62.1; H, 5.4. Required by 2:3 mixture of esters: C, 61.85; H, 5.4%). ν max (liquid film). 1730 (ester and ketone C=O) cm^{-1}.

3.7.2 3-Keto-2-methyl-3,4-dihydro-2H-1,5-benzodioxepin (LX)

Hydrolysis of the mixture of 2-ethoxycarbonyl- and 2-methoxycarbonyl-3-keto-2-methyl-3,4-dihydro-2H-1,5-benzodioxepin (7.5g), from the foregoing experiment, for 18 hr. with a 1:1 mixture of concentrated hydrochloric acid and ethanol (40 ml) afforded the title compound, 4.35g, (73% corrected), b.p. 78-84°/0.2 mm, m.p. 42-46°. G.l.c., column A at 120°, showed a single peak. Recrystallisation of a sample from light petroleum (b.p. 40-60°) furnished colourless prismatic needles, m.p. 50-51°. (Found: C, 67.2; H, 5.5. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.7%). ν max (KBr) 1750 (C=O), 1605, 1590, 1500 (>C=C<) and 1250 (-C=C-OR) cm^{-1}. λ max 274nm (ε 1760)[29a] τ (CCl_4) 3.0 (4H, s, aromatic), 5.0 (1H, q, >CH; J ~ 6Hz), 5.34 (2H, d, $-CH_2-$; J ~ 5Hz) and 8.54 (3H, d, CH_3; J ~ 6Hz).

A 2,4-dinitrophenylhydrazone was prepared (yellow plates from ethanol), m.p. 169-171°. (Found: C, 53.4; H, 4.0; N, 15.6. $C_{16}H_{14}N_4O_6$ requires C, 53.6; H, 3.9; N, 15.6%).

An oxime (colourless needles from dilute ethanol) was obtained, m.p. 152-154°. (Found: C, 62.4; H, 5.9; N, 7.3. $C_{10}H_{11}NO_3$ requires C, 62.2; H, 5.7; N, 7.25%). ν max (KBr) 3250 (OH), 1610, 1590, 1500 (>C=C<), and 1260 (-C=C-OR) cm^{-1}. λ max 275 nm (ε 2030)[29a].

3.7.3 trans-3-Hydroxy-2-methyl-3,4-dihydro-2H-1,5-benzodioxepin (LXII)

Reduction of 3-keto-2-methyl-3,4-dihydro-2H-1,5-benzodioxepin (0.82g, 0.005 mole) in dry ether (10 ml) with lithium aluminium hydride (0.115g, 0.003 mole) in dry ether (15 ml) as described in (3.2.1) produced cis/trans mixture of the title compound, 0.86g (95%), m.p. 87-99°. This was shown by g.l.c., column C at 130°, to consist of two isomers in the ratio of 3:7. The major component had the shorter retention time. Three recrystallisations from light petroleum (b.p. 60-80°) afforded the trans isomer as colourless plates m.p. 113.5-114.5°. It was shown by g.l.c. to be pure and have a retention time corresponding to that of the major component. (Found: C, 66.5; H, 6.8. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.7%). ν max (KBr) 3250 (OH), 1600, 1580, 1495 ($>C=C<$) and 1260 ($-C=\underset{|}{C}-OR$) cm^{-1}. λ max 274 nm (ε 1530)[29a]. τ (CCl_4) 3.1 (4H, s, aromatic), 5.65-6.45 (4H, m. $>\underset{|}{CH}-\underset{|}{CH}-CH_2-$), 7.77 (1H, s, OH) and 8.56 (3H, d, CH_3; J ~ 8Hz).

CHAPTER 4 Syntheses of some 3-keto-3,4-dihydro-2H-1,5-benzodioxepin derivatives substituted in the aromatic ring.

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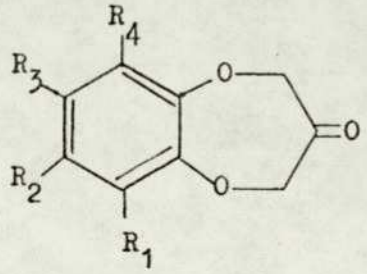
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CHAPTER 4 Syntheses of some 3-keto-3,4-dihydro-2H-1,5-benzodioxepin derivatives substituted in the aromatic ring

Consideration was then given to the preparation of a series of 3-keto-3,4-dihydro-2H-1,5-benzodioxepins of the general formula (I) substituted in the aromatic ring with from one to four methyl, t-butyl

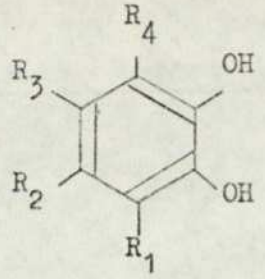


(I)

or phenyl groups in order to undertake further studies of the correlation between possible conformations of the dioxepin ring and the absorption in the 270 nm wave band previously discussed by Archer and Claret[3,18].

4.1 Syntheses of the appropriately substituted pyrocatechols (II a-p)

Of the substituted pyrocatechols (II a-p) required as intermediates for this part of the investigation only pyrocatechol itself (IIa), 3-methyl- (IIb), 4-methyl- (IIc), 4-t-butyl- (III) and 3,5-di-t-butyl-pyrocatechol (IIm) were commercially available; the remainder had to be synthesised. A literature search was therefore carried out in order to establish the most convenient laboratory synthesis of each individual pyrocatechol.



II

(a) $R_1 = R_2 = R_3 = R_4 = H$

(b) $R_1 = Me$, $R_2 = R_3 = R_4 = H$

(c) $R_1 = H$, $R_2 = Me$, $R_3 = R_4 = H$

(d) $R_1 = R_2 = Me$, $R_3 = R_4 = H$

(e) $R_1 = Me$, $R_2 = R_3 = Me$, $R_4 = H$

(f) $R_1 = Me$, $R_2 = R_3 = H$, $R_4 = Me$

(g) $R_1 = H$, $R_2 = R_3 = Me$, $R_4 = H$

(h) $R_1 = R_2 = R_3 = Me$, $R_4 = H$

(i) $R_1 = R_2 = Me$, $R_3 = H$, $R_4 = Me$

(j) $R_1 = R_2 = R_3 = R_4 = Me$

(k) $R_1 = \underline{t}$-Bu, $R_2 = R_3 = R_4 = H$

(l) $R_1 = H$, $R_2 = \underline{t}$-Bu, $R_3 = R_4 = H$

(m) $R_1 = \underline{t}$-Bu, $R_2 = H$, $R_3 = \underline{t}$-Bu, $R_4 = H$

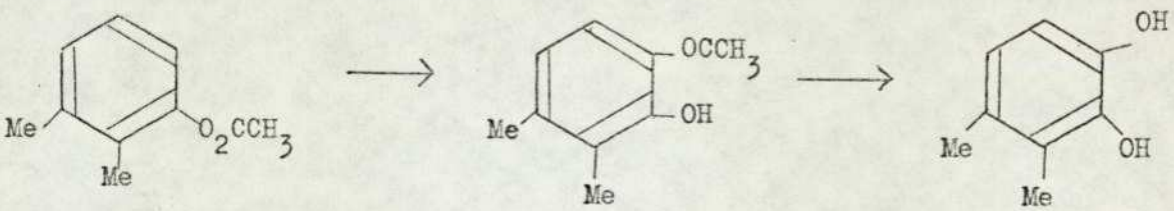
(n) $R_1 = \underline{t}$-Bu, $R_2 = R_3 = H$, $R_4 = \underline{t}$-Bu

(o) $R_1 = Ph$, $R_2 = R_3 = R_4 = H$

(p) $R_1 = H$, $R_2 = Ph$, $R_3 = R_4 = H$

4.1.1 3,4-Dimethylpyrocatechol (IId)

3,4- and/or 3,6-dimethylpyrocatechol (IId and/or IIf) was suspected as being present in the phenolic fractions of low-temperature carbonisation coal tar from North American coal[51]. It has since been prepared by two[52], three[53] and seven[54] stage syntheses. In this work the three stage preparation described by Baker and co-workers[53] (method 'A'; 4.1.1.1 - 4.1.1.3) was employed. The requisite starting material 2,3-dimethylphenylacetate (LXIII) was prepared in 91% yield by the



LXIII LXIV IId

acetylation of commercially available 2,3-dimethylphenol under Schotten-Baumann conditions. The Fries rearrangement of the ester (LXIII) proceeded smoothly and gave a similar yield of hydroxyketone (LXIV) (90.5%) to that reported[53] but was shown by g.l.c. to contain 20-25% of 2,3-dimethylphenol which, presumably was formed by hydrolysis of unrearranged ester (LXIII) during the isolation. Fractional distillation of this mixture gave 7% dimethylphenol and 68% of the hydroxyacetophenone (LXIV) of about 90% purity (g.l.c.) which was considered to be sufficiently pure for the next stage. In the Dakin oxidation of the latter compound with hydrogen peroxide in the presence of a base it was found that the

recommended[53] tetramethylammonium hydroxide could be conveniently replaced by its tetra-n-butyl-analogue. The 3,4-dimethylpyrocatechol (IId) obtained from six 0.03 mole experiments was of good quality although the yields were erratic (26.5 - 51%) but in two experiments when the input of hydroxyketone (LXIV) was raised to 0.1 mole, the yield of catechol was negligible. No satisfactory explanation can be offered for this.

The apparent dimorphic character reported[53] for this catechol (m.p.'s 61 and 84-84.5°) was also observed in this work (m.p.'s 55-57° and 83-84°).

As a result of experience gained in the preparation of 3,6-dimethylpyrocatechol (IIf) by the method of Loudon and Scott[55] (discussed fully later, 4.1.3) additional quantities of 3,4-dimethylpyrocatechol (IId) were prepared by this method from 2,3-dimethylphenol in an overall yield of 39% (method 'B'; 4.1.1.4 - 4.1.1.6).

3,4-Dimethylpyrocatechol (IId)

Method 'A'

4.1.1.1 2,3-Dimethylphenylacetate (LXIII)

This was prepared in 91% yield, b.p. 112°/10 mm., n_D^{25} 1.5020 (lit.,[56] b.p. 226-228°), by the acetylation of 2,3-dimethylphenol as described for phenyl acetate[57]. G.l.c., column A, at 150° showed it was $>$ 98% pure. ν max. (liquid film) 1770 (C=O)cm^{-1}.

4.1.1.2 2-Hydroxy-3,4-dimethylacetophenone (LXIV)

The Fries rearrangement of the foregoing ester (367.4g., 2.25 moles) with aluminium chloride (375g., 2.8 moles) at 155 - 165° for 1.5 hr. was carried out as described by Baker and co-workers[53]. The reaction mixture was added to ice-cold 4N hydrochloric acid and the organic layer was

extracted into methylene chloride, dried (Na_2SO_4) and evaporated. Distillation of the residual liquid gave a product, 333g., (91%), b.p. 100-140°/10 mm. G.l.c., column A at 160°, disclosed the presence of about 20% of 2,3-dimethylphenol. Fractionation through a Vigreux column afforded impure 2,3-dimethylphenol (67.4g., b.p. 110-129°/9 mm. [47g., m.p. 70-2°, after recrystallisation from light petroleum (b.p. 60-80°), which was identical (mixed m.p. and infra-red spectrum) with authentic 2,3-dimethylphenol], and 2-hydroxy-3,4-dimethylacetophenone, 252g. (68.5%), b.p. 120-122°/9-10 mm, n_D^{20} 1.5592. (lit., b.p. 145-148°/26 mm.,[53] n_D^{20} 1.5605[58]). G.l.c., column A at 160° showed it still contained about 10% 2,3-dimethylphenol. ν max. (liquid film) 3600-2800 (broad bonded OH) and 1640 (C=O) cm^{-1}.

4.1.1.3 3,4-Dimethylpyrocatechol (IId)

The method is a modification of that described by Baker and co-workers[53].

2-Hydroxy-3,4-dimethylacetophenone (4.92g., 0.03 mole) was dissolved in 10% tetra-n-butylammonium hydroxide solution (240 ml., 0.06 mole) and treated with 6% hydrogen peroxide solution (24 ml., 0.04 mole). After a few minutes the temperature rose and the solution became dark. When the initial reaction subsided the solution was warmed to 50-55° for 5 minutes and cooled. The solution was then acidified with 4N sulphuric acid, treated with a little sodium bisulphite which removed the dark colouration, and extracted with hot ethyl acetate (5 x 50 ml). The combined extracts were dried (Na_2SO_4) and evaporated to give a brown oil which was triturated with boiling light petroleum (b.p. 60-80°) (4 x 25 ml) and evaporated to about 10 ml. After refrigeration, 3,4-dimethylpyrocatechol,

1.1g (26.5%), m.p. 78-82° was collected. A sample, recrystallised from light petroleum (b.p. 40-60°) had m.p. 83-84°. In a later experiment, material of m.p. 55-57° [from light petroleum (b.p. 60-80°)] was obtained. However, this reverted to the higher melting form on further recrystallisation. (Baker and co-workers[53] also obtained samples of 3,4-dimethylpyrocatechol of m.p. 84-85° and 61°). ν max. (Nujol) 3480 and 3350 (free and intramolecularly bonded OH) and 1640 and 1590 (C=C) cm^{-1}. For n.m.r. results see Table 5. The following yields of crude 3,4-dimethylpyrocatechol were obtained from a further five 0.03 mole reactions: 1.6g. (39%), m.p. 78-82°; 2.1g. (51%), m.p. 70-75°; 1.9g (46%), m.p. 68-74°; 1.9g (46%), m.p. 80-82° and 1.5g. (36%), m.p. 77-81°.

3,4-Dimethylpyrocatechol (IId)

Method 'B'

Full experimental details are given later in 4.1.3.3 - 4.1.3.5.

4.1.1.4 2-(2",3"-Dimethylphenoxy)-5-nitrobenzophenone (LXIXa)

Scale: 0.1 mole. Yield 98%, m.p. 138-139° (colourless blades from methanol). (Found: C, 72.5; H, 5.2; N, 3.5. $C_{21}H_{17}NO_4$ requires C, 72.6; H, 4.9; N, 4.0%). ν max. (Nujol) 1670 (C=O) and 1255 (Ar-O-Ar) cm^{-1}.

4.1.1.5 2-(2"-Hydroxy-5",6"-dimethylphenoxy)-5-nitrobenzophenone (LXXIa)

Scale: 0.06 mole. Yield 80%, m.p. 129-130° [cream prisms from light petroleum (b.p. 80-100°) containing a little toluene]. (Found:

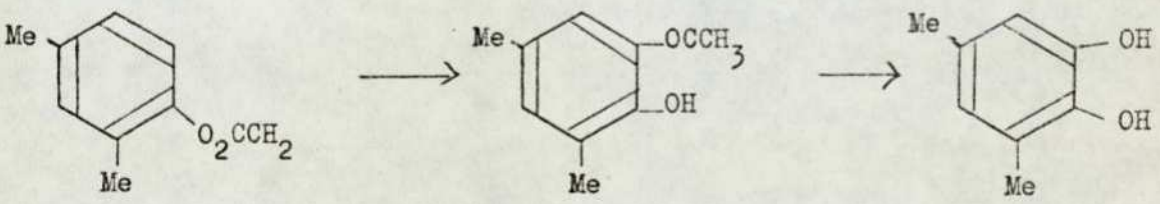
C, 69.3; H, 4.6; N, 3.8. $C_{21}H_{17}NO_5$ requires C, 69.4; H, 4.7; N, 3.9%). νmax. (Nujol) 3350 (OH), 1650 (C=O) and 1240 (Ar-O-Ar) cm^{-1}.

4.1.1.6 3,4-Dimethylpyrocatechol (IId)

Scale: 0.02 mole. Yield 65%, b.p. 98-102°/0.2mm, m.p. 56-57° [from light petroleum (b.p. 60-80°)]. After sublimation at 0.01mm (bath temperature 50°) it had m.p. 85-87° and was thereafter obtained in this form either by crystallisation or sublimation. (Literature melting points are recorded in Table 4). It was identical (mixed m.p. and infra-red spectrum) with 3,4-dimethylpyrocatechol prepared by method 'A' (4.1.1.1 - 4.1.1.3).

4.1.2 3,5-Dimethylpyrocatechol (IIe)

Of the methods reported[52,53,54,55,59,60] for preparing this catechol the three stage synthesis of Baker and co-workers[53] (method 'A' 4.1.2.1 - 4.1.2.3) was examined initially because of its apparent simplicity. The method was analogous to that employed for the preparation of 3,4-dimethylpyrocatechol (Id). Firstly 2,4-dimethylphenol was acetylated in 91% yield and the ester (LXV) was subjected to



LXV LXVI IIe

the Fries rearrangement to give a 94% yield of the hydroxy ketone (LXVI) in contrast to the 38% reported by Baker and co-workers[53].

Tetra-n-butylammonium hydroxide was again substituted for the recommended[53] tetramethyl compound in the Dakin oxidation of the hydroxyketone (LXVI). However, neither the yields (31-54%) nor the quality of the resultant 3,5-dimethylpyrocatechol (IIe) were satisfactory. In every case the crude product was shown by infra-red spectroscopy to be heavily contaminated with unreacted hydroxy-ketone (LXVI).

A further sample of this catechol (IIe) was prepared later, in low overall yield, from 3,5-dimethylphenol by the method of Loudon and Scott[55] (method 'B'; 4.1.2.4 - 4.1.2.6).

3,5-Dimethylpyrocatechol (IIe)

Method 'A'

4.1.2.1. 2,4-Dimethylphenyl acetate (LXV)

This compound was prepared in 91% yield, b.p. 106°/10mm, n_D^{26} 1.4965 (lit.,[61] 107.5 - 108.5°/13mm, $n_D^{15.5}$ 1.4990) by the acetylation of 2,4-dimethylphenol as described for phenyl acetate[57]. G.l.c. column A, at 150° showed the presence of <1.5% of two minor impurities. $\nu_{max.}$ (liquid film) 1770 (C=O) cm^{-1}.

4.1.2.2. 2-Hydroxy-3,5-dimethylacetophenone (LXVI)

2,4-Dimethylphenyl acetate (164g., 1 mole) and aluminium chloride (166.5g., 1.25 moles) were mixed and stirred with occasional cooling until an almost clear solution was obtained. The mixture was then heated on a steam bath to complete dissolution of the remaining aluminium chloride and immersed in an oil bath at 120 - 130° for 5 hr. After cooling, the reaction mixture was decomposed with ice-cold 4N hydrochloric acid and stored at room temperature overnight when the crystalline product was collected. This was dissolved in methylene chloride, dried (Na_2SO_4), evaporated and the residual black liquid (330g., ca 100%) was distilled

to give the crude hydroxy ketone, 309g. (94%), b.p. 140-150°/20mm, as a pale yellow solid. A portion (165g.) was recrystallised twice from light petroleum (b.p. 40-60°) (2 x 250 ml) to give 134g (76.5%) of pure 2-hydroxy-3,5-dimethylacetophenone, m.p. 52-53.5° (lit.,[53] m.p. 53-54°). ν max. (Nujol) 3500 - 2600 (broad bonded OH obscured by Nujol peak) and 1640 (C=O) cm^{-1}.

3,5-Dimethylpyrocatechol (IIe)

Method 'B'

Full practical details are described later in 4.1.3.3 - 4.1.3.5.

4.1.2.3 2-(3",5"-Dimethylphenoxy)-5-nitrobenzophenone (LXIXb)

Scale: 0.05 mole. Yield 98.5%, m.p. 118 - 119° [from benzene - light petroleum (b.p. 60-80°)] (lit.,[55] m.p. 117.5°). ν max. (Nujol) 1670 (C=O) and 1250 (Ar-O-Ar) cm^{-1}.

4.1.2.4 2-(2"-Hydroxy-3",5"-dimethylphenoxy)-5-nitrobenzophenone (LXXIb)

Scale: 0.04 mole. Yield 95%, m.p. 195 - 197° (colourless needles from aqueous ethanol) (lit.,[55] m.p. 166°). (Found: C, 69.5; H, 4.9; N, 4.0; Calc. for $C_{21}H_{17}NO_5$ C, 69.4; H, 4.7; N, 3.9%). ν max. (Nujol) 3450 and 3300 - 3000 (free and bonded OH respectively), 1650 (C=O) and 1250 (Ar-O-Ar) cm^{-1}.

4.1.2.5 3,5-Dimethylpyrocatechol (IIe)

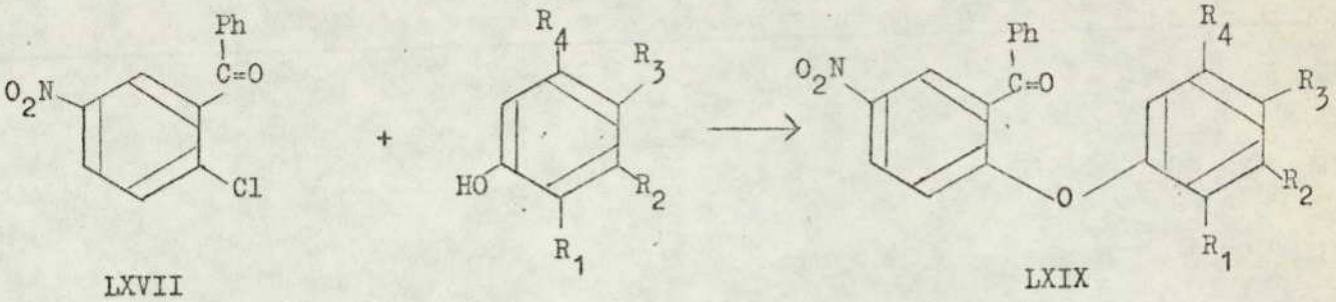
Scale: 0.033 mole. Yield 18%, b.p. 98-104°/0.2 mm, m.p. 68-70° [colourless needles from light petroleum (b.p. 60-80°) unaltered after sublimation at 0.01 mm (bath temperature 50°)]. Literature melting points are given in Table 4. It was identical with 3,5-dimethylpyrocatechol obtained by the Dakin reaction in method 'A' (4.1.2.3.).

4.1.3 3,6-Dimethylpyrocatechol (IIf)

This compound has been isolated from the phenolic fractions of low-temperature carbonisation coal tar[53]. It was first synthesised by Loudon and Scott[55] in undisclosed yield by a three stage process from 2,5-dimethylphenol (see below). Since then, alternative syntheses have been devised[52,53,54,62] starting from 2,5-dimethylphenol[52,53] or 3-methylpyrocatechol[53,54] but either the overall yields are low[52,53] or pressure equipment is necessary[62].

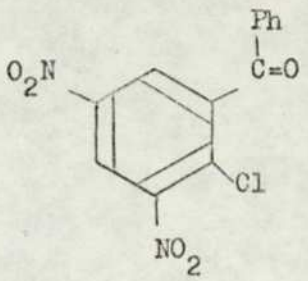
For this work the method of Loudon and Scott[55] was used. This method involved the reaction of the potassium salt of a suitably substituted phenol, having a vacant ortho position, with 2-chloro-5-nitrobenzophenone (LXVII), [2-chloro-3,5-dinitrobenzophenone (LXVIII) can also be used[63,64]] to give a 2-aryloxy-5-nitrobenzophenone (LXIX).

Stage 1



LXVII

LXIX



LXVIII

(a) $R_1=R_2=Me, R_3=R_4=H$

(b) $R_1=Me, R_2=H, R_3=Me, R_4=H$

(c) $R_1=Me, R_2=R_3=H, R_4=Me$

(d) $R_1=H, R_2=R_3=Me, R_4=H$

(e) $R_1=H, R_2=R_3=R_4=Me$

(f) $R_1=R_2=Me, R_3=H, R_4=Me$

(g) $R_1=\underline{t}\text{-Bu}, R_2=R_3=R_4=H$

(h) $R_1=H, R_2=\underline{t}\text{-Bu}, R_3=R_4=H$

(i) $R_1=R_2=H, R_3=\underline{t}\text{-Bu}, R_4$

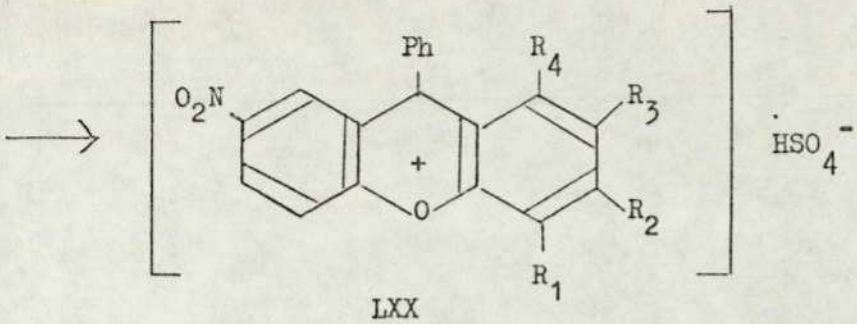
(j) $R_1=\underline{t}\text{-Bu}, R_2=R_3=H, R_4=\underline{t}\text{-Bu}$

(k) $R_1=Ph, R_2=R_3=R_4=H$

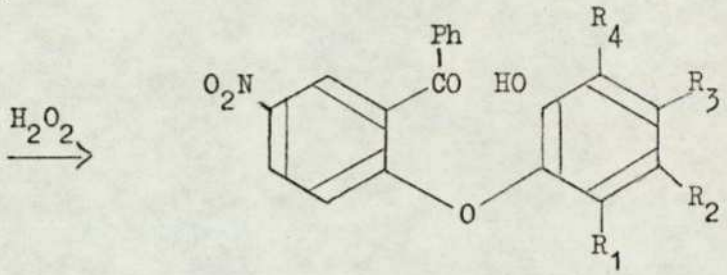
(l) $R_1=H, R_2=Ph, R_3=R_4=H$

(m) $R_1=R_2=H, R_3=Ph, R_4=H$

Stage 2



LXX



LXXI

(a) R_1=R_2=Me, R_3=R_4=H

(b) R_1=Me, R_2=H, R_3=Me, R_4=H

(c) R_1=Me, R_2=R_3=H, R_4=Me

(d) R_1=H, R_2=R_3=Me, R_4=H

(e) R_1=H, R_2=R_3=R_4=Me

(f) R_1=R_2=Me, R_3=H, R_4=Me

(g) R_1=t-Bu, R_2=R_3=R_4=H

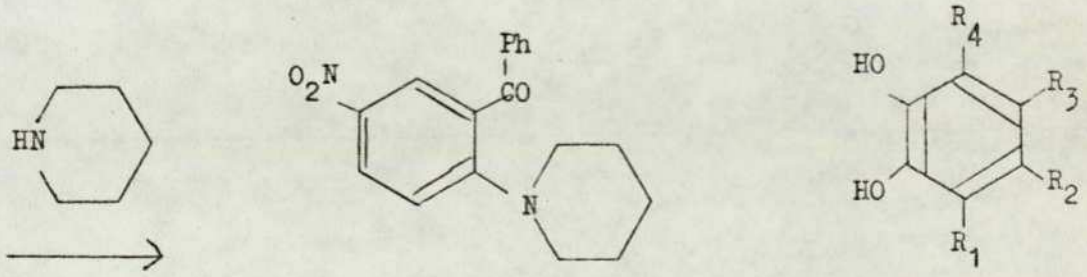
(h) R_1=H, R_2=t-Bu, R_3=R_4=H

(i) R_1=R_2=H, R_3=t-Bu, R_4=H

(j) R_1=Ph, R_2=R_3=R_4=H

(k) R_1=H, R_2=Ph, R_3=R_4=H

Stage 3



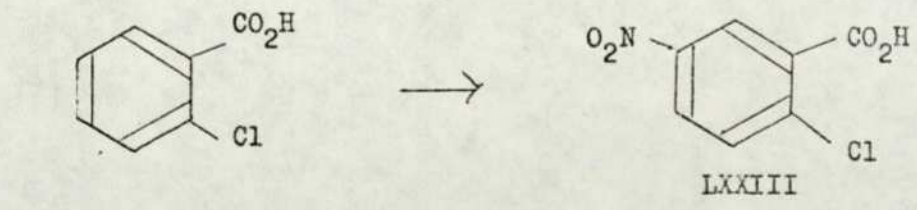
LXXII

II d-i,k,l,n-p.

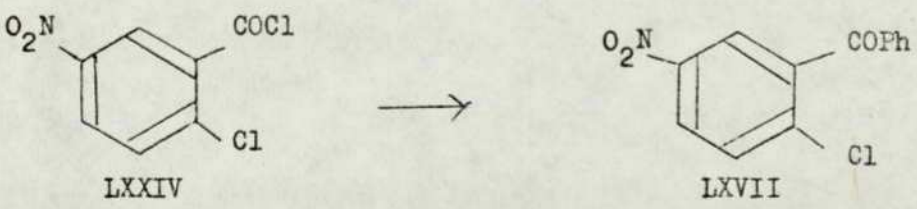
Cyclisation of this ketone with sulphuric acid produces an intermediate xanthylium salt (LXX) which can be hydroxylated *in situ* to a 2-(2"-hydroxyaryloxy)-5-nitrobenzophenone (LXXI). Finally, cleavage of the latter compound with piperidine gives the desired pyrocatechol (I) together with 2-piperidino-5-nitrobenzophenone (LXII).

Loudon and Scott[55,63] stated that the process was suitable for small scale preparations of substituted pyrocatechols but no exact yields were recorded in the examples they described although 'satisfactory' and 'high' returns were claimed[55,63] for Stages 1 and 2 respectively. In this work excellent yields were obtained from Stages 1 and 2 with inputs as high as 0.2 mole and satisfactory yields were realised from Stage 3 on up to 0.13 mole scale.

A supply of 2-chloro-5-nitrobenzophenone (LXVII) was therefore prepared by published methods or modifications thereof. Thus, 2-chlorobenzoic acid was nitrated[65] to the 5-nitro- derivative (LXXIII) in 79-87% yield



LXXIII



LXXIV LXVII

and converted into the acid chloride (LXXIV) with thionyl chloride containing a catalytic quantity of dimethyl formamide[66] in place of the

phosphorus pentachloride used originally[67]. The subsequent Friedel-Crafts reaction of the unisolated acid chloride (LXXIV) with benzene[67] gave an almost quantitative yield of the substituted benzophenone (LXVII). Reaction of the latter compound with 2,5-dimethylphenol produced the aryloxybenzophenone (LXIXc) in 80% yield which was then hydroxylated to the 2-(2"-hydroxyaryloxy)-benzophenone (LXXIc) in 99.5% yield. Finally, scission with boiling piperidine gave the required 3,6-dimethylpyrocatechol (IIf) in 58% yield (46% overall for the three step sequence).

4.1.3.1 2-Chloro-5-nitrobenzoic acid (LXXII)

The procedure of Rupe[65] was followed:-

A stirred solution of 2-chlorobenzoic acid (100g., 0.64 mole) in sulphuric acid (d = 1.84, 500 g) was nitrated at 5-10° by the dropwise addition of a mixture of nitric acid (d = 1.5, 75g) and sulphuric acid (d = 1.84, 150g). After 1 hour the solution was poured onto crushed ice and the white precipitate was collected, washed well with water and dried. It, 112g (87%) had m.p. 154-160°. The yields of products from two similar experiments were 102g, (79%), m.p. 158-165° and 107g, (83%), m.p. 154 - 158°. The three batches were combined and recrystallised from aqueous ethanol to give 305g, (79%) of 2-chloro-5-nitrobenzoic acid, m.p. 163-165°. (lit.,[68] m.p. 165°).

4.1.3.2 2-Chloro-5-nitrobenzophenone (LXVII)

A mixture of 2-chloro-5-nitrobenzoic acid (201.5g, 1 mole), thionyl-chloride (180g, 1.5 mole), benzene (100 ml) and dimethyl formamide (5 ml) was stirred and refluxed for 3 hours when the excess thionyl chloride and benzene were removed at reduced pressure. The residual 2-chloro-5-nitrobenzoyl chloride was dissolved in benzene (900 ml) and cooled in an

ice-bath. Aluminium chloride (201.5g, 1.5 moles) was then added to the stirred solution during ½ hour. The reaction was then allowed to attain room temperature and finally refluxed for 1 hr. After addition to a mixture of ice and 4N hydrochloric acid the organic phase was separated, combined with an additional benzene extraction and dried (Na_2SO_4). Evaporation of the solvent afforded an amber oil which was poured into a dish and allowed to solidify. It, 259.5g (99%), had m.p. 82-84° and a sample, after recrystallisation from methanol, gave colourless needles, m.p. 84-85° (lit.,[67] m.p.86°). ν max. (Nujol) 1670 (C=O) cm^{-1}. In repeat experiments on 1.1 and 1.5 mole scales the yields were 99%, m.p. 80-82° and 91.5%, m.p. 80-84° respectively.

4.1.3.3 2-(2",5"-Dimethylphenoxy)-5-nitrobenzophenone (LXIXc)

A mixture of 2,5-dimethylphenol (18.3g. 0.15 mole) and potassium hydroxide (85%; 8.0g, 0.12 mole) was fused by gentle heating and treated with 2-chloro-5-nitrobenzophenone (26.2g, 0.1 mole). The mixture was then warmed sufficiently to initiate and maintain the resultant reaction (5-10 mins) after which it was cooled and treated with aqueous sodium hydroxide solution. The solid was collected, washed well with water, and dried to give the crude product, 34g (98%), m.p. 112-114°. Recrystallisation from toluene-light petroleum (b.p. 80-100°) afforded 27.8g (80%) of the title compound, m.p. 118-119°. A sample from methanol gave colourless plates, m.p. 119-120° (lit.,[55] m.p. 120°). ν max. (Nujol) 1660 (C=O) and 1250 (Ar-O-Ar) cm^{-1}.

4.1.3.4 2-(2"-Hydroxy-3",6"-dimethylphenoxy)-5-nitrobenzophenone (LXXIc)

2-(2",5"-Dimethylphenoxy)-5-nitrobenzophenone (20.82g, 0.06 mole) was dissolved in sulphuric acid (d = 1.835; 40 ml) and warmed to 55-65°

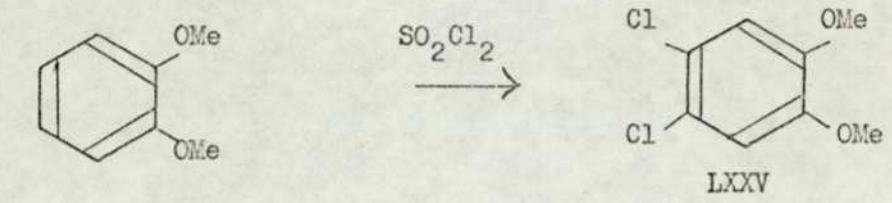
for ½ hr. The deep blood-red solution was then diluted with acetic acid (400 ml), cooled to 25° and treated dropwise over 5 min. with 30% hydrogen peroxide (12.5 ml, ca 0.125 mole) whilst the temperature of the solution was maintained between 25-35°. After ½-1hr. the amber liquid was poured into ice-water and the crude product was collected, by filtration. It was dissolved in ether, washed free of acetic acid with saturated sodium hydrogen carbonate solution and dried (Na_2SO_4). (This procedure was generally unnecessary in the other examples unless specifically stated). Evaporation of the ether gave the title compound, 21.6g (99.5%), m.p. 127-131°. A sample from methanol gave cream prisms, m.p. 131-132° (lit.,[55] m.p. 132°). ν max (Nujol) 3350 (OH), 1655 (C=O) and 1255 (Ar-O-Ar) cm^{-1}.

4.1.3.5. 3,6-Dimethylpyrocatechol (IId)

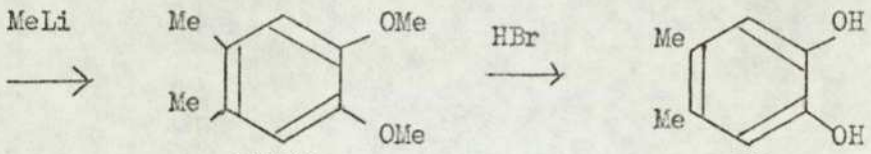
2-(2"-Hydroxy-3",6"-dimethylphenoxy)-5-nitrobenzophenone (18.1g, 0.05 mole) and piperidine (55 ml) were refluxed together for 1.5 hr. when the excess piperidine was removed at reduced pressure and the residual brown gum was partitioned between benzene and water. After washing the organic phase with 2N sodium hydroxide solution (X3), the combined aqueous extracts were acidified, treated with a little sodium bisulphite and extracted with methylene chloride (X5). The combined extracts were dried (Na_2SO_4) and evaporated to give the crude catechol, 4.0g (58%), m.p. 94-96°. Sublimation at 0.01 mm (bath temperature 80-90°) afforded colourless needles, m.p. 100-101°. (Literature melting points are given in Table 4. ν max (Nujol) 3350 (OH) cm^{-1}. The n.m.r. results are given in Table 5.

4.1.4 4,5-Dimethylpyrocatechol (IIg)

From the various syntheses recorded[54,55,69,70,71b,72] for this catechol a combination of the procedures described by Bruce and Sutcliffe[71b] and Karrer and Schick[70] (method 'C'; 4.1.4.1 - 4.1.4.3) was used. Veratrole was subjected to nuclear chlorination with sulphuryl chloride[71b,73] to give 4,5-dichloroveratrole (LXXV) in 87.5% yield.



LXXV



LXXVI IIg

Reaction of the latter compound with ethereal methyl-lithium[71b] afforded a 66% yield of 4,5-dimethylveratrole (LXXVI) which was smoothly demethylated to 4,5-dimethylpyrocatechol (IIg) in 71.5% yield (41.5% overall) with boiling 48% hydrobromic acid[70].

4,5-Dimethylpyrocatechol (IIg) was also prepared from 3,4-dimethylphenol in an overall yield of 37% by the three stage method of Loudon and Scott[55] (method 'B'; 4.1.4.4 - 4.1.4.6)

4.1.4 4,5-Dimethylpyrocatechol (IIg)

Method 'C'

4.1.4.1 4,5-Dichloroveratrole (LXXV)

This compound was obtained in 87.5% yield, m.p. 83-85° (lit.,[71a] 83.5°) by the chlorination of veratrole with sulphuryl chloride as described by Bruce and Sutcliffe[71a].

4.1.4.2 4,5-Dimethylveratrole (LXXVI)

The methylation of 4,5-dichloroveratrole with methyl-lithium as described by Bruce and Sutcliffe[71] afforded this compound in 53% yield, b.p. 76-86°/0.1mm., m.p. 38-40° (lit.,[71] b.p. 58-60°/0.2mm., m.p. 40-41°).

4.1.4.3 4,5-Dimethylpyrocatechol (IIg)

Demethylation of the foregoing ether with 48% hydrobromic acid as described by Karrer and Schick[70] gave the title compound in 71.5% yield, b.p. 122-128°/0.1mm, m.p. 84-86°. (lit.,[70] m.p. 86-87°). ν max. (Nujol). 3550, 3350 (free and bonded OH respectively), 1620 and 1590 (C=C) cm^{-1}. For the n.m.r. results see Table 5.

4.1.4 4,5-Dimethylpyrocatechol (IIg)

Method 'B'

4.1.4.4 2-(3",4"-Dimethylphenoxy)-5-nitrobenzophenone (LXIXd)

Scale: 0.1 mole. Yield 83.5% m.p. 131-132° [rectangular plates from benzene - light petroleum (b.p. 60-80°)] (lit.,[55] m.p. 133°). ν max. (Nujol) 1670 (C=O) and 1250 (Ar-O-Ar) cm^{-1}.

4.1.4.5 2-(2"-Hydroxy-4",5"-dimethylphenoxy)-5-nitrobenzophenone (LXXId)

Scale: 0.04 mole. Yield 96%, m.p. 166° (yellow needles from aqueous methanol) (lit.,[55] m.p. 166°). ν max (Nujol) 3350 (OH), 1650 (C=O) and 1250 (Ar-O-Ar) cm^{-1}.

4.1.4.6 4,5-Dimethylpyrocatechol (IIg)

Scale: 0.033 mole. Yield 46%, b.p. 114-120°/0.1mm, m.p. 85-86° after sublimation at 0.01 mm (bath temperature 75-80°) . See Table 4 for literature melting points. It was identical (mixed m.p. and infrared spectrum) with the material prepared by method 'A' (4.1.4.1 - 4.1.4.3).

4.1.5 3,4,5-Trimethylpyrocatechol (IIh)

This compound was first obtained in 1954 by Beer and co-workers[74] who used a five stage synthesis starting from 3,4,5-trimethylphenol (hemimellitenol). In this work the phenol was successfully converted into 3,4,5-trimethylpyrocatechol (IIh) by the method of Loudon and Scott[55]. Reaction of 3,4,5-trimethylphenol with 2-chloro-5-nitrobenzophenone (LXVII) yielded 82% of the ether (LXIXe), which was cyclised and hydroxylated to the hydroxy derivative (LXXIe) (94%) and finally cleaved with piperidine to give the requisite catechol (IIh) in 59% yield (45.5% overall for the three stages). It would appear that the sample of 3,4,5-trimethylpyrocatechol (IIh), m.p. 86-89°, isolated by Beer and associates[74] was impure since our material had m.p. 96-97°.

3,4,5-Trimethylpyrocatechol (IIh)

Method 'B'

4.1.5.1 2-(3",4",5"-Trimethylphenoxy)-5-nitrobenzophenone (LXIXe)

In order to conserve the 3,4,5-trimethylphenol equimolar quantities of the requisite reagents were employed. Scale: 0.1 mole. Yield 97%, m.p. 148.5 - 149.5° [colourless prisms from toluene - light petroleum (b.p. 60-80°)]. (Found: C, 73.2; H, 5.5; N, 4.2. $C_{22}H_{19}NO_4$ requires C, 73.1; H, 5.3; N, 3.9%). ν max. (Nujol) 1670 (C=O) and 1250 (Ar-O-Ar) cm^{-1}.

4.1.5.2 2-(2"-Hydroxy-3",4",5"-trimethylphenoxy)-5-nitrobenzophenone (LXXIe)

Scale: 0.06 mole. Yield 94%, m.p. 188-189° (colourless prisms from ethanol). (Found: C, 70.4; H, 4.8; N, 3.9. $C_{22}H_{19}NO_5$ requires C, 70.0; H, 5.1; N, 3.7%). ν max. (Nujol) 3450 (OH), 1660 (C=O) and 1250 (Ar-O-Ar) cm^{-1}.

4.1.5.3 3,4,5-Trimethylpyrocatechol (IIh)

Scale: 0.1 mole. Yield 59%, m.p. 96-97° [colourless needles after sublimation at 0.01mm (both temperature 80°) and recrystallisation from light petroleum (b.p. 60-80°)] (lit.,[74] m.p. 86-89°). (Found: C, 71.4; H, 7.7. Calc. for $C_9H_{12}O_2$ C, 71.0; H, 7.95%). ν max. (Nujol) 3450 and 3400 (free and bonded OH respectively) and 1620 and 1610 (C=C) cm^{-1}. The n.m.r. data are given in Table 5.

4.1.6 3,4,6-Trimethylpyrocatechol (IIi)

Three methods for preparing this catechol have been described in the literature[64,72,74] involving two[72,73] and five[74] stage reactions on 2,4,5-trimethylphenol (Ψ-cumenol) or a three stage sequence from

2,3,5-trimethylphenol (iso-ψ-cumenol)[64].

In the preparation of 3,4,6-trimethylpyrocatechol (IIi) from 2,3,5-trimethylphenol described by Loudon and McCapra[64] the more reactive 2-chloro-3,5-dinitrobenzophenone (LXVIII) was introduced at Stage 1 of the original method of Loudon and Scott[55] and phenylhydrazine was used for the cleavage at Stage 3. However, we found that these modifications were unnecessary and 3,4,6-trimethylpyrocatechol (IIi) was in fact obtained in an overall yield of 56.5% from 2,3,5-trimethylphenol when the Loudon and Scott[55] reaction sequence was applied. After rigorous purification the pure catechol had m.p. 111-112° (lit., 110°[64] and 109-110°[72]); the figures of 118-120° recorded by Beer and co-workers[74] appear to be incorrect but the possibility that this was due to polymorphism cannot be ruled out.

3,4,6-Trimethylpyrocatechol (IIi)

Method 'B'

4.1.6.1 2-(2",3",5"-Trimethylphenoxy)-5-nitrobenzophenone (LXIXe)

The modification described in 4.1.5.1 was used. Scale: 0.1 mole. Yield 95.5%, m.p. 165-166° [cream needles from toluene-light petroleum (b.p. 60-80°) or ethanol]. (Found: C, 73.4; H, 5.4; N, 4.0. $C_{22}H_{19}NO_4$ requires C, 73.1; H, 5.3; N, 3.9%). ν max (Nujol) 1660 (C=O) and 1250 (Ar-O-Ar) cm^{-1}.

4.1.6.2 2-(2"-Hydroxy-3",5",6"-trimethylphenoxy)-5-nitrobenzophenone (LXXIe)

Scale: 0.06 mole. Yield 99%, m.p. 148-149° (pale yellow needles from methanol). (Found: C, 70.4; H, 5.2; N, 4.0. $C_{22}H_{19}NO_5$ requires C, 70.0; H, 5.1; N, 3.7%). ν max. (Nujol) 3450 (OH), 1660 (C=O) and 1250 (Ar-O-Ar) cm^{-1}.

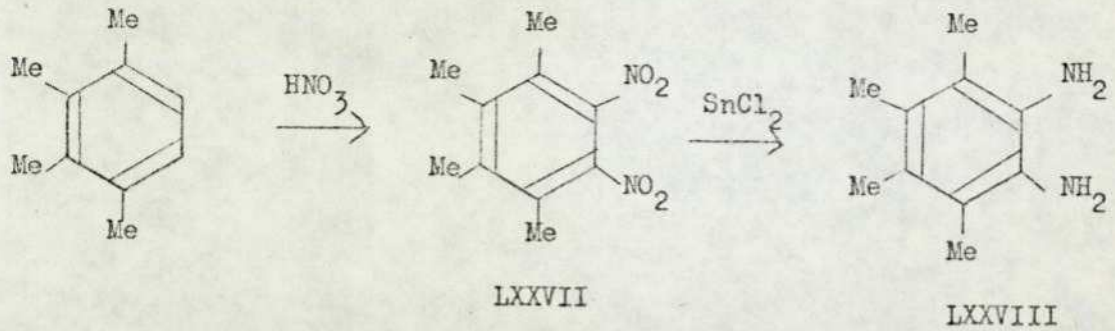
4.1.6.3 3,4,6-Trimethylpyrocatechol (IIi)

Scale: 0.1 mole. Yield 66.5%, m.p. 111-112° [colourless needles from light petroleum (b.p. 80-100°) followed by three sublimations at 0.01 mm. (bath temperature 100°)]. Literature melting points are recorded in Table 4. (Found: C, 71.1; H, 8.05. Calc. for $C_9H_{12}O_3$ C, 71.0; H, 7.95%). ν max (Nujol) 3350 (OH) cm^{-1}. See Table 5 for the n.m.r. results.

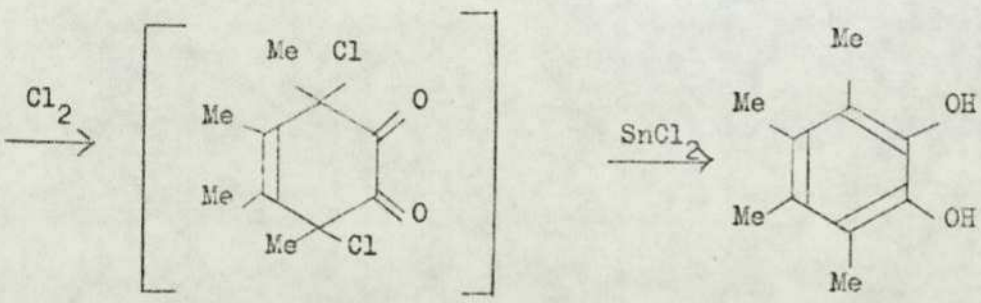
4.1.7 Tetramethylpyrocatechol (IIj)

The only synthesis of this catechol cited in the literature was that described by Smith and Hac[75] in 1934.

Several minor modifications were found to be necessary when the reaction sequence was repeated here. Firstly, prehnitene (1,2,3,4-tetramethylbenzene) was nitrated with nitric acid (d = 1.5) in chloroform to



LXXVII LXXVIII



LXXIX II(j)

give a 94% yield of the corresponding dinitro compound (LXXVII). Reduction to the diamine (LXXVIII) was effected with stannous chloride but the

product was heavily contaminated with tin due, possibly, to the presence of some stannichloride complex whereas the material obtained by Smith and Hac[75] was claimed to be almost tin free (c.f. reduction of dinitrodurene with stannous chloride which gave the stannichloride salt[76]). Treatment with 20% sodium hydroxide solution removed the tin and afforded 81% of the free base (LXXVIII) which was reconverted into its dihydrochloride salt. Oxidation of this with a stream of chlorine gave the intermediate dichlorodione (LXXIX) which was reduced in situ with stannous chloride yielding 48-58.5% of the tetramethylpyrocatechol (IIj) whose properties agreed closely with those recorded[75].

Tetramethylpyrocatechol (IIj)

4.1.7.1 Dinitroprehnitene (LXXVII)

Prehnitene was nitrated by the method previously used by Smith and Dobrovolny[76] for the nitration of durene. The total yield of crude dinitroprehnitene from eight 0.1 mole experiments was 168.7g. (94%), m.p. 167-172°. Recrystallisation of a sample from methanol gave almost colourless needles, m.p. 176-177° (lit.,[75] m.p. 176°). ν max. (Nujol) 1540 and 1360 ($-NO_2$) cm^{-1}.

4.1.7.2 Diaminoprehnitene (LXXVIII)

cf. Smith and Hac[75].

A suspension of dinitroprehnitene (44.8g, 0.2 mole) in hot ethanol (200 ml) was added rapidly to a boiling solution of stannous chloride dihydrate (300g, 1.33 moles) in hydrochloric acid (d = 1.18, 390 ml). When the vigorous reaction moderated the flask was cooled in ice and the product was collected and dried. The yield was 60.5g. ($>$ 100% if

dihydrochloride). In a repeat experiment on the same scale the yield was 70.5g (theory for stannichloride complex, 70.8g). As both products appeared to be heavily contaminated with tin compounds they were combined, treated with 20% sodium hydroxide solution and extracted with hot toluene. Evaporation of the combined extracts at reduced pressure gave 53g (81%) of diaminoprehnitene, m.p. 135-138°. A sample, recrystallised from toluene had m.p. 143-144° (lit.,[75] m.p. 144°). ν max. (Nujol) 3450 and 3350 ($-NH_2$) cm^{-1}. The free base (ca 0.32 mole) was dissolved in ethanol, treated with hydrochloric acid (d = 1.18, 65 ml, ca 0.65 mole) and evaporated to dryness in vacuo. After trituration with ether, the dihydrochloride, 62g (65%) was obtained as rectangular plates m.p. 200°. (Found: C, 50.9; H, 7.9; Cl, 29.7; N, 12.0. Calc. for $C_{10}H_{18}Cl_2N_2$ C, 50.6; H, 7.65; Cl, 29.9; N, 11.8%).

4.1.7.3 Tetramethylpyrocatechol (IIj)

cf. Smith and Hac[75].

A stirred suspension of diaminoprehnitene dihydrochloride (23.7g, 0.1 mole) in glacial acetic acid (200 ml) and hydrochloric acid (d = 1.18, 20 ml) was treated with a slow stream of chlorine for 6 hr. After removal of the ammonium chloride (7.1g, 66.5%) and aeration of the filtrate, a solution of stannous chloride dihydrate (95g, 0.42 mole) in hydrochloric acid (d = 1.18, 180 ml) was added. The mixture was then heated on a steam bath for 5 hr. diluted to 2 litres with water and refrigerated overnight. Filtration gave 9.7g (58.5%) of brown crystalline material, m.p. 102-104°. Recrystallisation from light petroleum (b.p. 80-100°) (200 ml) afforded pure tetramethylpyrocatechol, 7.1g (43%) as colourless needles, m.p. 110-111°. (Lit.,[75] m.p. 111°). ν max. (Nujol) 3350 (OH) cm^{-1}. See Table 5 for n.m.r. data. In a repeat experiment the yield of crude product was 8.1g (48%) which gave 6.2g (37%), m.p. 109-111°), after recrystallisation.

4.1.8 3-t-Butylpyrocatechol (IIk)

This catechol has been obtained by the alkylation of pyrocatechol with isobutene in the presence of various catalysts[77,78,79] and more recently in 57% yield by the Dakin oxidation of 3-t-butylsalicylaldehyde[52].

In this study we found it convenient to use the three-step Loudon and Scott[55] process and succeeded in obtaining the requisite 3-t-butylpyrocatechol (IIk) from commercially available 3-t-butylphenol in an overall yield of 46.5%. The catechol (Ik) was an almost colourless liquid and was shown to be chromatographically pure (g.l.c.) Its structure was confirmed by nuclear magnetic resonance spectroscopy (see Table 5) and the spectrum was similar to that reported[52].

3-t-Butylpyrocatechol (IIk)

Method 'B'

4.1.8.1 2-(2"-t-Butylphenoxy)-5-nitrobenzophenone (LXIXg)

Scale: 0.2 mole. The crude product was obtained as an oil. It was partitioned between toluene and 20% sodium hydroxide solution when the organic phase was separated, dried (Na_2SO_4) and evaporated in vacuo. Distillation gave the title compound in 81% yield, b.p. 230-234°/0.01mm which set to a hard glass. Crystallisation from methanol afforded colourless prisms, m.p. 91-92°. (Found: C, 73.6; H, 5.7; N, 3.7. $C_{23}H_{21}NO_4$ requires C, 73.6; H, 5.6; N, 3.7%) ν max (Nujol) 1660 (C=O) and 1250 (Ar-O-Ar)cm^{-1}.

4.1.8.2 2-(2"-Hydroxy-6"-t-butylphenoxy)-5-nitrobenzophenone (LXXIg)

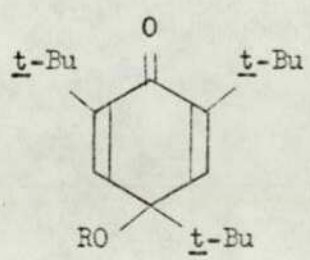
Scale: 0.12 mole. Yield 99%, m.p. 164-165° (colourless needles from aqueous methanol). (Found: C, 71.0; H, 5.5; N, 3.7. $C_{23}H_{21}NO_5$ requires C, 70.6; H, 5.4; N, 3.6%). ν max (Nujol) 3350 (OH), 1640 (C=O) and 1255 (Ar-O-Ar) cm^{-1}.

4.1.8.3 3-t-Butylpyrocatechol (IIk)

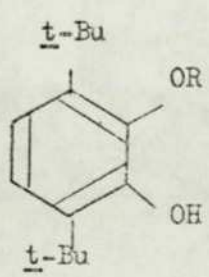
Scale: 0.13 mole. Yield 58%, b.p. 92-96°/0.5mm, n_D^{25} 1.5335 (lit.,[52] b.p. 140-146°/20mm). G.l.c., column A, at 175° gave only one peak. (Found: C, 72.0; H, 8.4. $C_{10}H_{14}O_2$ requires C, 72.3; H, 8.5%). ν max. (liquid film) 3500 (OH), 1620, 1585 and 1470 (C=C)c The n.m.r. results are recorded in Table 5.

4.1.9 3,6-Di-t-butylpyrocatechol (IIn)

This compound has been obtained by the action of isobutene on pyrocatechol in the presence of aluminium phenoxide at elevated temperatures and pressures[80]. Similar conditions have also been utilised by Czechoslovakian workers[79]. 3,6-Di-t-butylguaiacol (LXXXI, R=Me) had been isolated from the photolysis of 2,4,6-tri-t-butyl-4-methoxy-2,5-cyclohexadienone (LXXX, R=Me)[81] and the corresponding 4-acetoxy compound (LXXX, R=Ac) gives some 3,6-di-t-butylpyrocatechol monoacetate (LXXXI, R=Ac)



LXXX

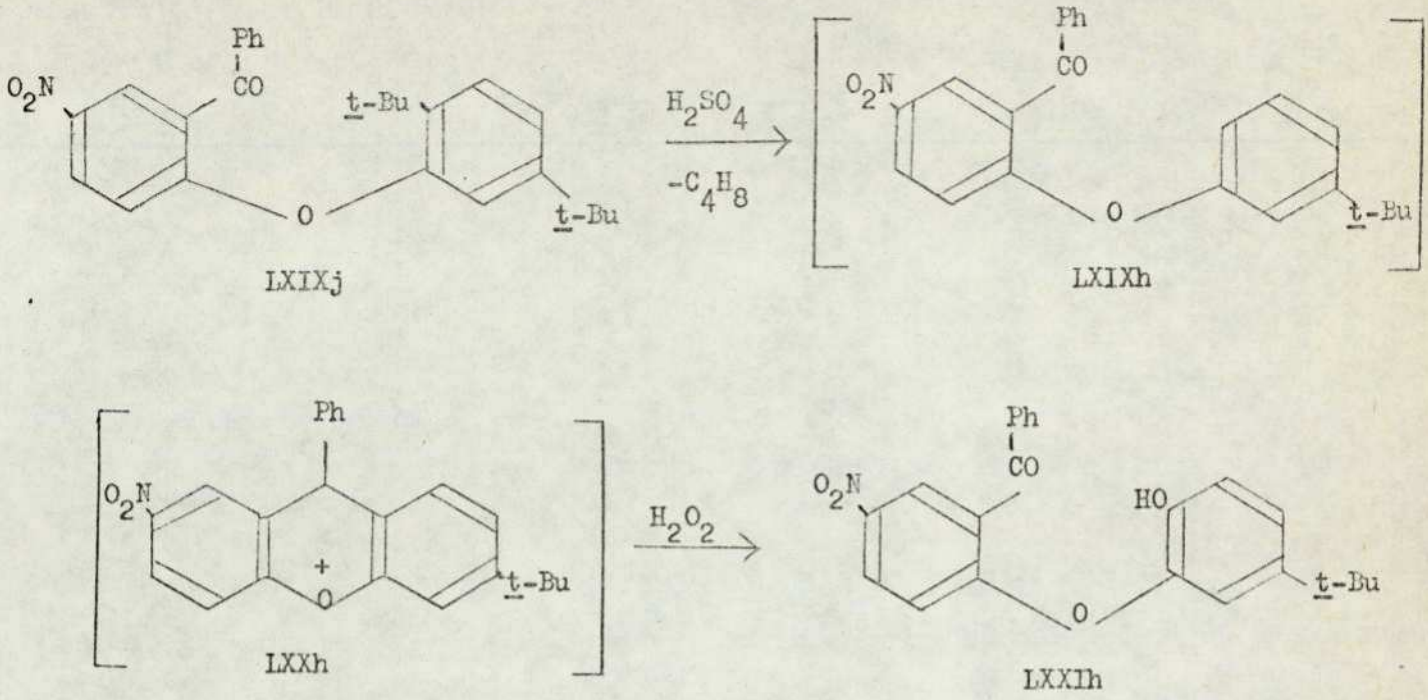


LXXXI

under similar conditions[82].

As none these procedures was considered to be suitable, the method of Loudon and Scott[55] was considered in the hope that commercially available 2,5-t-butylphenol would provide the required pyrocatechol (IIn). In view of the inability of this 'crypto' phenol[83] to give the potassium salt on fusion with solid potassium hydroxide in the usual way, the technique of Carpenter co-workers[84] was used whereby a toluene solution of the phenol was treated dropwise with aqueous potassium hydroxide solution with simultaneous azeotropic removal of the water followed by distillation of the solvent. Reaction of the resultant potassium 2,5-di-t-butyl phenate with 2-chloro-5-nitrobenzophenone (LXVII) gave 66.5% of the aryloxybenzophenone (LXIXj) the infra-red spectrum (C=O at 1675 cm^{-1}) and elemental analysis of which were consistent with its structure. The crystalline product, m.p. 135.5-136.5°, isolated from the ensuing cyclisation and hydroxylation step revealed hydroxyl and carbonyl absorptions at 3400 and 1660 cm^{-1} respectively which were observed for all the other analogues but elemental analysis figures revealed that the product had an empirical formula $C_{23}H_{21}NO_5$ which indicated the loss of one t-butyl group.

Removal of the 5"-t-butyl group was ruled out since the new compound was different from the corresponding 2-(2"-hydroxy-6"-t-butylphenoxy)-5-nitrobenzophenone (LXXIg), m.p. 164-165°, prepared from o-t-butylphenol (4.1.8.2). Therefore, addition of the 2",5"-di-t-butylphenoxy compound (LXIXj) to sulphuric acid caused initial displacement of the 2"-t-butyl group followed by cyclisation at this vacated site paralleling the results of Loudon and Scott[55] for the cyclisation of the 3"-phenoxy compound (LXIXl). Analogous dealkylations of t-butylated aromatic compounds with conventional[85], or Lewis[86], acids have been reported. Additional



confirmation of the structure (LXXIh) resulted from its reaction with piperidine which gave 71% of almost chromatographically pure 4-t-butylpyrocatechol (III) identical in every respect (mixed m.p., infra-red and nuclear magnetic resonance spectra) with an authentic commercial sample and with 4-t-butylpyrocatechol (III) prepared from p-t-butylphenol by the Loudon and Scott[55] procedure (4.1.9.4 - 4.1.9.5). Further attempts to synthesise 3,6-di-t-butylpyrocatechol (IIn) were not pursued.

Attempted preparation of 3,6-di-t-butylpyrocatechol (IIn)

Method 'B'

4.1.9.1 2-(2",5"-Di-t-butylphenoxy)-5-nitrobenzophenone (LXIXj)

An attempt to fuse together potassium hydroxide and 2,5-di-t-butylphenol in the usual way failed to give the required potassium salt but it was readily formed by the method of Carpenter and co-workers[84].

A refluxing solution of 2,5-di-t-butylphenol (30g, 0.15 mole) in toluene (250 ml) was treated dropwise with a solution of potassium hydroxide (85%; 9.8g, 0.15 mole) in water (50 ml) and the water was collected in a Dean-Stark trap. The toluene was removed in vacuo when the residual salt was powdered and intimately mixed with 2-chloro-5-nitrobenzophenone (39.2g, 0.15 mole). Gentle heating was then applied to initiate and complete the ensuing reaction. After partitioning the reaction mixture between benzene and water the organic phase was separated, dried (Na_2SO_4) and evaporated. Crystallisation of the residue from light petroleum (b.p. 60-80°) yielded 43g (66.5%) of the title compound, m.p. 115-125°. Additional recrystallisations from ligroin afforded colourless needles, m.p. 136-137°. (Found: C, 75.2; H, 6.8; N, 3.2. $C_{27}H_{29}NO_4$ requires C, 75.15; H, 6.8; N, 3.25%). $\nu_{max.}$ (Nujol) 1675 (C=O) and 1260 (Ar-O-Ar) cm^{-1}.

4.1.9.2 Hydroxylation of 2-(2",5"-di-t-butylphenoxy)-5-nitrobenzophenone (LXIXj)

2-(2",5"-Di-t-butylphenoxy)-5-nitrobenzophenone (21.5g, 0.05 mole) was hydroxylated as described in experiment 4.1.1.5 and diluted with water to give a sticky brown solid. This was extracted into toluene which was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4) and evaporated in vacuo. The residual brown oil was dissolved in boiling

light petroleum (b.p. 80-100°), clarified with charcoal, filtered and evaporated to give a yellow oil (23g). A 1g. sample was dissolved in ligroin containing a little toluene and furnished cream plates, m.p. 135.5 - 136.5° which proved to be 2-(2"-hydroxy-5"-t-butylphenoxy)-5-nitrobenzophenone (LXXIh). (Found: C, 70.7; H, 5.35; N, 3.25. $C_{23}H_{21}NO_5$ requires C, 70.6; H, 5.4; N, 3.6%). νmax (Nujol) 3400 (OH) 1660 (C=O) and 1265 (Ar-O-Ar) cm^{-1}.

4.1.9.3 Scission of 2-(2"-hydroxy-5"-t-butylphenoxy)-5-nitrobenzophenone (LXXIh) with piperidine.

The crude oil (22g, ca 0.056 mole) from the preceding experiment (4.1.9.2) was refluxed with piperidine (3 volumes) and worked up as described above (3.1.1.6) to give 6.65g (71%) of a colourless oil, b.p. 115-120°/0.01 mm which was shown by g.l.c., column A at 170°, to be at least 99% pure. It solidified and had m.p. 54-55° after crystallisation from light petroleum (b.p. 60-80°) and proved identical (mixed m.p., infra-red and nuclear magnetic resonance spectrum) with an authentic sample of 4-t-butylpyrocatechol (m.p. 54-56°). νmax (Nujol) 3350 (OH), and 1590 (>C=C<) cm^{-1}. N.m.r. results are recorded in Table 5.

The two compounds described below have been included here for convenience; they were prepared by method 'B'.

4.1.9.4 2-(4"-t-Butylphenoxy)-5-nitrobenzophenone (LXIXi)

Scale: 0.04 mole. Yield 93%, m.p. 129-130° [rectangular plates from toluene - light petroleum (b.p. 80-100°)]. (Lit.,[55] m.p. 85°). (Found: C, 73.4; H, 5.9; N, 3.9. Calc. for $C_{23}H_{21}NO_4$ C, 73.6; H, 5.6, N, 3.7%). νmax (Nujol) 1670 (C=O) and 1260 (Ar-O-Ar) cm^{-1}.

4.1.9.5 2-(2"-Hydroxy-4"-t-butylphenoxy)-5-nitrobenzophenone (LXXIi)

Scale: 0.006 mole. Yield 76.5%, m.p. 119-121° which underwent softening at 111° [pale yellow needles from light petroleum (b.p. 80-100°)] . (Lit.,[55] m.p. 115°). ν max (Nujol) 3400 (OH), 1665 (C=O) and 1260 (Ar-O-Ar) cm^{-1}.

4.1.10 3-Phenylpyrocatechol (IIo)

This catechol was prepared in 58% overall yield from commercially available 2-hydroxybiphenyl by the now well-tried synthesis of Loudon and Scott[55]. The m.p. of our material was 112-113° and agreed with that given by other workers[55,87,88], who employed alternative syntheses[87,88]. The m.p. of 57-59° reported for this compound by Japanese workers[89] is incorrect and suggests that they did not in fact obtain 3-phenylpyrocatechol (IIo). (2-hydroxybiphenyl has m.p. 56°!)[90].

4.1.10.1 2-(2"-Biphenylyloxy)-5-nitrobenzophenone (LXIXk)

Scale: 0.2 mole. Yield 87%, m.p. 98-99° [cream prisms from toluene-light petroleum (b.p. 60-80°) or methanol.] (Lit.,[55] m.p. 97-98°). ν max (Nujol) 1675 (C=O) and 1260 (Ar-O-Ar) cm^{-1}.

4.1.10.2 2-(2"-Hydroxy-6"-biphenylyloxy)-5-nitrobenzophenone (LXXIj)

Scale: 0.12 mole. Yield 96.5%, m.p. 147-148° [colourless needles from benzene-light petroleum (b.p. 60-80°)] . (Lit.,[55] m.p. 41°). (Found: C, 73.1; H, 4.5; N, 3.1. Calc. for $C_{25}H_{17}NO_5$ C, 73.0; H, 4.2; N, 3.4%). ν max (Nujol) 3350 (OH), 1670, 1655 (split C=O) and 1255 (Ar-O-Ar)cm^{-1}.

4.1.10.3 3-Phenylpyrocatechol (IIo)

Scale: 0.1 mole. Yield 86%, m.p. 112-113° [colourless prisms from light petroleum (b.p. 60-80°) or by sublimation at 0.01 mm (bath temperature 100°)]. (lit.,[55] m.p. 111°). ν max. (Nujol) 3450 and 3340 (free and bonded OH respectively), 1585 and 1575 (C=C) cm^{-1}. See Table 5 for the n.m.r. data.

4.1.11 4-Phenylpyrocatechol (IIp)

Although a number of different syntheses of this catechol have been reported[55,87,91,92,93,94] we again considered Loudon and Scott's method[55] the most suitable for our requirements. 4-Phenylpyrocatechol (IIp) was thus obtained from commercially available 4-hydroxybiphenyl in an overall yield of 58% by the now familiar three step reaction sequence.

4.1.11.1 2-(4"-Biphenylyloxy)-5-nitrobenzophenone (LXIXm)

Scale: 0.2 mole. Yield 80.5%, m.p. 125-126° [off-white needles from toluene-light petroleum (b.p. 80-100°)] (lit.,[55] m.p. 126°). ν max (Nujol) 1670 (C=O) and 1255 (Ar-O-Ar) cm^{-1}.

4.1.11.2 2-(2"-Hydroxy-4"-biphenylyloxy)-5-nitrobenzophenone (LXXIk)

Scale: 0.12 mole. This compound was obtained in 85.5%. After recrystallisation from toluene-light petroleum (b.p. 80-100°) it gave yellow needles which melted in the range 103-108°. When dried at 100° the colour faded and the cream needles had m.p. 125-126° (lit.,[55] m.p. 119°) ν max (Nujol). 3400 (OH), 1660 (C=O) and 1250 (Ar-O-Ar) cm^{-1}.

4.1.11.3 4-Phenylpyrocatechol (IIp)

Scale: 0.1 mole. Yield 79%, m.p. 139-140° (colourless plates from aqueous methanol) (lit., m.p. 135°[55], 141°[93]). ν_{max} (Nujol) 3350 (OH) and 1660 (C=C) cm^{-1}. The n.m.r. results are given in Table 5.

4.1.12 Some physical constants of the substituted pyrocatechols

During the course of the literature survey on the pyrocatechols (IIa - p) described above it became apparent that some of the physical constants such as melting points that were recorded differed from those obtained in this work. As considerable care had been exercised in purifying samples of the pyrocatechols synthesised in this work it was considered worthwhile comparing the results with published values. Characteristic colour reactions produced with ferric chloride are also recorded (Table 4). In addition the 60 MHz nuclear magnetic resonance spectra of the commercially available pyrocatechols (II a - c, l, m) and those synthesised in this work (II d - k, o, p) have been recorded in Table 5. The spectral data for the latter compounds were consistent with their structures. In an attempt to assign the methyl resonances in 3,4-dimethyl-, 3,4,5-trimethyl-, 3,4,6-trimethyl- and tetramethyl-pyrocatechols (II d, h - j) the chemical shift of each methyl substituent was calculated using the additive effects of hydroxyl and methyl chemical shift constants, derived from published correlation tables,[95a] on the toluene methyl signal (7.66 τ)[95b]. However, the results tended to be inconclusive because of the small differences involved. Calculated values have been included in Table 5 for comparison with the observed values and some tentative assignments have been made where possible.

TABLE 4

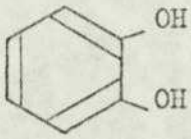
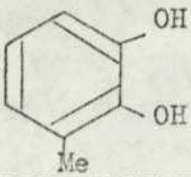
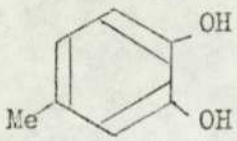
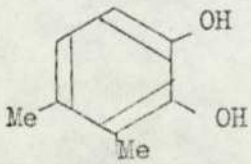
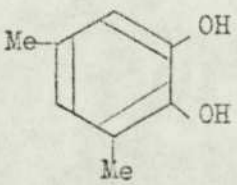
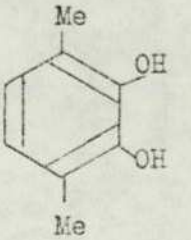
Pyrocatechol (II)	m.p. * (this work and method used)	m.p. (lit.)	Colour with alcoholic $FeCl_3$ and on dilution with water
(a) 	Ex. BDH Ltd. 105°	-	Blue ⟶ yellowish green
(b) 	Ex Koch-Light Ltd.	-	Blue green ⟶ yellow
(c) 	Ex Koch-Light 65-7°	-	Blue green ⟶ yellow green
(d) 	A 56-7° and 85-7° B 55-7° 83-4°	84-5°(52) 61 and (53) 84-5° 57° (54)	Blue green ⟶ yellow
(e) 	A 55-57° B 70-2°	71°(52) 73-4°(54) 55° 70.5-71°(55) 73-4°(59)	Olive green ⟶ yellow
(f) 	B 100-1°	101-3°(52) 100, 101 & 104°(53) 92°(54) 104°(55) 100-100.5°(62)	Olive green ⟶ orange

TABLE 4 (cont.)

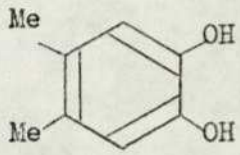
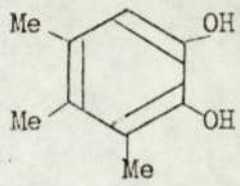
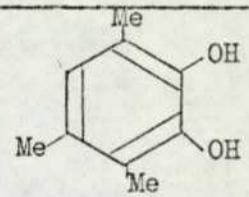
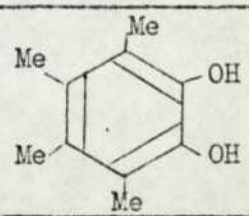
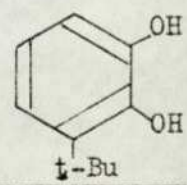
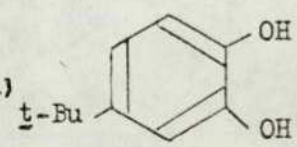
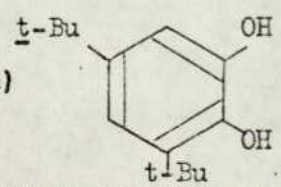
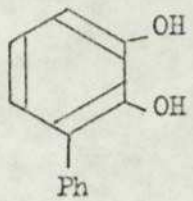
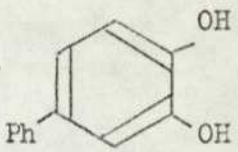
Pyrocatechol (II)	m.p.* (this work and method used)	m.p. (lit.)	Colour with alcoholic $FeCl_3$ and on dilution with water
(g) 	C 84-6° B 85-6°	87°(54) 85-6°(55) 79-82°(69) 86-7°(70) 86-7°(71) 87-8°(72)	Blue green ⟶ yellow
(h) 	B 96-7°	86-9°(74)	Yellowish-green → orange
(i) 	B 111-12°	110°(64) 109-110°(72) 118-120°(74)	Yellowish-green → orange
(j) 	110-11°	111°(75)	Olive green ⟶ orange
(k) 	B b.p. 92-6°/0.5 mm n_D^{25} 1.5335	b.p. 140-6°/20 mm(52)	Green ⟶
(l) 	Ex. BDH Ltd. 56-60°	-	-
(m) 	Ex. Fluka	-	-

TABLE 4 (cont.)

Pyrocatechol (II)	m.p.* (this work and method used)	m.p. (lit.)	Colour with alcoholic $FeCl_3$ and on dilution with water
(n) 	B 112-3°	113-4°(87) 111°(55) 114°(88) 57-9°(89)	Olive green ⟶ dark blue
(o) 	B 138-9°	136-136.5°(91) 144.8-149.2°(92) 141°(93) 139-140°(87) 135°(55) 138-140° and 136-8°(94)	Olive green ⟶ dark blue

* Corrected.

TABLE 5

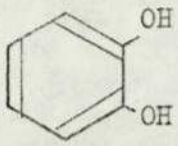
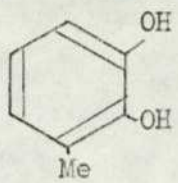
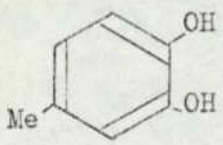
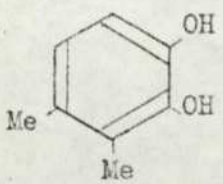
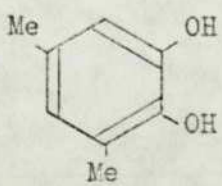
Pyrocatechol (II)	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$ [a]		
	aromatic protons	phenolic protons	protons of aromatic substituent(s)
(a) 	3.29 τ, 4H, s	4.88 τ, 2H, s	-
(b) 	3.24 - 3.38 τ, 3H, m	4.41 τ, 2H, s	7.80 τ, 3H, s (calculated value, 7.78 τ) [b]
(c) 	3.16 - 3.5 τ 3H, m	4.38 τ, 2H, b.s.	7.79 τ, 3H, s (calculated value 7.77 τ) [b]
(d) 	3.4 τ, 2H, s	4.6 τ, 2H, s	7.81 τ, s, 3-Me [c] 7.84 τ, s, 4-Me [c] } 6H (calculated for 3-Me, 7.83 τ and for 4-Me, 7.82 τ) [b]
(e) 	3.46 τ, 2H, s	4.8 τ, 2H, b.s.	7.80 τ, 6H, s (calculated for 3-Me, 7.85 τ and for 5-Me, 7.84 τ) [b]

TABLE 5 (Cont.)

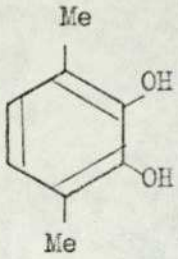
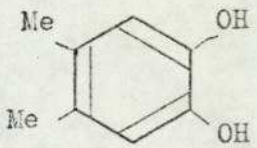
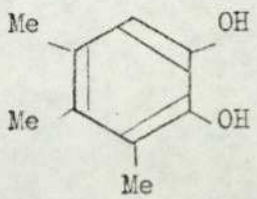
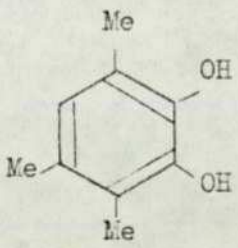
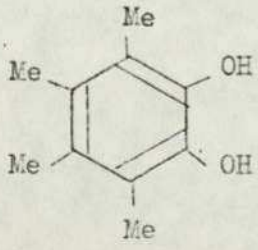
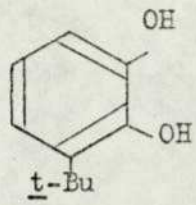
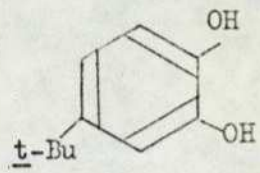
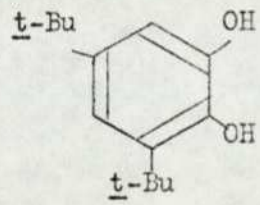
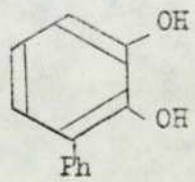
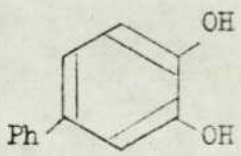
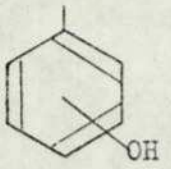
Pyrocatechol (II)	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$ [a]		
	aromatic protons	phenolic protons	protons of aromatic substituent(s)
(f) 	3.45 τ, 2H, s	4.95 τ, 2H, s	7.81 τ, 6H, s (calculated value 7.82 τ)[b]
(g) 	3.35 τ, 2H, s	4.92 τ, 2H, s	7.86 τ, 6H, s (calculated value 7.82 τ)[b]
(h) 	3.5 τ, 1H, s	4.77 τ, 2H, s	7.85 τ, 6H, s 7.91 τ, 3H, s (calculated values 3-Me, 7.90 τ; 4-Me, 7.87 τ; 5-Me, 7.89 τ)[b]
(i) 	3.46 τ, 1H, s	4.9 τ, 2H, s	7.82 τ, 6H, s 7.85 τ, 3H, s (calculated values. 3-Me, 7.87 τ; 4 and 6-Me, 7.89 τ)[b]
(j) 	-	5.1 τ, 2H, s	7.84 τ, 2 7.86 τ, s } 12H (calculated values 3 and 6-Me, 7.94 τ 4 and 5-Me, 7.94 τ)[b]

TABLE 5 (cont.)

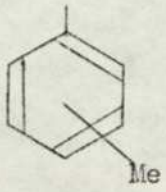
Pyrocatechol (II)	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$[a]		
	aromatic protons	phenolic protons	protons of aromatic substituents
(k) 	3.05 - 3.25τ 3H,m	4.37τ,2H,s	8.77τ,9H,s
(l) 	3.08 - 3.25τ 3H,m	4.36τ,2H,s	8.76τ,9H,s
(m) 	3.10 - 3.28τ 2H,q J meta≃2.4Hz	4.57τ,2H 5.06τ,1H both broad singlets	8.59τ,9H,s 8.75τ,9H,s
(n) 	3.17τ,3H,m	4.57τ,2H,s	2.57τ,5H,m
(o) 	Ill defined multiplet centred at 2.9τ	not evident[d]	Broad singlet at 2.52τ

a. Concentrations of ca 10-15% w/v were used.

b. The following chemical shift constants[95a] were used in the calculations



	δ
o	+0.05 ppm
m	+0.07 ppm
p	+0.04 ppm



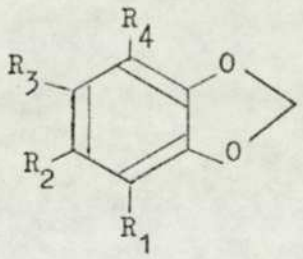
	δ
o	+ 0.05 ppm
m	+ 0.07 ppm
p	+ 0.04 ppm

c. Tentative assignments.

d. Because of the low solubility of this compound in $CDCl_3$ the spectrum was poor. In the absence of the hydroxyl protons integration of the remaining areas was not attempted.

4.2 Syntheses of the substituted 1.3-benzodioxoles (VII a - m)

The substituted 1.3-benzodioxoles (VII a - m) were required as planar reference compounds in connection with subsequent ultra-violet absorption studies (Chapter 5). All were prepared by the methylenation of the appropriately substituted pyrocatechols (II a-m) using the method of Bonthrone and Cornforth[96].



VII

(a) $R_1 = R_2 = R_3 = R_4 = H$

(b) $R_1 = Me, R_2 = R_3 = R_4 = H$

(c) $R_1 = H, R_2 = Me, R_3 = R_4 = H$

(d) $R_1 = R_2 = Me, R_3 = R_4 = H$

(e) $R_1 = Me, R_2 = H, R_3 = Me, R_4 = H$

(f) $R_1 = Me, R_2 = R_3 = H, R_4 = Me$

(g) $R_1 = H, R_2 = R_3 = Me, R_4 = H$

(h) $R_1 = R_2 = R_3 = Me, R_4 = H$

(i) $R_1 = R_2 = Me, R_3 = H, R_4 = Me$

(j) $R_1 = R_2 = R_3 = R_4 = Me$

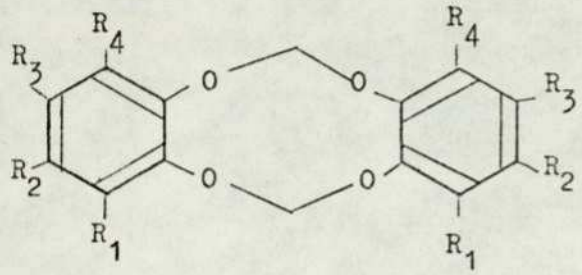
(k) $R_1 = \underline{t}\text{-Bu}, R_2 = R_3 = R_4 = H$

(l) $R_1 = H, R_2 = \underline{t}\text{-Bu}, R_3 = R_4 = H$

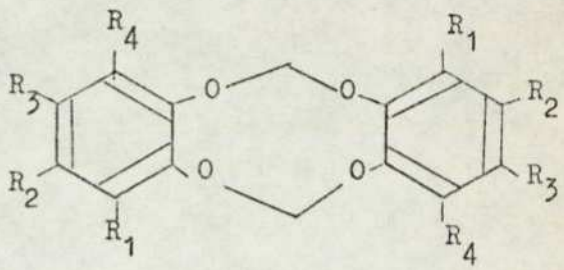
(m) $R_1 = \underline{t}\text{-Bu}, R_2 = H, R_3 = \underline{t}\text{-Bu}, R_4 = H$

The method involved heating a solution of the dianion of the appropriate Pyrocatechol with methylene chloride in dimethyl sulphoxide at 120° for several hours. Satisfactory yields (36-79%) of the dioxoles were obtained even when the

catechol input was as little as 600 mg. In most cases the products were isolated in a high state of purity by steam distillation followed by redistillation, crystallisation or sublimation where appropriate. In view of the small scale on which these reactions were performed no attempt was made to isolate any of the dimeric 2,7-dibenzo- [1,3,6,8] -tetroxecins (LXXXII a-m or LXXXIII a-m) that can also be formed[18,96,97].



LXXXII



LXXXIII

(a) $R_1 = R_2 = R_3 = R_4 = H$

(b) $R_1 = Me$, $R_2 = R_3 = R_4 = H$

(c) $R_1 = H$, $R_2 = Me$, $R_3 = R_4 = H$

(d) $R_1 = R_2 = Me$, $R_3 = R_4 = H$

(e) $R_1 = Me$, $R_2 = H$, $R_3 = Me$, $R_4 = H$

(f) $R_1 = Me$, $R_2 = R_3 = H$, $R_4 = Me$

(g) $R_1 = H$, $R_2 = R_3 = Me$, $R_4 = H$

(h) $R_1 = R_2 = R_3 = Me$, $R_4 = H$

(i) $R_1 = R_2 = Me$, $R_3 = H$, $R_4 = Me$

(j) $R_1 = R_2 = R_3 = R_4 = Me$

(k) $R_1 = \underline{t}\text{-Bu}$, $R_2 = R_3 = R_4 = H$

(l) $R_1 = H$, $R_2 = \underline{t}\text{-Bu}$, $R_3 = H$, $R_4 = H$

(m) $R_1 = \underline{t}\text{-Bu}$, $R_2 = H$, $R_3 = \underline{t}\text{-Bu}$, $R_4 = H$

The following 1,3-benzodioxoles were prepared by the method of Bonthrone and Cornforth[96]. Infra-red and nuclear magnetic resonance spectra for all the compounds are recorded in Tables 6 and 7 respectively. Ultra-violet spectral results are given later in Chapter 5, Table 29.

4.2.1 1,3-Benzodioxole (VIIa)

A solution of pyrocatechol (11.0g, 0.1 mole) and methylene chloride (10.2g, 0.12 mole) in dimethyl sulphoxide (150 ml), under nitrogen, was treated with powdered sodium hydroxide (8.4g, 0.21 mole) and heated for 2 hr. under reflux in an oil bath at 120°. The black solution was steam distilled and the distillate was extracted with ether (3 x 10 ml) dried (Na_2SO_4) and evaporated. Distillation of the residue afforded 6.1g (55%) of 1,3-benzodioxole as a colourless liquid, b.p. 172-174°/755 mm (b.p. 65-66°/10 mm), $n_D^{22.5}$ 1.5380. (Lit.,[96] b.p. 173-175°/760 mm, 60°/9 mm, n_D^{21} 1.5377). G.l.c., column A at 120° showed only one peak. The infra-red spectrum was identical with that published[98].

4.2.2 4-Methyl-1,3-benzodioxole (VIIb)

This compound was available from a previous investigation[18]. It was redistilled [b.p. 76-78°/10 mm, 192-194°/772 mm, $n_D^{22.5}$ 1.5305 (lit.,[3] b.p. 45°/1.2mm, n_D^{26} 1.5288), g.l.c., column A at 150° showed only one peak] and its physical constants were redetermined.

4.2.3 5-Methyl-1,3-benzodioxole (VIIc)

This compound was also available from a previous investigation[18]. It was redistilled [b.p. 75-6°/10mm, 194-196°/756 mm, n_D^{23} 1.5302 (lit.,[96] b.p. 196-197°/753.5 mm, n_D^{20} 1.5308). g.l.c., column A at 150° gave a single peak] and its physical constants were redetermined.

The following compounds were prepared as described for 1,3-benzodioxole (VIIa), (example 4.2.1).

4.2.4 4,5-Dimethyl-1,3-benzodioxole (VIId)

Scale: 0.03 mole. Yield 65%, colourless liquid, b.p. 99-100°/11 mm, n_D^{27} 1.5304. G.l.c., column A at 140° gave a single peak. (Found: C, 71.7; H, 6.4. $C_9H_{10}O_2$ requires C, 72.0; H, 6.7%).

4.2.5 4,6-Dimethyl-1,3-benzodioxole (VIIe)

Scale: 0.025 mole. Yield 66%, colourless liquid, b.p. 93-94°/10 mm, n_D^{23} 1.5260. G.l.c., column A at 150° gave a single peak. (Found: C, 72.0; H, 7.0. $C_9H_{10}O_2$ requires C, 72.0; H, 6.7%).

4.2.6 4,7-Dimethyl-1,3-benzodioxole (VIIf)

Scale: 0.01 mole. Yield, 56% as a colourless liquid, b.p. 90-91°/10 mm, n_D^{25} 1.5228. G.l.c., column A at 150° showed only one peak. (Found: C, 71.8; H, 6.9, $C_9H_{10}O_2$ requires C, 72.0; H, 6.7%).

4.2.7 5,6-Dimethyl-1,3-benzodioxole (VIIg)

Scale: 0.01 mole. Yield, 59%, as colourless needles, m.p. 49-50° after sublimation at 0.01 mm (bath temperature 40-45°). G.l.c., column A at 150° gave one peak. (Found: C, 72.1; H, 6.85. $C_9H_{10}O_2$ requires C, 72.0; H, 6.7%).

4.2.8 4,5,6-Trimethyl-1,3-benzodioxole (VIIh)

Scale: 0.015 mole. Yield, 36%, b.p. 116-118°/10 mm, m.p. 31-32° [colourless prisms from light petroleum (b.p. 40-60°)]. G.l.c., column A at 160°, gave a single peak. (Found: C, 73.1; H, 7.3. $C_{10}H_{12}O_2$ requires C, 73.1; H, 7.4%).

4.2.9 4,5,7-Trimethyl-1,3-benzodioxole (VIIi)

Scale: 0.015 mole. Yield, 43%, of a colourless liquid, b.p. 113-114°/10 mm, n_D^{27} 1.5267. G.l.c., at 150° gave a single peak. (Found: C, 73.3; H, 7.3. $C_{10}H_{12}O_2$ requires C, 73.1; H, 7.4%).

4.2.10 4,5,6,7-Tetramethyl-1,3-benzodioxole (VIIj)

Scale: 0.004 mole. Yield, 79%, of colourless prisms, m.p. 70-71°, after sublimation at 0.01mm (bath temperature 60°). G.l.c., column A, at 170°, showed a single peak. (Found: C, 74.3; H, 8.0. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%).

4.2.11 4-t-Butyl-1,3-benzodioxole (VIIk)

Scale: 0.02 mole. This compound was obtained in 47% yield as a colourless liquid, b.p. 107°/10 mm, $n_D^{22.5}$ 1.5160. G.l.c., column A, at 150° gave one peak only. (Found: C, 73.8; H, 7.7. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%).

4.2.12 5-t-Butyl-1,3-benzodioxole (VIIl)

Scale: 0.1 mole. This compound was obtained as a colourless liquid in 55% yield, b.p. 117°/10 mm, $n_D^{22.5}$ 1.5168. G.l.c., column A at 150° gave only one peak. (Found: C, 74.3; H, 8.2. $C_{11}H_{14}O_2$ requires

C, 74.1; H, 7.9%).

4.2.13 4,6-Di-t-butyl-1,3-benzodioxole (VIIm)

Scale: 0.1 mole. A 68.5% yield of this compound was obtained as a colourless liquid, b.p. 143-144°/10mm, n_D^{23} 1.5055. G.l.c., column A, at 210° gave a single peak. (Found: C, 76.6; H, 9.2. $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.5%).

4.2.14 Some infra-red and nuclear magnetic resonance spectral data for the substituted 1,3-benzodioxoles (VII a-m).

The infra-red spectra of 1,3-benzodioxole (VIIa) and the mono, di tri and tetramethyl- analogues (VII b-j) showed a single strong absorption in the range 1231-1270 cm^{-1} typical of aralkyl ethers[38b] but in the spectra of the three t-butyl- analogues (VII k-m) three bands were observed close to this range (see Table 6). Considerable variations occurred in the intensities of bands in the range 1650-1450 cm^{-1}, a region associated with >C=C< stretching vibrations[38a]. These bands have also been recorded in Table 6 together with the bands which appeared in the 1000-700 cm^{-1} region. These are due to the out-of-plane deformation vibrations of hydrogen atoms remaining on the ring[38g]. Their position is determined almost wholly by the positions rather than the nature of the substituents, consequently they provide an excellent means of recognising the type of substitution and would be valuable in identifying these compounds.

Ultra-violet absorption measurements on the extent of the absorption in the 270 nm region are discussed in Chapter 5.

TABLE 6

Infra-red frequencies (cm^{-1}) of some bands in the substituted 1,3-benzodioxoles (VII a-m).

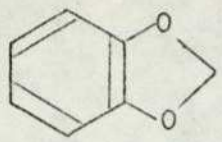
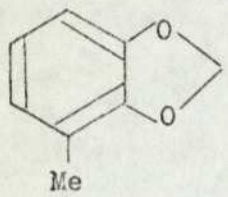
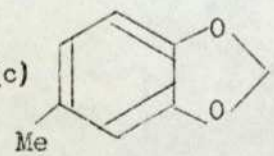
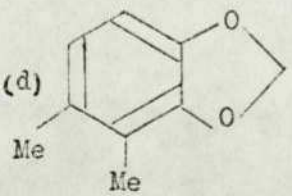
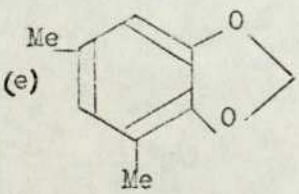
1,3-Benzodioxole (VII)	Phase	>C=C< 1650-1450 cm^{-1} stretching vibrations	>C=C-OR Stretching Vibrations	1000 - 700 cm^{-1} Out-of-plane deformations
(a) 	neat film	1620 w 1600 w 1500 s 1480 vs	1230 vs	1000 w, 937 vs, 910 w, 855 vs, 800 m, 740 vs, 715 w.
(b) 	"	1635 m 1600 m 1450 vs	1245 vs	950 s, 925 m, 830 m, 857 vs, 845 w, 720 s.
(c) 	"	1600 w 1480 s 1430 s	1240 vs	935 s, 915 s, 850 m, 805 s, 795 s, 750 w.
(d) 	"	1640 w 1580 w 1500 m 1480 s 1470 vs	1250 vs	975 m, 940 s, 880 m, 795 s, 756 w, 744 w, 726 w.
(e) 	"	1640 s 1610 m 1490 vs 1430 vs	1270 vs	980 s, 935 vs 835 vs, 733 w, 724 s.

TABLE 6 (Cont.)

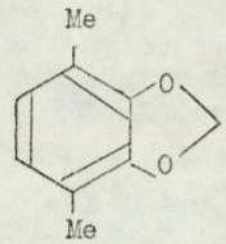
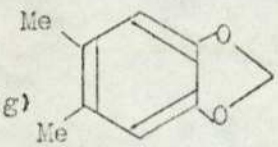
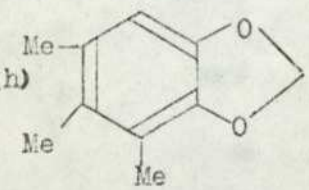
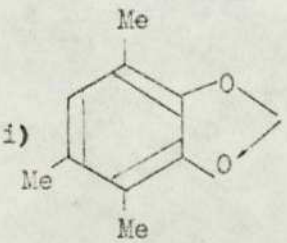
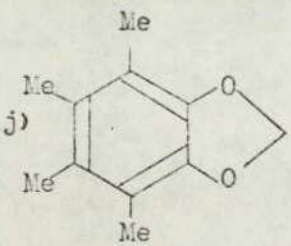
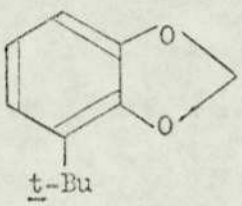
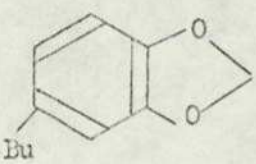
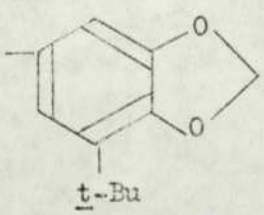
1,3-Benzodioxole (VII)	Phase	>C=C< 1650-1450 cm^{-1} Stretching Vibrations	>C=C-OR Stretching Vibrations	1000-700 cm^{-1} Out-of-plane deformations
(f) 	neat film	1650 w 1600 w 1500 m 1450 s 1440 vs	1250 vs	965 vs, 925 m, 785 s, 747 w, 733 m
(g) 	Nujol*	1610 w 1500 s 1495 vs	1245 vs	990 w, 940 s, 845 s, 840 m, 755 m.
(h) 	neat film	1635 w 1495 m 1470 vs 1440 s	1260 s	995 w, 953 m, 922 s, 840 m, 825 m, 755 w, 730 w, 723 w.
(i) 	melt	1650 w 1605 w 1495 s 1450 vs 1410 vs	1245 vs	1000 m, 965 m, 930 m, 846 m, 745 w, 730 w
(j) 	Nujol*	1610 w 1430 s	1270 m	953 m, 875 w, 820 w, 723 w

TABLE 6 (Cont.)

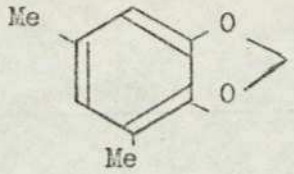
1,3-Benzodioxole (VII)	Phase	>C=C< 1650-1450 cm^{-1} Stretching Vibrations	>C=C-OR Stretching Vibrations	1000-700 cm^{-1} Out-of-plane deformations
(k) 	neat film	1625 m 1590 s 1485 s 1440 vs	1270 m 1250 vs 1230 vs	965 vs, 940 s, 870 w, 837 s, 810 m, 775 vs, 728 vs.
(l) 	"	1605 w, 1500 s 1490 vs 1430 s	1280 m 1250 vs 1225 vs	940 s, 908 s, 860 m, 826 m, 808 s, 725 w
t-Bu (m) 	"	1635 w 1590 m 1485 s 1465 s 1420 vs	1280 s 1260 s 1230 s	975 vs, 945 m, 910 w, 853 m, 825 m, 815 w, 743 m, 725 w.

w = weak, m = medium, s = strong, vs = very strong.

* Some bands in this region may be obscured by the Nujol peak.

The nuclear magnetic resonance spectra of all the compounds were consistent with their structures and have been recorded in Table 7. The protons of the methylenedioxy group resonated as a singlet at 4.1 - 4.3 τ in agreement with the reported values[95c]. Identification of the proton resonances of the aromatic substituents has been made with the aid of chemical shift constants either from published correlation tables alone or in conjunction with spectral data from this investigation. When the reported methyl[95a] and methoxyl[99] chemical shift constants for the toluene methyl signal (7.66τ)[95b] were applied to the substituted 1,3-benzodioxoles (VII) a satisfactory agreement was found for the observed and calculated signal positions which enabled a confident signal assignment to be made for the majority of the compounds with the exception of the 4,5,7-trimethyl compound (VII i) when the results were inconclusive (see Table 7). A much closer agreement between the observed and estimated values for the resonance positions of the substituents was obtained when the o/m and m/p effects of the methylenedioxy group on the toluene methyl signal (7.66τ)[95b] were employed in place of the methoxyl constants. The requisite shift constants were readily calculated by subtracting the methyl τ value of toluene (7.66 τ)[95b] from that observed in 4-methyl- and 5-methyl-1,3-benzodioxoles (VIIb and c). The chemical shift constant thus calculated for a methylenedioxy group o/m to a toluene methyl group amounted to +0.16 ppm and was used, together with the appropriate methyl increment(s) to estimate the chemical shift(s) of the methyl group(s) at the 4 and 7 position(s). The m/p chemical shift constant, +0.09 ppm, was similarly employed to predict the positions of the 5 and 6 methyl substituents. The following is a typical calculation:

Compound:



VIIe

4-Methyl

Toluene methyl position[95b]	7.66 τ	
o/m methylenedioxy increment[100]	+ 0.16 ppm	
m-methyl increment[95a]	+ 0.07 ppm	
Total	7.89 τ	(Observed: 7.87 τ)

6-Methyl

Toluene methyl position[95b]	7.66 τ	
m/p methylene dioxy increment[100]	+ 0.09 ppm	
m-methyl increment[95a]	+ 0.07 ppm	
Total	7.82 τ	(Observed: 7.82 τ)

Deviations from the observed values were less than 0.07 ppm by this approach but inconclusive results were again noted for the 4,5,7-trimethyl-compound (VIIi) (see Table 7). Similar principles were used to calculate the chemical shifts of the t-butyl groups in 4,6-di-t-butyl-1,3-benzodioxole (VIIm). In this case subtraction of the alkyl proton signal position in t-butyl benzene (8.67 τ)[101] from the corresponding signal in 4-t-butyl- (VIIk) and 5-t-butyl-1,3-benzodioxole (VIIl) gave the o/m (+ 0.01 ppm) and m/p (+ 0.06 ppm) shift constants respectively and when used with the appropriate increment for an additional m-t-butyl group (see footnote d,

Table 7) enabled a confident assignment to be made for the two t-butyl signals in the spectrum of the di-t-butyl- compound (VIIm)(see Table 7).

TABLE 7

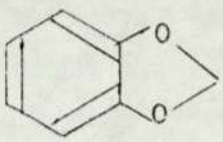
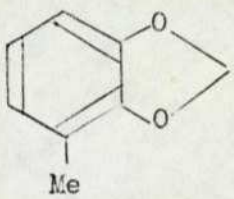
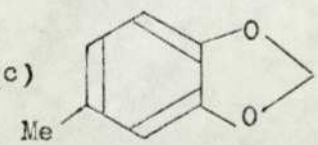
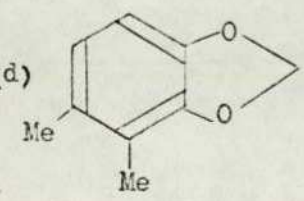
1,3-Benzodioxole (VII)	60 MHz ^{1}H n.m.r. spectra in CCl_4 [a]		
	aromatic protons	$-OCH_2-O-$	protons of aromatic substituent(s)
(a) 	3.28 τ, 4H, s	4.19 τ, 2H, s	-
(b) 	3.1-3.5 τ, 3H, m	4.16 τ, 2H, s	7.82 τ, 3H, s (Calcd. value, 7.97 τ)[b]
(c) 	3.2-3.6 τ, 3H, m	4.16 τ, 2H, s	7.75 τ, 3H, s (Calcd. value, 7.91 τ)[b]
(d) 	3.54 τ, 2H, s	4.19 τ, 2H, s	7.86 τ, 3H, s, 5-Me. (Calcd. value 7.96 τ[b]; 7.80 τ[c]). 7.92 τ, 3H, s 4-Me (Calcd. value 8.02 τ[b]; 7.87 τ[c]).

TABLE 7 (Cont.)

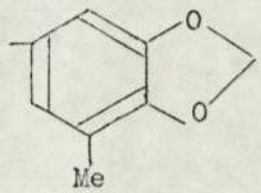
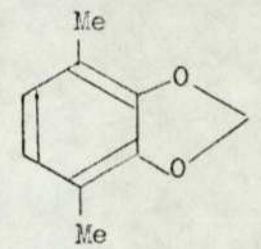
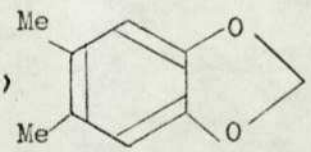
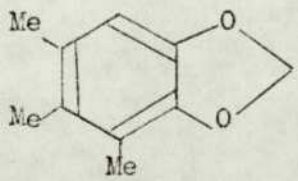
1.3-Benzodioxole (VII)	60 MHx ^{1}H n.m.r. spectra in CCl_4 [a]		
	aromatic protons	$-OCH_2-O-$	protons of aromatic substituent(s)
(e) 	3.67τ,2H,s	4.24τ,2H,s	7.82τ,3H,s 6-Me. (Calcd. value 7.98τ[b]; 7.82τ[c]). 7.87τ,3H,s 4-Me. (Calcd. value, 8.04τ[b], 7.89τ[c]).
(f) 	3.58τ,2H,s	4.16τ,2H,s	7.86τ,6H,s (Calcd. values, 8.01τ[b]; 7.86τ[c]).
(g) 	3.50τ,2H,s	4.21τ,2H,s	7.86τ,6H,s (Calcd. values, 7.96τ[b]; 7.80τ[c]).
(h) 	3.63τ,1H,s	4.23τ,2H,s	7.85τ,3H,s 5-Me. (Calcd. value, 8.01τ[b]; 7.85τ[c]). 7.89τ,3H,s 6-Me. (Calcd. value, 8.03τ[b]; 7.87τ[c]). 7.96τ,3H,s 4-Me. (Calcd. value, 8.09τ[b]; 7.94τ[c]).

TABLE 7 (Cont.)

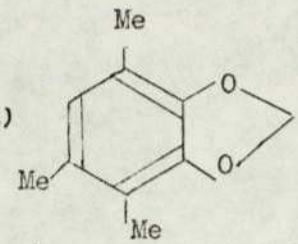
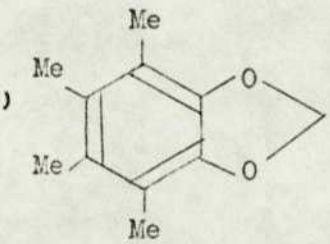
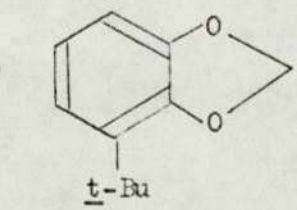
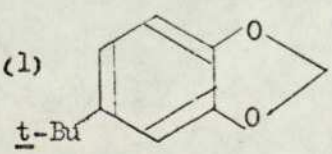
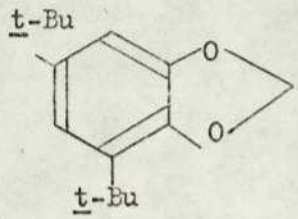
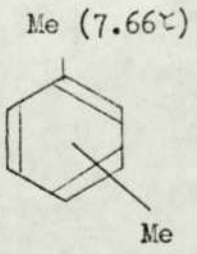
1,3-Benzodioxole (VII)	60 MHz ^{1}H n.m.r. spectra in CCl_4 [a]		
	aromatic protons	$-OCH_2-O-$	protons of aromatic substituent(s)
(i) 	3.71τ, 1H, s	4.22τ, 2H, s	7.90τ, 6H, s 7.96τ, 3H, s (Calcd. values: 4-Me, 8.09τ[b]; 7.91τ[c]. 5-Me, 8.03τ[b]; 7.87τ[c]. 7-Me, 8.08τ[b]; 7.93τ[c]).
(j) 	-	4.2τ, 2H, s	7.91τ, 12H, s (Calcd. values 4 and 7-Me, 8.13τ[b], 7.98τ[c]. 5 and 6-Me 8.08τ[b], 7.92τ[c]).
(k) 	3.38 τ, 3H, s	4.16τ, 2H, s	8.68τ, 9H, s
(l) 	3.19-3.4τ, 3H, s	4.17τ, 2H, s	8.73τ, 9H, s

TABLE 7 (Cont.)

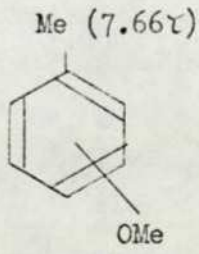
1,3-Benzodioxole (VII)	60 MHz ^{1}H n.m.r. spectra in CCl_4 [a]		
	aromatic protons	$-OCH_2-O-$	protons of aromatic substituent(s)
(m) 	3.31τ, 2H, s	4.18τ, 2H, s	8.65τ, 9H, s 4-t-Bu (Calcd. value, 8.70τ)[d] 8.72τ, 9H, s 6-t-Bu (Calcd. value 8.75τ)[d]

a. Concentrations of ca 10-15% were used.

b. The following methyl[95a] and methoxyl[99] chemical shift constants were employed for these calculations.



	δ
o	+ 0.05 ppm
m	+ 0.07 ppm
p	+ 0.04 ppm



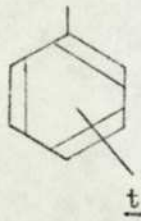
	δ
o	+ 0.21 ppm
m	+ 0.11 ppm
p	+ 0.14 ppm

c. Chemical shift constants for the o/m and m/p effects of the methylenedioxy group on the toluene methyl signal were obtained by subtracting the position of the methyl proton signal (7.66τ)[95b] from the corresponding signals in 4-methyl- (VIIb) and 5-methyl-1,3-benzodioxole (VIIc) respectively. The o/m constant (+ 0.16 ppm) was used to

calculate the chemical shift(s) of the 4 and 7 methyl group(s); the m/p constant (+ 0.09 ppm) to estimate the chemical shifts of the 5 and 6 methyl substituents.

The methyl chemical shift constants used are recorded in footnote b.

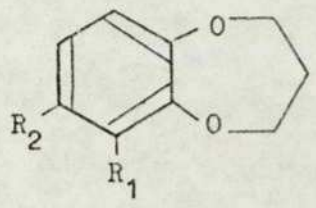
d. The appropriate o/m and m/p chemical shift constants used to calculate the chemical shifts of the two t-butyl groups were obtained by subtracting the position of the alkyl proton signal of t-butylbenzene (8.67τ)[101] from the corresponding signals in 4-t-butyl- (VIIk) and 6-t-butyl-1,3-benzodioxole (VIIl). The o/m constant (+ 0.01 ppm) was used to calculate the chemical shift of the 4-t-butyl group; the m/p constant (+ 0.06 ppm) was used for the 6-t-butyl substituent. The appropriate m-t-butyl chemical shift constant was taken from published data[101].



	δ
o	-0.21 ppm
m	+0.02 ppm
p	+0.02 ppm

4.3 Preparations of some 3,4-dihydro-2H-1,5-benzodioxepins (VIII a-c)

These compounds were required for the ultra-violet studies described in Chapter 5. Only the parent compound (VIII a) had to be prepared and



VIII

(a) $R_1 = R_2 = H$

(b) $R_1 = Me$, $R_2 = H$

(c) $R_1 = H$, $R_2 = Me$

this was obtained by reaction of pyrocatechol with 1,3-dibromopropane[102]. The 6- and 7-methyl- analogues (VIII b,c) were available from a previous investigation[18].

4.3.1 3,4-Dihydro-2H-1,5-benzodioxepin (VIII a)

This compound was obtained by the reaction of pyrocatechol (11.0g, 0.1 mole) with 1,3-dibromopropane (20.2g, 0.1 mole) as described by Ghosh[102]. It (12.5g, 83%) had b.p. 230-232°/772 mm, 106-108°/10 mm (lit.,[21] b.p. 103°/10 mm), $n_D^{21.5}$ 1.5445 (lit.,[103] n_D 1.5430). G.l.c., column A at 140° gave one peak. The infra-red spectrum was identical with that obtained by Archer[18]. For ultra-violet spectral data see Chapter 5, Table 31.

4.3.2 6-Methyl-3,4-dihydro-2H-1,5-benzodioxepin (VIII b)

This compound was available from a previous study[18]. It was redistilled, b.p. 115-117°/10 mm, n_D^{22} 1.5380 (lit.,[3] b.p. 83°/1.5 mm, n_D^{23} 1.5374). G.l.c., column A, at 170°, gave one peak only. See Chapter 5, Table 31. for ultra-violet spectral data.

4.3.3 7-Methyl-3,4-dihydro-2H-1,5-benzodioxepin (VIII c)

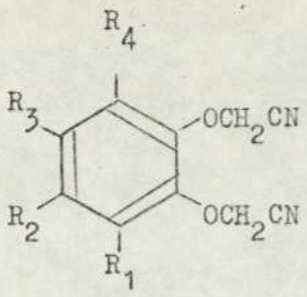
This material was also available from previous work[18]. It was redistilled and had b.p. 116-117°/10 mm, n_D^{22} 1.5363 lit.,[3] b.p. 85-86°/1.0 mm, n_D^{23} 1.5368). G.l.c., column A, at 170°, showed one peak. Ultra-violet spectral information is recorded in Chapter 5, Table 31.

4.4 Preparations of the substituted o-phenylenedioxydiacetonitriles (III b-o)

The substituted o-phenylenedioxydiacetonitriles (III b-o) described below were all prepared using the conditions which were developed earlier for the parent compound (IIIa) (see Chapter 2.1). In most cases the yields were satisfactory (56 - > 90%) and little difficulty was encountered in the isolation or purification of the compounds; for most, crystallisation was usually sufficient but others, especially the low melting (III b, f) and liquid compounds (III k, l, n), required passage through a column of neutral alumina followed by distillation before chromatographically (g.l.c.) pure material was obtained.

4.4.1 o-Phenylenedioxydiacetonitrile (IIIa)

The preparation of this compound was described earlier (2.1.1.2);



III

(a) $R_1 = R_2 = R_3 = R_4 = H$

(b) $R_1 = Me$, $R_2 = R_3 = R_4 = H$

(c) $R_1 = H$, $R_2 = Me$, $R_3 = R_4 = H$

(d) $R_1 = R_2 = Me$, $R_3 = R_4 = H$

(e) $R_1 = Me$, $R_2 = H$, $R_3 = Me$, $R_4 = H$

(f) $R_1 = Me$, $R_2 = R_3 = H$, $R_4 = Me$

(g) $R_1 = H$, $R_2 = R_3 = Me$, $R_4 = H$

(h) $R_1 = R_2 = R_3 = Me$, $R_4 = H$

(i) $R_1 = R_2 = Me$, $R_3 = H$, $R_4 = Me$

(j) $R_1 = R_2 = R_3 = R_4 = Me$

(k) $R_1 = \underline{t}$-Bu, $R_2 = R_3 = R_4 = H$

(l) $R_1 = H$, $R_2 = \underline{t}$-Bu, $R_3 = R_4 = H$

(m) $R_1 = \underline{t}$-Bu, $R_2 = H$, $R_3 = \underline{t}$-Bu, $R_4 = H$

(n) $R_1 = Ph$, $R_2 = R_3 = R_4 = H$

(o) $R_1 = H$, $R_2 = Ph$, $R_3 = R_4 = H$

similar conditions and precautions were followed during the preparation of the following analogues. Nuclear magnetic resonance spectral data for all the compounds are recorded in Table 8. Ultra-violet spectral results are given in Chapter 5, Table 28.

4.4.2 3-Methyl-o-phenylenedioxydiacetonitrile (IIIb)

Scale: 0.333 mole. Yield 56.5%, b.p. 148-150°/0.5 mm, m.p. 34-35° [colourless needles from light petroleum (b.p. 60-80°)]. (Found: C, 65.4; H, 4.9; N, 13.9. $C_{11}H_{10}N_2O_2$ requires C, 65.3; H, 5.0; N, 13.9%).

4.4.3 4-Methyl-o-phenylenedioxydiacetonitrile (IIIc)

Scale: 0.333 mole. Yield 87.5%, m.p. 86-87° (off-white plates from aqueous ethanol). (Found: C, 65.2; H, 4.8; N, 13.8. $C_{11}H_{10}N_2O_2$ requires C, 65.3; H, 5.0; N, 13.9%).

4.4.4 3,4-Dimethyl-o-phenylenedioxydiacetonitrile (IIId)

Scale: 0.1 mole. Yield 89%, m.p. 81-82° [colourless silky needles from carbon tetrachloride-light petroleum (b.p. 60-80°)]. (Found: C, 67.0; H, 5.7; N, 12.75. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 13.0%).

4.4.5 3,5-Dimethyl-o-phenylenedioxydiacetonitrile (IIIe)

Scale: 0.1 mole. Yield 90%, m.p. 61-62°, [colourless blades from carbon tetrachloride-light petroleum (b.p. 60-80°)]. (Found: C, 66.2; H, 5.6; N, 12.7. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 13.0%).

4.4.6 3,6-Dimethyl-o-phenylenedioxydiacetonitrile (IIIf)

Scale: 0.04 mole. Yield 65%, b.p. 152-158°/0.05 mm, m.p. 61-62° [colourless needles from carbon tetrachloride-light petroleum (b.p. 60-80°)]. (Found: C, 66.2; H, 5.6; N, 13.2. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 13.0%).

4.4.7 4,5-Dimethyl-o-phenylenedioxydiacetonitrile (IIIg)

Scale: 0.05 mole. Yield 80%, m.p. 107-108° (colourless needles from aqueous methanol). (Found: C, 66.6; H, 5.5; N, 13.3. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 13.0%).

4.4.8 3,4,5-Trimethyl-o-phenylenedioxydiacetonitrile (IIIh)

Scale: 0.05 mole. Yield 78%, m.p. 78-79° [colourless filaments from light petroleum (b.p. 60-80°)]. (Found: C, 68.1; H, 6.4; N, 12.3. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%).

4.4.9 3,4,6-Trimethyl-o-phenylenedioxydiacetonitrile (IIIi)

Scale 0.05 mole. Yield 74%, m.p. 79-80° [colourless needles from light petroleum (b.p. 60-80°)]. (Found: C, 68.05; H, 6.2; N, 12.15. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%).

4.4.10 3,4,5,6-Tetramethyl-o-phenylenedioxydiacetonitrile (IIIj)

Scale 0.025 mole. The yield, after a 24 hr. reaction time, was 56%, m.p. 112-113° (colourless prisms from methanol). (Found: C, 68.8; H, 6.9; N, 11.65. $C_{14}H_{16}N_2O_2$ requires C, 68.8; H, 6.6; N, 11.5%).

4.4.11 3-t-Butyl-o-phenylenedioxydiacetonitrile (IIIk)

Scale: 0.05 mole. Yield 58%, b.p. 166-172°/0.05 mm, m.p. 55-56° [colourless needles from light petroleum (b.p. 60-80°)]. G.l.c., column A, at 220° gave a single peak. (Found: C, 68.5; H, 6.5; N, 11.4. $C_{14}H_{16}N_2O_2$ requires C, 68.8; H, 6.6; N, 11.5%).

4.4.12 4-t-Butyl-o-phenylenedioxydiacetonitrile (IIIl)

Scale: 0.2 mole. This compound was obtained as a colourless liquid in 90% yield, b.p. 162-164°/0.6 mm, n_D^{25} 1.5163. G.l.c., column A, at 220° disclosed < 0.1% of impurity. (Found: C, 68.7; H, 6.8; N, 11.7. $C_{14}H_{16}N_2O_2$ requires C, 68.8; H, 6.6; N, 11.5%).

4.4.13 3,5-Di-t-butyl-o-phenylenedioxydiacetonitrile (IIIm)

Scale: 0.1 mole. The yield of crude material was almost quantitative. It had m.p. 96-97° [colourless needles from light petroleum (b.p. 60-80°)]. (Found: C, 71.8; H, 8.05; N, 9.4. $C_{18}H_{24}N_2O_2$ requires C, 72.0; H, 8.05; N, 9.3%).

4.4.14 3-Phenyl-o-phenylenedioxydiacetonitrile (IIIn)

Scale: 0.075 mole. Yield 80.5%, b.p. 194-198°/0.01 mm, m.p. 59-60° [colourless plates from carbon tetrachloride-light petroleum (b.p. 60-80°)]. (Found: C, 72.6; H, 4.3; N, 10.9. $C_{16}H_{12}N_2O_2$ requires C, 72.7; H, 4.6; N, 10.6%).

4.4.15 4-Phenyl-o-phenylenedioxydiacetonitrile (IIIo)

Scale: 0.05 mole. Yield 79.5%, m.p. 84-85° [colourless prisms from benzene-light petroleum (b.p. 60-80°)]. (Found: C, 72.4; H, 4.4; N, 10.9. $C_{16}H_{12}N_2O_2$ requires C, 72.7; H, 4.6; N, 10.6%).

4.4.16 Discussion of nuclear magnetic resonance spectral data of the substituted o-phenylenedioxydiacetonitriles (III a-o).

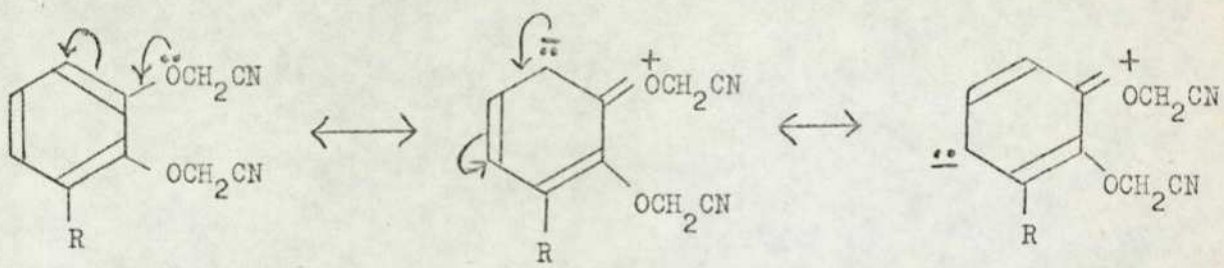
A notable feature of all these compounds (III a-o) was the absence of any C≡N absorption in their infra-red spectra near 2200 cm^{-1}. This was not unexpected since a marked quenching of the C≡N absorption intensity often occurs when an oxygen-containing group is attached to the same carbon atom as the nitrile group[38h]. In fact infra-red spectroscopy was of little diagnostic value for this class of compound.

Far more useful information was obtained from the nuclear magnetic resonance spectra of these compounds. The results are recorded in Table 8, and in every case were consistent with the proposed structures. The precise assignment of signals, particularly for many of the unsymmetrically substituted methyl-compounds (III b,c,d,e,h,i) and t-butyl-analogues (III k,l,m), proved difficult because of small changes that the number and position(s) of the aromatic substituent(s) exerted on the electronic and/or steric effects of the molecules and the consequent effects these produced on the chemical shifts of certain protons. Attempts have been made to interpret some of the spectra in Table 8 but it must be emphasised that many of these are tentative speculations.

One interesting feature observed for most of the unsymmetrically substituted o-phenylenedioxydiacetonitriles (III b-e,h-i,k-o) was the non-equivalence of the methylene protons which, in most cases, appeared

as a pair of two-proton singlets. The small differences (0.02 - 0.07τ) observed between these signals in the unsymmetrical methyl- and t-butyl- members of the series (III b-e,h,k,l,m) made positive identifications hazardous but tentative assignments based on the following arguments have been made and are discussed below.

Ultra-violet spectral results (see Chapter 5) indicated that the presence of a 3-methyl- or 3-t-butyl- substituent in the o-phenylenedioxy-diacetonitriles forced the 2-OCH_2CN into an orthogonal conformation and prevented mesomeric contributions from the oxygen electrons. In contrast the 1-OCH_2CN group can become co-planar with the aromatic ring and enable delocalisation of its oxygen electrons to occur.

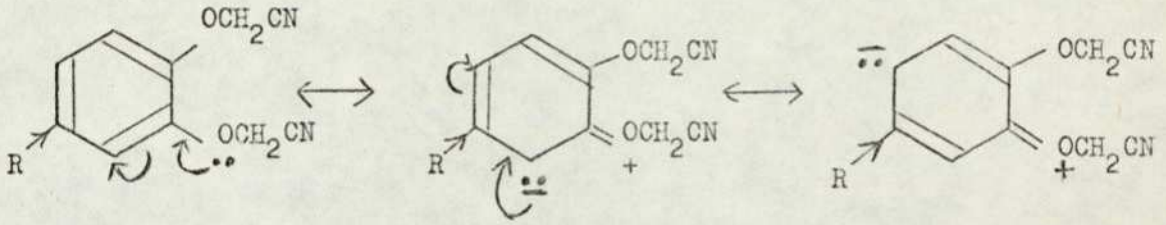


R = Me or t-Bu

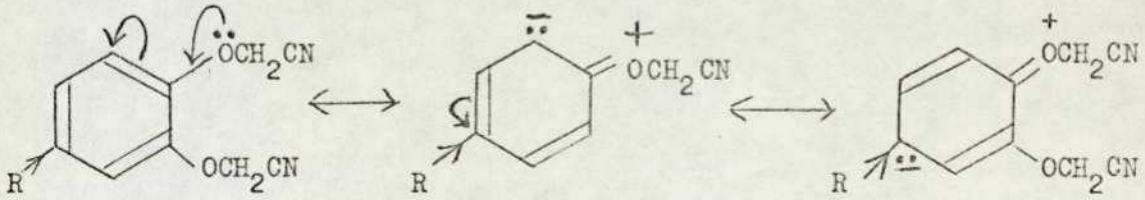
Consequently the methylene protons of the 1-OCH_2CN group could experience a slightly more deshielded environment and thus resonate at a lower field than the corresponding protons of the 2-OCH_2CN group. The same argument can also be extended satisfactorily to the 3,4-dimethyl- (IIId), 3,5-dimethyl- (IIIe), 3,4,5-trimethyl- (IIIh) and 3,5-di-t-butyl- (IIIm) analogues.

In the case of the 4-methyl- (IIIb) and 4-t-butyl- (IIIl) analogues mesomeric effects involving the 1-OCH_2CN group are less favourable than

those from the 2-OCH_2CN function because of direct competition from the electron donating 4-alkyl substituent.



mesomerism favourable from '2'-oxygen



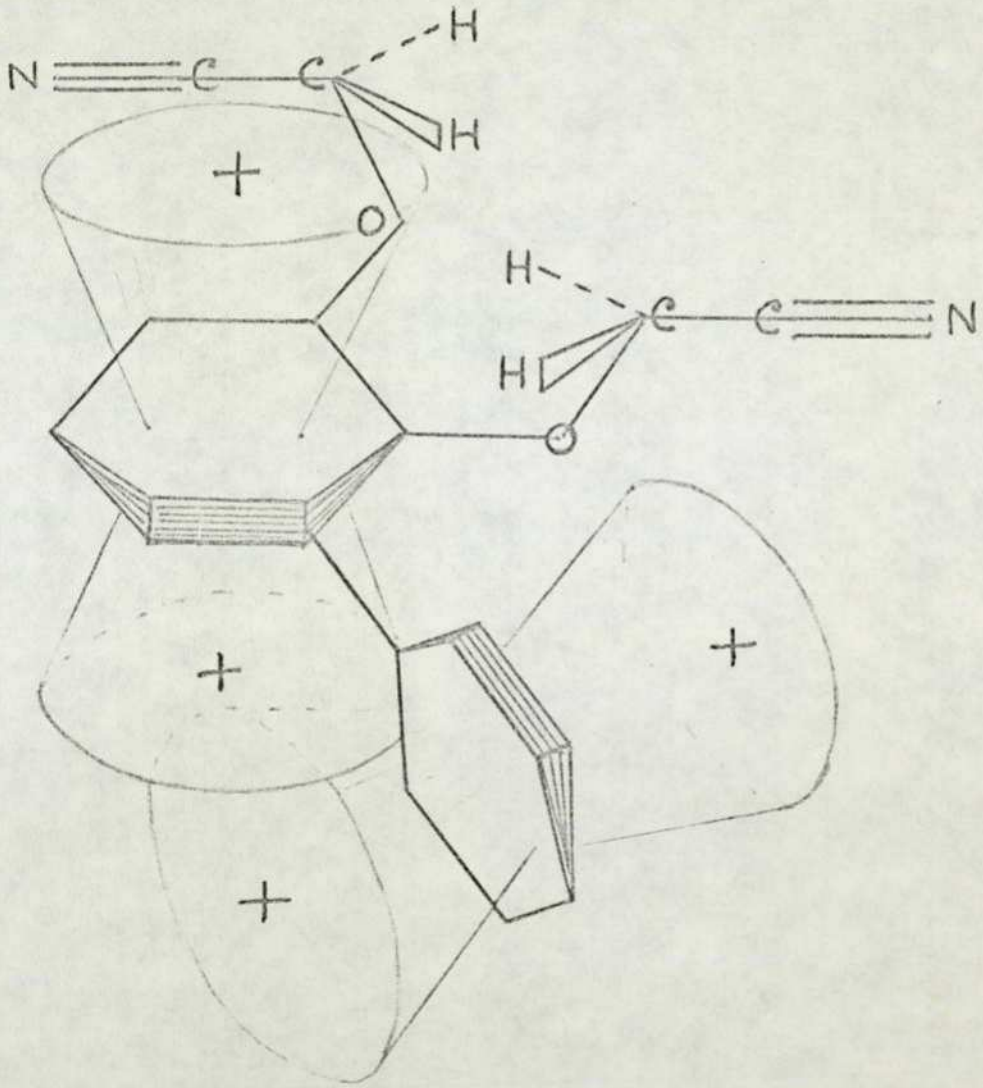
mesomerism less favourable from '1'-oxygen

R = Me or t-Bu

Consequently the methylene protons of the 2-OCH_2CN group would be slightly more deshielded and resonate at a lower field than the protons of the 1-OCH_2CN group.

However, these ideas do not account for the marked variations observed for the methylene proton resonances in the spectra of the 4-phenyl- (IIIo) and 3-phenyl-o-phenylenedioxydiacetonitrile (IIIn). In the former compound these appeared as a four-proton singlet at 5.19 τ whereas in the latter

isomer a pair of two-proton singlets were observed at 5.16 and 5.62 τ . From Dreiding models it can be seen that for non-bonded interactions to be minimal the 2-OCH_2CN group must approach an orthogonal conformation with the plane of the aromatic ring and the 3-phenyl ring can be so



Not to scale

oriented that the methylene protons of the 2-substituent could experience the long range shielding effect from this ring[95d]. This factor could explain the larger difference in the chemical shifts observed for the methylene proton signals in this compound.

In calculating approximate values for the chemical shifts of the nuclear alkyl proton substituents use was again made of the cumulative effect of methyl[95a] and methoxyl[99] chemical shift constants on the toluene methyl proton resonance (7.66τ)[95a]. Results are recorded in Table 8. In view of the successful use of the o/m and m/p chemical shift constants of the methylenedioxy group in estimating the chemical shift of the individual methyl and t-butyl signals in the series of substituted 1,3-benzodioxoles (VII a-m) (see 4.2.14) the same approach was again used in this series. In calculating the chemical shift(s) of the methyl protons at the 3 and 6 position(s) a shift constant of +0.06 ppm, arising from the combined o/m effect of the two $-OCH_2CN$ groups on the position of the toluene methyl proton signal (7.66τ)[95a] was employed together with the appropriate increment(s) for any additional methyl group(s). The chemical shift constant for the combined m/p effect of the two $-OCH_2CN$ substituents on the toluene methyl resonance was +0.01 ppm and was applied in calculating the chemical shifts of the 4 and 5 methyl protons. Analogous calculations were used for predicting the chemical shifts of the t-butyl groups in 3,5-di-t-butyl-o-phenylenedioxydiacetonitrile (IIIm). The chemical shift constants for the o/m (-0.06 ppm) and m/p (+0.04 ppm) effects of the two $-OCH_2CN$ groups on the alkyl proton resonance of t-butylbenzene (8.67τ)[101], together with the appropriate chemical shift increment for an additional m-t-butyl substituent (+0.02τ), enabled a confident assignment of the 3- and 5-t-butyl- groups to be made (see Table 8).

TABLE 8

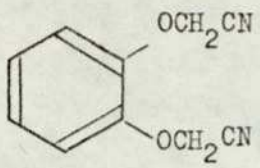
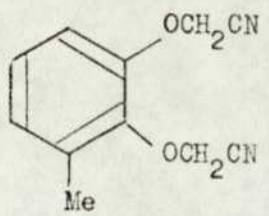
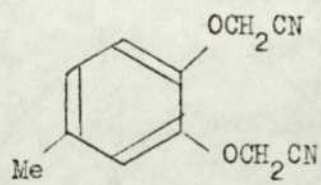
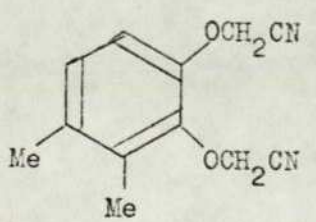
Dinitrile (III)	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$ [a]		
	aromatic protons	$-O-\underline{CH_2}-CN$	protons of aromatic substituent(s)
(a) 	3.0τ, 4H, s	5.32τ, 4H, s	-
(b) 	2.80-3.15τ 3H, m	5.30τ, 2H, s 1-OCH_2CN [b] 5.34τ, 2H, s 2-OCH_2CN [b]	7.72τ, 3H, s (Calcd. value, 7.97τ) [c]
(c) 	2.93-3.23τ 3H, m	5.24τ, 2H, s 2-OCH_2CN [b] 5.26τ, 2H, s 1-OCH_2CN [b]	7.67τ, 3H, s (Calcd. value, 7.91τ) [c]
(d) 	3.13τ, 2H, q J ortho ≃ 8Hz	5.25τ, 2H, s 1-OCH_2CN [b] 5.29τ, 2H, s 2-OCH_2CN [b]	7.76τ, 6H, s (Calcd. value, for 3-Me: 7.77τ [d] 8.02τ [c], 4-Me: 7.72τ [d], 7.96τ [c]).

TABLE 8 (Cont.)

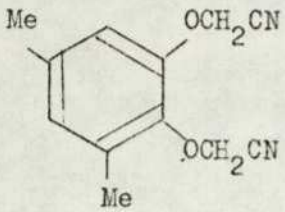
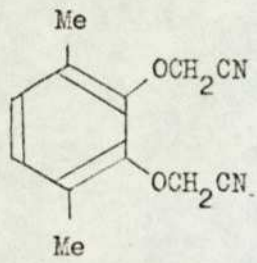
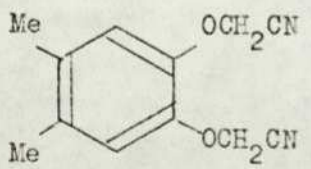
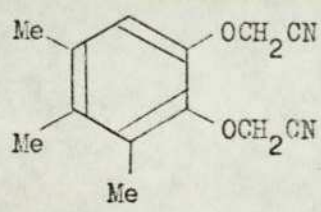
Dinitrile (III)	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$ [a]		
	aromatic protons	$-O-CH_2-CN$	protons of aromatic substituent(s)
(e) 	3.28 τ, 2H, d J meta ≃ 3Hz	5.22 τ, 2H, s 1-OCH_2CN [b] 5.29, 2H, s 2-OCH_2CN [b]	7.70 τ, 6H, s (Calcd. for 3-Me: 7.79 τ [d], 8.04 τ [c] 5-Me: 7.74 τ [d], 7.98 τ [c]).
(f) 	3.09 τ, 2H, s	5.30 τ, 4H, s	7.70 τ, 6H, s (Calcd. value: 7.76 τ [d] and 8.01 τ [c]).
(g) 	3.15 τ, 2H, s	5.25 τ, 4H, s	7.78 τ, 6H, s (Calcd. value: 7.72 τ [d] and 7.96 τ [c]).
(h) 	3.29 τ, 1H, s	5.25 τ, 2H, s 1-OCH_2CN [b] 5.31 τ, 2H, s 2-OCH_2CN [b]	7.74 τ, 6H, s 7.87 τ, 3H, s Calcd. for 3-Me: 7.84 τ [d] and 8.09 τ [c]. 4-Me: 7.77 τ [d] and 8.03 τ [c] 5-Me: 7.79 τ [d] and 8.09 τ [c]).

TABLE 8 (Cont.)

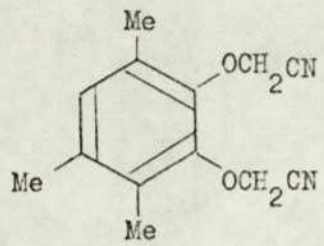
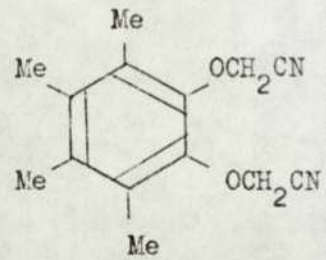
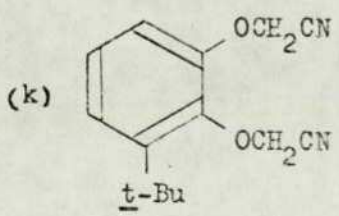
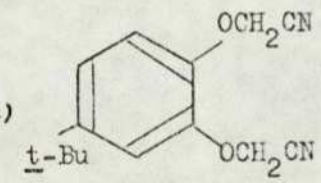
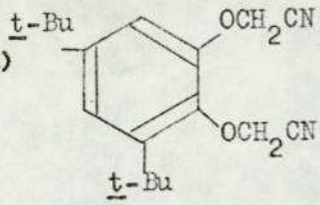
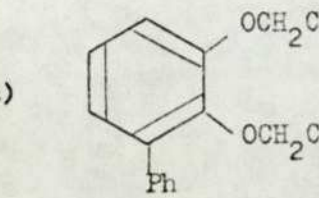
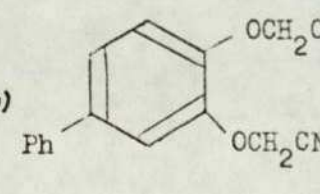
Dinitrile (III)	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$ [a]		
	aromatic protons	$-OCH_2-CN$	protons of aromatic substituent(s)
(i) 	3.17τ, 1H, s	5.30τ, 4H, s	7.73τ, 3H, s 7.79τ, 6H, s (Calcd. for 3-Me: 7.81τ [d] and 8.09τ [c]. 4-Me: 7.79τ [d] and 8.03τ [c] 6-Me: 8.08τ [d] and 8.08τ [c]).
(j) 	—	5.31τ, 4H, s	7.74τ, 6H, s 4,5-Me_2. (Calcd. for 4,5-Me_2: 7.84τ [d] and 8.08τ [c]). 7.81τ, 6H, s 3,6-Me_2 (Calcd. for 3,6-Me_2: 7.88τ [d] and 8.13τ [c]).
(k) 	2.89 - 3.10τ 3H, m	5.21τ, 2H, s 1-OCH_2CN [b] 5.25τ, 2H, s 2-OCH_2CN [b]	8.61τ, 9H, s

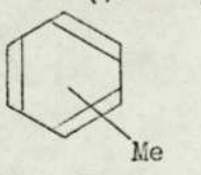
TABLE 8 (Cont.)

Dinitrile (III)	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$ [a]		
	aromatic protons	-O-CH_2-CN	protons of aromatic substituent(s)
(l) 	2.70 - 3.0τ 3H, m	5.22τ, 2H, s 2-OCH_2CN [b] 5.25τ, 2H, s 1-OCH_2CN [b]	8.71τ, 9H, s
(m) 	2.85 - 3.01τ 2H, q J meta ≃ 2.4Hz	5.15τ, 2H, s 1-OCH_2CN [b] 5.22τ, 2H, s 2-OCH_2CN [b]	8.59τ, 9H, s 3-t-Bu (Calcd. value, 8.63τ [e]). 8.67τ, 9H, s 5-t-Bu (Calcd. value 8.73τ [e]).
(n) 	2.87τ, 3H, m	5.16τ, 2H, s 1-OCH_2CN 5.62τ, 2H, s 2-OCH_2CN	2.56τ, 5H, s
(o) 	2.40 - 3.0τ 8H, m (All aromatic protons).	5.19τ, 4H, s	-

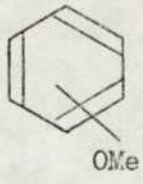
a. Concentration of ca 10-15% w/v were employed.

b. Tentative assignments.

c. Approximate chemical shifts were calculated using the following methyl[95a] and methoxyl[99] chemical shift constants.

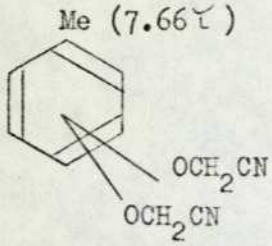


	δ
o	+0.05 ppm
m	+0.07 ppm
p	+0.04 ppm



	δ
o	+0.2 ppm
m	+0.11 ppm
p	+0.14 ppm

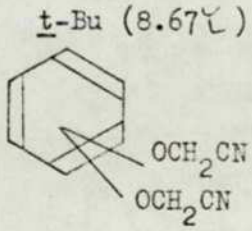
d. Chemical shifts were estimated with the aid of the following chemical shift constants.



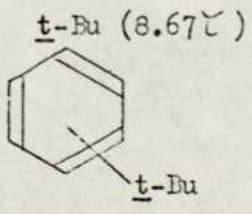
	δ
2,3-	+0.06 ppm
3,4-	+0.01 ppm

and were calculated as described in the text, page 153. The appropriate methyl chemical shift constants are given in footnote c.

e. The chemical shifts of the t-butyl groups were calculated from the following chemical shift constants as described in the text, page 153



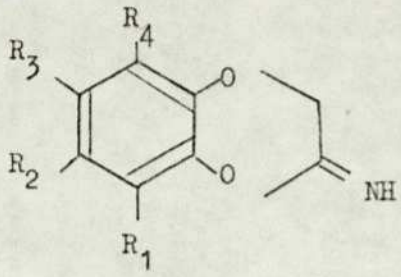
	δ
2,3-	-0.06 ppm
3,4-	+0.04 ppm



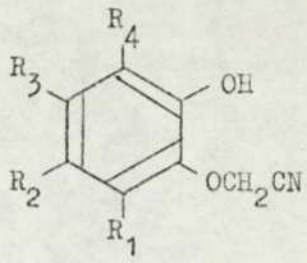
	δ
o	-0.21 ppm
m	+0.02 ppm

4.5 Isolation and identification of some 2,4,6-tris-(o-hydroxyphenoxymethyl)-1,3,5-triazines. (IV a-d)

During the preparations of 4-t-butyl- and 3,4,5,6-tetramethyl-o-phenylenedioxydiacetonitriles (III j and m) an insoluble by-product was isolated from both reactions. Initially these compounds were considered to be the 'iminobenzodioxans' (LXXXIVb and/or c, and d) on the basis



LXXXIV



LXXXV

(a) $R_1 = R_2 = R_3 = R_4 = H$

(b) $R_1 = H$, $R_2 =$ t-Bu, $R_3 = R_4 = H$

(c) $R_1 = R_2 = H$, $R_3 =$ t-Bu, $R_4 = H$

(d) $R_1 = R_2 = R_3 = R_4 = Me$

of their spectral and physical similarities to '2-iminobenzodioxan' (LXXXIVa) obtained in 32% yield by Archer and Claret[18,22] from a similar reaction between chloroacetonitrile and pyrocatechol in the absence of the potassium iodide catalyst. However, it now appears that earlier[18,22] spectral evidence was incorrectly interpreted because of the influence of an erroneous mass spectrometry result. This gave a molecular weight of 149 which was precisely the value required for either o-hydroxyphenoxyacetonitrile (LXXXV) or the cyclic imine (LXXXIVa). The nuclear magnetic resonance spectrum (60 MHz) of the compound in dimethyl sulphoxide gave signals at 3.05 τ (4H, s, aromatic), 4.62 τ (2H, s, $-OCH_2$) and 0.65 τ (1H, s)[18,22]. Initially[18], this latter signal was correctly diagnosed as a phenolic

hydroxyl proton and was considered to be indicative of o-hydroxyphenoxy-acetonitrile (LXXXV) but because of its insolubility in sodium hydroxide solution it was assigned the cyclic 'iminobenzodioxan' structure (LXXXIVa). Surprisingly, no mention was made[18,22] of a characteristic[38i] infra-red =NH absorption expected for this type of structure although the strong band at 1550 cm^{-1} was attributed[18,22] to a C=N stretching vibration.

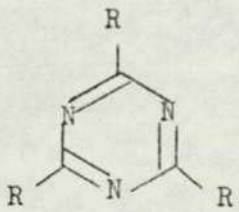
Elementary analysis results indicated that the by-products isolated in this work both had an empirical formula $C_{12}H_{15}NO_2$ and on the basis of the previous evidence[18,22] were, at this time, believed to be the 'iminobenzodioxans' (LXXXIVb and/or c, and d) but the high melting points, $> 200^{\circ}$, and poor solubilities of these compounds in common organic solvents such as alcohols, ketones, etc., did not appear to be compatible with the properties of a simple imine structure such as (LXXXIV). Furthermore they failed to display any of the basic properties expected of an imine. In fact they were only readily soluble in hot acetic acid and dimethyl sulphoxide; boiling 2-methoxyethanol was actually used to recrystallise both 'iminobenzodioxans' (LXXXIVb and/or c, and d).

High resolution mass spectrometry was particularly informative and gave a molecular weight of 615.3295 for the t-butyl- compound (LXXXIVb and/or c) and 615.3314 for the tetramethyl- analogue (LXXXIVd) which, in each case, was three times the mass of 205.1103 calculated for the imine structures.

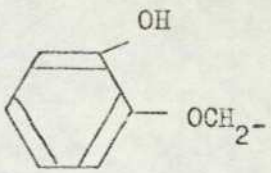
In view of this result the preparation of the 'iminobenzodioxan' (LXXXIVa) described by Archer and Claret[22] was repeated and there was obtained a similar yield (26,5%) of material with the same melting point, 170-172°, as previously reported[22] but high resolution mass spectrometry gave a molecular weight of 447.1421 which was treble that of 149.043

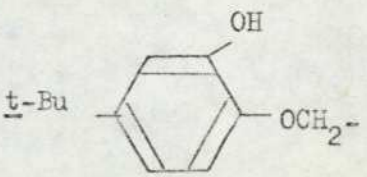
calculated for the 'iminobenzodioxan' structure (LXXXIVa) assigned originally.

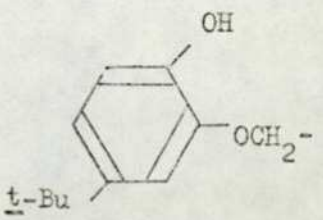
Reassessment of the previously reported[18,22] chemical properties together with infra-red, nuclear magnetic resonance and mass spectral data observed in this work revealed that the 'iminobenzodioxans' were in fact the sym-triazines (IVa, b and/or c, and d).

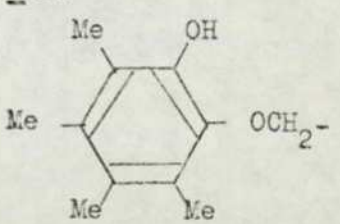


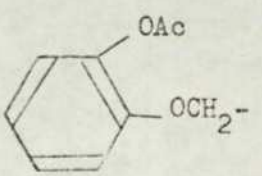
IV

(a) R = 

(b) R = 

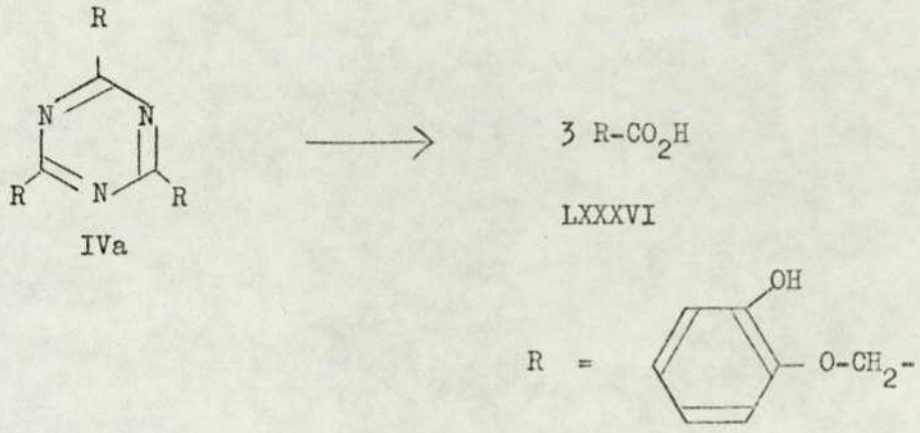
(c) R = 

(d) R = 

(e) R = 

All three 'trimers' were insoluble in cold dilute sodium hydroxide solution and mineral acids. In addition their poor solubilities in common organic solvents resembled the solubility characteristics reported[104a] for other high molecular weight sym-triaryl-triazines.

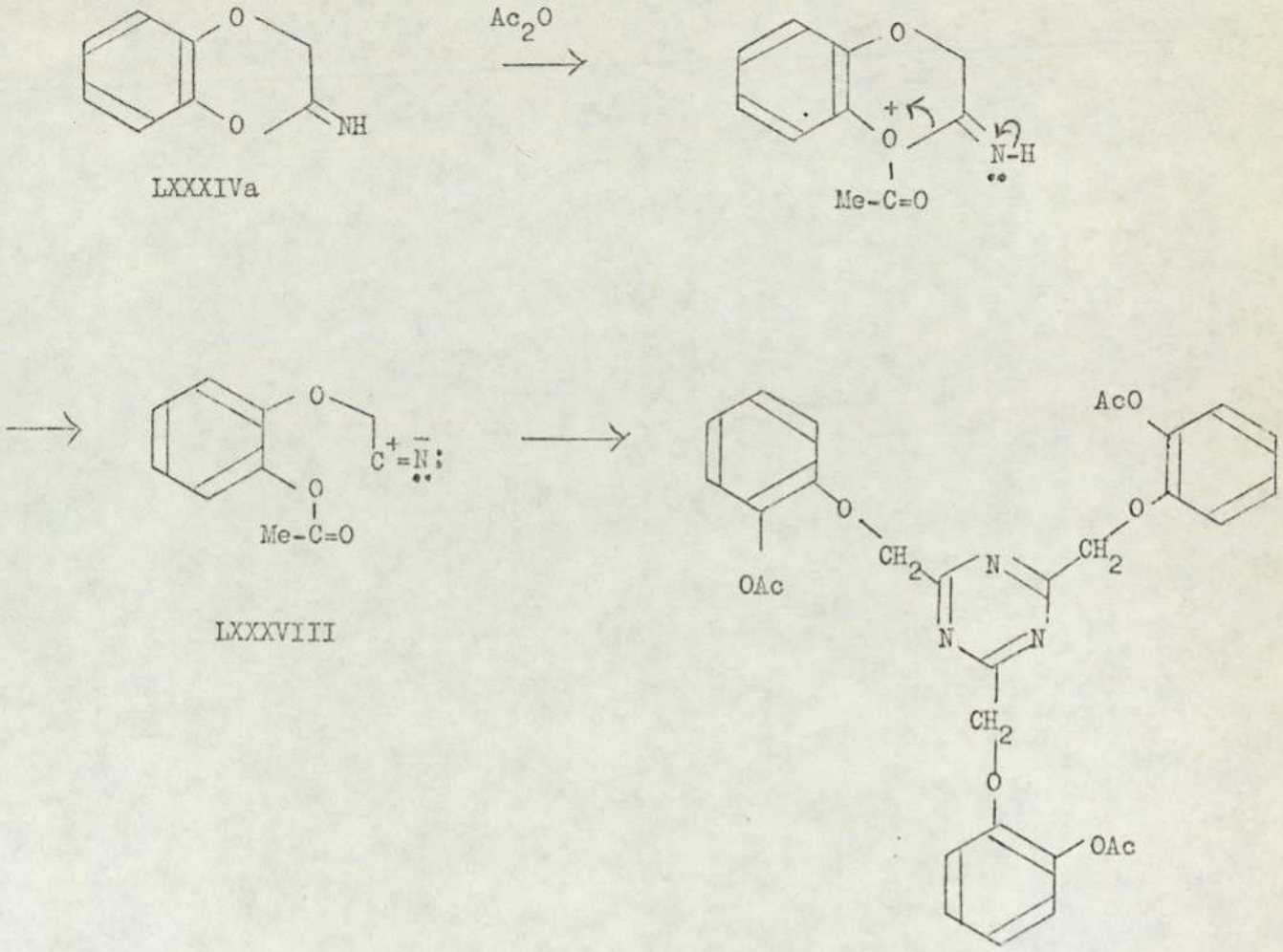
Acid hydrolysis of sym-triaryl-triazines to carboxylic acids has been



IVa

used extensively to establish the presence of a triazine ring[104b]. In the case of the compound (IVa), acid degradation gave o-hydroxyphenoxyacetic acid (LXXXVI)[18,22] which, although not conclusive by itself was not inconsistent with the revised triazine formulation.

The infra-red spectra of the three trimers, either in Nujol or methylene chloride solution, revealed a peak near 3300 cm^{-1} which, from its position, suggested an intramolecularly hydrogen bonded hydroxyl group[38c]. This absorption disappeared after the trimer (IVa) was reacted with acetic anhydride but an intense absorption appeared at 1760 cm^{-1} typical of a phenolic ester carbonyl group[38j]. The properties of this compound agreed with those of 2,4,6-tris-(2-acetoxyphenoxymethyl)-1,3,5-triazine (IVe) similarly prepared by Archer and Claret[18,22], who believed that it was formed during the acetylation of the 'iminobenzodioxan' (LXXXIVa). To explain this, they suggested[22] a reaction mechanism in which the triazine



LXXXIVa

LXXXVIII

IVe

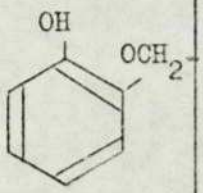
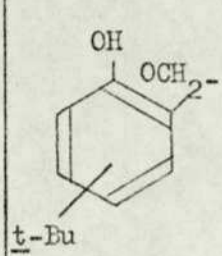
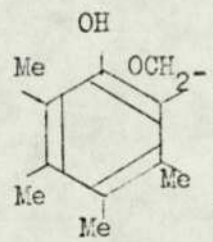
(IVe) resulted from the trimerisation of the intermediate (LXXXVIII) containing a charged imine system, $-\overset{+}{C}=\overset{-}{N}$, formed by attack by acetylium ion at O-1 (see LXXXVII), followed by ring opening and deprotonation of the nitrogen atom (by acetate ion). In fact the triacetate was none other than the normal acetylation product of the triazine (IVa). The pronounced infra-red absorption near 1550 cm^{-1} present in all four triazines (IV a-e) was within the range of 1500-1560 cm^{-1} quoted for a characteristic frequency in nineteen substituted sym-triazines compiled by Schroeder[105]. The band was assigned to the C=N stretching mode (in

plane vibration of the triazine ring).

The 100 MHz nuclear magnetic resonance spectra of the three compounds are recorded in Table 9 and were consistent with the proposed triazine structures (IV a-d). In fact the simplicity and symmetry of the three spectra, apart from the t-butyl- compound (IVb and/or C), which probably contained isomers, made it difficult to conceive how the results could support a structure other than a sym-triazine.

The mass spectra of the three trimers were also consistent with the sym-triazine formulation and are recorded in Tables 10-12. Inspection of their fragmentation patterns revealed that a parallel sequence of eliminations could be postulated for each compound. Mass spectral data for the triazine (IVa) indicated that the peaks at m/e 339 (I=17%), 231 (I=28%) and 123 (I=20%) were compatible with the consecutive loss of three o-quinone fragments (3 x 108 mass units) from the parent ion (m/e 447, I=100%) and could be rationalised by two similar mechanisms depicted in Figures 4 and 5. In the case of the t-butyl- compound (IVb and/or c) the parent ion (m/e 615, I=34%) suffered three successive losses of 164 mass units to give peaks at m/e 451 (I=33%), 287 (I=42%) and 123 (I=65%) This corresponded to the elimination of three t-butyl-o-quinone units, as shown in Figure 6, by either of the mechanisms proposed in Figures 4 and 5. An analogous fragmentation sequence was also observed for the tetramethyl-compound (IVd) (see Figure 7) and involved the stepwise elimination, from the parent ion (m/e 615, I=9%), of three tetramethyl-o-quinone groups each of 164 mass units to give peaks at m/e 451 (I=47%), 287 (I=70%) and 123 (I=100%). The mechanisms outlined in Figures 4 and 5 were again consistent with the observed spectral data. The occurrence of a high proportion of the abundant ions in the schemes outlined in Figures 4-7 and the presence of a particularly abundant ion at m/e 123 in all three spectra (I=42% for IVa, I=65% for IVb and/or c, and I=100% for IVd),

TABLE 9

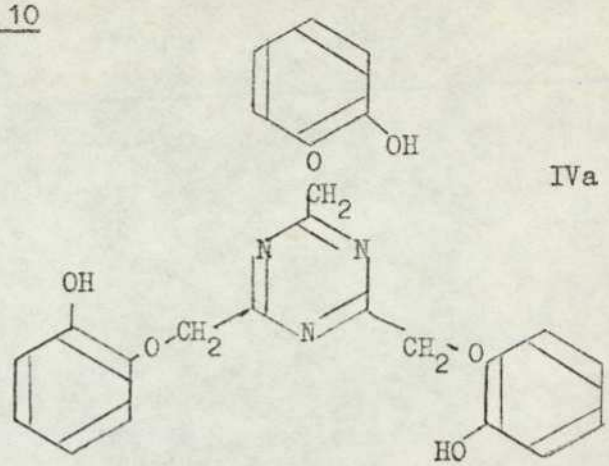
Compound (IV) R	100 MHz ^{1}H n.m.r. spectra in DMSO-d_6			
	proton signals			
	aromatic	OH	OCH_2	substituent
(a) 	3.0-3.4 τ 4H multiplet	0.8 τ* 1H broad singlet	4.72 τ* 2H singlet	-
(b) and/or (c) 	2.9-3.4 τ+ 3H multiplet	0.85 τ+ 1H broad singlet	4.72 and 4.78 τ+ 2H 2 peaks in ratio of 1:3	8.78 and 8.82 τ+ 9H 2 peaks in ratio of 3:1
(d) 	-	1.0 τ* 1H singlet	4.9 τ* 2H singlet	7.81 τ, 3H 7.93 τ, 9H singlets

* These protons exchanged with D_2O

\+ Addition of D_2O caused precipitation of the compound

TABLE 10

Mass spectrum of



IVa

m/e	I(%)	m/e	I(%)
449	5	149	4
448	28	148	3
447	100	133	3
340	3	123	20
339	17	122	19
338	32	121	42
320	4	110	21
232	4	109	10
231	28	95	4
230	22	82	3
229	32	81	17
213	10	80	6
200	3	66	4
190	3	65	5
189	3	54	9
172	5	53	3
150	3	52	4

Only peaks > m/e 50 and I > 3% noted.

Measured mass: 447.1421

Calculated mass: 447.130

$C_{24}H_{21}N_3O_6$

Solvent: Acetone

Ion source: 200°

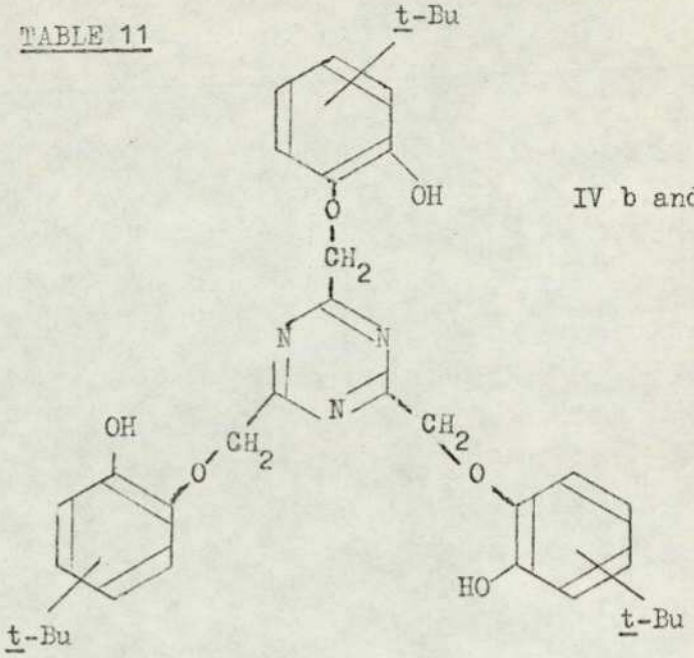
Electron energy: 70 eV

Trap current: 100 μA

Probe

TABLE 11

Mass spectrum of



IV b and/or c

m/e	I(%)	m/e	I(%)	m/e	I(%)
617	5	167	4	95	7
616	15	166	34	93	7
615	34	165	5	91	7
452	10	163	4	83	5
451	33	162	4	82	6
450	23	152	11	81	13
449	3	151	100	80	5
433	4	150	7	79	7
288	10	137	4	77	10
287	42	135	6	69	5
286	28	133	4	67	5
285	16	124	5	65	5
272	4	123	65	57	16
271	4	122	20	55	8
270	8	121	5	54	9
269	16	111	8	53	5
256	5	110	10	51	5
213	11	109	5		
211	13	107	8		
190	13	105	9		
178	7				
177	39				

TABLE 11 (Cont.)

Only peaks > m/e 50 and I > 3% noted.

Measured mass: 615.3295
Calculated mass: 615.3308
} $C_{36}H_{45}N_3O_6$

Ion source: 240°C

Electron energy: 70 eV

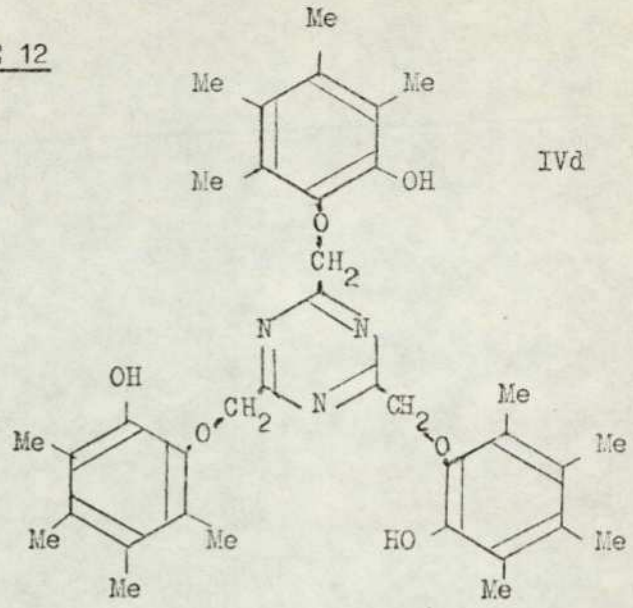
Trap current: 100 μA

Probe:

Solvent: Chloroform

TABLE 12

Mass spectrum of



IVd

m/e	I/(%)	m/e	I(%)	m/e	I(%)
616	4	179	8	107	6
615	9	178	50	105	13
452	13	177	4	104	3
451	47	167	12	103	5
450	7	166	85	95	13
449	10	165	53	93	13
448	3	164	11	91	18
288	15	163	4	83	7
287	70	138	3	82	10
286	47	137	20	81	20
285	30	136	17	79	10
284	5	135	10	78	3
272	3	133	5	77	15
271	3	124	26	69	4
270	4	123	100	67	6
269	7	122	18	66	3
251	8	121	11	65	6
215	8	120	5	55	5
205	5	119	6	54	10
204	5	109	4	53	8
189	3	108	4	52	3
188	3			51	6

TABLE 12 (Cont.)

Only peaks > m/e 50 and I > 3% noted.

Measured mass: 615.3314
Calculated mass: 615.3308
} $C_{36}H_{45}N_3O_6$

Ion Source: 220°C

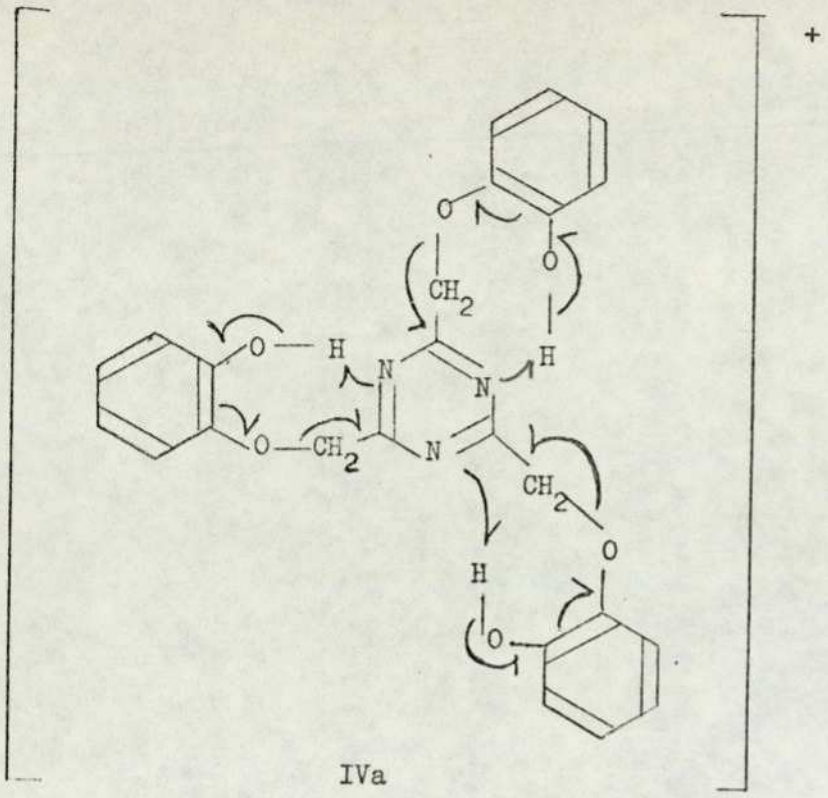
Electron energy: 70 eV

Trap current: 100 μA

Probe:

Solvent: Chloroform

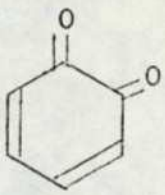
FIGURE 4 *



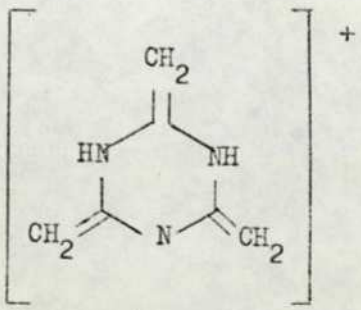
IVa

m/e 447

three consecutive losses of



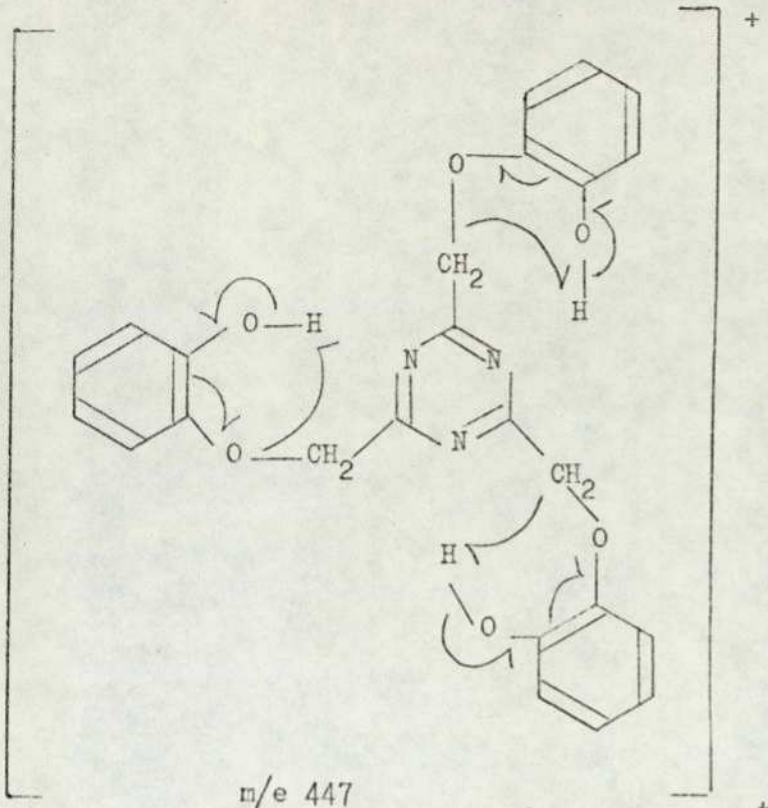
(108)



m/e 123

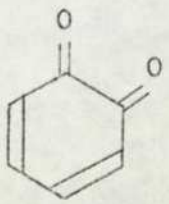
* A fish-hook arrow denotes a one electron shift.

FIGURE 5 *

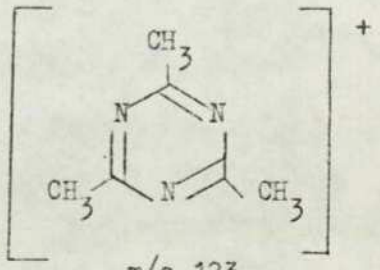


m/e 447

three consecutive losses of



(108)



m/e 123

* A fish-hook arrow denotes a one electron shift

FIGURE 6

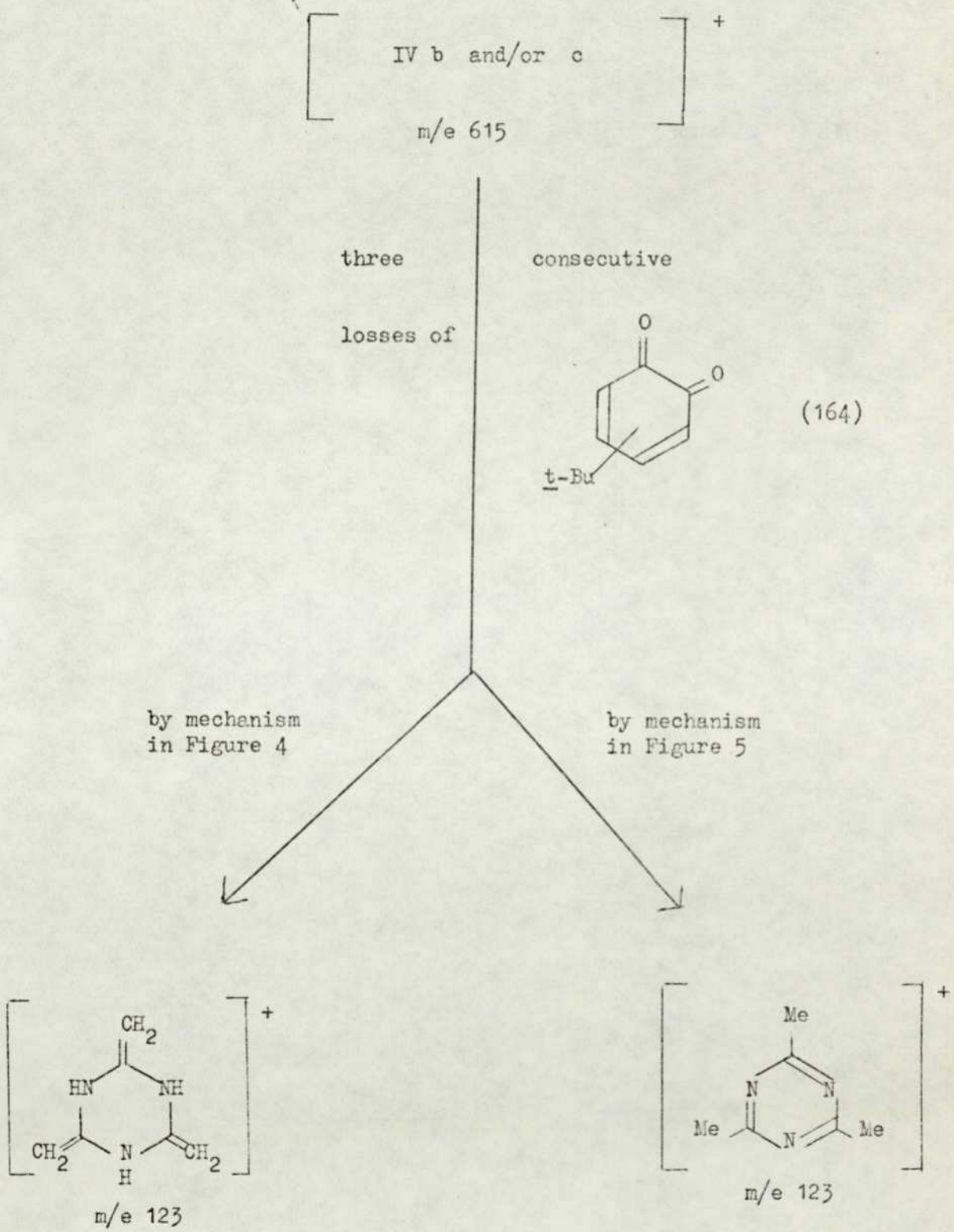
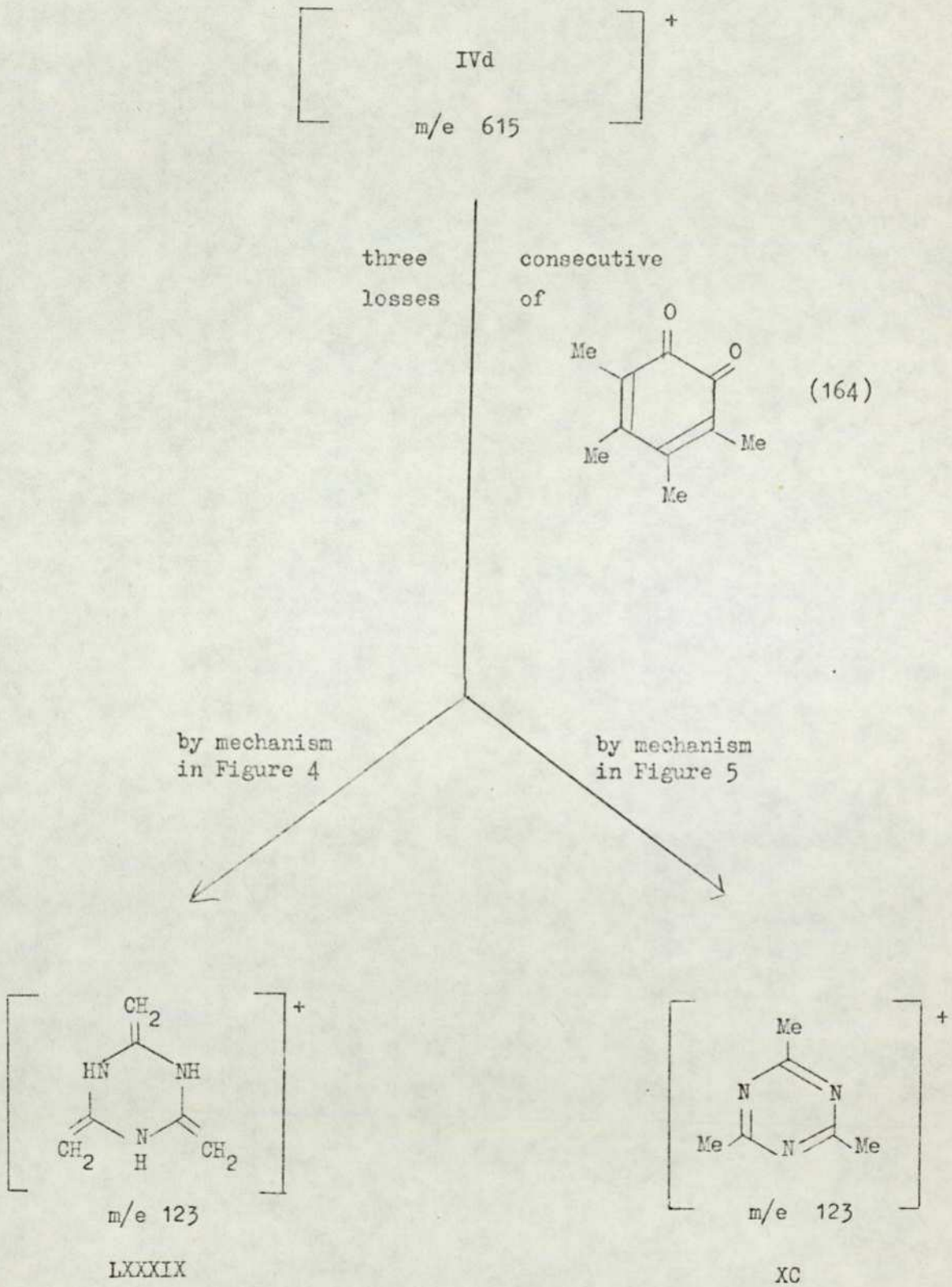
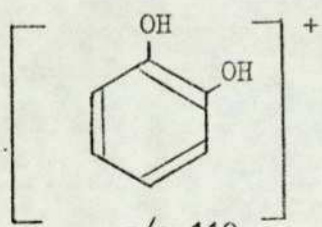

IV b and/or c
m/e 615
three
losses of
consecutive
O
O
t-Bu
(164)
by mechanism
in Figure 4
by mechanism
in Figure 5
CH2
HN
NH
CH2
N
H
CH2
m/e 123
Me
N
N
Me
N
Me
m/e 123

FIGURE 7

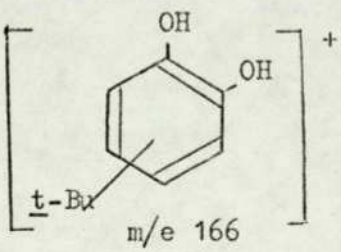

IVd
m/e 615
three losses
consecutive of
(164)
by mechanism in Figure 4
by mechanism in Figure 5
m/e 123
LXXXIX
m/e 123
XC

associated with the triazine fragments (LXXXIX or XC), was considered to be strong evidence in favour of sym-triazine structures (IV a, b and/or c and d). The appearance of other relatively prominent ions at m/e 110 (I=21%) in the trimer (IVa), m/e 166 (I=34%) in (IVb and/or c) and m/e 166 (I=85%) in (IVd) has been attributed to the species (XCI), (XCII) and (XCIII) respectively.



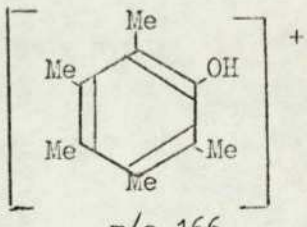
m/e 110

XCI



m/e 166

XCII

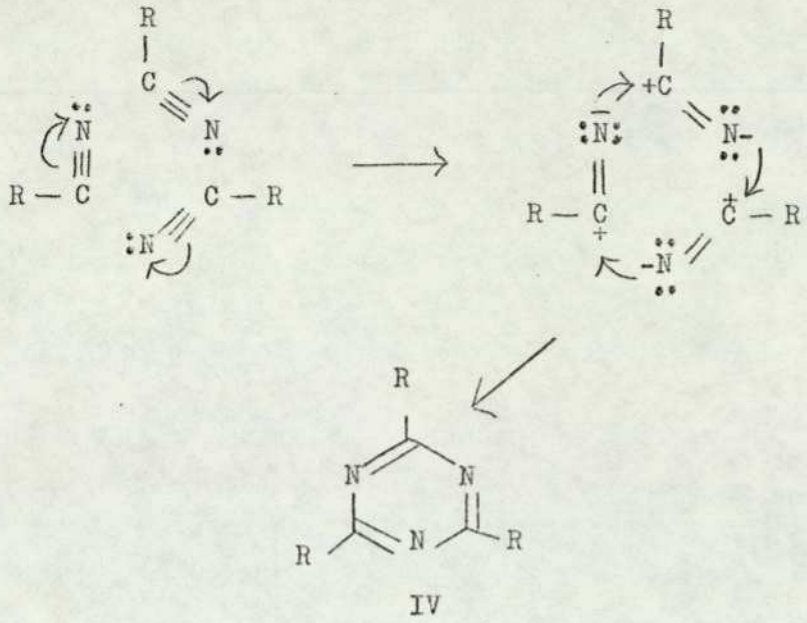


m/e 166

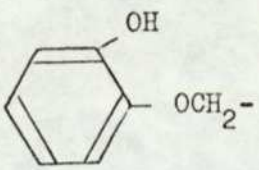
XCIII

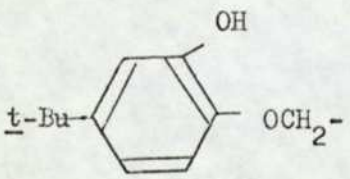
A fragment at m/e 57 (I=16%) in the spectrum of the triazine (IVb and/or c) but absent in the two analogues (IVa and IVd) originated from the expulsion of $[C_4H_9]^+$ from the t-butyl substituent. The identification of peaks arising from the rupture of the pyrocatechol and triazine portions of the molecules was not attempted.

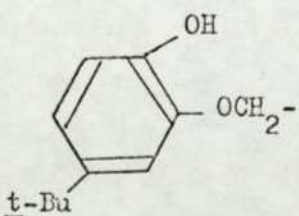
Although nitriles having no α-hydrogens can be trimerised to sym-triazines rather easily with strong acids[106], less easily by alkali-metals[107], or strong bases[108], those possessing one or two α-hydrogen atoms required extremely high pressures (> 7000 atmospheres) to effect their trimerisation[109]. In view of these reports it was surprising that the sym-triazines (IVa, b and/or c and d) were formed under such mild reaction conditions and for this reason the direct trimerisation of the intermediate o-hydroxyphenoxyacetonitriles (LXXXVa, b and/or c and d) seemed unlikely. Closely related to the trimerisation of the

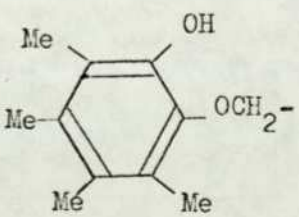


IV

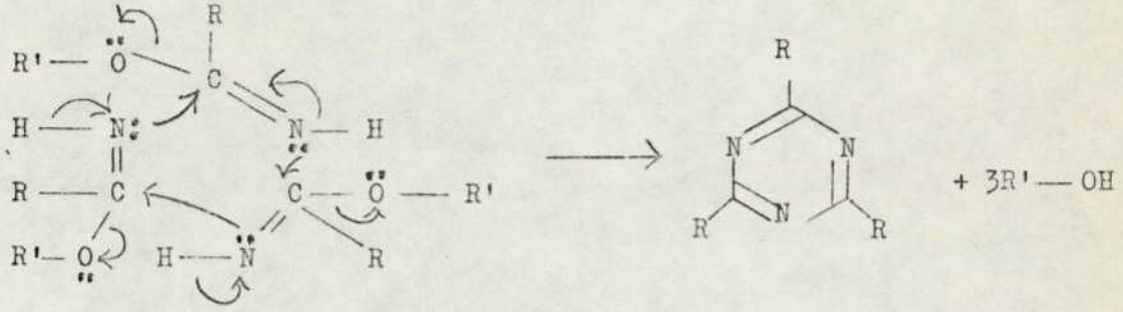
(a) R = 

(b) R = 

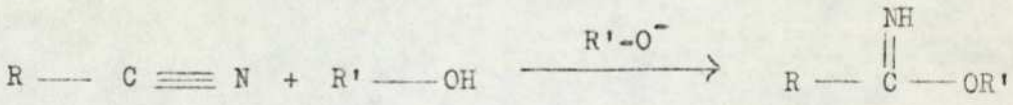
(c) R = 

(d) R = 

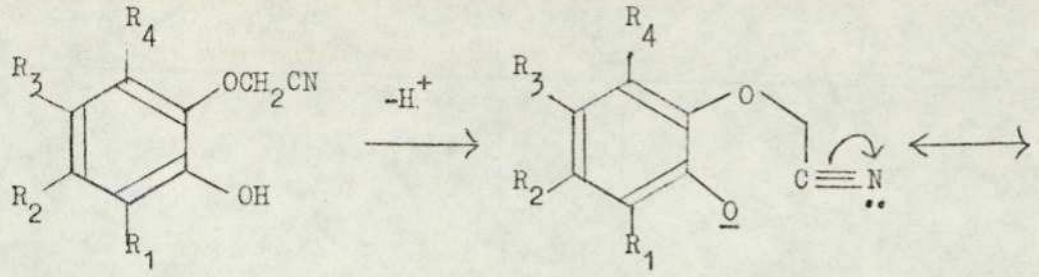
nitriles is the preparation of trisubstituted-sym-triazines by the cyclisation of imidates. This reaction was first observed by Pinner[110,111] in 1877 and was later developed by him as a preparative method[112]. It involved treatment of an imidate salt with alkali and the following reaction mechanism can explain the formation of the triazine.



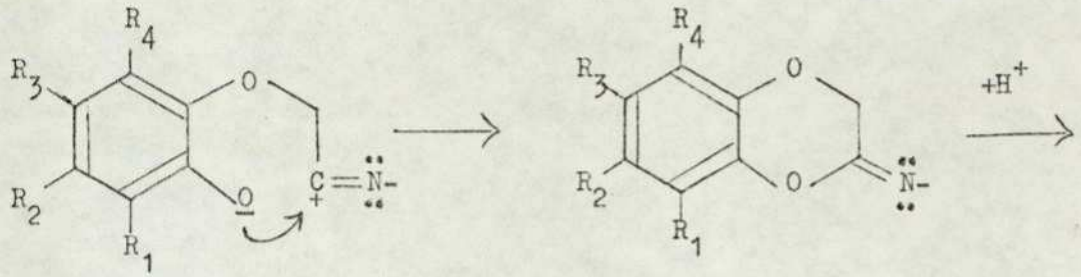
It is also known[113] that electronegatively substituted aliphatic and aromatic nitriles react with alcohols in the presence of basic catalysts to give imidates in up to quantitative yields.

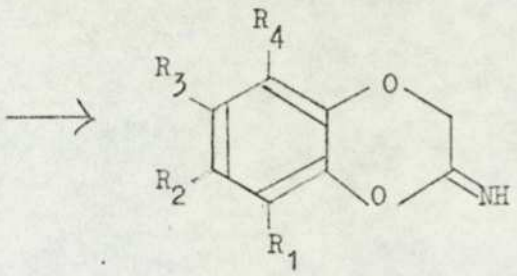


Since the reactions of pyrocatechols with chloroacetonitrile were carried out in the absence of alcohols the presence of simple imidate esters was precluded. However, it is conceivable that the intermediate o-hydroxyphenoxyacetonitriles (LXXXVa, b and/or c and d) could undergo intramolecular cyclisation to form the iminobenzodioxans (LXXXIV a, b and/or c and d) which are themselves imidates.



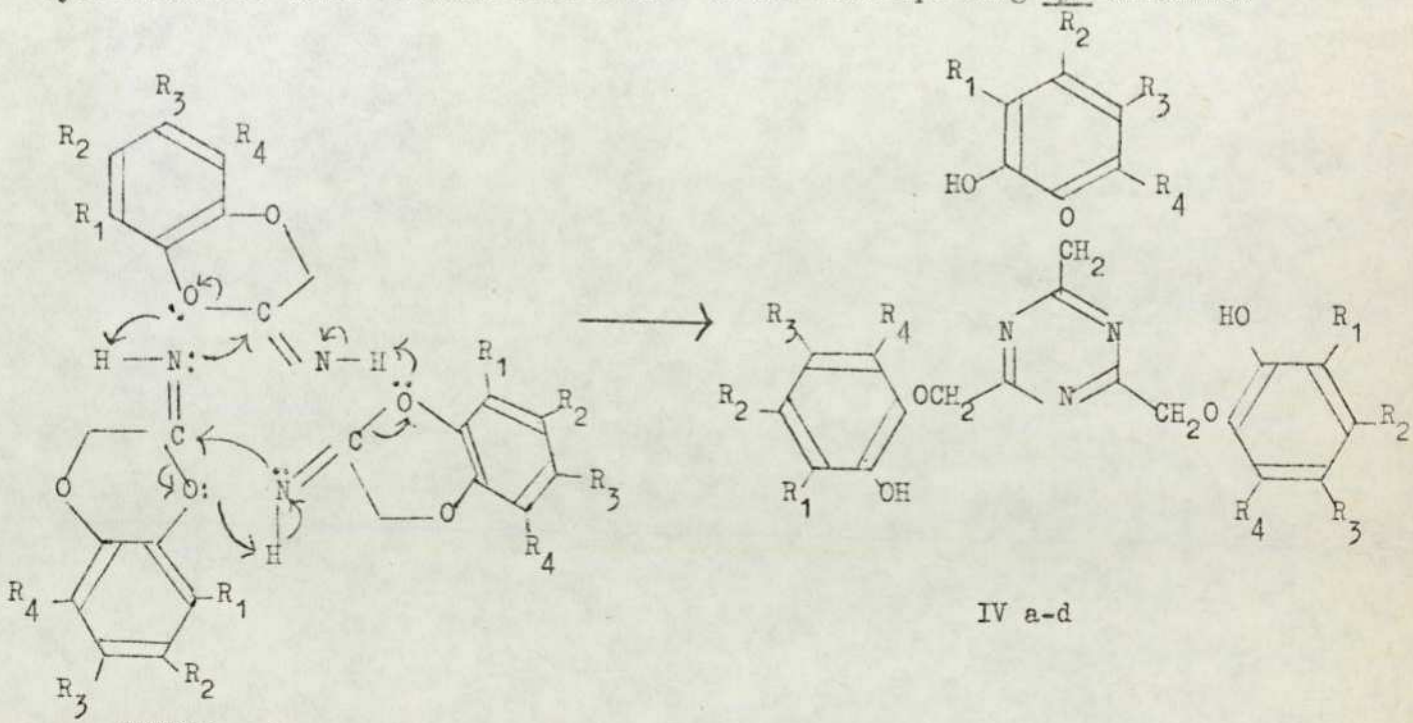
LXXXV a-d





LXXXIV a-d

Cyclisation of these 'iminobenzodioxans' to the corresponding sym-triazines

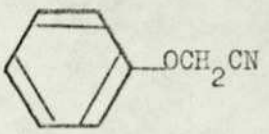


LXXXIV a-d

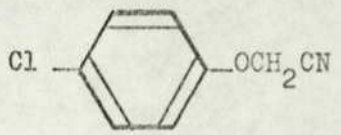
IV a-d

(IV a, b and/or c and d) under the influence of the basic reaction conditions could then proceed as shown above.

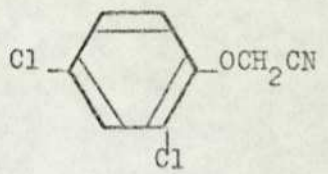
After this aspect of the work was completed we became aware of a paper by French workers[114] concerning the alcoholysis of aryloxyacetonitriles under basic conditions. They found that when phenoxyacetonitrile and its 4-chloro- and 2,4-dichloro-analogues were refluxed with sodium ethoxide solution for 3-5 hr. nitrile polymers of unknown structure were obtained.



$\longrightarrow$ $(C_8H_7NO_2)_n$ m.p. 140°

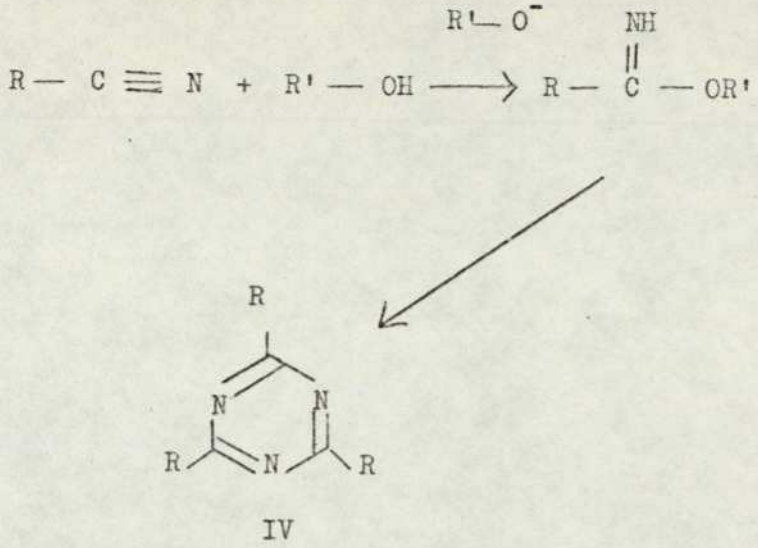


$\longrightarrow$ $(C_8H_6ClNO_2)_n$ m.p. 181°

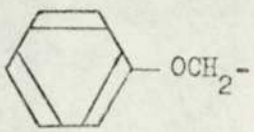


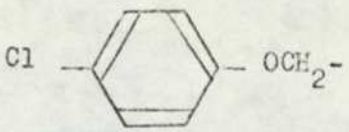
$\longrightarrow$ $(C_8H_5Cl_2NO_2)_n$ m.p. 166°

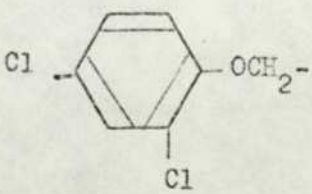
With the knowledge that electronegatively substituted acetonitriles can undergo base catalysed addition of alcohols to give imidates[113] and that these can subsequently yield sym-triazines in the presence of base[110,111,112] it seemed likely that the nitrile polymers isolated by the French workers were in fact the sym-triazines (IV f-h). Their formation can be expressed as follows:-



IV

(f) R = 

(g) R = 

(h) R = 

The high melting points and low solubilities of the compounds in water and alcohol were also consistent with the triazine structures (IV f-h).

4.5.1 2,4,6-Tris-(2-hydroxyphenoxymethyl)-1,3,5-triazine (IVa)

A mixture of pyrocatechol (22.0g, 0.2 mole), chloroacetonitrile (22.6g. 0.3 mole), anhydrous potassium carbonate (20.7g, 0.15 mole) and acetone (150 ml) was stirred and refluxed for 5 hr. cooled and filtered. The acetone was evaporated and the residue was triturated with hot acetic acid (75 ml). After cooling, the buff crystals, 7.9g (26.5%), m.p. 153-158°, were collected. Recrystallisation from acetic acid afforded fawn needles m.p. 170-172° (lit.,[18,104] m.p. 172-173°). ν max. (CH_2Cl_2) 3300 (OH) and 1550 (C=N) cm^{-1}. N.m.r. spectral data are recorded in Table 9. Mass spectral information for this compound is given in Table 10.

4.5.2 2,4,5-Tris-(2-acetoxyphenoxymethyl)-1,3,5-triazine (IVe)

The foregoing compound (4g) was refluxed in acetic anhydride for 4 hr. cooled, poured into water when the sticky solid was collected. Recrystallisation from methanol gave colourless needles, 2.35g, (46%), m.p. 107-108°, (lit.,[18,104] m.p. 105-106°). ν max. (Nujol) 1760 (C=O) and 1560 (C=N) cm^{-1}.

4.5.3 2,4,6-Tris-(4 and/or 5-t-butyl-2-hydroxyphenoxymethyl)-1,3,5-triazine (IV b and/or c)

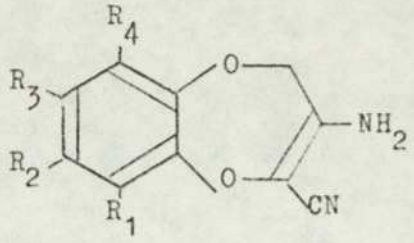
This compound (0.98g, 18.5%), m.p. 204-208° (from 2-methoxyethanol) was obtained when 4-t-butylpyrocatechol (4.15g, 0.025 mole) was reacted using the conditions described in the next example (4.5.4). (Found: C, 70.3; H, 7.6; N, 6.6. $C_{36}H_{45}N_3O_6$ requires C, 70.2; H, 7.4; N, 6.8%). ν max (CH_2Cl_2) 3350-3300 (OH) and 1550 (C=N) cm^{-1}. See Table 9 for the n.m.r. results and Table 12 for the mass spectrometry data.

4.5.4 2,4,6-Tris-(2-hydroxy-3,4,5,6-tetramethylphenoxymethyl)-1,3,5-triazine (IVd)

A stirred mixture of tetramethylpyrocatechol (8.3g, 0.05 mole), chloroacetonitrile (5.65g, 0.075 mole), potassium carbonate (8.4g, 0.06 mole), potassium iodide (0.8g) and acetone (80 ml) was refluxed for 6 hr., filtered hot and evaporated to a semi-solid. The residue was partitioned between toluene and sodium hydroxide solution. After separation, the organic phase was evaporated *in vacuo* and the residue was triturated with light petroleum (b.p. 80-100°) and refrigerated the fawn product (8.85 g) was collected and recrystallised from 2-methoxyethanol to give material m.p. 204-206° (prior darkening and softening at 200°). (Found: C, 69.8; H, 7.5; N, 6.8. $C_{38}H_{45}N_3O_6$ requires C, 70.2; H, 7.4; N, 6.5%). ν max (CH_2Cl_2) 3300-3250 (OH) and 1550 (C=N) cm^{-1}. See Table 9 for the n.m.r. results and Table 12 for the mass spectrometry data.

4.6 Preparations of the substituted 3-amino-2H-1,5-benzodioxepin-4-carbonitriles (V b-z)

Thorpe cyclisations of the substituted o-phenylenedioxydiacetonitriles (III b-o) were readily effected with sodium hydride in dimethyl sulphoxide using the conditions developed earlier for the parent compound (Va) (Chapter 2.1.1).



V

(a) $R_1 = R_2 = R_3 = R_4 = H$

(b) $R_1 = Me, R_2 = R_3 = R_4 = H$

(c) $R_1 = H, R_2 = Me, R_3 = R_4 = H$

(d) $R_1 = H, R_2 = Me, R_3 = R_4 = H$

(e) $R_1 = R_2 = H, R_3 = Me, R_4 = H$

(f) $R_1 = R_2 = Me, R_3 = R_4 = H$

(g) $R_1 = R_2 = H, R_3 = R_4 = Me$

(h) $R_1 = Me, R_2 = H, R_3 = Me, R_4 = H$

(i) $R_1 = H, R_2 = Me, R_3 = H, R_4 = Me$

(j) $R_1 = Me, R_2 = R_3 = H, R_4 = Me$

(k) $R_1 = H, R_2 = R_3 = Me, R_4 = H$

(l) $R_1 = R_2 = R_3 = Me, R_4 = H$

(m) $R_1 = H, R_2 = R_3 = R_4 = Me$

(n) $R_1 = R_2 = Me, R_3 = H, R_4 = Me$

(o) $R_1 = Me, R_2 = H, R_3 = R_4 = Me$

(p) $R_1 = R_2 = R_3 = R_4 = Me$

(q) R_1 = t-Bu, R_2 = R_3 = R_4 = H

(r) R_1 = R_2 = R_3 = H, R_4 = t-Bu

(s) R_1 = H, R_2 = t-Bu, R_3 = R_4 = H

(t) R_1 = R_2 = H, R_3 = t-Bu, R_4 = H

(u) R_1 = t-Bu, R_2 = H, R_3 = t-Bu, R_4 = H

(v) R_1 = H, R_2 = t-Bu, R_3 = H, R_4 = t-Bu

(w) R_1 = Ph, R_2 = R_3 = R_4 = H

(x) R_1 = R_2 = R_3 = H, R_4 = Ph

(y) R_1 = H, R_2 = Ph, R_3 = R_4 = H

(z) R_1 = R_2 = H, R_3 = Ph, R_4 = H

Generally yields approached or were greater than 90% and the crude products were shown by thin layer chromatography to be essentially pure except for some coloured impurity which was subsequently removed by recrystallisation or sublimation. In most cases purification of the mixed isomers was not attempted and they were used directly for the preparations of the appropriate ketones (I b-o).

4.6.1 3-Amino-2H-1,5-benzodioxepin-4-carbonitrile (Va)

The preparation of this compound was fully described in Chapter 2.1.1.2. Details of its nuclear magnetic resonance spectrum are given in Table 13.

Similar conditions were employed to prepare the substituted members of the series described below.

4.6.2 3-Amino-6-methyl- (Vb) and 3-amino-9-methyl-2H-1,5-benzodioxepin-4-carbonitrile (Vc)

Scale: 0.1 mole. The yield of mixed isomers was 87%, m.p. 147-155°. A sample was sublimed at 0.01 mm (bath temperature 140-150°) affording a

white solid, m.p. 148-154°. T.l.c., solvent A, gave a single spot, Rf. 0.5 (Found for mixed isomers: C, 65.6; H, 5.1; N, 13.9. $C_{11}H_{10}N_2O_2$ requires C, 65.3; H, 5.0; N, 13.9%). ν max (Nujol) 3450, 3350 (NH_2), 3225 (C=C ?), 2190 (C≡N), 1650 (NH_2) and 1625 (C=C) cm^{-1}. N.m.r. spectral data for the mixture are shown in Table 13.

Separation of 3-amino-9-methyl-2H-1,5-benzodioxepin-4-carbonitrile (Vc)

After six recrystallisations of the mixed isomers from slightly aqueous methanol, a sample was raised to a constant m.p. of 177-178° (colourless blades). T.l.c., solvent A, showed one spot, Rf. 0.5. (Found: C, 65.2; H, 4.9; N, 13.9%). ν max (Nujol) 3400, 3325 (NH_2), 3200 (C=C ?), 2180 (C≡N), 1660 (NH_2) and 1625 (C=C) cm^{-1}. Details of the 220 MHz n.m.r. spectrum are recorded in Table 14.

Attempted isolation of 3-amino-6-methyl-2H-1,5-benzodioxepin-4-carbonitrile (Vb)

The filtrates from the foregoing recrystallisations were combined, evaporated to dryness and recrystallised from toluene. The collected solid was discarded and the filtrate was then evaporated. The residue was recrystallised twice from toluene and twice from aqueous methanol giving off-white needles, m.p. 141-142°. T.l.c., solvent A, gave one spot only, Rf. 0.5. (Found: C, 65.1, H, 4.9; N, 13.8%). ν max (Nujol) 3400, 3300 (NH_2), 3200 (C=C ?), 2200 (C≡N), 1650 (NH_2) and 1625 (C=C) cm^{-1}. The 220 MHz n.m.r. spectrum revealed the presence of about 40% of the higher melting isomer. See Table 14 for the results.

4.6.3 3-Amino-7-methyl- (Vd) and 3-amino-8-methyl-2H-1,5-benzodioxepin-4-carbonitrile (Ve)

Scale: 0.1 mole. The yield of mixed isomers was 88%, m.p. 130-140° Sublimation at 0.1 mm (bath temperature 130°) afforded an off-white solid,

m.p. 138-144°. T.l.c., solvent A, revealed one spot, Rf 0.56. (Found for mixture: N, 13.9. $C_{11}H_{10}N_2O_2$ requires N, 13.9%). ν max (Nujol) 3450, 3350 (NH_2), 3250 (C=C ?), 2190 (C≡N), 1650 (NH_2) and 1625 (C=C) cm^{-1}. See Table 13 for n.m.r. data on the mixture.

Separation of 3-amino-?-methyl-2H-1,5-benzodioxepin-4-carbonitrile (Vd or e) 'α'-isomer

A sample of the mixed isomers was recrystallised seven times from aqueous methanol until a constant m.p. of 171-173° (colourless blades) was attained. (Found: C, 65.1; H, 4.7; N, 14.0. $C_{11}H_{10}N_2O_2$ requires C, 65.3; H, 5.0; N, 13.9%). ν max (Nujol) 3400, 3300 (NH_2), 3200 (C=C ?), 2190 (C≡N), 1650 (NH_2) and 1625 (C=C) cm^{-1}. The 220 MHz n.m.r. spectrum is recorded in Table 15.

Attempted separation of 3-amino-?-methyl-2H-1,5-benzodioxepin-4-carbonitrile (Vd or e), 'β'-isomer

The combined filtrates from above were evaporated to dryness and recrystallised from toluene. The material that separated was collected and discarded. Evaporation of the filtrate followed by four recrystallisations of the residue from aqueous methanol gave off-white needles, m.p. 135-136° (Found: C, 65.1; H, 4.9; N, 13.6. $C_{11}H_{10}N_2O_2$ requires C, 65.3; H, 5.0; N, 13.9%). ν max (Nujol) 3400,3300 (NH_2), 3200 (C=C ?), 2190 (C≡N), 1650 (NH_2) and 1625 (C=C) cm^{-1}. From the 220 MHz n.m.r. spectrum recorded in Table 15 it was evident that the material contained ca 50% of the other isomer.

In all the subsequent preparations the sodium hydride was washed free of mineral oil with ligroin (X3) before addition of the dimethyl sulphoxide.

4.6.4 3-Amino-6,7-dimethyl- (Vf) and 3-amino-8,9-dimethyl-2H-1,5-benzodioxepin-4-carbonitrile (Vg)

Scale: 0.075 mole. The yield of mixed isomers was 89%, m.p. 139-147°. Sublimation at 0.1 mm (bath temperature 130°) raised the m.p. to 148-159°. (Found for mixed isomers: C, 66.7; H, 5.8; N, 13.2. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 13.0%). νmax (Nujol) 3400, 3300 (NH_2), 3200 (C=C ?), 2200 (C≡N), 1660 (NHz) and 1625 (C=C) cm^{-1}. N.m.r. data for the mixture are given in Table 13.

4.6.5 3-Amino-6,8-dimethyl- (Vh) and 3-amino-7,9-dimethyl-2H-1,5-benzodioxepin-4-carbonitrile (Vi)

Scale: 0.075 mole. The mixed isomers were obtained in 87% yield, m.p. 113-119°. Sublimation at 0.01 mm (bath temperature 110-120°) gave a cream solid, m.p. 121-128°. (Found for mixed isomers: C, 66.5; H, 5.6; N, 12.7. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 13.0%). ν max (Nujol) 3450, 3350 (NH_2), 3200 (C=C ?), 2200 (C≡N), 1650 (NH_2) and 1625 (C=C) cm^{-1}. See Table 13 for n.m.r. data on the mixture.

4.6.6 3-Amino-6,9-dimethyl-2H-1,5-benzodioxepin-4-carbonitrile (Vj)

Scale: 0.025 mole. Yield 91.5%, m.p. 120-121° (colourless blades from dilute ethanol). (Found: C, 66.5; H, 5.6; N, 13.05. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 13.0%). νmax (Nujol) 3400, 3300 (NH_2), 3190 (C=C ?), 2190 (C≡N), 1650 (NH_2) and 1625 (C=C) cm^{-1}. See Table 13 for the n.m.r. results.

4.6.7 3-Amino-7,8-dimethyl-2H-1,5-benzodioxepin-4-carbonitrile (Vk)

Scale: 0.05 mole. Yield 95%, m.p. 185-186° (colourless blades from aqueous ethanol). (Found: C, 66.6; H, 5.6; N, 12.6. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 13.0%). νmax (Nujol) 3400, 3300 (NH_2)

3200 (C=C ?), 2190 (C≡N), 1650 (NH_2) and 1625 (C=C) cm^{-1}. The n.m.r. details for this compound are recorded in Table 13.

4.6.8 3-Amino-6,7,8-trimethyl- (Vl) and 3-amino-7,8,9-trimethyl-2H-1,5-benzodioxepin-4-carbonitrile (Vm)

Scale: 0.03 mole. The crude product was dissolved in boiling carbon tetrachloride, clarified with charcoal, filtered and evaporated to dryness. Trituration of the residue with light petroleum (b.p. 60-80°) gave the mixed isomers (74%) m.p. 125-140°. Sublimation at 0.01 mm (bath temperature 140°) gave a cream solid, m.p. 141-163°. (Found for mixed isomers: N, 12.4. $C_{13}H_{14}N_2O_2$ requires N, 12.2%). ν max (Nujol) 3450, 3350 (NH_2), 3250 (C=C ?) 2200 (C≡N), 1660 (NH_2) and 1625 (C=C) cm^{-1}. The n.m.r. results for the mixture are given in Table 13.

4.6.9 3-Amino-6,7,9-trimethyl- (Vn) and 3-amino-6,8,9-trimethyl-2H-1,5-benzodioxepin-4-carbonitrile (Vo)

Scale: 0.03 mole. The purification procedure described in the preceding example was used and the yield was 59.5%. Sublimation at 0.01 mm (bath temperature ca 100°) afforded a cream solid m.p. 93-106°. (Found for mixed isomers: N, 11.9. $C_{13}H_{14}N_2O_2$ requires N, 12.2%). ν max (Nujol) 3450, 3350 (NH_2) 3250 (C=C ?), 2210 (C≡N), 1660 (NH_2) and 1625 (C=C) cm^{-1}. N.m.r. data for this mixture are recorded in Table 13.

4.6.10 3-Amino-6,7,8,9-tetramethyl-2H-1,5-benzodioxepin-4-carbonitrile (Vp)

Scale: 0.025 mole. Yield 94%, m.p. 179-180° (colourless plates from methanol). (Found: C, 68.7; H, 6.6; N, 11.3. $C_{14}H_{16}N_2O_2$ requires C, 68.8; H, 6.6; N, 11.5%). ν max (Nujol) 3450, 3350 (NH_2), 3250 (C=C ?), 2200 (C≡N), 1640 (NH_2) and 1625 (C=C) cm^{-1}. See Table 13 for the n.m.r. results.

4.6.11 3-Amino-6-t-butyl- (Vq) and 3-amino-9-t-butyl-2H-1,5-benzodioxepin-4-carbonitrile (Vr)

Scale: 0.025 mole. The crude mixed isomers were obtained as a sticky solid. This was extracted into ether, dried (Na_2SO_4) and evaporated to give the product (93.5%) as a pale brown gum. An elemental analysis of this material was not obtained. ν max (neat film) 3400, 3300 (NH_2), 3200 (C=C ?), 2200 (C≡N), 1650 (NH_2) and 1625 (C=C) cm^{-1}. Details of the n.m.r. spectrum are given in Table 13.

4.6.12 3-Amino-7-t-butyl- (Vs) and 3-amino-8-t-butyl-2H-1,5-benzodioxepin-4-carbonitrile (Vt)

Scale: 0.1 mole. The yield of mixed isomers was 84%, m.p. 112-124°. An attempt to sublime this material at 0.01 mm was unsuccessful. No elemental analysis was obtained for the material. ν max (Nujol) 3450, 3350 (NH_2), 3200 (C=C ?), 2200 (C≡N), 1650 (NH_2) and 1625 (C=C) cm^{-1}. See Table 13 for n.m.r. results.

4.6.13 3-Amino-6,8-di-t-butyl- (Vu) and 3-amino-7,9-di-t-butyl-2H-1,5-benzodioxepin-4-carbonitrile (Vv)

Scale: 0.05 mole. The crude product was obtained as a brown solid which was difficult to filter. It was dissolved in ether, dried (Na_2SO_4) and evaporated to a brown gum (96.5%). It was readily soluble in light petroleum (b.p. 60-80°). No elemental analysis was obtained on this mixture. ν max (film) 3450, 3350 (NH_2), 3250 (C=C ?), 2200 (C≡N) cm^{-1}. The n.m.r. results are recorded in Table 13.

4.6.14 3-Amino-6-phenyl- (Vw) and 3-amino-9-phenyl-2H-1,5-benzodioxepin-4-carbonitrile (Vx)

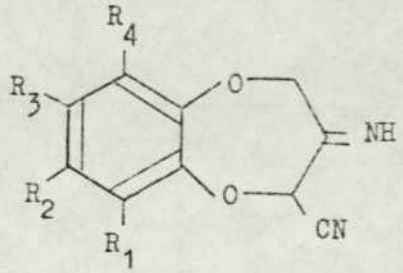
Scale: 0.04 mole. The crude product was extracted with toluene, boiled, clarified with charcoal, filtered and evaporated in vacuo to an orange oil (91%). Elemental analyses were not carried out on this mixture. ν max (film) 3500, 3400 (NH_2), 3250 (C=C ?), 2210 (C≡N) cm^{-1}. See Table 13 for the n.m.r. data.

4.6.15 3-Amino-7-phenyl- (Vy) and 3-Amino-8-phenyl-2H-1,5-benzodioxepin-4-carbonitrile (Vz)

Scale: 0.04 mole. The crude mixture of isomers, 88.5%, m.p. 155-165°, was dissolved in ether, filtered and evaporated to dryness to give a pale fawn solid, m.p. 163-186°. An elemental analysis was not obtained. ν max (Nujol) 3450, 3350 (NH_2), 3250 (C=C ?), 2200 cm^{-1}. See Table 13 for n.m.r. results.

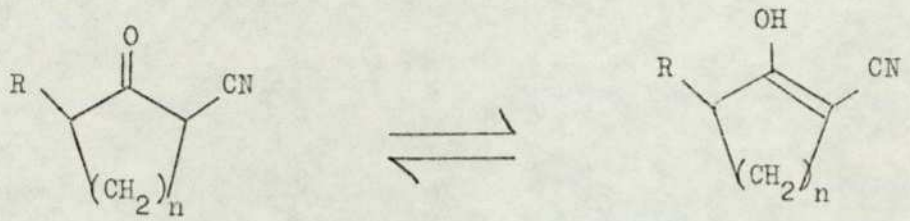
4.6.16 Some infra-red and nuclear magnetic resonance spectral data.

The high melting points observed for many of the enaminonitriles and the relatively vigorous conditions that were required to achieve hydrolysis of the amino group (4.7) suggested that they existed almost exclusively as the enaminonitrile tautomers (V a-z). Spectroscopic evidence confirmed this and ruled out the presence of the unconjugated iminonitrile form (XCIV).



(XCIV)

The infra-red spectra, in Nujol, of all the compounds including the mixtures of isomers (V a-z) exhibited only one -C≡N absorption. If the compounds had in fact been mixtures of the tautomeric forms it would be reasonable to expect two -C≡N absorptions for the different forms as was observed for some tautomeric 2-cyanocycloalkanones (XCV)[116,117].



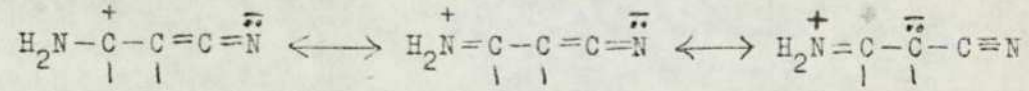
XCV

R = H, n = 2,3,4,5,6

R = Me, n = 3

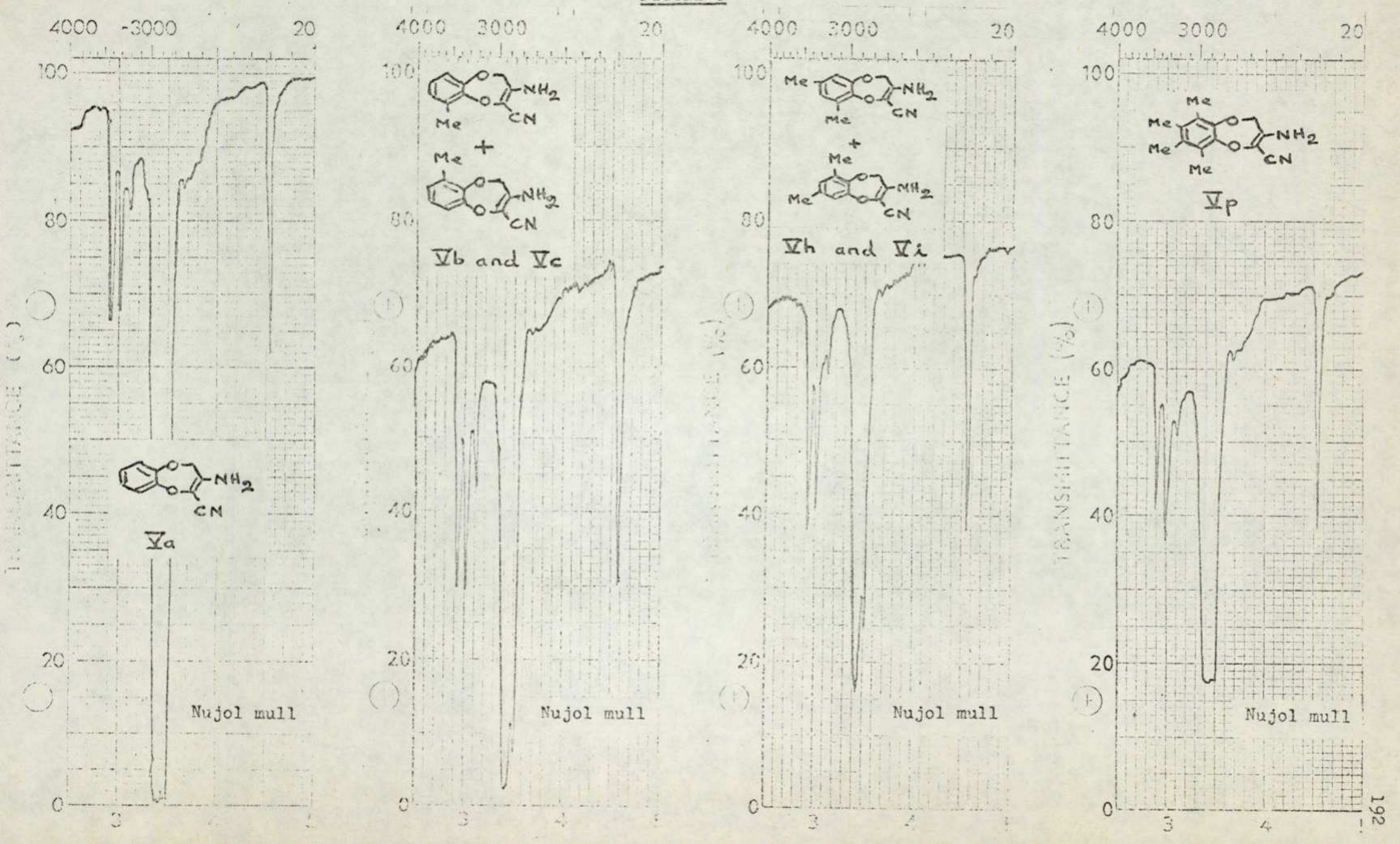
R = Ph, n = 3

The position of 2190-2200 cm^{-1} observed in this work for the -C≡N absorption in the enaminonitriles (V a-z) is similar to that recorded by Baldwin[115] for some cyclic enaminonitriles. The depression of the -C≡N frequency by 15-25 cm^{-1} below the value of 2215 cm^{-1} quoted by Bellamy[38k] for normally conjugated aliphatic nitriles had been attributed[115] to the contribution by charge-separated resonance structures to the ground state of the molecule.



However, examination of the NH stretching region tended to contradict the above evidence since all the enaminonitriles displayed three distinct bands in this region, (see Figure 8 for some examples). The two higher frequency bands were similar in intensity and were characteristic of a primary $-NH_2$

FIGURE 8


4000
3000
20
100
80
60
40
20
0
TRANSMITTANCE (%)
Va
Nujol mull
Vb and Vc
Nujol mull
Vh and Vi
Nujol mull
Vp
Nujol mull
NH2
CN
Me

group[381], whereas the lower frequency absorption was more variable in intensity and suggested the presence of some unconjugated iminonitrile (XCIV). Spectral data for seventeen enaminonitriles compiled from literature sources by Baldwin[115] showed that this lower frequency band was present in only one of the spectra. The absence of a second infra-red -C≡N absorption in this example coupled with the observation that in its nuclear magnetic resonance spectrum the $-NH_2$ group integrated for two protons with respect to the remaining aromatic and methylene protons was not considered consistent with the iminonitrile structure[115]. It was suggested[115] that this third, lower frequency, band in the NH stretching region originated from C=C, which was increased in intensity by the enhanced conjugation within the molecule. This idea may explain the presence of the third, lower frequency, band in the enaminonitriles (V a-z) examined in this work. The nuclear magnetic resonance spectra (60 MHz) of the enaminonitriles, including the mixed isomers, were examined in deuterochloroform and all showed a broad signal in the 5.7-6.1 τ region typical of the $-NH_2$ group. The area of this signal compared with that of the heterocyclic methylene proton singlet, or singlets in the case of some mixed isomers, integrated in the ratio of 1:1 whereas the ratio for the corresponding iminonitrile structure (XCIV) would have been 1:2. The possibility that the imino proton and the methine proton had the same chemical shifts seemed unlikely. This evidence confirmed that the compounds existed almost exclusively as the enaminonitrile tautomers (V a-z).

Nuclear magnetic resonance spectroscopy readily established that cyclisation of the unsymmetrically substituted o-phenylenedioxydiacetonitriles (III b-e, h, i, k-o) had given approximately 1:1 mixtures of the two possible enaminonitriles. This ratio was expected and showed that nuclear substitution of the dinitriles (III) had not affected to any marked degree which methylene group was involved in the initial carbanion formation.

Spectral data for all the enaminonitriles (V a-z) have been recorded in Table 13 and it can be seen that because of small differences in the chemical shifts experienced by certain aromatic, methylene, methyl or t-butyl protons of individual isomers in each mixture there occurred in all but one of the mixtures examined at least one signal that could be relied upon to confirm the presence of the two isomers.

Assignment of the methylene proton signals to the appropriate isomers in the mixtures (Vb and c, d and e, f and g, q and r, s and t, and w and x) was not attempted. However, the results (Table 13) clearly indicated a tendency for the methylene proton signals to move up-field (increased shielding) with progressive nuclear substitution.

Confident assignments for some of the alkyl proton signals have been made where possible based on chemical shift data from this investigation supplemented by chemical shift constants from published correlation tables but in most cases the small differences observed for the chemical shifts of these protons, especially in mixtures of the polyalkylated compounds, prevented any conclusive identification being reached.

Predictions for the chemical shifts of some of the alkyl protons were greatly simplified by information obtained from the 60 MHz nuclear magnetic resonance spectra of the 6,9-dimethyl- (Vj) and 6,7,8,9-tetramethyl- (Vp) analogues. In both of these compounds one of the methyl groups resonated about 0.1 τ lower than the other(s) and in each case this was attributed to long-range deshielding of the 6-methyl protons either by diamagnetic anisotropic properties of the 4-cyano group[118] which, in Dreiding models, is situated about 3 Å away from these nuclei or as a result of the direct electrostatic effect of the appreciable dipole of the nitrile group[95e]. On the basis of this evidence the methyl resonances visible at 7.70 and 7.81 τ in the mixture of enaminonitriles (V b and c) were allocated to the

TABLE 13

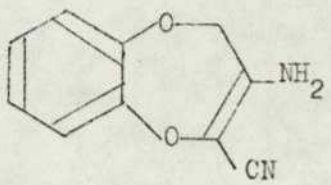
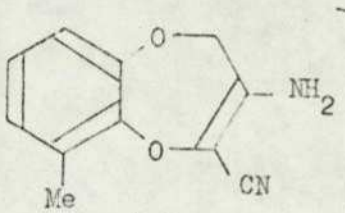
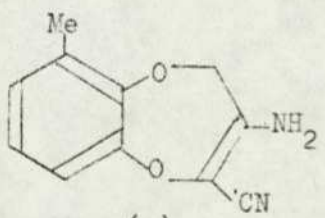
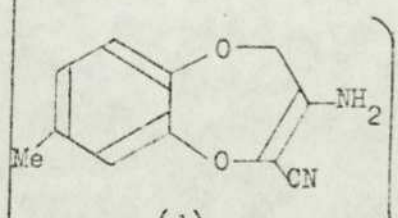
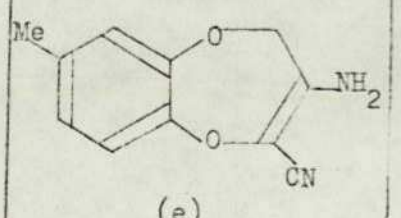
Compound (V)	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$ [a]			
	aromatic protons	O-CH_2-	-NH_2	protons of aromatic substituent(s)
 (a)	3.05 τ, bs 4H	5.16 τ, s, 2H	5.90 τ, bs, 2H	-
 (b)  (c)	3.14 and 3.19 τ, singlets of equal area, 3H	5.16 and 5.20 τ, singlets of equal area, 2H	5.94 τ, bs, 2H	7.70 τ(6-Me) [b] and 7.81 τ (9-Me) [b], singlets of equal area, 3H
 (d)  (e)	3 - 3.4 τ, m, 3H	5.19 and 5.21 τ, singlets of equal area, 2H	5.89 τ, bs 2H	7.76 τ, s, 3H (7 and 8-Me)

TABLE 13 (Cont.)

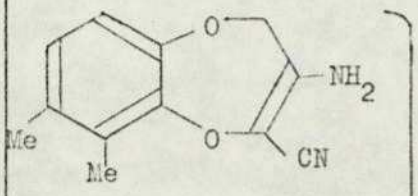
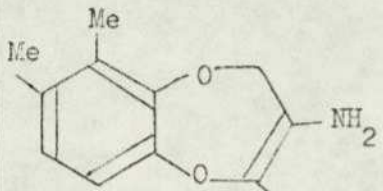
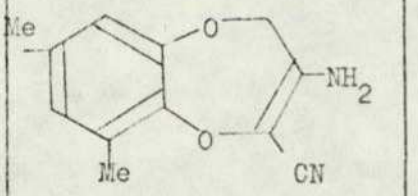
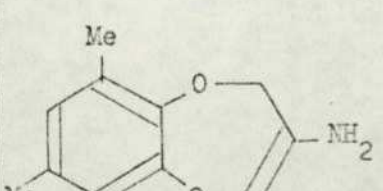
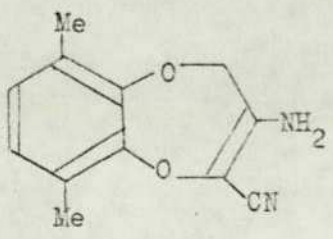
Compound V	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$[a]			
	aromatic protons	$-O-\underline{CH}_2-$	$-\underline{NH}_2$	protons of aromatic substituent(s)
 (f)  (g)	3.25 τ bs, 2H	5.20 and 5.26 τ singlets of equal area, 2H	6.05 τ bs, 2H	7.79 and 7.81 τ singlets in ratio 3:1, 6H. (Calcd. for 6-Me, 7.75 τ; 7 and 8-Me 7.81 τ; 9-Me, 7.86 τ)[c]
 (h)  (i)	3.31 and 3.46 τ, singlets of equal area, 2H	5.23 τ, s, 2H	5.99 τ, bs, 2H	7.76 τ (6-Me)[d], 7.81 τ (7- and 8-Me)[d] and 7.86 τ (9-Me)[d]. All singlets in ratio of 1:2:1. 6-H. (Calcd. for 6-Me, 7.77 τ; 7- and 8-Me, 7.83 τ; 9-Me, 7.88 τ)[c]
 (j)	3.26 τ, s, 2H	5.22 τ, s, 2H	6.05 τ, bs, 2H	7.74 τ, s, 3H, (6-Me)[b]. 7.85 τ, s, 3H, (9-Me)[b]. (Calcd. for 6-Me, 7.74 τ; 9-Me, 7.86 τ)[c]

TABLE 13 (Cont.)

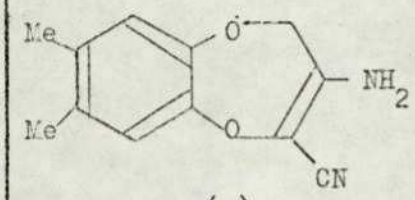
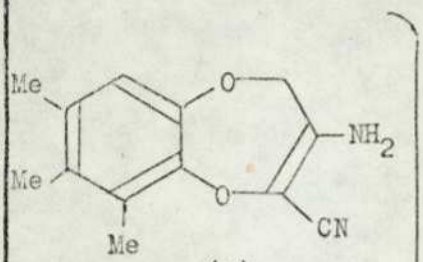
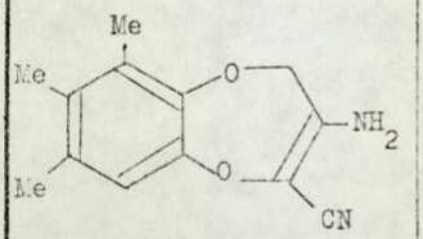
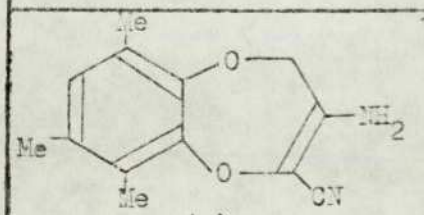
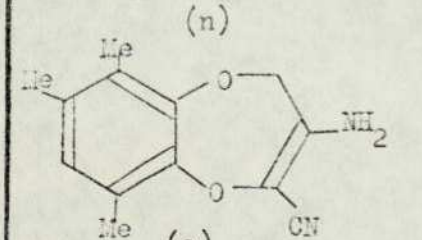
Compound (V)	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$ [a]			
	aromatic protons	$-OCH_2-$	$-NH_2$	Protons of aromatic substituent(s)
 (k)	3.18 τ, s, 6-H[b]; 3.34 τ, s, 9-H[b] — 2H	5.27 τ, s, 2H	5.96 τ, bs, 2H	7.85 τ, s, 6H (7 and 8-Me)[c] (Calcd for 7- and 8-Me, 7.81 τ)[c]
 (l)	3.36 τ, s, 6-H[b]; 3.40 τ, s, 9-H[b] — 1H	5.27 τ s, 2H	6.03 τ, s, 2H	7.79 (6-Me)[d,e] 7.82, 7.88 and 7.89 τ, singlets in ratio 1:3:1:1 9H Isomer Vl (Calcd. for 6-Me, 7.82 τ; 7-Me, 7.86 τ; 8-Me, 7.88 τ)[c]
 (m)				Isomer Vm (Calcd. for 7-Me, 7.88 τ; 8-Me, 7.86 τ; 9-Me, 7.93 τ)[c]
 (n)	3.33 τ, s; 3.39 τ, s — 1H	5.33 τ, s 2H	6.02 τ bs 2H	7.78, 7.85 and 7.94 τ, singlets in ratio 1:4:1 9H Isomer Vn (Calcd. for 6-Me 7.79 τ; 7-Me 7.88 τ; 9-Me, 9-Me, 7.92 τ)[c]
 (o)				

TABLE 13 (Cont.)

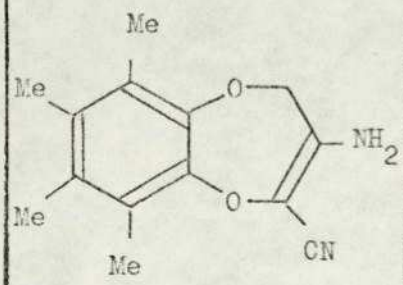
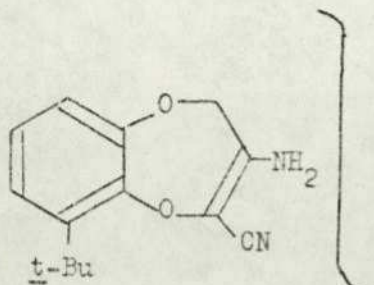
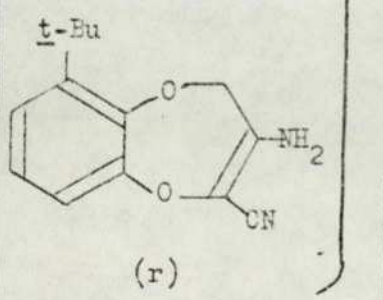
Compound (V)	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$ [a]			
	aromatic protons	-O-$\underline{CH}_2$-	-$\underline{NH}_2$	protons of aromatic substituent(s)
Isomer (Vo) continued				Isomer Vo (Calcd. for 6-Me, 7.81τ; 8-Me, 7.88τ; 9-Me, 7.90τ)[c]
 (p)	-	5.36τ, s, 2H	6.30τ bs 2H	7.77τ (6-Me)[b] and 7.86τ (7,8,9-Me_3)[b], singlets in ratio 1:3, 12H (Calcd. for 6-Me, 7.86τ; 7- and 8-Me, 7.93τ; 9-Me, 7.97τ)[c]
 (q) +  (r)	2.92-3.14τ m 3H	5.24 and 5.29τ, singlets of ~ equal area, 2H	5.86τ, bs 2H	8.57τ (6-$\underline{t}$-Bu)[b] and 8.64τ (9-$\underline{t}$-Bu)[b], singlets of equal area, 9H

TABLE 13 (Cont.)

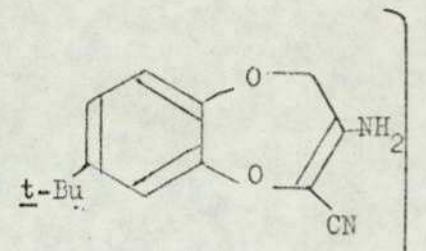
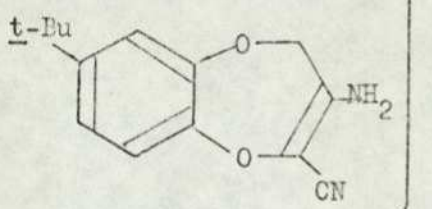
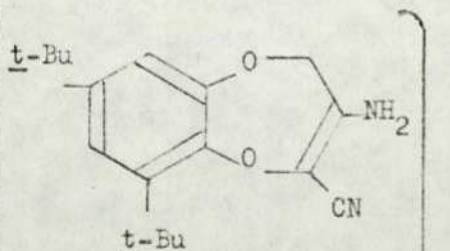
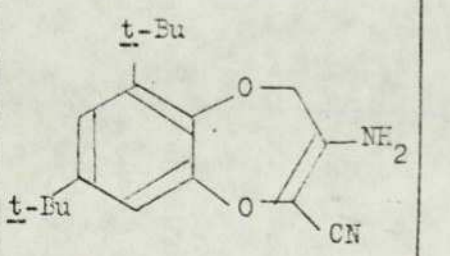
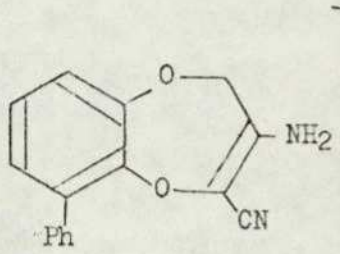
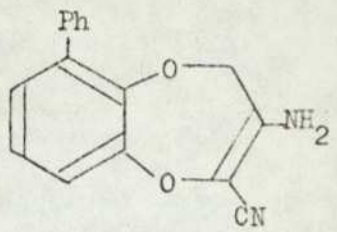
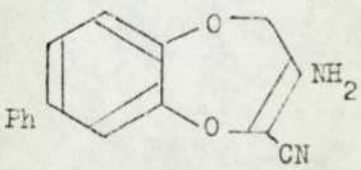
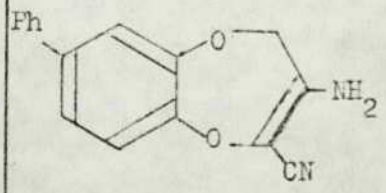
Compound (V)	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$ [a]			
	aromatic protons	-O-CH-2	$-NH_2$	protons of aromatic substituent(s)
 (s)  (t)	2.90-3.20 τ m, 3H	5.19 and 5.23 τ singlets of ~ equal area, 2H	5.71 τ bs, 2H	8.75 τ, s, 9H (7- and 8-t-Bu)
 (u)  (v)	2.8-3.35 τ broad signal [f], 2H	5.3 τ s, 2H	4.8-5.5 τ broad signal 2H	8.58 τ (6-t-Bu) [g] 8.62 τ (9-t-Bu) [g] 8.77 τ (7- and 8-t-Bu) [g] singlets in approximate ratio of 1:1:2 18H (Calcd. for 6-t-Bu, 8.59 τ; 7- and 8-t-Bu, 8.77 τ; 9-t-Bu, 8.66 τ) [h]

TABLE 13 (Cont.)

Compound V	60 MHz ^{1}H n.m.r. spectrum in $CDCl_3$ [a]			
	aromatic protons	$-O-CH_2-$	$-NH_2$	protons of aromatic substituent(s)
 (w)  (x)	2.7-3.1 τ m, 3H	5.25 and 5.32 τ, singlets of equal area, 2H	5.82 τ bs, 2H	2.59 τ (6-Ph)[b] and 2.62 τ (9-Ph)[b], singlets of equal area, 5H
 (y)  (z)	Broadened singlet at 2.58 τ superimposed on multiplet at 2.4-3.1 τ 8H	5.13 τ, s, 2H	5.81 τ, bs, 2H	see under aromatic protons

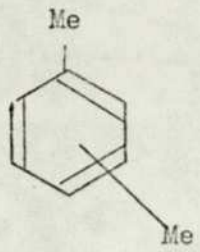
Footnotes

(a) Concentrations of 10-15% w/v were used.

(b) Reasons for these assignments are discussed in the text (4.6.16).

(c) Assignments are based on the chemical shifts calculated in footnote (d).

(d) Chemical shifts for the 6- and 9-methyl- protons in compounds (Vf-p) were calculated by adding the appropriate chemical shift constants[95a]



	δ
o	+0.05 ppm
m	+0.07 ppm
p	+0.04 ppm

for additional methyl substituents to the methyl resonance positions of 7.70 and 7.81 τ observed for the 6- and 9-methyl- compounds (V b and c) respectively. Chemical shifts for the 7- and 8-methyl- protons in compounds (V f-p) were similarly estimated from the methyl signal position of 7.76 τ found for the 7- and 8-methyl isomers (V d and e).

(e) Tentative assignment.

(f) Poorly resolved spectrum.

(g) Assignments were based on the calculations described in footnote (h).

(h) Chemical shifts for the t-butyl protons at positions 6 and 9 in these two isomers were calculated by adding the chemical shift constant for an additional m-t-butyl group (+0.02 ppm)[101] to the alkyl proton resonance positions of 8.57 and 8.64 τ observed for the 6- and 9-t-butyl isomers, (V q and r) respectively. The chemical shifts for the 7- and 8-t-butyl protons were calculated in an identical fashion from the t-butyl resonance position of 8.75 τ observed for the 7- and 8-t-butyl- compounds (V s and t).

6- and 9-methyl protons respectively. These same values, together with the appropriate chemical shift increments for additional methyl substituents, were then used to calculate the resonance positions of the 6- and 9-methyl groups in other members of this series (V f and g, V h and i, V l and m, V n and o and V p). Chemical shifts for the methyl groups at the 7- and 8- positions in the compounds (V f and g, V h and i, V k, V l and m, V n and o and V p) were similarly estimated from the resonance position of 7.76 τ observed for both methyl signals in the mixture of 7- and 8-methyl isomers (Vd and e). The lower field alkyl proton resonance in the spectrum of the 6- and 9-t-butyl enaminonitriles (V q and r) was also assigned to the 6-t-butyl group of isomer (Vq) since at this position these protons could experience long-range deshielding from diamagnetic anisotropic effects[118] or direct electrostatic forces[95e] of the 4-cyano group situated about 2.5Å away. The chemical shifts for the t-butyl protons in the mixture of di-t-butyl isomers (V u and v) were calculated in a similar manner to those of the corresponding methyl analogue (see footnote h in Table 13). Good agreement for the predicted and observed chemical shifts of the nuclear alkyl protons was evident in Table 13 for compounds (V h and i, V j and V u and v) thus permitting confident spectral assignments to be made but in compounds (Vf and g, V k, V l and m, V n and o and V p), all of which possess at least one pair of o-dimethyl groups, the agreement between the predicted and observed chemical shifts was less satisfactory and precise assignments were inconclusive. Nevertheless some tentative identifications have been made where possible.

Allocation of the low field aromatic signal to the 6-H in compound (V k) and to isomer (V m) in the mixture of trimethyl-enaminonitriles (Vl and m) has also been based on long-range deshielding that a proton at this position could suffer from diamagnetic anisotropic[118] or electrostatic effects[95e] of the 4-cyano group situated approximately 4 Å

away but it should be noted that this is close to the limit over which such effects can operate[120]. For the same reasons[118,95e] the lower field phenyl resonance in the mixed isomers (V w and x) was attributed to the 6-phenyl protons of isomer (Vx).

Attempts to separate two of these mixtures (V b and c) and (V d and e) into their pure components was partially successful. Six recrystallisations of the crude mixture containing (V b and c) were necessary before material with a constant m.p. of 177-178° was obtained. This was shown by its 220 MHz ^{1}H nuclear magnetic resonance spectrum to be a pure compound (see Table 14 for spectral data) and because it displayed the higher field methyl resonance (see above, p 194) it was considered to be the 9-methyl isomer (Vc). A second component, isolated from the filtrates, was raised to a constant m.p. of 141-142° after repeated recrystallisations but this was shown by its 220 MHz ^{1}H nuclear magnetic resonance spectrum to be a 60:40 mixture of the 6-methyl- isomer (Vb) (see Table 14 for spectral data) and its 9-methyl- relative (Vc) respectively.

TABLE 14

220 MHz 'H n.m.r. spectra[a] (in $CDCl_3$)[b]
3-amino-6-methyl- (Vb)[c] and 3-amino-9-methyl-2-H-1,5-benzodioxepin-4-carbonitrile (Vc)

Isomer	aromatic protons	$-CH_2-$	$-NH_2$	$-CH_3$
(Vb) m.p. -	3.1 - 3.25τ 3H, m	5.18τ 2H, s	6.0τ 2H, s	7.71τ 3H, s
(Vc) m.p. 177 - 178°	3.1 - 3.25τ 3H, m	5.14τ 2H, s	6.0τ 2H, s	7.83τ 3H, s

a Determined by the Physico-chemical Measurements Unit, Harwell.

b $CHCl_3$ peak appeared at 2.74τ. Tetramethyl silane was used as an internal standard (10τ).

c Data for this isomer were obtained by subtracting the spectrum of the 9-methyl- isomer (Vc) from that of the mixture.

Separation of the 7- and 8-methyl- isomers (Vd and e) was similarly attempted. Here again, one isomer of m.p. 171-173°, designated the 'α'-isomer, was isolated and shown by its 220 MHz 'H nuclear magnetic resonance spectrum to be pure (see Table 15) but the 'β'-isomer, m.p. 135-136°, which was isolated from the filtrates was found to contain an equal amount of the 'α'-isomer. Because such small differences existed between the structures of the two isomers and their respective spectra there appeared to be no firm basis for even a speculative structural proposal to be made.

TABLE 15

220 MHz 'H n.m.r. spectra[a] (in C_6D_6)[b] of 3-amino-7-methyl- (Vd) and 3-amino-8-methyl-2H-1,5-benzodioxepin-4-carbonitrile (Ve)

Isomer	aromatic protons	$-CH_2-$	$-NH_2$	$-CH_3$
'α' m.p. 171-173°	3.30 - 3.52τ 3H, m	6.14τ 2H, s	7.21τ 2H, bs	8.15τ 3H, s
'β'[c] m.p. -	3.20 - 3.67τ 3H, m	6.10τ 2H, s	7.2τ 2H, bs	8.11τ 3H, s

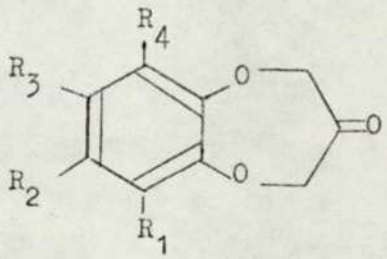
a Determined by the Physico-chemical Measurements Unit, Harwell.

b The benzene peak appeared at 2.86τ; tetramethylsilane was the internal standard (10τ).

c Information for this isomer was obtained by subtracting the spectrum of the 'α'-isomer from that of the mixture.

4.7 Syntheses of the substituted 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (I b-o).

The substituted 3-keto-3,4-dihydro-2H-1,5-benzodioxepins (I b-o) were obtained in 28-73% yields by hydrolysis of the appropriate



(a) $R_1 = R_2 = R_3 = R_4 = H$

(b) $R_1 = Me$, $R_2 = R_3 = R_4 = H$

(c) $R_1 = H$, $R_2 = Me$, $R_3 = R_4 = H$

(d) $R_1 = R_2 = Me$, $R_3 = R_4 = H$

(e) $R_1 = Me$, $R_2 = H$, $R_3 = Me$, $R_4 = H$

(f) $R_1 = Me$, $R_2 = R_3 = H$, $R_4 = Me$

(g) $R_1 = H$, $R_2 = R_3 = Me$, $R_4 = H$

(h) $R_1 = R_2 = R_3 = Me$, $R_4 = H$

(i) $R_1 = R_2 = Me$, $R_3 = H$, $R_4 = Me$

(j) $R_1 = R_2 = R_3 = R_4 = Me$

(k) $R_1 = t$-Bu, $R_2 = R_3 = R_4 = H$

(l) $R_1 = H$, $R_2 = t$-Bu, $R_3 = R_4 = H$

(m) $R_1 = t$-Bu, $R_2 = H$, $R_3 = t$-Bu, $R_4 = H$

(n) $R_1 = Ph$, $R_2 = R_3 = R_4 = H$

(o) $R_1 = H$, $R_2 = Ph$, $R_3 = R_4 = H$

enaminonitrile(s) (V b-z) with orthophosphoric acid in acetic acid as described for the parent compound (Ia) (2.1.3). Purification was best accomplished by passing a solution of the crude ketone in benzene or toluene through a short column of neutral alumina to remove coloured and polar impurities followed by distillation and/or crystallisation. Nearly all the substituted ketones possessed a strong odour reminiscent of water melons; a property which was also claimed[23] in a patent for the 7-methyl ketone (Ic). All the ketones were characterised as their 2,4-dinitrophenylhydrazones and a number as their oximes. Sharp melting points were observed for the former derivatives and for the oximes derived from the symmetrically substituted ketones (Ia,f,g) but often those prepared from unsymmetrically substituted ketones (I b,c,d,e,k,l,n,o) melted over wide ranges. This was attributed to the presence of both geometrical isomers (E and Z forms).

4.7.1 3-Keto-3,4-dihydro-2H-1,5-benzodioxepin (Ia)

The preparation of this compound by the acid hydrolysis of 3-amino-2H-1,5-benzodioxepin-4-carbonitrile (Va) has already been described together with its infra-red, ultra-violet and nuclear magnetic resonance spectra (2.1.3).

The analogues (Ib-o) described below were similarly prepared from the appropriately substituted enaminonitriles or mixtures thereof.

Ultra-violet spectral data for the ketones are recorded and discussed in Chapter 5 (Table 32).

2,4-Dinitrophenylhydrazone derivatives were prepared by a recommended procedure[121]. Oximes (XXVIII b-g, j-o, R=OH) were obtained using the same conditions described for the parent compound (XXVIIIa, R=OH) (see 3.5.1); their ultra-violet spectral data are also recorded and discussed in Chapter 5 (Table 34).

4.7.2 3-Keto-6-methyl-3,4-dihydro-2H-1,5-benzodioxepin (Ib)

Scale: 0.05 mole. Yield 63%, b.p. 82-84°/0.2mm, n_D^{20} 1.5445. G.l.c., column A, at 150° showed < 1% impurity of shorter retention time. (Found: C, 67.6; H, 5.6. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.7%). ν_{max} (liquid film) 1740 (C=O) cm^{-1}. See Table 16 for the n.m.r. data.

The 2,4-dinitrophenylhydrazone (yellow needles from ethanol) had m.p. 155-157°. (Found: C, 53.5; H, 3.8; N, 15.8. $C_{16}H_{14}N_4O_6$ requires C, 53.6; H, 3.9; N, 15.6%).

The oxime (XXVIII b, R=OH), (96%, colourless needles, from dilute ethanol) had m.p. 133-134°. (Found: C, 62.1; H, 5.7; N, 7.4. $C_{10}H_{11}NO_3$ requires C, 62.2; H, 5.7; N, 7.25%).

4.7.3 3-Keto-7-methyl-3,4-dihydro-2H-1,5-benzodioxepin (Ic)

Scale: 0.05 mole. Yield 55%, b.p. 90-94°/0.5mm, m.p. 38-39° [colourless prisms from light petroleum (b.p. 40-60°)]. (Found: C, 67.4; H, 5.6. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.7%). ν max (KBr) 1750 (C=O) cm^{-1}. See Table 16 for n.m.r. information.

The 2,4-dinitrophenylhydrazone, (yellow needles from ethanol) had m.p. 180-181°. (Found: C, 53.45; H, 3.8; N, 15.8. $C_{16}H_{14}N_4O_6$ requires C, 53.6; H, 3.9; N, 15.6%).

The oxime (XXVIII c, R=OH), (96%, colourless needles from dilute ethanol or ligroin) had m.p. 105-110°. (Found: C, 62.0; H, 5.7; N, 7.4. $C_{10}H_{11}NO_3$ requires C, 62.2; H, 5.7; N, 7.25%).

4.7.4 6,7-Dimethyl-3-keto-3,4-dihydro-2H-1,5-benzodioxepin (Id)

Scale: 0.05 mole. Yield 54%, b.p. 100-106°/0.1mm, m.p. 32° [colourless prisms from light petroleum (b.p. 40-60°)]. (Found: C, 68.6; H, 6.2. $C_{11}H_{10}O_3$ requires C, 68.7; H, 6.3%). ν max (melt) 1250 (C=O) cm^{-1}. The n.m.r. results are shown in Table 16.

It formed a 2,4-dinitrophenylhydrazone (orange-yellow needles from aqueous ethanol), m.p. 186-188°. (Found: C, 54.9; H, 4.5; N, 15.0. $C_{17}H_{16}N_4O_6$ requires C, 54.8; H, 4.3; N, 15.05%).

The oxime (XXVIIId, R=OH) (colourless needles from aqueous ethanol) had m.p. 139-140°. (Found: C, 63.8; H, 6.1; N, 6.7. $C_{11}H_{13}NO_3$ requires C, 63.75; H, 6.3; N, 6.8%).

4.7.5 6,8-Dimethyl-3-keto-3,4-dihydro-2H-1,5-benzodioxepin (Ie)

Scale: 0.05 mole. Yield 48%, b.p. 100-105°/0.01 mm, m.p. 35-36° [colourless prisms from light petroleum (b.p. 40-60°)]. (Found: C, 68.7; H, 6.45. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%). ν max (melt) 1750 (C=O) cm^{-1}. The n.m.r. results are recorded in Table 16.

The 2,4-dinitrophenylhydrazone (yellow silky needles from ethanol) had m.p. 198-199°. (Found: C, 54.9; H, 4.1; N, 14.95. $C_{17}H_{16}N_4O_6$ requires C, 54.8; H, 4.3; N, 15.05%).

It gave an oxime (XXVIIIe, R=OH) (colourless needles from dilute ethanol), m.p. 140-142°. (Found: C, 63.8; H, 6.5; N, 7.0. $C_{11}H_{13}NO_3$ requires C, 63.75; H, 6.3; N, 6.8%).

4.7.6 6,9-Dimethyl-3-keto-3,4-dihydro-2H-1,5-benzodioxepin (If)

Scale: 0.02 mole. Yield 63.5%, b.p. 88-96°/0.1 mm, m.p. 54-55° [colourless needles after sublimation at 0.01 mm (bath temperature 40°)]. (Found: C, 68.5; H, 6.0. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%). νmax (KBr) 1740 (C=O) cm^{-1}. N.m.r. data are recorded in Table 16.

The 2,4-dinitrophenylhydrazone (yellow needles from ethanol) had m.p. 206°. (Found: C, 55.1; H, 4.7; N, 15.0. $C_{17}H_{16}N_4O_6$ requires C, 54.8; H, 4.3; N, 15.05%).

An oxime (XXVIIIf, R=OH) (colourless needles from dilute ethanol) had m.p. 146-147°. (Found: C, 63.9; H, 6.0; N, 6.6. $C_{11}H_{13}NO_3$ requires C, 63.75; H, 6.3; N, 6.8%).

4.7.7 7,8-Dimethyl-3-Keto-3,4-dihydro-2H-1,5-benzodioxepin (Ig)

This compound was obtained in 72.5% yield, b.p. 108-112°/0.01 mm, m.p. 57-58° [colourless needles from light petroleum (b.p. 60-80°)]. (Found: C, 68.5; H, 6.5. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%). ν max (KBr) 1740 (C=O) cm^{-1}. See Table 16 for the n.m.r. results.

The 2,4-dinitrophenylhydrazone (yellow needles from ethanol) had m.p. 220-221° (decomp.). (Found: C, 54.8; H, 4.2; N, 15.4. $C_{17}H_{16}N_4O_6$ requires C, 54.9; H, 4.3; N, 15.05%).

It gave an oxime (XXVIIIg, R=OH) (colourless needles from aqueous ethanol) of m.p. 154-155°. (Found: C, 63.9; H, 6.4; N, 6.55. $C_{11}H_{13}NO_3$ requires C, 63.75; H, 6.3; N, 6.8%).

4.7.8 3-Keto-6,7,8-trimethyl-3,4-dihydro-2H-1,5-benzodioxepin (Ih)

Scale: 0.02 mole. Yield 28%, m.p. 57.5-58.5° [colourless prismatic needles from light petroleum (b.p. 60-80°)]. (Found: C, 70.0; H, 7.0. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%). ν max (Nujol) 1740 (C=O) cm^{-1}. See Table 16 for the n.m.r. results.

The 2,4-dinitrophenylhydrazone (yellow needles from aqueous acetic acid), m.p. 219-220°. (Found: C, 55.8; H, 4.9; N, 14.4. $C_{18}H_{18}N_4O_6$ requires C, 55.95; H, 4.7; N, 14.5%).

The oxime (XXVIIIh, R=OH) was not prepared.

4.7.9 3-Keto-6,7,9-trimethyl-3,4-dihydro-2H-1,5-benzodioxepin (Ii)

Scale: 0.015 mole. Yield 29%, m.p. 62-63° [colourless plates either sublimation at 0.01 mm (bath temperature 50-55°) or from light petroleum (b.p. 40-60°)]. (Found: C, 69.7; H, 6.85. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%). ν max (Nujol) 1740 (C=O) cm^{-1}. N.m.r. spectral data are recorded in Table 16.

It formed a 2,4-dinitrophenylhydrazone (yellow needles from ethanol), m.p. 184-186°. (Found: C, 56.0; H, 4.9; N, 14.8. $C_{18}H_{18}N_4O_6$ requires C, 55.95; H, 4.7; N, 14.5%).

The oxime (XXVIIIi, R=OH) was not prepared.

4.7.10 3-Keto-6,7,8,9-tetramethyl-3,4-dihydro-2H-1,5-benzodioxepin (Ij)

Scale: 0.02 mole. Yield 28%, m.p. 116-117°. [colourless needles from light-petroleum (b.p. 80-100°)]. (Found: C, 70.8; H, 7.6. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%). ν max (Nujol) 1720 (split C=O) cm^{-1}. The n.m.r. results are recorded in Table 16.

The 2,4-dinitrophenylhydrazone (yellow needles from ethanol) had m.p. 194-195°. (Found: C, 56.7; H, 4.9; N, 14.1. $C_{19}H_{20}N_4O_6$ requires C, 57.0; H, 5.0; N, 14.0%).

The oxime (XXVIIIj, R=OH) (colourless filaments from aqueous ethanol) had m.p. 175°. (Found: C, 66.1; H, 7.35; N, 5.9. $C_{13}H_{17}NO_3$ requires C, 66.4; H, 7.3; N, 5.95%).

4.7.11 6-t-Butyl-3-keto-3,4-dihydro-2H-1,5-benzodioxepin (Ik)

Scale: 0.023 mole. Yield 43.5%, b.p. 93-95°/0.01 mm, m.p. 52-53° [colourless prisms after sublimation at 0.01 mm (bath temperature 45°).] (Found: C, 70.65; H, 7.4. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%). νmax (Nujol) 1760 (C=O) cm^{-1}. See Table 16 for the n.m.r. results.

A 2,4-dinitrophenylhydrazone (yellow prisms from methanol) was obtained, m.p. 189-190°. (Found: C, 56.85; H, 5.0; N, 14.0. $C_{19}H_{20}N_4O_6$ requires C, 57.0; H, 5.0; N, 14.0%).

The oxime (XXVIIIk, R=OH) (colourless needles from dilute ethanol) had m.p. 90-93°. (Found: C, 66.3; H, 7.2; N, 6.2. $C_{13}H_{17}NO_3$ requires C, 66.4; H, 7.3; N, 5.95%).

4.7.12 7-t-Butyl-3-keto-3,4-dihydro-2H-1,5-benzodioxepin (Il)

Scale: 0.05 mole. Yield 66.5%, b.p. 116-122°/0.05 mm, m.p. 96-97° [colourless prisms from light petroleum (b.p. 60-80°)]. (Found: C, 70.7; H, 7.25. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%). ν max (Nujol) 1740 (C=O) cm^{-1}. N.m.r. spectral information can be found in Table 16.

It gave a 2,4-dinitrophenylhydrazone (yellow needles from ethanol) m.p. 174-175°. (Found: C, 57.3; H, 5.2; N, 14.3. $C_{19}H_{20}N_4O_6$ requires C, 57.0; H, 5.0; N, 14.0%).

The oxime (XXVIIIl, R=OH) (colourless plates from ethanol) had m.p. 114-119° with prior softening at 110°. (Found: C, 66.1; H, 7.1; N, 6.2. $C_{13}H_{17}NO_3$ requires C, 66.4; H, 7.3; N, 5.95%).

4.7.13 6,8-Di-t-butyl-3-keto-3,4-dihydro-2H-1,5-benzodioxepin (Im)

Scale: 0.04 mole. Yield 55%, b.p. 120-125°/0.5mm, m.p. 92.5-93.5° [colourless needles from light petroleum (b.p. 60-80°)]. (Found: C, 73.6; H, 8.9. $C_{17}H_{24}O_3$ requires C, 73.9; H, 8.75%). ν max (Nujol) 1740 (C=O) cm^{-1}. N.m.r. results are recorded in Table 16.

The 2,4-dinitrophenylhydrazone (yellow needles from methanol) had m.p. 202-203°. (Found: C, 60.8; H, 6.0; N, 12.0. $C_{23}H_{28}N_4O_6$ requires C, 60.5; H, 6.2; N, 12.3%).

The oxime (XXVIII m, R=OH) (colourless blades from dilute ethanol) melted in the range 154-168°. (Found: C, 69.9; H, 8.4; N, 4.6. $C_{17}H_{25}NO_3$ requires C, 70.1; H, 8.65; N, 4.8%).

4.7.14 3-Keto-6-phenyl-3,4-dihydro-2H-1,5-benzodioxepin (In)

Scale: 0.035 mole. Yield 37%, b.p. 150-154°/0.01 mm, n_D^{25} 1.6100. G.l.c., column A, at 220°, gave a single peak. (Found: C, 74.7; H, 4.95. $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0%). ν max (liquid film) 1740 (C=O) cm^{-1}. See Table 16 for the n.m.r. results.

The 2,4-dinitrophenyl hydrazone (yellow needles from ethanol) had m.p. 194-195°. (Found: C, 60.1; H, 3.7; N, 13.4. $C_{21}H_{16}N_4O_6$ requires C, 60.0; H, 3.8; N, 13.3%).

The crude oxime (XXVIII n, R=OH) had m.p. 110-113°. After recrystallisation from ligroin it furnished colourless plates, m.p. 111-120°. (Found: C, 70.3; H, 5.0; N, 5.8. $C_{15}H_{13}NO_3$ requires C, 70.6; H, 5.1; N, 5.5%).

4.7.15 3-Keto-7-phenyl-3,4-dihydro-2H-1,5-benzodioxepin (Io)

Scale: 0.03 mole. The yield of crude product was 51%. After chromatography on neutral alumina (75g; ether as eluant) the pure ketone (39%) was obtained as colourless blades, m.p. 113-114°. (Found: C, 74.7; H, 4.9. $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0%). ν max (Nujol) 1740 (C=O) cm^{-1}. See Table 16 for the n.m.r. details.

It gave a 2,4-dinitrophenylhydrazone (yellow needles from ethanol), m.p. 222-224° (Found: C, 60.2; H, 4.0; N, 13.6. $C_{21}H_{16}N_4O_6$ requires C, 60.0; H, 3.8; N, 13.3%).

The oxime (XXVIII o, R=OH) (colourless blades from aqueous ethanol) had m.p. 177-179°. (Found: C, 71.6; H, 5.1; N, 5.2. $C_{15}H_{13}NO_3$ requires C, 70.6; H, 5.1; N, 5.5%).

4.7.16 Some infra-red and nuclear magnetic resonance spectral data.

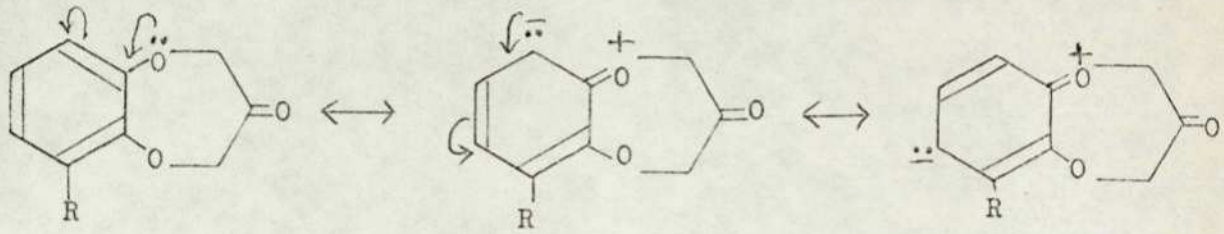
The infra-red spectra of the substituted ketones (I b-o) all showed a characteristic ketonic[38f] carbonyl absorption near 1750 cm^{-1} with the exception of the tetramethyl compound (Ij) which exhibited a distinct doublet near 1720 cm^{-1}.

Ultra-violet spectral determinations were also carried out on all the ketones but these results are discussed separately in Chapter 5.

Nuclear magnetic resonance spectroscopy confirmed the structures of all the ketones described here and the results have been tabulated (Table 16). In the spectra of the symmetrical ketones (I a,f,g,j) the protons of the two methylene groups in the heterocyclic ring appeared as a four proton singlet at 5.28-5.47τ depending upon the number(s) and position(s) of the nuclear substituent(s), whereas two distinct 2-proton singlets were observed for all but two of the unsymmetrical compounds (I b-e, h, k-n). In view of the particularly

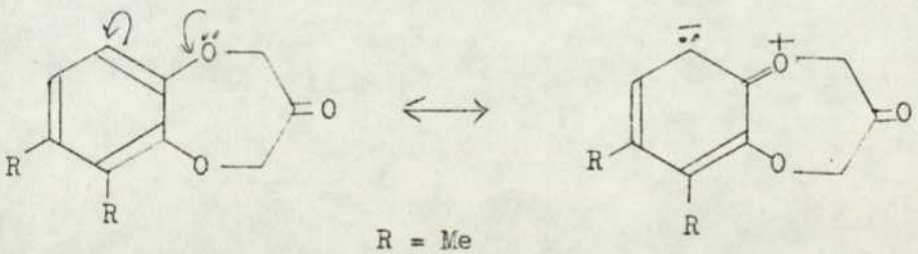
small differences in the chemical shifts of these two signals (0.02-0.06 τ) precise spectral assignments proved difficult. However, possible explanations to account for these small variations are discussed below and some tentative assignments have been proposed.

Ultra-violet absorption studies on the ketones (I a-m) (see Chapter 5) indicated that the presence of an alkyl substituent at position 6 prevented mesomerism between the oxygen at the neighbouring 5 position and the aromatic ring but did not interfere with effective mesomeric contributions from the oxygen at the 1 position



R = Me or t-Bu

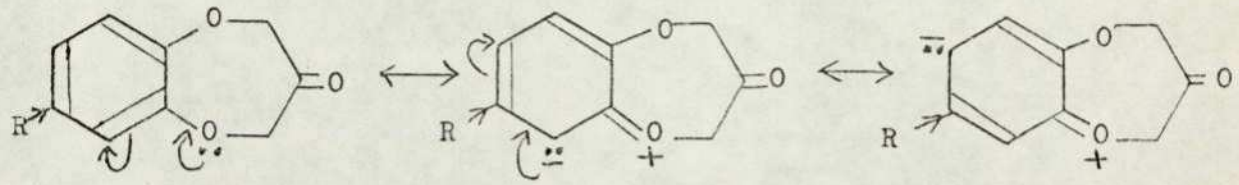
even when a 7-alkyl substituent was present.



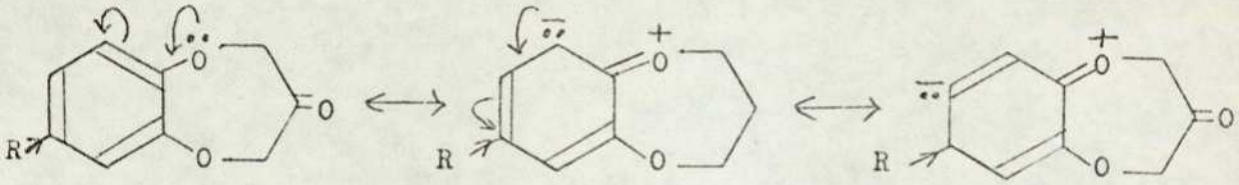
R = Me

Consequently in the 6-methyl- and 6-t-butyl- ketones (Ib and k) the methylene protons at the 2 position would experience a relatively greater degree of deshielding than the protons at position 4 and thus resonate at a lower field. This explanation can also be extended satisfactorily to the 6,7-dimethyl-,6,8-dimethyl-,6,7,8-trimethyl- and 6,8-di-t-butyl- analogues (I d,e,h and m) all of which lack an alkyl substituent at position 9 thereby enabling mesomeric effects to operate from the 1-oxygen. With the 7-methyl- and 7-t-butyl- ketones (Ic and l)

mesomeric effects from the oxygen at position 1 are probably less favourable than those involving the oxygen at position 5 because of competition from the electron donating 7-alkyl substituent.



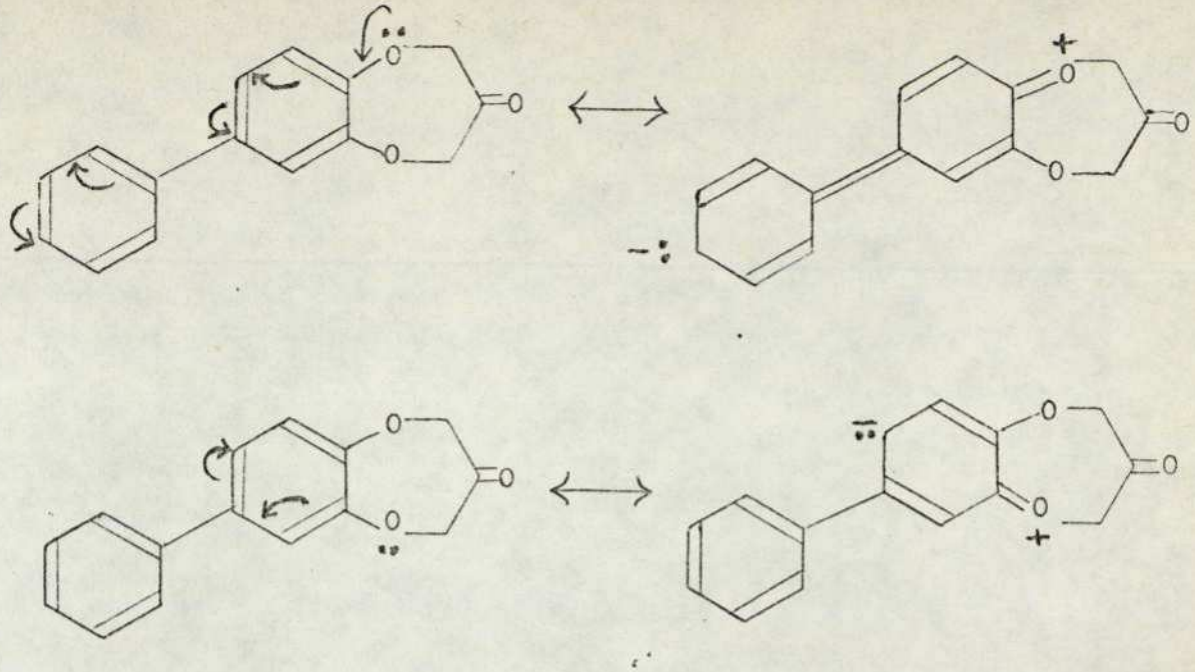
mesomerism favourable from 5-oxygen



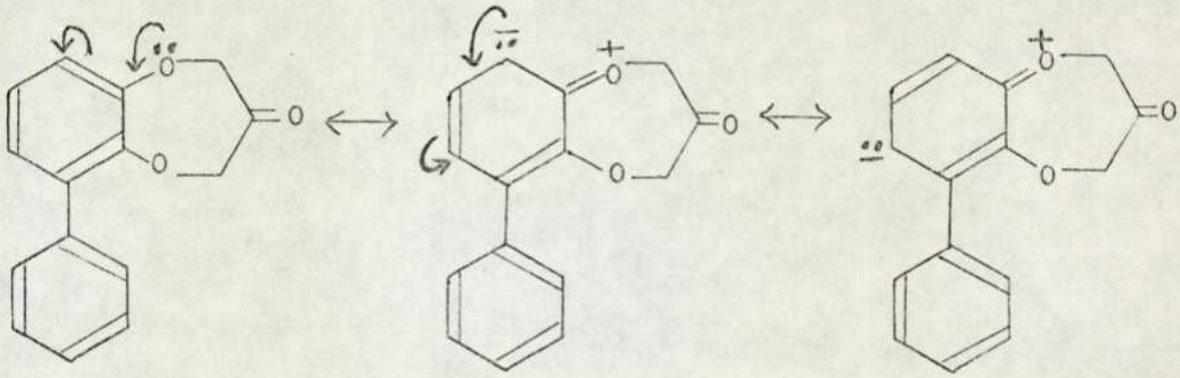
mesomerism less favourable from 1-oxygen

R = Me or t-Bu

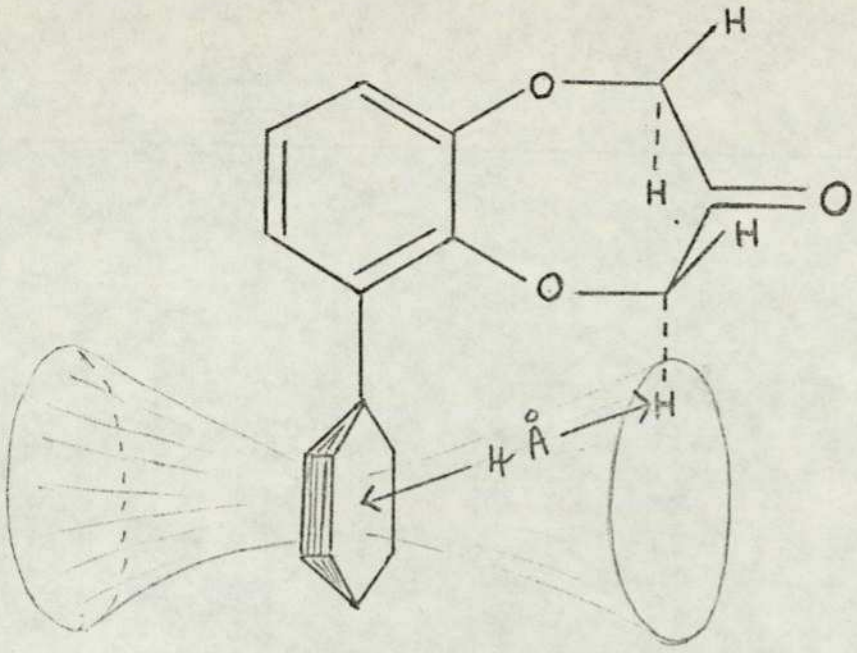
This would cause the protons at position 4 to be relatively more deshielded than those at position 2 and thus resonate at a lower field. In the case of the 7-phenyl- ketone (Io) the protons of both methylene groups had the same chemical shifts whereas a difference of 0.12 τ was observed between the resonances of the corresponding protons in the 6-phenyl- isomer (In); the biggest difference recorded in the series. With the 7-phenyl- compound (Io) mesomeric effects are possible from either ether function with the net



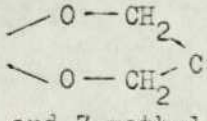
result that both pairs of methylene protons may well suffer a similar degree of deshielding. In contrast mesomerism in the 6-phenyl- ketone (In) would probably be confined to the oxygen at position 1 with the result that



the protons at position 2 would be relatively more deshielded than those located at position 4. An additional steric factor may also operate in this compound. Examination of a Drieding model of this ketone (In) revealed that for non-bonded interactions to be minimal the 6-phenyl group would have to be twisted out of the plane of the other aromatic ring and could then be favourably oriented for the protons at position 4, which are



situated about 4 Å from its centre, to experience the long-range screening effect from this ring[95d] with the result that these nuclei would accordingly resonate at the higher field. This together with the mesomeric effects discussed earlier could possibly explain the enhanced differences in chemical shifts observed for the pairs of methylene protons in this compound. Assignment of the nuclear alkyl proton resonances was also attempted by applying the cumulative effects of the methoxyl[99] and methyl[95a] chemical shift constants as discussed for the substituted 1,3-benzodioxoles (VII a-m) (see 4.2.14). Comparison of the calculated and observed values enables a fairly positive identification of many of the methyl signals to be made even though estimated values tended to be 0.08-0.24 τ higher than the observed figures. Variations were greatest as nuclear substitution increased. Even better agreement between the calculated and observed values was obtained when the chemical shift effects exerted by the



system on the methyl proton resonances of the 6-methyl- and 7-methyl- ketones (I b and c), compared with that of toluene (7.66 τ)[95b], were substituted for the chemical shift increments of the methoxyl groups.

The chemical shift constants arising from the o/m and m/p effects of 'dioxepinone' fusion were +0.15 and +0.12 ppm respectively. The former value together with the appropriate additive effects of further methyl substitution[95a] were used to calculate the resonance positions of the 6 and/or 9- methyl groups whereas the latter figure was used for estimating the chemical shifts of the 7- and/or 8-methyl groups (for an example of a typical calculation see 4.2.14). In view of the particularly small differences that were noted between the observed and calculated values for the methyl resonances of the two trimethyl- ketones (I h and i) signal assignments are considered as tentative. Identification of both t-butyl- groups in the spectrum of the 6,8-di-t-butyl- ketone (Im) was also based on calculations involving chemical shift values of -0.03 ppm and +0.05ppm observed in this work[100] for the effect of o/m and m/p 'dioxepinone' fusion respectively on the alkyl proton signal position of t-butylbenzene (8.67τ)[101] together with the reported[101] increment of +0.02 ppm for an additional m-t-butyl group. Results (see Table 16) indicated that the 6-t-butyl group resonated at the lower field.

TABLE 16

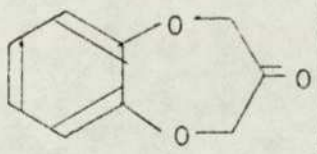
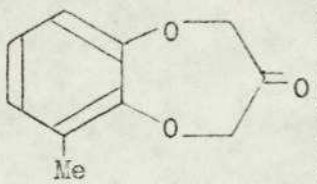
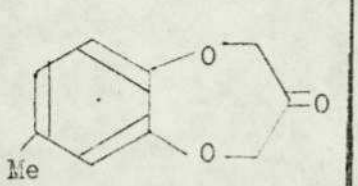
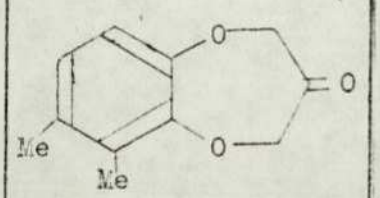
Ketone (I)	60 MHz ^{1}H n.m.r. spectra in CCl_4 [a]		
	aromatic protons	methylene protons	protons of aromatic substituent(s)
 (a)	3.08 τ, 4H, s	5.28 τ, 4H, s	-
 (b)	3.09 - 3.23 τ 3H, s	5.41 τ, s 2-CH_2 [b] 5.45 τ, s 4-CH_2 [b] } 4H	7.81 τ, 3H, s (Calcd. value 7.97 τ)[c]
 (c)	3.08 - 3.42 τ 3H, s	5.43 τ, 2 4-CH_2 [b] 5.45 τ, s 2-CH_2 [b] } 4H	7.78 τ, 3H, s (Calcd. value 7.91 τ)[c]
 (d)	3.38 τ, 2H, s	5.38 τ, s, 2-CH_2 [b] 5.44 τ, s 4-CH_2 [b] } 4H	7.84 τ, s, 7-Me 7.91 τ, s 6-Me } 6H (Calcd. for 6-Me 8.02 τ[c] and 7.86 τ[d] 7-Me: 7.96 τ[c] and 7.83 τ[d]).

TABLE 16 (Cont.)

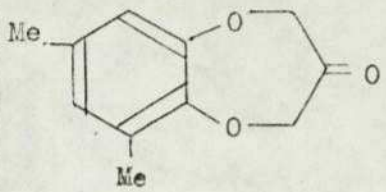
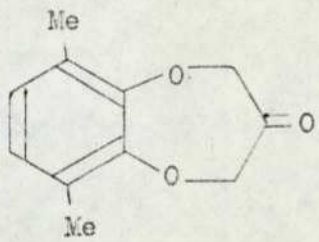
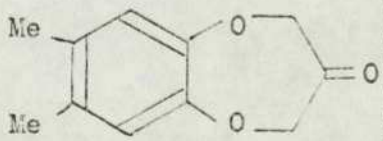
Ketone (I)	60 MHz ^{1}H n.m.r. spectra in CCl_4 [a]		
	aromatic protons	methylene protons	protons of aromatic substituent(s)
 (e)	3.45τ, 2H, s	5.42τ, s, 2-CH_2 [b]; 5.44τ, s, 4-CH_2 [b]; 4H	7.81τ, s, 8-Me; 7.85τ, s, 6-Me; 6H (Calcd. for 8-Me: 7.98τ [c] and 7.85τ [d] 6-Me: 8.04τ [c] and 7.88τ [d]).
 (f)	3.38τ, 2H, s	5.40τ, 4H, s	7.85τ, 6H, s (Calcd. for 6,9-Me_2: 8.01τ [c], 7.85τ [d]).
 (g)	3.35τ, 2H, s	5.47τ, 4H, s	7.88τ, 6H, s (Calcd.for 7,8-Me_2: 7.96τ [c], 7.83τ [d]).

TABLE 16 (Cont.)

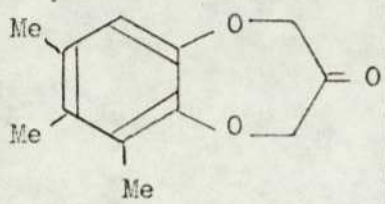
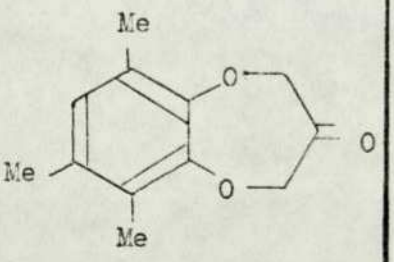
Ketone (I)	60 MHz ^{1}H n.m.r. spectra in CCl_4 [a]		
	aromatic protons	methylene protons	protons of aromatic substituent(s)
 (h)	3.44 τ, 1H, s	5.45 τ, s, 2-CH_2 [b] 4H 5.49 τ, s, 4-CH_2 [b]	7.85 τ, s, 7-Me [b] 7.88 τ, s, 8-Me [b] 7.93 τ, s, 6-Me [b] } 9H (Calcd. for 7-Me 8.01 τ [c], and 7.88 τ [d]; 8-Me: 8.03 τ [c], and 7.90 τ [d]; 6-Me: 8.09 τ [c], and 7.93 τ [d]).
 (i)	3.46 τ, 1H, s	5.39 τ, 4H, s	7.87 τ, s, 6,7-Me_2 [b] } 6H 7.92 τ, s, 9-Me } 3H (Calcd. for 6-Me: 8.06 τ [c] and 7.90 τ [d] 7-Me: 8.03 τ [c] and 7.90 τ [d] 9-Me: 8.08 τ [c] and 7.92 τ [d])

TABLE 16 (Cont.)

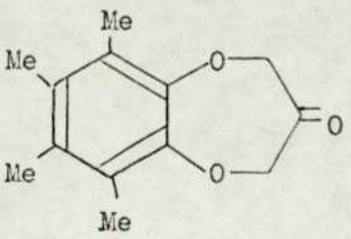
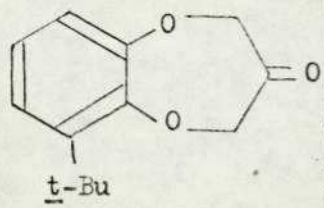
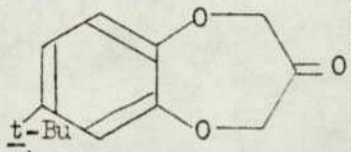
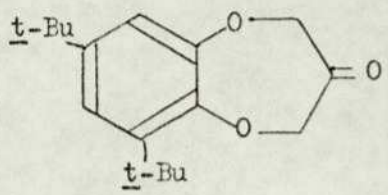
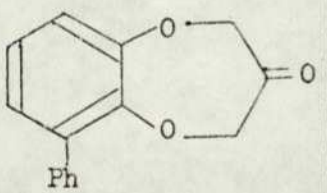
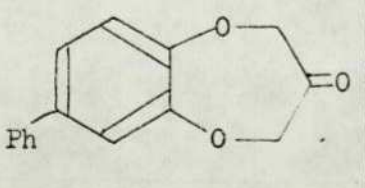
Ketone (I)	60 MHz ^{1}H n.m.r. spectra in CCl_4 [a]		
	aromatic protons	methylene protons	protons of aromatic substituent(s)
 (j)	-	5.44τ, 4H, s	7.89τ, 12H, s (Calcd. for 6,9-Me_2: 8.13τ [c] and 7.97τ [d] 7,8-Me_2: 8.08 [c] and 7.95τ [d]).
 (k)	3.07τ, 3H, m	5.36τ, s, 2-CH_2 [b]; 5.38τ, s, 4-CH_2 [b]; 4H	8.64τ, 9H, s
 (l)	3.1τ, 3H, m	5.37τ, s, 4-CH_2 [b]; 5.39τ, s, 2-CH_2 [b]; 4H	8.72τ, 9H, s

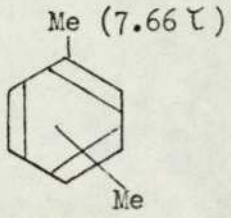
TABLE 16 (Cont.)

Ketone (I)	60 MHz ^{1}H n.m.r. spectra in CCl_4 [a]		
	aromatic protons	methylene protons	protons of aromatic substituent(s)
 (m)	3.12 τ, 2H, q, J meta ~2.4 Hz	5.34 τ, s, 2-CH_2 [b]; 5.38 τ, s, 4-CH_2 [b] } 4H	8.64 τ, s, 6-t-Bu; 8.73 τ, s, 8-t-Bu } 18H (Calcd. for 6-t-Bu: 8.66 [e]; 8-t-Bu: 8.74 [e]).
 (n)	3.11 τ, 3H, s	5.43 τ, 2H, s, 2-CH_2 [b]; 5.55 τ, 2H, s, 4-CH_2 [b]	2.72 τ, 5H, s
 (o)	2.3 - 3.0 τ, 8H, m. All aromatic protons	5.37 τ, 4H, s	-

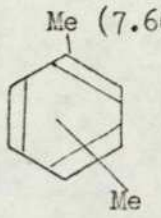
(a) Concentrations of 10-15% w/v were employed.

(b) Tentative assignments only.

(c) Chemical shifts for the methyl protons were calculated by adding the appropriate methyl[95a] and methoxyl[99] chemical shift constants



	δ
o	0.05 ppm
m	0.07 ppm
p	0.04 ppm

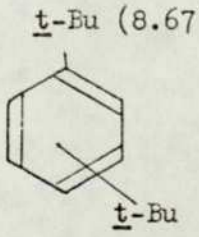


	δ
o	0.2 ppm
m	0.11 ppm
p	0.14 ppm

to the resonance position of 7.66τ reported for the toluene methyl signal.

(d) Chemical shifts for the 6- and 9-methyl protons were readily estimated by adding the requisite methyl chemical shift constants in note (c) to the resonance position of 7.81τ observed for the methyl group of 3-keto-6-methyl-3,4-dihydro-2H-1,5-benzodioxepin (Ib); chemical shifts for the 7- and 8-methyl substituents in ketones (I d, e, g, h, i and j) were similarly calculated from the methyl signal position (7.76τ) of the 7-methyl ketone (Ic).

(e) The chemical shifts of the 6- and 8-t-butyl substituents in this ketone (Im) were calculated by adding the reported[101] chemical shift constant for an additional m-t-butyl group



	δ
o	-0.21 ppm
m	+0.02 ppm
p	+0.02 ppm

to the signal positions of 8.64 and 8.72τ observed[100] for the 6- and 7-t-butyl ketones (I k and l) respectively.

4.8 Preparations of some 3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepins (XV a-l)

The secondary alcohols described below were prepared by the reduction of the appropriate 3-keto compounds with lithium aluminium hydride using the conditions of Nystrom and Brown[41]. They were required for subsequent ultra-violet studies the spectral details of which are discussed in Chapter 5. The presence of a hydroxyl group was confirmed by infra-red spectroscopy and additional confirmatory structural evidence was obtained from their nuclear magnetic resonance spectra (Table 17). Spectral assignments for the alkyl substituents were based on chemical shifts calculated as described in footnotes (b), (c) and (d) of Table 17. For convenience the ultra-violet spectral data have been recorded in Chapter 5, Table 33.

4.8.1 3-Hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (XV a)

The preparation of this compound together with its infra-red, ultra-violet and nuclear magnetic resonance spectral results were described earlier (3.2.1). The n.m.r. spectral data have also been included in Table 17.

The following analogues were similarly prepared:

4.8.2 3-Hydroxy-6-methyl-3,4-dihydro-2H-1,5-benzodioxepin (XVb)

Scale: 0.00625 mole. Yield 89%, m.p. 50-51° [colourless plates from light petroleum (b.p. 40-60°)]. (Found: 66.6; H, 6.6. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.7%). ν max (Nujol) 3400 (OH) cm^{-1}. See Table 17 for the n.m.r. results.

4.8.3 3-Hydroxy-7-methyl-3,4-dihydro-2H-1,5-benzodioxepin (XVc)

Scale: 0.005 mole. Yield 94.5%, m.p. 77-78° [colourless needles from light petroleum (b.p. 60-80°)] . (Found: C, 66.7; H, 6.75. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.7%). ν max (Nujol) 3350 (OH) cm^{-1}. N.m.r. results are shown in Table 17.

4.8.4 6,7-Dimethyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (XVd)

Scale: 0.002 mole. Yield 97%, m.p. 66-66.5° [colourless prisms from light petroleum (b.p. 60-80°)] . (Found: C, 68.1; H, 7.4. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.3%). ν max (Nujol) 3300 (OH) cm^{-1}. The n.m.r. results are given in Table 17.

4.8.5 6,8-Dimethyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (XVe)

Scale: 0.002 mole. Yield 98%, m.p. 72-72.5° [colourless prisms from light petroleum (b.p. 60-80°)] . (Found: C, 68.2; H, 7.3. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.3%). ν max (Nujol) 3300 (OH) cm^{-1}. Details of the n.m.r. spectrum are in Table 17.

4.8.6 6,9-Dimethyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (XV f)

Scale: 0.002 mole. Yield 93%, m.p. 68-69° [colourless prisms from light petroleum (b.p. 60-80°)] . (Found: C, 68.1; H, 7.3. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.3%). ν max (Nujol) 3500 (OH) cm^{-1}. See Table 17 for the n.m.r. results.

4.8.7 7,8-Dimethyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (XVg)

Scale: 0.02 mole. Yield 99%, m.p. 87.5 - 88.5° [colourless needles from light petroleum (b.p. 60-80°)] . (Found: C, 67.4; H, 7.3%). ν max (Nujol) 3300 (OH) cm^{-1}. N.m.r. results are recorded in Table 17.

4.8.8 3-Hydroxy-6,7,8,9-tetramethyl-3,4-dihydro-2H-1,5-benzodioxepin (XVh)

Scale: 0.001 mole. Yield 94.5%, m.p. 99-100° [colourless prisms from light petroleum (b.p. 60-80°)]. (Found: C, 70.0; H, 8.4. $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.2%). νmax (Nujol) 3450 (OH)cm^{-1}. Details of the n.m.r. spectrum are to be found in Table 17.

4.8.9 6-t-Butyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (XVi)

Scale: 0.0015 mole. An almost quantitative yield of this compound was obtained, m.p. 73-74° [colourless plates from light petroleum (b.p. 60-80°)]. (Found: C, 70.1; H, 8.3. $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.2%). νmax (Nujol) 3500 (OH) cm^{-1}. See Table 17 for the n.m.r. results.

4.8.10 7-t-Butyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (XVj)

Scale: 0.002 mole. Yield 97%, m.p. 73.5 - 74.5° [colourless needles from light petroleum (b.p. 60-80°)]. (Found: C, 70.1; H, 8.1. $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.2%). ν max (Nujol) 3450 (OH) cm^{-1}. See Table 17 for the n.m.r. results.

4.8.11 6,8-Di-t-butyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (XVk)

Scale: 0.002 mole. Yield 97.5%, m.p. 136-137° [colourless needles from light petroleum (b.p. 60-80°)]. (Found: C, 73.5; H, 9.4. $C_{17}H_{26}O_3$ requires C, 73.3; H, 9.4%). ν max (Nujol) 3500 (OH) cm^{-1}. The n.m.r. results are given in Table 17.

4.8.12 3-Hydroxy-7-phenyl-3,4-dihydro-2H-1,5-benzodioxepin (XVl)

Scale: 0.002 mole. Yield 89%, m.p. 82-83° [colourless prismatic needles from light petroleum (b.p. 80-100°)]. (Found: C, 74.4; H, 5.9. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%). νmax (Nujol) 3350 (OH) cm^{-1}. For the n.m.r. results see Table 17.

4.8.13 Some nuclear magnetic resonance spectral data

TABLE 17

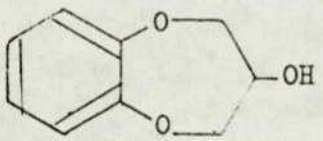
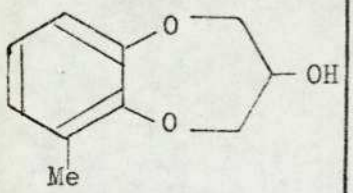
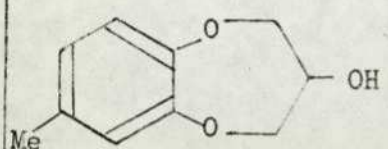
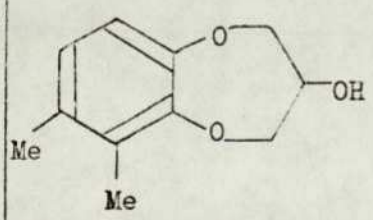
Compound (XV)	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$ [a]			
	aromatic protons	-O-CH_2 \ CH- -O-CH_2 /	Hydroxyl proton	Protons of aromatic substituents
 (a)	3.03τ, 4H, s	5.82τ, 5H, m	6.9τ, 1H, bs	–
 (b)	3.17τ, 3H, s	5.83τ, 5H, s	6.87 and 7.0τ, 1H d	7.76τ, 3H, s. (Calcd. value 7.97τ)[b]
 (c)	3.2τ, 3H, m	5.88τ, 5H, m	7.06τ, 1H, s	7.76τ, 3H, s. (Calcd. value 7.91τ)[b]
 (d)	3.26τ, 2H, s	5.85τ, 5H, m	7.18τ, 1H, s	7.82τ, s, 7-Me; 7.85τ, s, 6-Me } 6H (Calcd. for 6-Me: 8.02τ[b], and 7.81τ[c], 7-Me: 7.96τ[b] and 7.81τ[c])

TABLE 17 (Cont.)

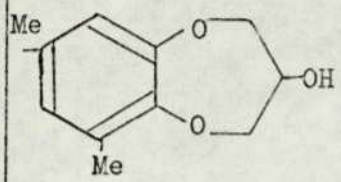
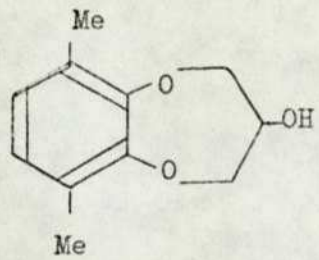
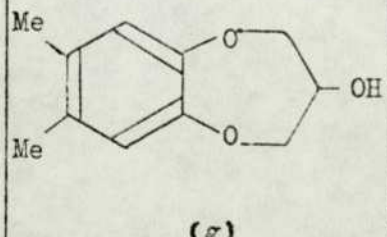
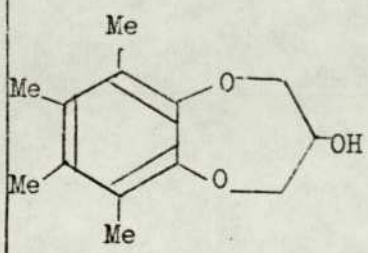
Compound (XV)	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$ [a]			
	aromatic protons	-O-CH_2-CH-O-CH_2-	Hydroxyl proton	Protons of aromatic substituent(s)
 (e)	3.36τ, 2H, s	5.9τ, 5H, m	7.81τ, 1H, bs	7.81τ, 6H, s (Calcd. for 6-Me: 8.04τ [b], and 7.83τ [c] 8-Me: 7.98τ [b], and 7.83τ [c])
 (f)	3.28τ, s, 2H	5.85τ, 5H, m	6.75τ. 1H, s	7.81τ, 6H, s (Calcd. for 6,9-Me_2: 8.01τ [b] 7.80τ [c]).
 (g)	3.27τ, 2H, s	5.94τ, 5H, s	7.1τ, 1H, bs	7.88τ, 6H, s (Calcd. for 7,8-Me_2: 7.96τ [b], 7.81τ [c]).
 (h)	—	5.85τ, 5H, m	6.9τ, 1H, s	7.84τ, 12H, poorly resolved doublet (Calcd. for 6,9-Me_2: 8.13τ [b], 7.92τ [c] 7,8-Me_2: 8.08τ [b], 7.93τ [c]).

TABLE 17 (Cont.)

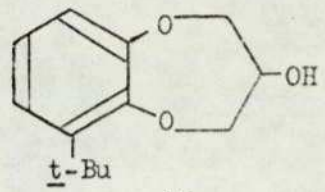
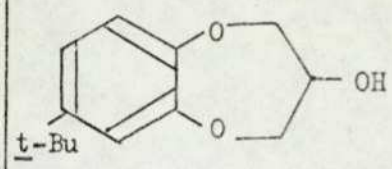
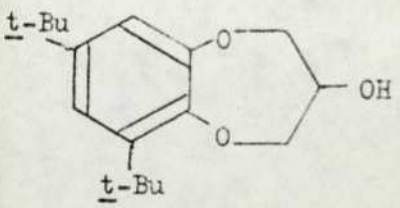
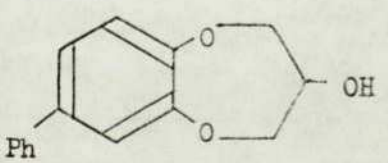
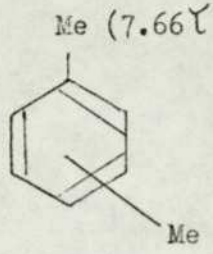
Compound (XV)	60 MHz ^{1}H n.m.r. spectra in $CDCl_3$ [a]			
	Aromatic protons	-O-CH_2 \ CH- / -O-CH_2	Hydroxyl protons	Protons of aromatic substituent(s)
 (i)	3.1τ, 3H, m	5.85τ, 5H, m	7.10τ, 1H, s	8.64τ, 9H, s
 (j)	3.0τ, 3H, m	5.84τ, 5H, m	7.05τ, 1H, bs	8.72τ, 9H, s
 (k)	2.95τ, 2H, q J_{meta} ~1.8Hz	5.9τ, 5H, m	7.2τ, 1H, bs	8.57τ, 9H, s 6-t-Bu 8.67τ, 9H, s 8-t-Bu (Calcd. for 6-t-Bu: 8.66τ[d] 8-t-Bu: 8.74τ[d]).
 (l)	2.35-3.05τ, 8H, m All aromatic protons	5.77τ, 5H, m	7.05τ, 1H, bs	-

TABLE 17 (Cont.)

(a) Concentrations of 10-15% w/v were used.

(b) The chemical shifts were calculated as described in Table 16, footnote (c).

(c) Chemical shifts for the 6/9-methyl and 7/8-methyl groups were obtained by adding the pertinent methyl chemical shift constants[95a]



	δ
o	0.05 ppm
m	0.07 ppm
p	0.04 ppm

to the methyl resonance position of 7.76τ observed in both the 6- and 7-methyl alcohols (XV b and c).

(d) The chemical shifts of the 6- and 8-t-butyl substituents in this alcohol (XV k) were estimated by adding the reported[101] chemical shift constant for an additional m-t-butyl group (+ 0.02 ppm) to the resonance positions of 8.64 and 8.72τ found for the 6- and 7-t-butyl compounds (XV i and j) respectively.

CHAPTER 5. ULTRA-VIOLET SPECTRAL DATA AND CONFORMATIONAL STUDIES ON THE (AR)-METHYL-o-PHENYLENEDIOXYDIACETONITRILES AND SOME (AR)-ALKYL-3-SUBSTITUTED-3,4-DIHYDRO-2H-1,5-BENZODIOXEPINS.

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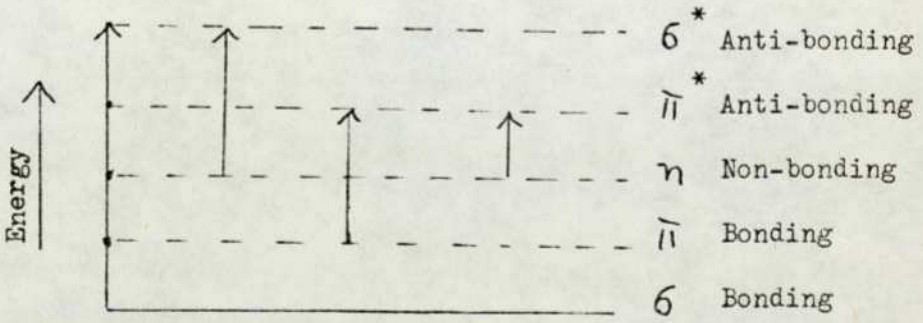
CHAPTER 5

Ultra-violet spectral data and conformational studies on the (ar)-methyl-o-phenylenedioxydiacetonitriles and some (ar)-alkyl-3-substituted-3,4-dihydro-2H-1,5-benzodioxepins.

5.1 Introduction

The ultra-violet absorption spectrum of the unsubstituted benzene ring shows two intense absorption bands at about 180 nm ($\leq$ 47,000) and 200 nm (Σ 7000) and a third weak absorption band near 260 nm ($\leq$ 200). All three bands are associated with the π electron system and arise from the promotion of an electron from a bonding π orbital to an antibonding π^* orbital and can in principle occur in any molecule containing a π electron system. The relative positions of the energy levels corresponding to the different types of molecular orbitals in organic molecules are shown in Figure 9.

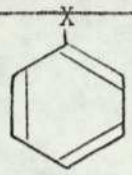
Figure 9



Relative energies of molecular orbitals and possible transitions between the orbitals.

Introduction of halogen or alkyl groups into the aromatic nucleus causes a slight shift of the 260 nm band to longer wavelength (bathochromic or red shift) with a small increase in the extinction coefficient.

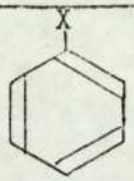
Table 18 [120b]

	Primary band $\lambda_{max}^{nm}(\varepsilon)$	Secondary band $\lambda_{max}^{nm}(\varepsilon)$	Bathochromic shift (λ) relative to benzene	
			primary band	secondary band
X = H	204 (7400)	254 (200)	0	0
Me	207 (7000)	261 (225)	3	7
Et*	208 (7800)	260 (220)	4	6
I	207 (7000)	257 (700)	3	3
Cl	210 (7400)	264 (190)	6	10
Br	210 (7900)	261 (190)	6	7

* For ethanol solution. All other data in this Table are for solutions in water containing a little methanol.

In contrast substitution by groups carrying non-bonding or π electrons such as -OH, -O-Alk, $-NH_2$ or -CHO, -COR causes a very pronounced bathochromic shift and a greatly enhanced absorption.

TABLE 19 [120b]

	Primary band λ_{max}^{nm} (ε)	Secondary band λ_{max}^{nm} (ε)	Bathochromic shift (λ) relative to benzene	
			primary band	secondary band
X = H	204 (7400)	254 (200)	0	0
OH	211 (6200)	270 (1450)	7	16
OMe	217 (6400)	269 (1420)	13	15
NH_2	230 (8600)	280 (1430)	26	26
CHO	250 (11400)	280* (1100)	46	26
COR	246 (9800)	280* (1100)	42	26

* For ethanol solutions. All other data in this table are for solutions in water containing a little methanol.

In 1954 Braude and co-workers developed a theory of electronic spectral effects arising from changes in steric conformation of conjugated systems, X-Y, about a single bond. These can give rise to two types of spectral effects:-

Type (1), changes in absorption intensity with little or no wavelength shift.

Type (2), changes in absorption intensity accompanied by wavelength shifts.

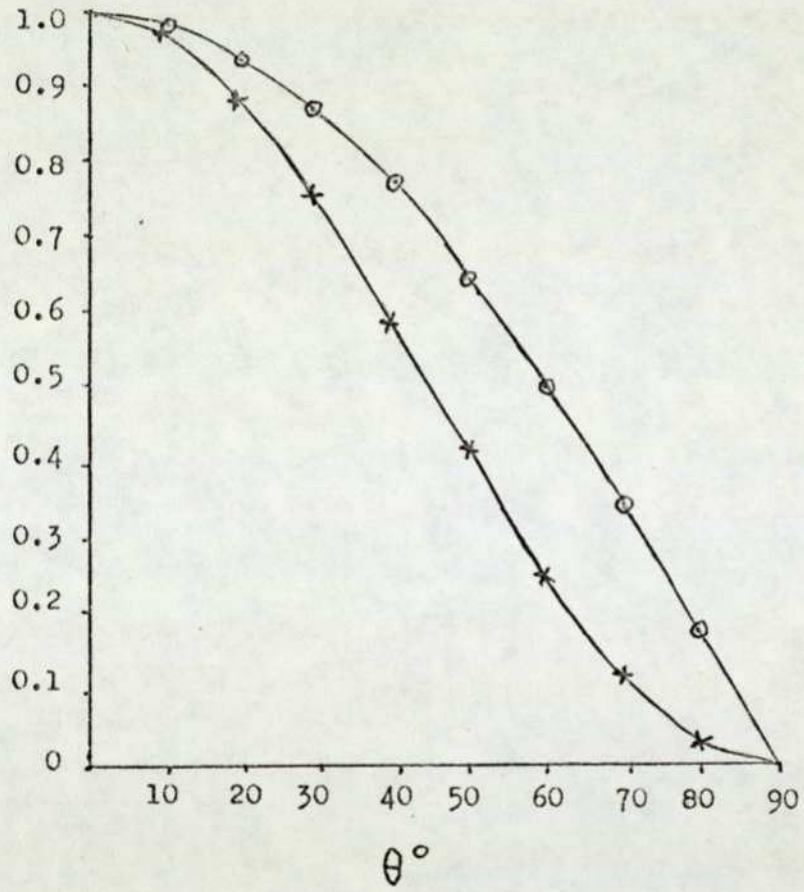
Type (2) effects result from transitions between non-planar ground and excited states and are not relevant to the following discussion.

Type (1) effects are produced by transitions between non-planar ground states and uniplanar, or near-planar, excited states and the absorption intensity (ε) of a conjugated chromophore is at its maximum when the substituent group is co-planar with the aromatic ring (i.e., the mean interplanar angle or angle of twist, Θ, is 0°) and is negligible when the angular distortion, θ, is 90°. It was suggested by Braude and co-workers[122] that Θ could be calculated from the empirical relationship $\cos\Theta = \varepsilon/\varepsilon_{o}$, where ε was the extinction coefficient of the compound in question and the extinction coefficient of a suitable reference compound which was assumed to be planar (i.e. $\Theta = 0^{\circ}$). $\cos\Theta$ was chosen as the simplest function having a maximum value of 1 when $\Theta = 0^{\circ}$ and a minimum value of zero when $\Theta = 90^{\circ}$ (see Figure 10); it was pointed out that the $\cos^{2}\Theta = \varepsilon/\varepsilon_{o}$ expression would also satisfy these requirements but would lead to values for Θ some 10-15° lower in the intermediate range $\Theta \sim$ 40-60° (see Fig. 10). This latter relationship was subsequently preferred by Braude and Sondheimer[123] since it describes the behaviour of a function of Θ which decreases from unity to zero in going from 0° to 90° but which again attains unity on further increase to 180°, assuming that the substituent group was rotated continuously about the bond joining it to the aromatic ring. Thus the $\cos^{2}\Theta$ function is symmetrical about 90° which it must be if the twist occurs about a bond lying on the rotational axis of the molecule.

The two equations were used by Braude and co-workers[122,123] to calculate the conformations of some substituted benzaldehydes and acetophenones and agreement with Θ calculated from dipole moment data and molecular models was found to be satisfactory. The $\cos^{2}\Theta$ relationship has been applied to a variety of aromatic compounds[123-132] and in slightly

Figure 10

Plot of θ against $\cos\theta$ and $\cos^2\theta$



⊙ = $\cos\theta$

\+ = $\cos^2\theta$

modified form to cyclic monophenolic ethers[126-132] but in few of the references cited were the calculated values of Θ compared with evaluated by other methods; generally the calculated values were correlated qualitatively with other factors (e.g. size of ortho-substituent[129]) to demonstrate a trend. In certain cases, particularly where Θ normally has one or two well-defined values, measurements on molecular models showed reasonable agreement with the calculated values[132].

Both the Cos Θ and Cos^2 Θ relationships were derived empirically and in order to determine which is the more generally applicable Archer[18] compared the calculated values of Θ from each expression with those determined independently by other methods. Unfortunately, at that time no suitable compounds had been examined by X-ray crystallography which would have given a direct measurement of Θ in the solid state, however values of Θ for a variety of compounds in solution were determined by Suzuki[133] using molecular orbital calculations, and values of Θ were available for phenylcyclohexene derivatives, calculated by Garbisch[134,135] from the chemical shifts experienced by an olefinic proton in the vicinity of a benzene ring.

The extinction coefficients of some of the compounds examined by Suzuki[133] and Garbisch[134,135] were used to calculate values of Θ by means of both the Cos Θ and Cos^2 Θ relationships and the results were compared with those obtained by molecular orbital calculations or proton chemical shift data (see Table 20 and Figs. 11 and 12). From these graphs it was evident that values of Θ derived from the Cos $\Theta = \varepsilon/\varepsilon_o$ relationship were more consistent with values determined by other methods except when Θ is small, when the Cos^2 $\Theta = \varepsilon/\varepsilon_o$ expression gives a better correlation. It is also evident from the curves that Θ and ε are related by a function which tends to Cos $\Theta = \varepsilon/\varepsilon_o$ when

TABLE 20

Comparison of the angles of twist (Θ), calculated from the Cos and $Cos^2\ \Theta$ expressions, with values found by molecular orbital calculations[133] and proton chemical shift measurements[134,135].

Compound		ε_{max} (e)	Θ (in degrees)		
			Calcd. by MO or PMR	from Cos Θ	from $Cos^2\ \Theta$
Fluorene	(a)	19,000			
Diphenyl (in solution)	(b)	16,600	23,25	28	20
Diphenyl (vapour at 170°)	"	12,050	43,45	49	36
2-Methyldiphenyl	"	10,500	58,59	57	42
2-Ethyldiphenyl	"	10,500	61,62	57	42
2-n-Propyldiphenyl	"	10,000	"	58	43
2-iso-Propyldiphenyl	"	11,000	"	55	40
2-n-Butyldiphenyl	"	10,500	"	57	42
2,2'-Dimethyldiphenyl	"	6,800*	70-72	70	54
2,2'-Diethyldiphenyl	"	6,800*	"	71	56
Styrene	(a)	14,600			
α-Methylstyrene	(b)	11,400	33	38	28
α-Ethylstyrene	(b)	10,100	38	46	34
o-Methylstyrene	(b)	12,600(d)	31	30	22
α-n-Propylstyrene	(b)	9,390	40	50	37
1-Phenylcyclohexene	(c)	12,300	20	33	23
6-Methyl-1-phenyl-cyclohexene	"	11,200	43	40	29
6-iso-Propyl-1-phenyl-cyclohexene	"	10,500	43	40	32
6-t-Butyl-1-phenyl-cyclohexene	"	10,000	48	47	34
o-Methyl-1-phenyl-cyclohexene	"	5,630*	69	67	52
o,o'-Dimethyl-1-phenylcyclohexene	"	No A band	90	90	90
6-Methyl-1,6-diphenylcyclohexene	"	9,780	48	48	35
trans-Stilbene	(a)	27,900			
α-Methylstilbene	(b)	21,000	35	41	29
α,α'-Dimethylstilbene	"	12,270	58	64	48

Cont.

TABLE 20 (Cont.)

Compound	ε_{max} [e]	θ (in degrees)		
		Calcd. by MO or PMR	from Cos	from Cos^2
α-Methyl-α'-ethylstilbene (b)	11,950	61	65	49
α,α'-Diethylstilbene "	11,090	63	67	51
p,p-Diphenylstilbene (a)	50,000			
α,α'-Dimethyl-p-p'-diphenylstilbene (b)	29,000	57	55	40

(a) Reference compound assumed to be planar.

(b) θ for these compounds was obtained by molecular orbital calculations[133].

(c) θ for these compounds was obtained from proton chemical shift data[134,135]

(d) Ref. 125

(e) The values of ε max were taken from reference 133.

* Inflexion.

FIGURE 11

Correlation between calculated values of Θ with those estimated from Cos Θ expression (From Table 20).

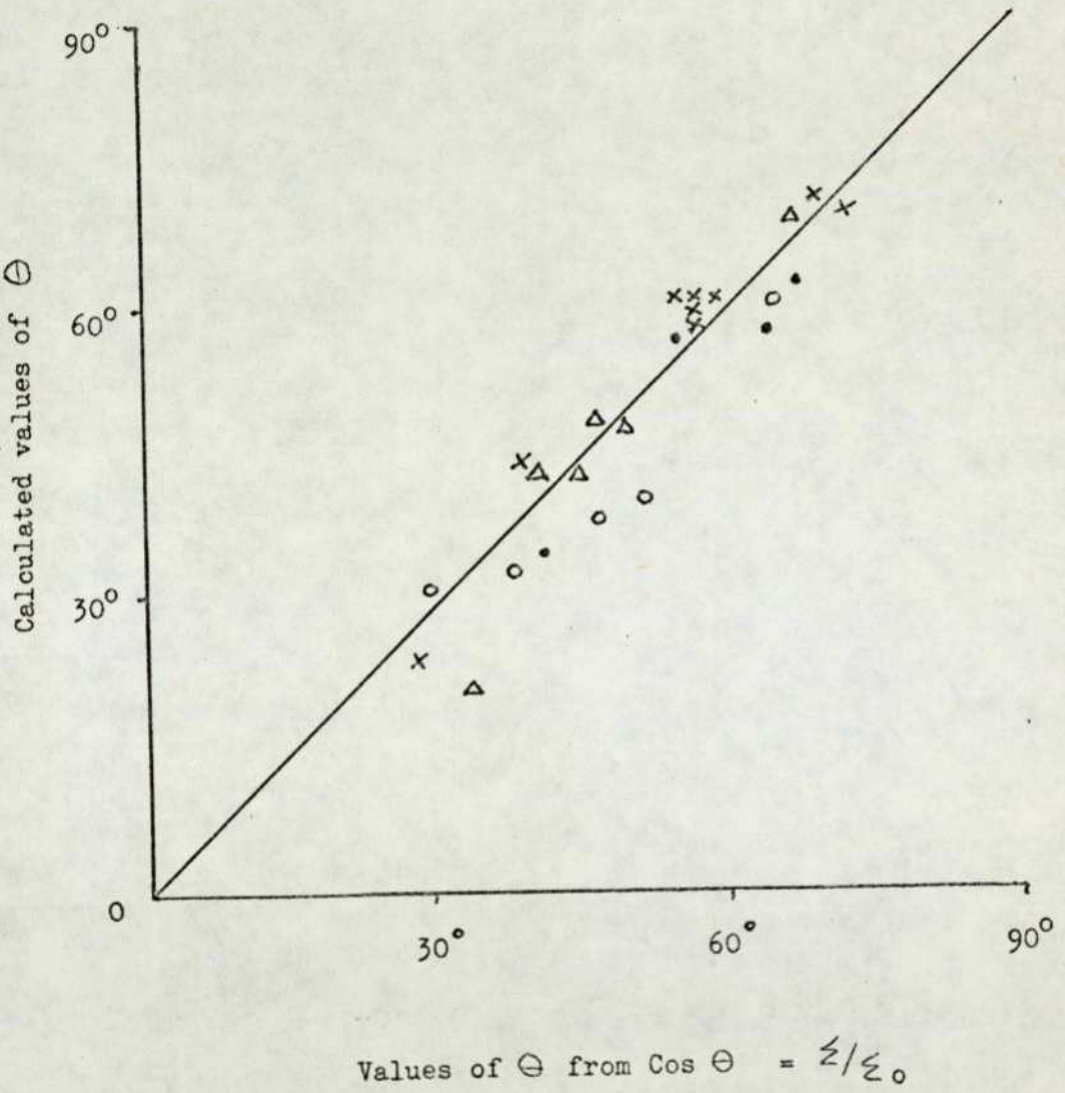
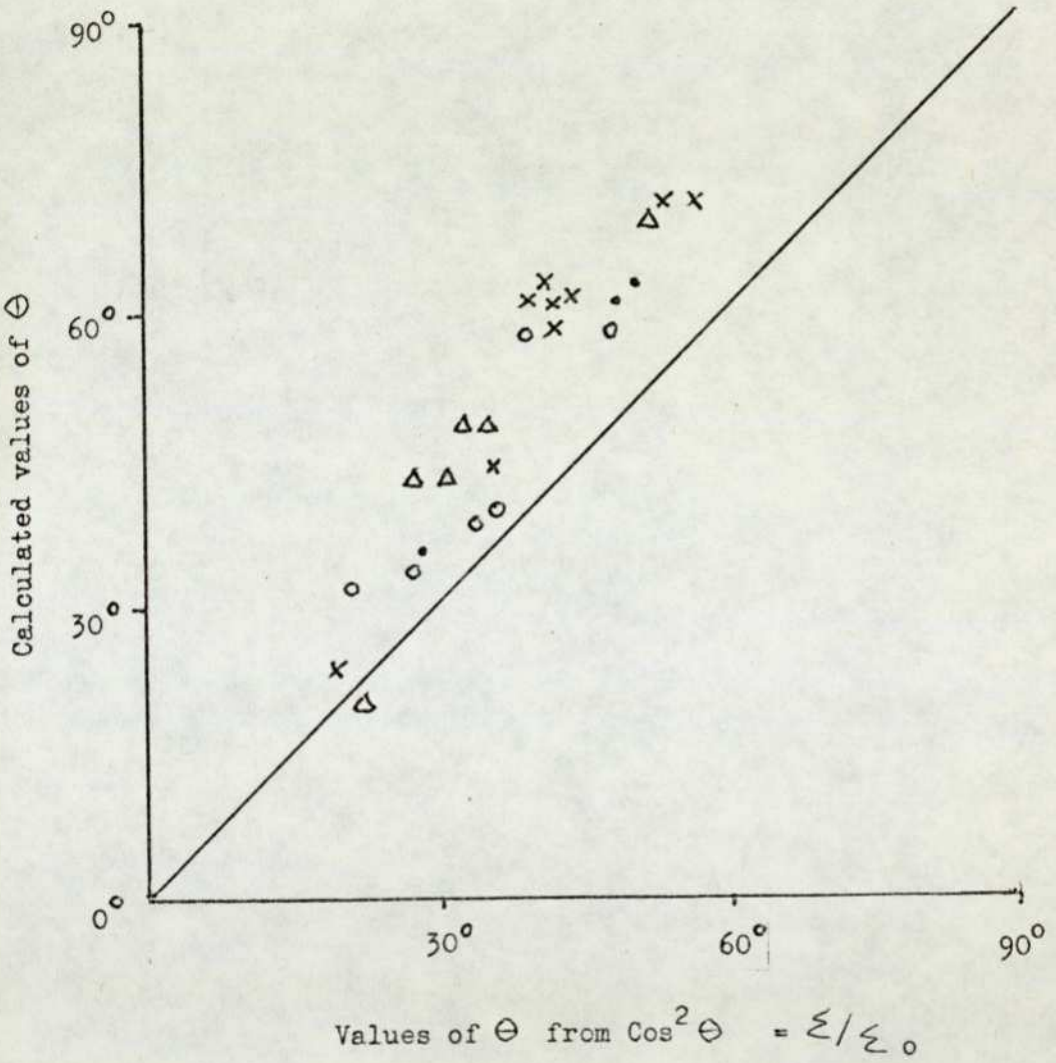


FIGURE 12

Correlation between calculated values of Θ with those estimated from the $Cos^2 \Theta$ expression (from Table 20).



Θ is large ($\varepsilon / \varepsilon_o$ is small) and tends to $\cos^2\Theta = \varepsilon/\varepsilon_o$ when is small ($\varepsilon/\varepsilon_o$ tends to unity). The functions themselves show the greatest divergence when Θ is 45^o (see Figure 10). McRae and Goodman[136], using molecular orbital calculations, showed that the intensity of a transition causing absorption of ultra-violet light varied as $\cos^2\Theta$ for small values of Θ but that for larger angles of twist there would be marked deviations from the $\cos^2\Theta$ values. Investigations by Frolen and Goodman[137] on the ultra-violet absorption spectra of substituted anisoles led to similar conclusions. These observations supported the trends indicated in Figs. 11 and 12.

Two assumptions are implicit in the use of either equation:-

(i) It is essential that the extinction coefficient for a planar reference compound (ε_o) can be determined.

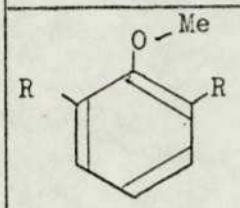
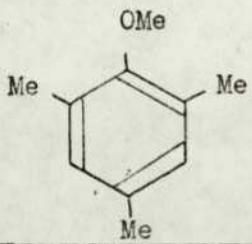
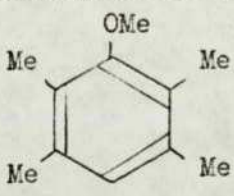
(ii) It is assumed that when Θ is 90^o the extinction coefficient of the compound at the wavelength under examination is zero. This may not always be strictly true as may be seen from the small extinction coefficients observed for some di-<u>ortho</u>-substituted anisoles in the 270 nm region (see Table 21). This small absorption has been attributed to the contribution by the alkyl groups and to correct for this factor Clarke and Williams[132] proposed that the equation

$$\cos^2\Theta = \frac{(\varepsilon \text{ corr} - \varepsilon \text{ min})}{(\varepsilon_o - \varepsilon \text{ min})}$$

should be used where ε corr is the extinction coefficient for the chromophore corrected for the 'non-steric' effects of each substituent and ε min is the residual absorption when Θ is 90^o.

TABLE 21

Molar extinction coefficients of some 2,6-disubstituted anisoles.

Compound	Solvent	λ (nm) ε	Reference
			
R = Me	cyclohexane	268 (389) 273 (347)	138
R = Et	"	267 (417) 273 (380)	138
R = i-Pr	"	265 (427) 273 (389)	138
R = t-Bu	"	275 (324)	138
	ethanol	268 (575)* 277 (501)*	139
	ethanol	270.5 (300) 278 (300)	139

* A para-methyl substituent in anisoles has been reported[132] to produce a non-steric increase in the absorption of 260.

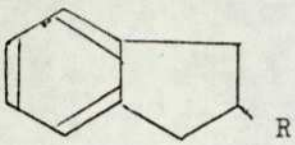
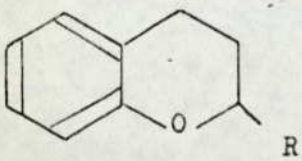
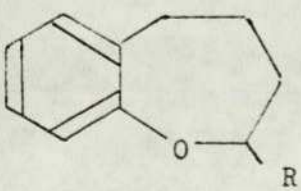
Studies by Frolen and Goodman showed that for a series of anisoles the intensity of the ultra-violet absorption near 260 nm is due to a $\pi \rightarrow \pi^*$ transition and is dependent upon the conformation about the phenyl-O bond. The intensity of this chromophore was subsequently used by Clarke and Williams[132] to determine the conformation of an number of heterocyclic analogues of choline phenyl ether in an attempt to establish a relationship between conformation and biological activity in a series of choline aryl ethers of pharmacological interest. Their results indicated that the interplanar angle, Θ, for the heterocyclic compounds using the modified $\text{Cos}^2\Theta$ equation agreed favourably with values of Θ measured from photographs of Dreiding models (see Table 22), whereas, in fact, the $\text{Cos}\ \Theta$ expression gives a better correlation with the measured angle for the homochroman series.

It was evident from published data that measurement of the intensity of the ultra-violet induced Ph-O $\pi \rightarrow \pi^*$ transition had been applied mainly to the conformational analysis of mono-phenolic ethers[132] and only to a limited extent in deducing the conformations of cyclic monophenolic ethers[126,132].

In an earlier investigation in this laboratory, Archer[18] undertook the preparation of a variety of cyclic catecholic ethers since it was considered that examination of the intensity of the Ph-O chromophore should in principle allow the conformation of such compounds to be determined and compared with values measured on Dreiding models. To determine Θ for this series of compounds it was necessary to obtain a value for ε_o from a suitable planar reference compound. For this it was assumed that the five-membered rings (n = 2 for the cyclic monoethers and n = 1 for the cyclic diethers) in the compounds in Table 23 were co-planar with the aromatic ring and an average value of 3100 l mol^{-1} cm^{-1} was derived for ε_o.

TABLE 22

Angles of twist for some cyclic ethers calculated from ultra-violet spectral data[132] by the $\text{Cos}^2\,\Theta = \varepsilon/\varepsilon_o$ relationship and by the $\text{Cos}\,\Theta = \varepsilon/\varepsilon_o$ expression.

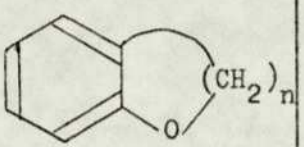
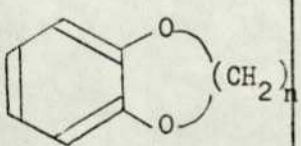
Compound	calculated from:		Θ measured from Dreiding model
	$\text{Cos}^2\,\Theta$	$\text{Cos}\,\Theta$	
			
R = H	0	0	0
R = $-CO_2H$	0	0	0
R = $-CH_2NMe_3Br$	0	0	0
			
R = H	34	46.5	37
R = $-CO_2H$	35	47.5	37
R = $-CH_2NMe_3Br$	34	46.5	37
			
R = H	62	77	73
R = $-CO_2H$	62.5	77.5	73
R = $-CH_2NMe_3Br$	63.5	78.5	73

Values of Θ are expressed in degrees.

TABLE 23

Calculated values of θ compared with values of θ measured on Dreiding models.

(Values of θ are expressed in degrees).

Compound	ε_{max}[a]	θ measured on model	θ calculated from:			
			Cos θ		Cos^2 θ	
			(c)	(d)	(c)	(d)
						
n = 2	3090	0	0	0	0	0
3	2125	37	46.8	49.6	34.6	36.4
4	678	73	77.4	82.8	62.2	69.3
						
n = 1	3122	0	0	0	0	0
2	2340	20	41	43.5	29.7	31.5
3	1360	64(73)[e]	64	68.2	48.5	52.4
4	1660[b]	60	57.6	61.3	43.0	46.6
5	1322	65	64.8	69.0	49.2	53.2

(a) All ε max values in hexane from reference 140

(b) Determined in hexane from reference 18.

(c) Calculated taking εmin as zero.

(d) Calculated taking εmin as 330.

(e) Revised value.

The use of ε max instead of the integrated band area A, where $A = \int_a^b \varepsilon \, dv$ (ν is the wavenumber in cm^{-1} and a and b define the total band width), as an indication of the oscillator strength of the transitions has been considered a justifiable assumption[123,132] providing the bands being compared are of substantially the same electronic origin and the band widths at half maximum height are constant for the compounds under examination. The band widths at half-peak height for the compounds examined by Archer were in the range 2710-3280 cm^{-1}, similar to those found previously for anisole derivatives (2500-2961cm^{-1})[132].

The use of ultra-violet absorption spectra for the estimation of angles of twist has been criticised[141] on the grounds that the separation of the appropriate band from other bands is not always possible. However, it was found that the band under consideration (λ max ca 270nm) was in fact separated from the next absorption band (λ max ca 200 nm) by a well defined minimum in the 245 nm region.

From the results compiled[18] in Table 23 from published data[140] it is apparent that the Cos θ equation showed a better correlation with the calculated values of θ and the angles measured from Dreiding models in seven or higher membered rings whereas the $Cos^2 \theta$ equation gave a better correlation for the six-membered ring; this applied equally to values of θ calculated from both the corrected and uncorrected values of ε and ε_o. The effect of correction was to increase all the angles by about 3-5°, depending upon the value of ε, but the measured values of θ remained essentially unchanged.

The majority of the compounds prepared and examined by Archer[18] were derivatives of 3,4-dihydro-2H-1,5-benzodioxepin (VIII a) containing one or more substitutuents in the heterocyclic ring which would be expected to produce conformational changes in the heterocyclic ring and thus affect

the value of the extinction coefficients of these compounds.

Dreiding molecular models of 3,4-dihydro-2H-1,5-benzodioxepin (VIII a) show that the heterocyclic ring can exist in two well-defined symmetrical, strainless conformations, (boat and chair) in each of which the protons of the heterocyclic ring are fully staggered (Figs. 13 and 14). A third conformation (skew) can be made in which the benzodioxepin ring protons are slightly less staggered (Fig. 15) but in which some degree of strain is clearly evident in the model. The three models correspond to the 'chair', 'boat' and 'twist-boat' conformations of the unsaturated ring systems studied by Friebolin and his co-workers[142]. The 'boat' conformation was, by analogy with the carbocyclic compound, benzocycloheptane, considered to be of minor importance owing to steric factors[142]. Models of the 'chair' and 'skew' conformations were photographed from a point in the plane of the benzene ring on the axis of the phenyl-O ring. The angles thus obtained by Archer[18] for the symmetrical 'skew' and 'chair' forms were 44 and 64° respectively and were essentially unchanged when the tetrahedral angle at C(3) was increased from 109-120° ($sp^3 \longrightarrow sp^2$) by the introduction of C=O, C=N or C=C (see Figs. 16 and 17). It is considered pertinent at this stage to mention that routine remeasurement of the twist angle for the 'chair' form of 3,4-dihydro-2H-1,5-benzodioxepin (VIII a) in the present work disclosed that the value of 64° obtained by Archer[18] was incorrect. It is possible that the error arose from the use of distorted Dreiding units or as a result of a photographic error. In this work the bond angles of the Dreiding units were carefully checked before remeasuring the angle of twist on the stereomodel. The revised value for the interplanar angle thus obtained was 73°.

The angles measured for the two conformations were then used[18] in conjunction with the value of 3100 l mol^{-1} cm^{-1} for ε_b, [i.e., the molar extinction coefficient of the planar reference compound,

FIGURE 13

Boat form of 3,4-dihydro-2H-1,5-benzodioxepin (VIII a)

(From a Dreiding model)

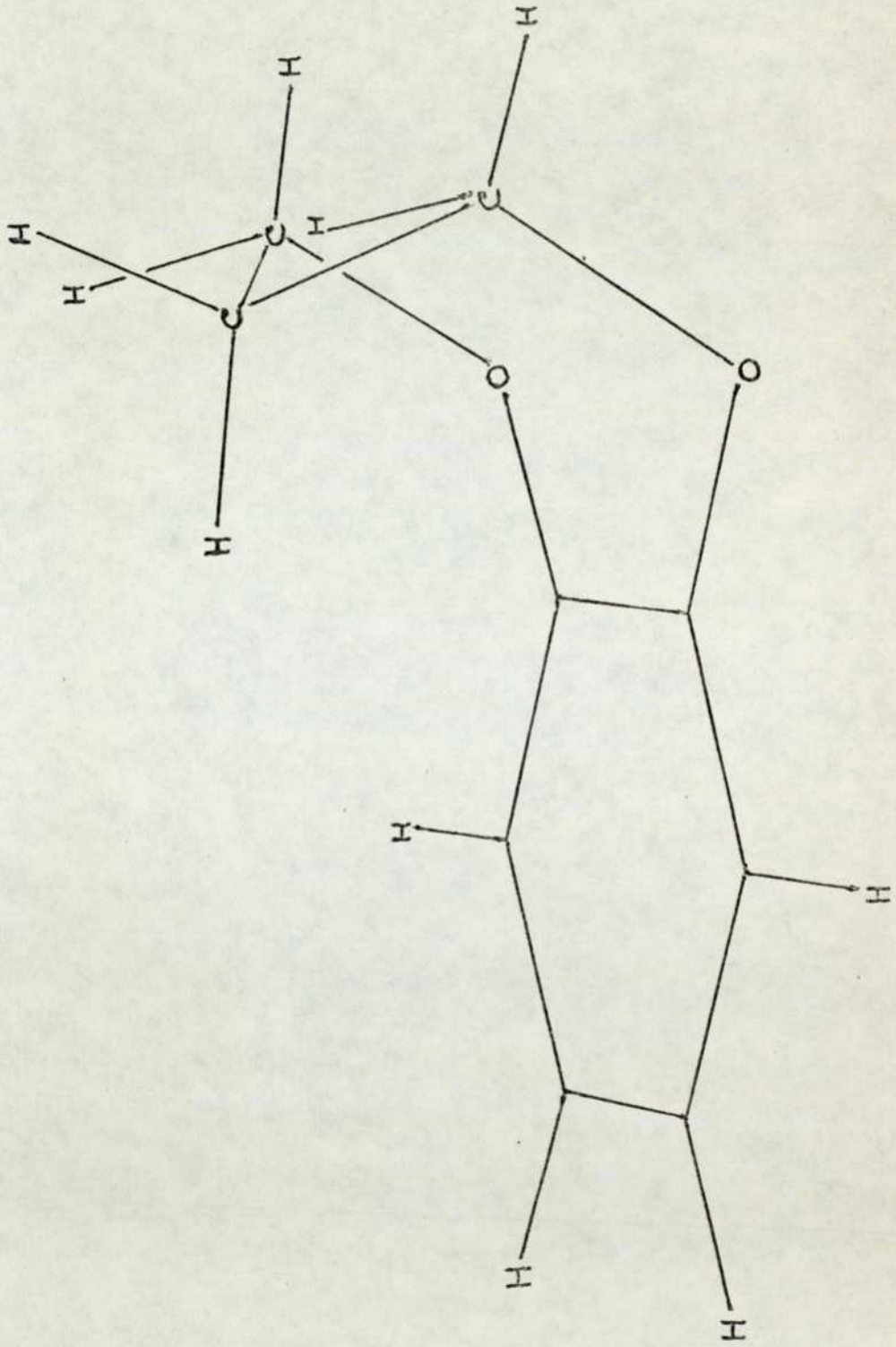


FIGURE 14

Chair form of 3,4-dihydro-2H-1,5-benzodioxepin (VIII a)

(From a Dreiding model)

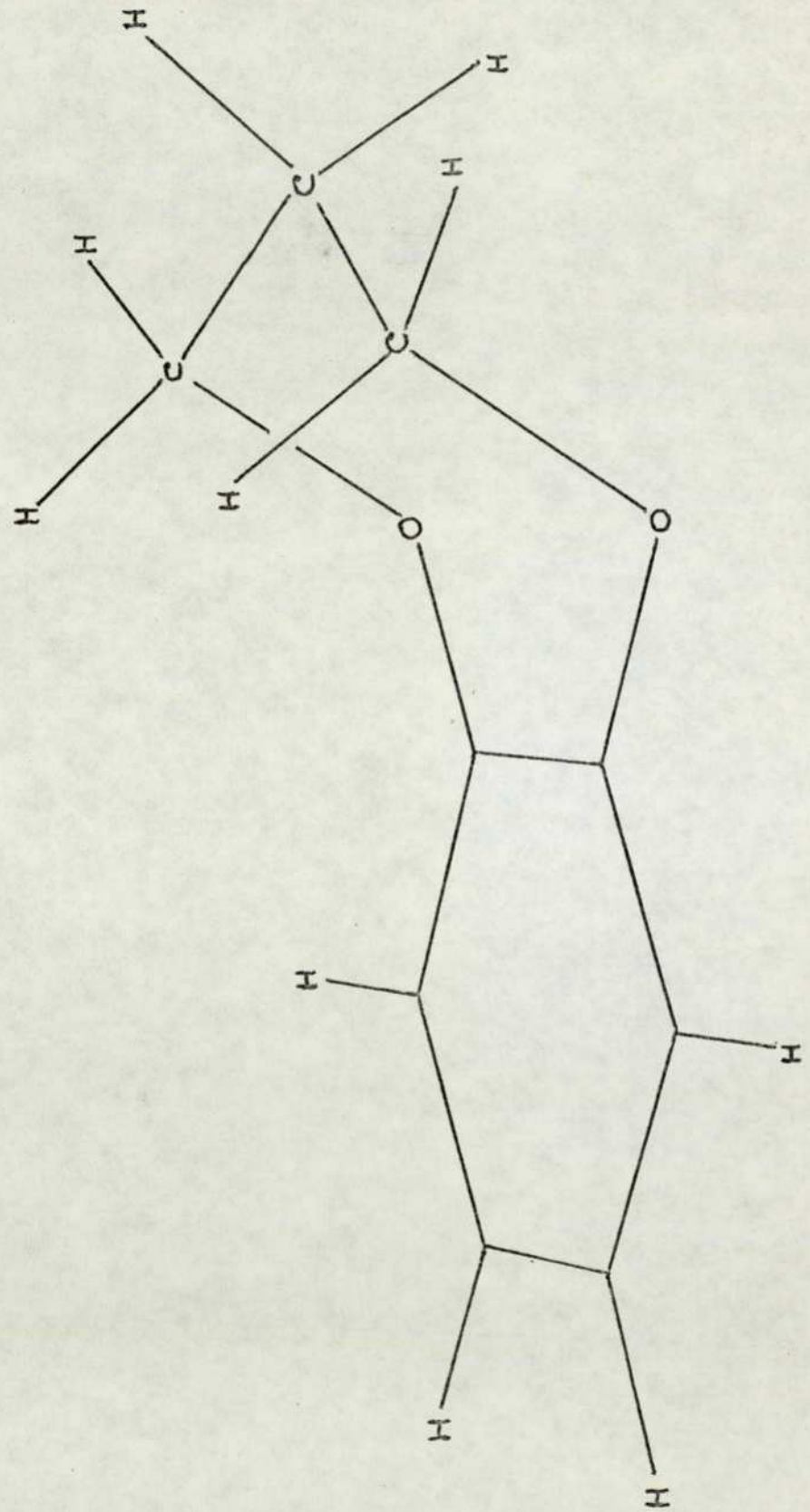


FIGURE 15

Skew form of 3,4-dihydro-2H-1,5-benzodioxepin (VIII a)

(From a Dreiding model)

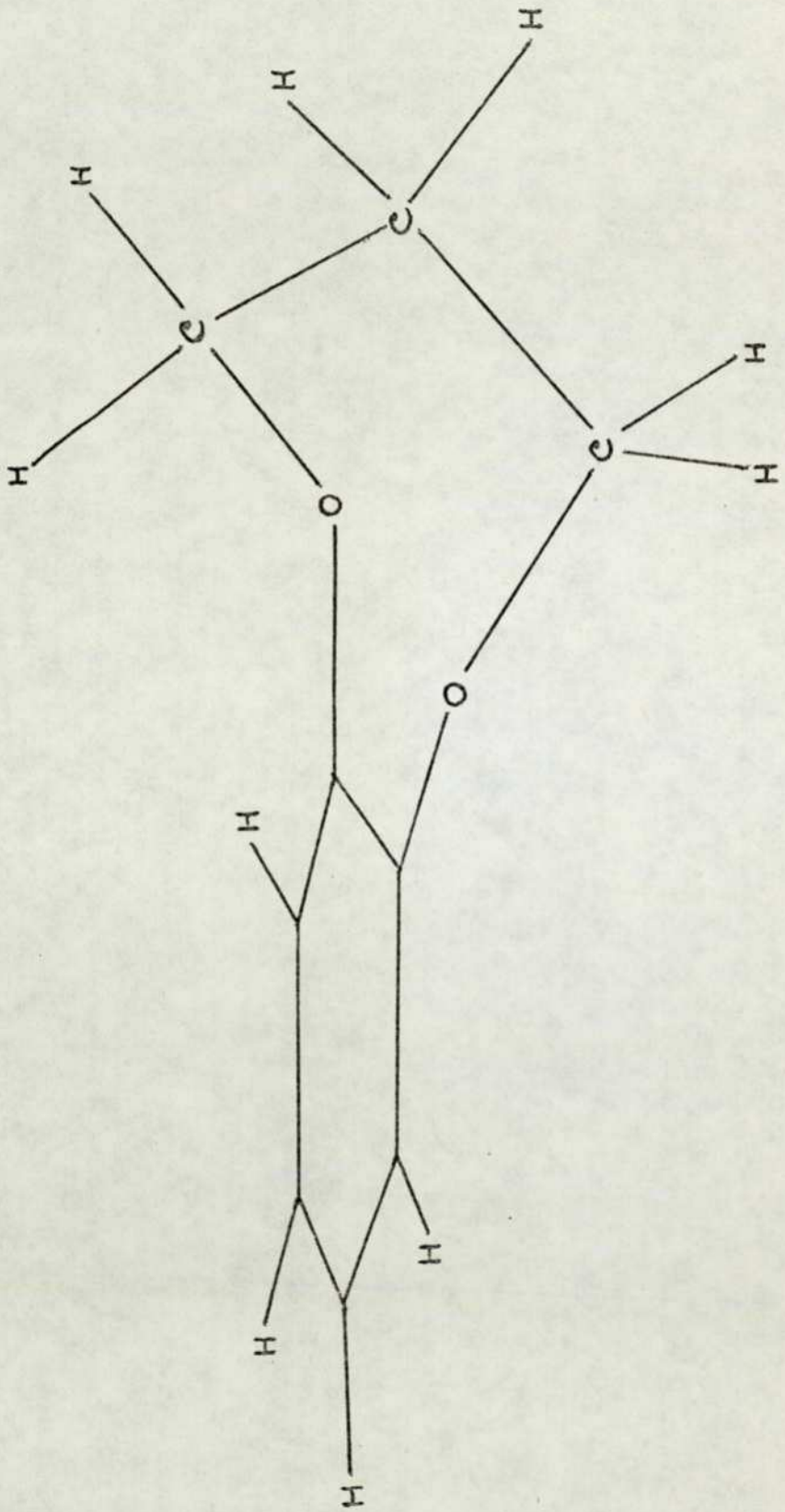


FIGURE 16

Skew form of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (Ia)

(From a Dreiding model)

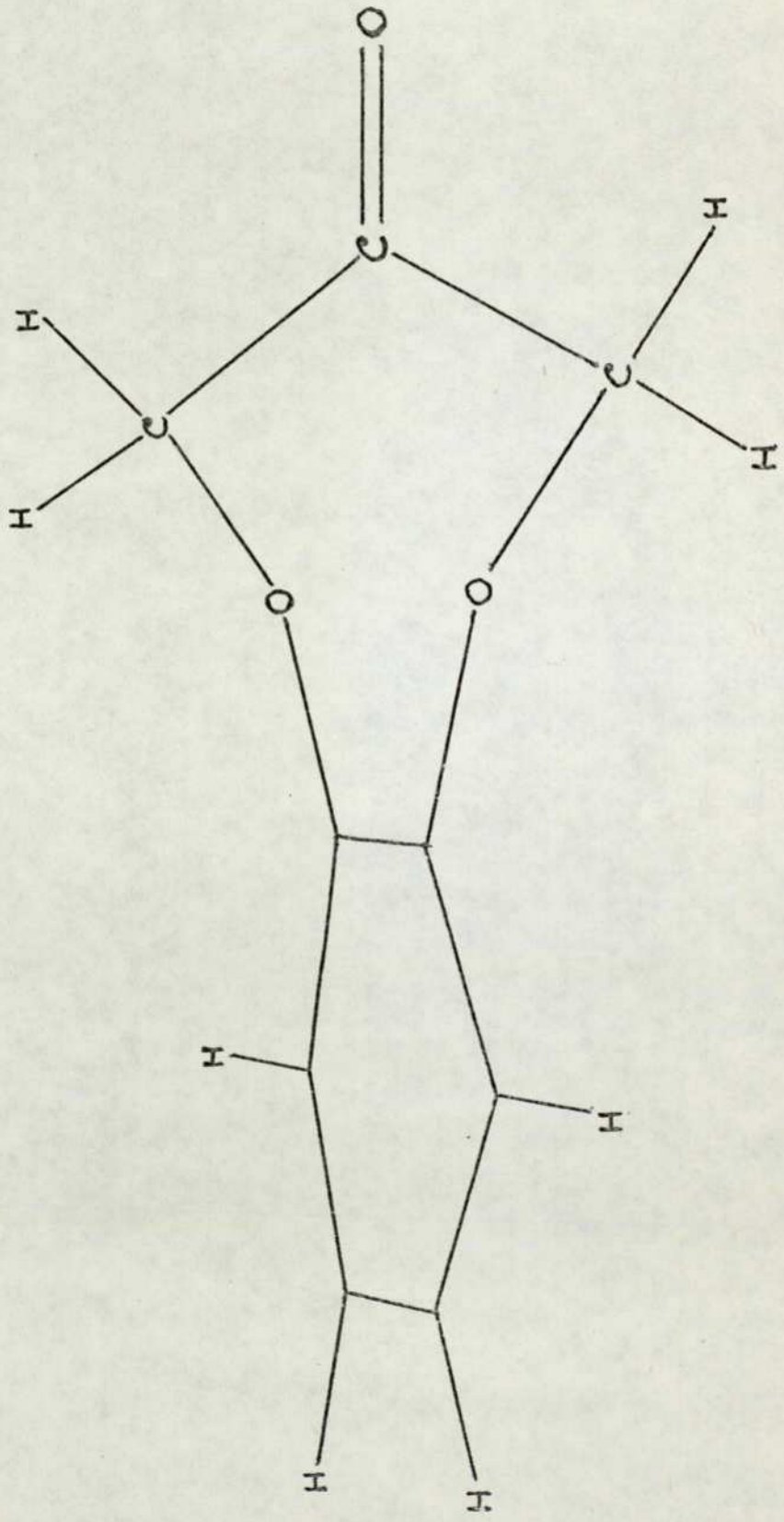
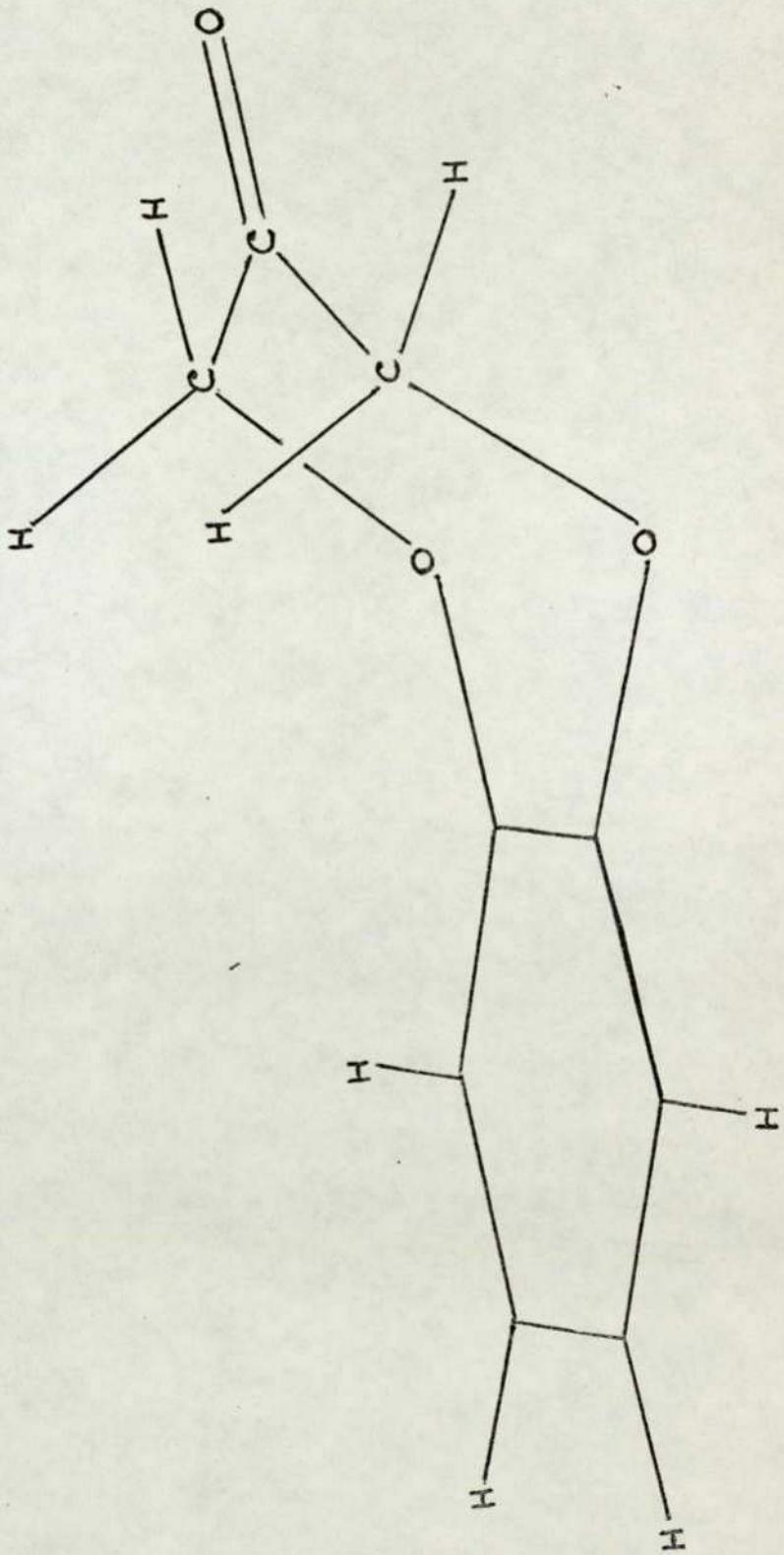


FIGURE 17

Chair form of 3-keto-3,4-dihydro-2H-1,5-benzodioxepin (Ia)

(From a Dreiding model)



1,3-benzodioxole (VIIa)] to calculate the extinction coefficients for the two extreme conformations of the dihydrobenzodioxepin ring. When the $Cos^2\theta$ equation was used, values of ε for the 'chair' and 'skew' forms were 595 and 1604 l mol^{-1} cm^{-1} respectively; using the $Cos\,\theta$ expression the corresponding values were 1360 and 2230 l mol^{-1} cm^{-1}. Since the majority of extinction coefficients for the variously substituted dihydrobenzodioxepins in Table 24 were in the range 1300-2400 l mol^{-1} cm^{-1} Archer[3,18] concluded that the $Cos\,\theta$ equation gave a more accurate indication of the angle of twist and hence the conformation of the heterocyclic ring than the $Cos^2\theta$ expression. The compounds examined by Archer[18] in Table 24 fell into three main groups:- (i) those with extinction coefficients of about 1300-1400 (compounds 1 - 11) (ii) those with extinction coefficients of about 2300 (compounds 28-32) and (iii) those with intermediate values (compounds 12-27).

The extinction coefficients of the compounds in the first group suggest that they have the 'chair' conformation similar to those found[142,146-148] and calculated[149] for carbocyclic and heterocyclic analogues.

The high extinction coefficients of the compounds in the second group were considered as indicative of the 'skew' conformation.

Compounds in the third group with extinction coefficients in the range 1400-2100 were considered to be mixtures of the 'skew' and 'chair' forms, the relative percentage of each being determined by the steric preference of the substituent(s) in the heterocyclic ring.

The previous investigation[18] was also extended to a limited number of cyclic catecholic ethers containing substituents in the aromatic ring and when the appropriate values of ε_o were employed an approximate agreement was observed between the measured and calculated values of θ (see Table 25). One noticeable feature observed for the few compounds derived from 3-methyl-pyrocatechol was the marked decrease in their extinction coefficients; this has previously been reported[132] for cyclic analogues of anisole.

TABLE 24 [18]

Extinction coefficients of some dihydrobenzodioxepins with substituents in the heterocyclic ring (determined in methanol).

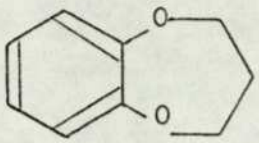
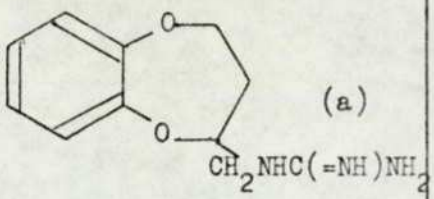
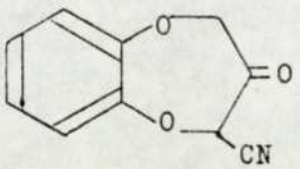
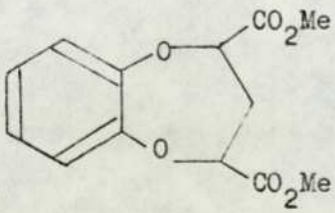
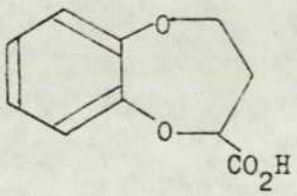
Compound	λ max(nm)	(ε)
1. 	274	1340
2.  (a)	273	1090
3. 	271	1240
4. 	271.5	1310
5. 	272.5	1320

TABLE 24 (Cont.)

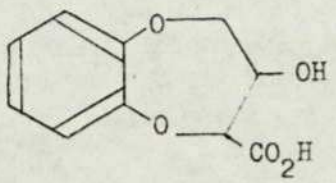
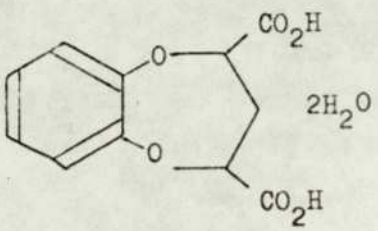
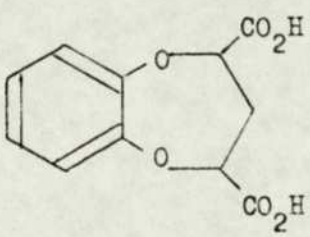
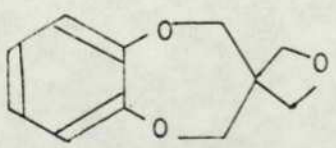
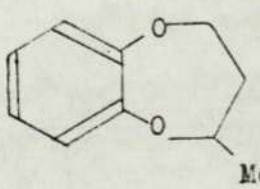
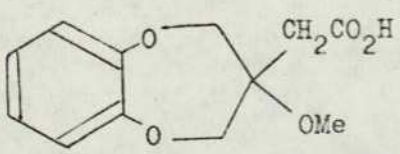
Compound	λ max (nm)	(ε)
6. 	272.5	1330
7. 	272	1320
8. 	272	1340
9. 	273	1350
10. 	274	1360
11. 	271	1380

TABLE 24 (Cont.)

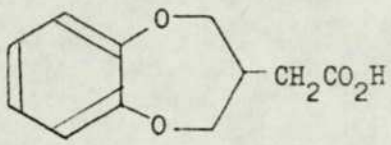
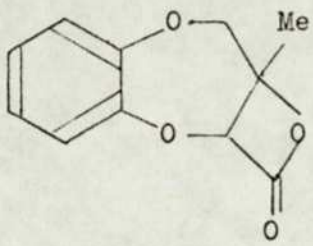
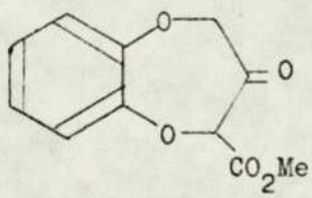
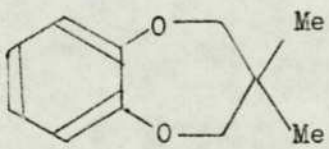
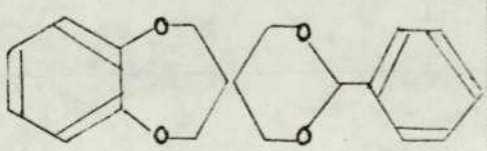
Compound	λ max(nm)	(ε)
12. 	273.5	1484
13 	272	1487
14 	272	1600
15 	274.5	1636
16 	273	1665

TABLE 24 (Cont.)

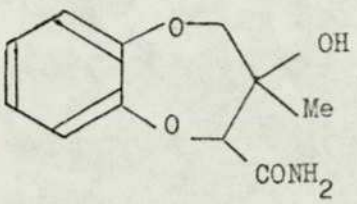
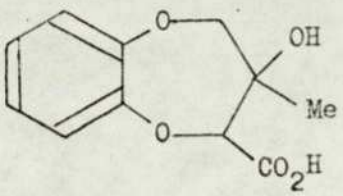
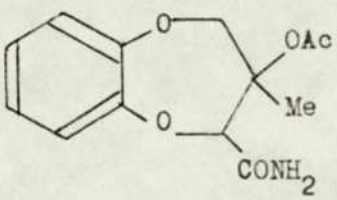
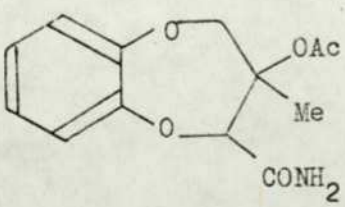
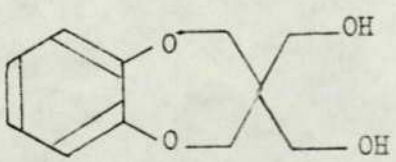
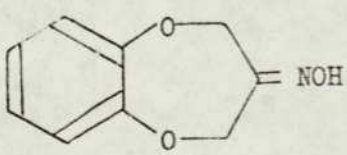
Compound	λ max(nm)	(ε)
17. 	272	1672
18. 	273	1675
19. 	272	1680
20. 	272	1690
21. 	274	1770
22. 	273	1805

TABLE 24 (Cont.)

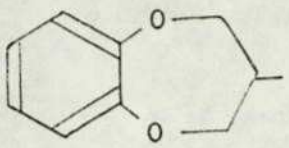
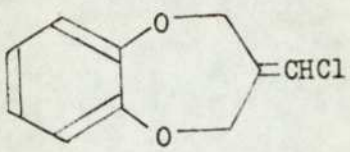
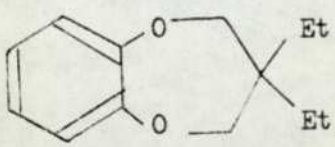
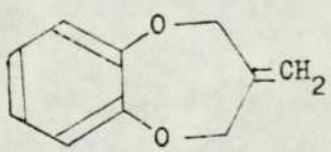
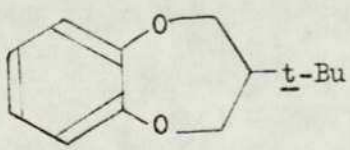
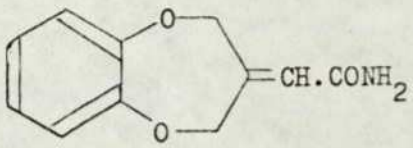
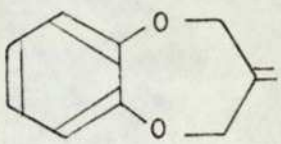
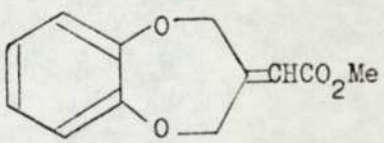
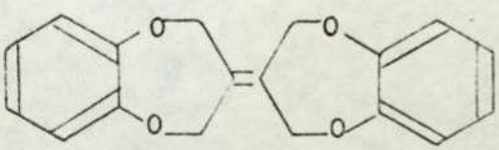
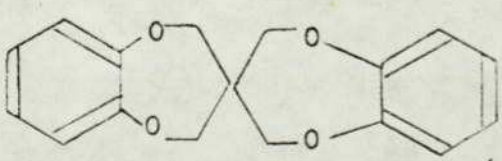
Compound	max(nm)	(ε)
23  (b)	274	1885
24 	274	1900
25 	275	1900
26  (b)	274	1923
27 	275	2020

TABLE 24 (Cont.)

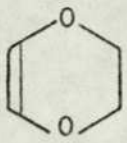
Compound	max(nm)	(ε)
28 	273	2240
29 	273	2280
30 	272	2380
31 	275	4650
32  (c)	274	4900

(a) Reference 144.

(b) Personal communication to A.W. Archer[18] from Professor M. Muhlstadt, Karl Marx University, Leipzig. See also reference 20.

(c) In dioxan, reference 145.

Ford and co-workers[150] have recently determined the conformation of 1,4-dioxene (XCVI) by an analysis of the high resolution for infra-red spectrum of its vapour and found that the stable conformation is



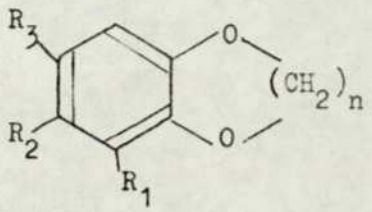
XCVI

'skew' with an angle of twist of 48.54°. In view of the structural resemblance of this compound to the 1,4-benzodioxans studied by Archer[18] it has been suggested[152] that a similar conformation and angle of twist would be anticipated for these compounds. If this were so then it would appear that Dreiding molecular models do not accurately depict the conformation of the 1,4-benzodioxan molecule. On the other hand the angle of twist calculated from the Cos θ equation[18] agrees quite favourably with that established by the infra-red study[150] (see Table 25 where n = 2).

X-ray crystallographic studies, carried out independently in these laboratories by Steward and co-workers[152], on the crystalline 3,4-dihydro-2H-1,5-benzodioxepin-2,4-dicarboxylic acid (compound 8, Table 24), which from its molar extinction coefficient was previously considered[18] to exist in the chair conformation, revealed that the compound has the 'skew' conformation (twisted half-chair) with a twist-angle of approximately 40°. On the basis of these findings it was suggested[152] that use of the $\text{Cos}^2\,\theta$ equation would have indicated the 'skew' conformation. However, because the 'skew' arrangement is indicated in the crystalline state there is no reason to expect the compound to retain the same conformation in solution. It was also suggested[152] that in solution the system is in fact time-averaging about the 'skew', rather than the 'chair' conformation.

TABLE 25

Values of Θ calculated for some pyrocatechol ethers substituted in the aromatic ring, compared with values of Θ calculated for the correspondingly unsubstituted compounds.



Compound	ε (a) $l\ mol^{-1}\ cm^{-1}$	Θ Calculated from Cos Θ	Θ Measured from model
n = 1			
$R_1 = R_2 = R_3 = H$	3320	0 (b)	0
$R_1 = Me, R_2 = R_3 = H$	2655	"	"
$R_1 = H, R_2 = Me, R_3 = H$	3660	"	"
$R_1 = H, R_2 = COMe, R_3 = H$	7140 (c)	"	"
$R_1 = H, R_2 = R_3 = Br$	4260	"	"
n = 2			
$R_1 = R_2 = R_3 = H$	2480	42	20
$R_1 = Me, R_2 = R_3 = H$	1580	51	"
$R_1 = H, R_2 = Me, R_3 = H$	2660	43	"
$R_1 = H, R_2 = COMe, R_3 = H$	4525 (c)	51	"
$R_1 = H, R_2 = R_3 = Br$	3530	34	"

TABLE 25 (Cont.)

Compound	ε (a) $l\ mol^{-1}\ cm^{-1}$	θ Calculated from Cos θ	θ Measured from model
n = 3			
$R_1 = R_2 = R_3 = H$	1340	66	64 (73) (d)
$R_1 = Me, R_2 = R_3 = H$	764	73	" "
$R_1 = H, R_2 = Me, R_3 = H$	1575	64	" "
$R_1 = H, R_2 = COMe, R_3 = H$	3600 (c)	59	" "
$R_1 = H, R_2 = R_3 = Br$	2300	57	" "
n = 4			
$R_1 = R_2 = R_3 = H$	1480	64	60
$R_1 = Me, R_2 = R_3 = H$	950	69	"
$R_1 = H, R_2 = Me, R_3 = H$	1690	63	"
$R_1 = H, R_2 = R_3 = Br$	2380	56	"

(a) Determined in methanol from reference 18.

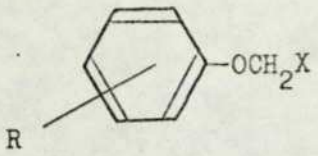
(b) ε taken as ε_o for these compounds.

(c) Determined in hexane from ref. 151.

(d) Revised value; see Chapter 5.3.

5.2 Discussion of the ultra-violet spectra and conformations of some ar-methyl-o-phenylenedioxydiacetonitriles (III a-j).

Measurement of the intensity of the Ph-O $\pi \rightarrow \pi^*$ transition near 260 nm has been used to study the conformations of a series of aromatic ethers[132].



X = H X = -CO2H X = -CH2CH2NMe3Br X = -CHCH2NMe3Br

R = 2-Me, 3-Me, 4-Me, 2,4-Me2, 2,5-Me2, 3,5-Me2 and 2,4,6-Me3

R = H and 2-Me

It was therefore expected that examination of the intensity of the Ph-O chromophore in the series o-phenylenedioxydiacetonitriles (III a-j) whose preparation was described in Chapter 4.3, would provide useful information concerning the conformations of these compounds, particularly when nuclear substituents, such as methyl groups, flanked either one or both $-OCH_2CN$ groups.

Initially the ultra-violet spectra of anisole and veratrole were compared with phenoxyacetonitrile[153] and o-phenylenedioxydiacetonitrile (IIIa) in the 260-280 nm region to observe whether the cyano group produced any distinctive changes in their absorption spectra. It is evident from the spectra recorded in Fig. 18 that the absorption curves for anisole and phenoxyacetonitrile are very similar and that the two diethers clearly resemble each other but the absorption bands of both nitriles were displaced to slightly shorter wavelengths and reduced in intensity by about 30% (see Table 26).

Figure 18

Ultra-violet spectra of anisole, veratrole, phenoxyacetonitrile and o-phenylenedioxydiacetonitrile (IIIa).

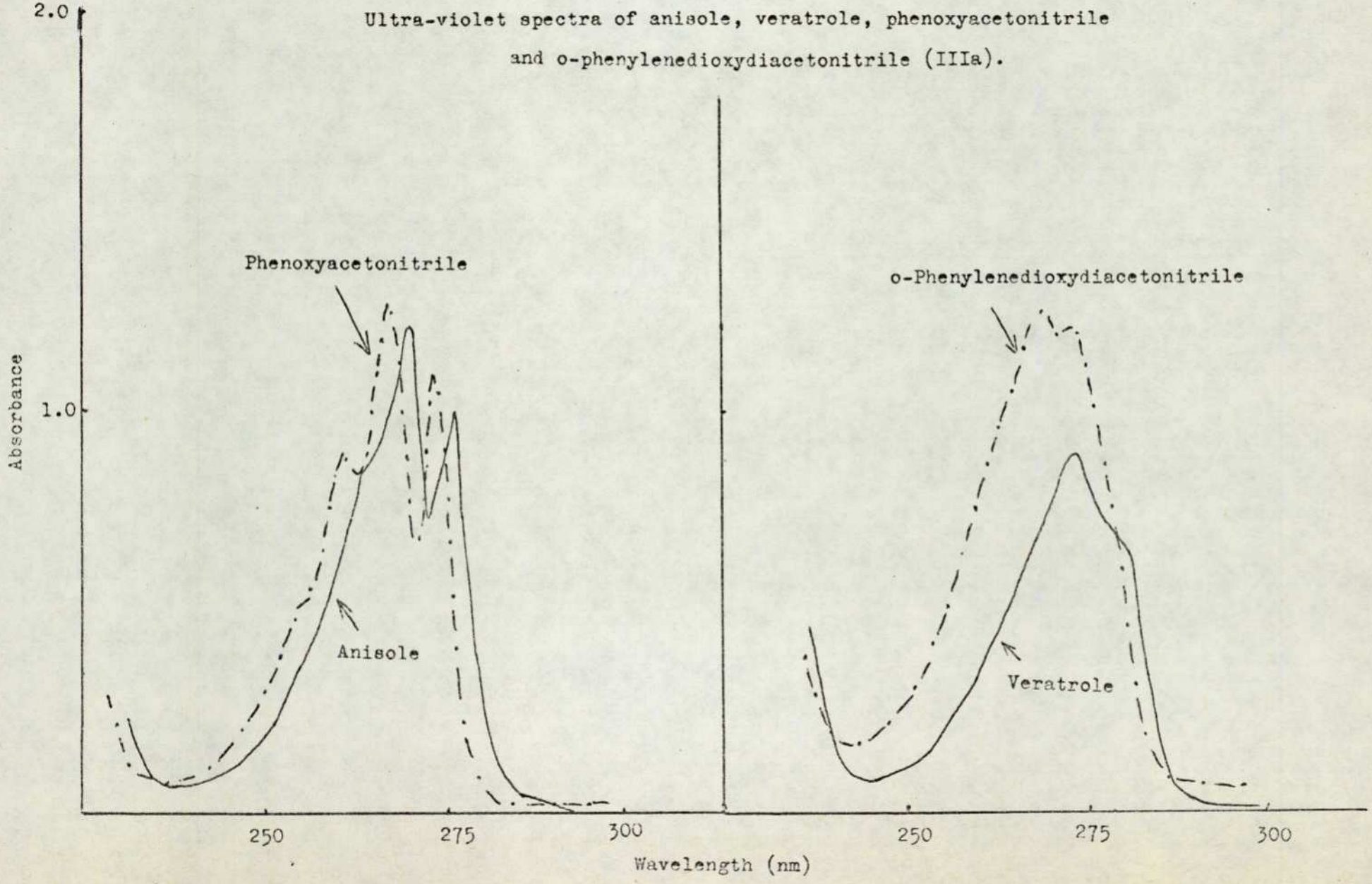
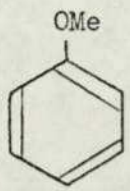
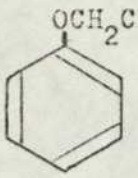
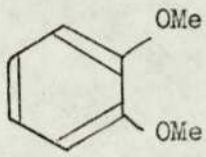
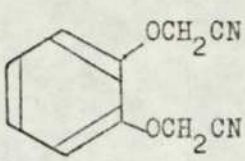


TABLE 26 (a)

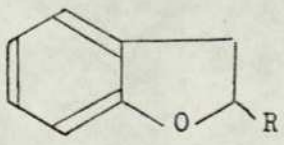
Compound	λ max nm (ε)	Compound	λ max nm (ε)
	264.5 sh (1310) 270.5 * (1850) 277 (1580)		261.5 (1109) 267.5* (1291) 274 (895)
	273.5 * (2270) 279 sh (1805)		269 * (1440) 273.5 (1380)

* Principal peak.

(a) In methanol.

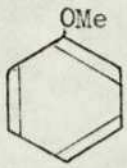
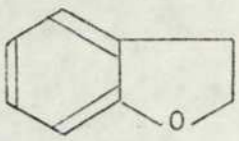
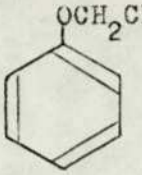
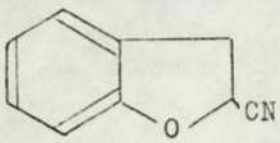
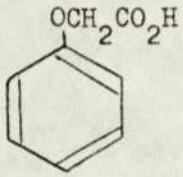
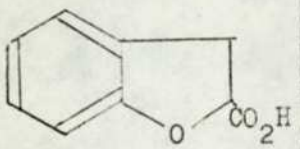
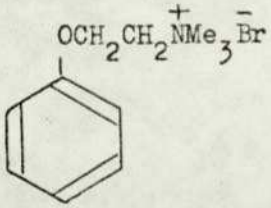
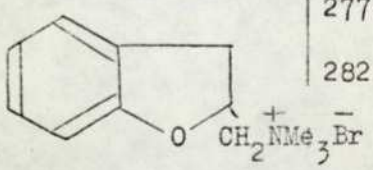
Hypsochromic shifts and hypochromic effects are both indicative of decreased conjugation within the molecule and in the case of the nitriles it can be attributed to the inductive effect of the cyano group reducing the ease of electron release from the ether-oxygen atom to the benzene ring.

Angles of twist for anisole, phenoxyacetic acid and β-phenoxyethyltrimethylammonium bromide were calculated by Clarke and Williams[132] using the $\cos^2\theta$ equation and the appropriate ε_o values for the planar reference compounds (see Table 27); values of 44.5°, 46.5° and 43.5° respectively were obtained. Although the planar reference compound, 2-cyano-3,4-dihydrobenzofuran (XCVII R = -CN), corresponding to phenoxyacetonitrile has



XCVII

TABLE 27

Compound	λ max (nm) (ε)	Compound	λ max (nm) (ε)
 (a)	265 (1125) 271 * (1579) 277.5 (1475)		274 (2250) 283 *(3095) 289 (3055)
 (b)	261.5 (1109) 267.5* (1291) 274 (895)		276(d) (2700)(d)
 (a)	270* (1275) 276 (1140)		279* (2670) 285 (2375)
 (c)	264 (1045) 269* (1410) 275.5 (1145)		277.5* (2680) 282.5 sh (2350)

* Indicates the peak taken as a measure of absorption intensity.

(a) Recorded in n-hexane[132].

(b) " " methanol.

(c) " " distilled water[132].

(d) Predicted values.

TABLE 28 (a)

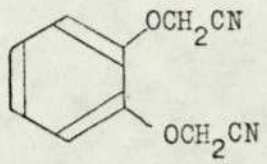
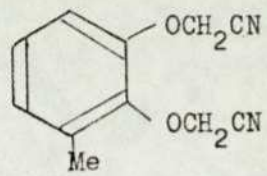
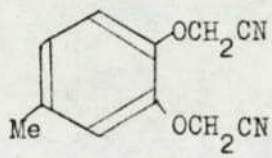
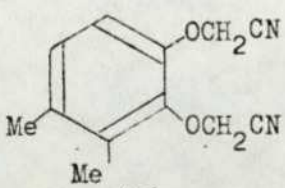
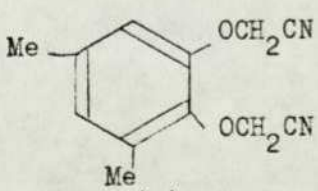
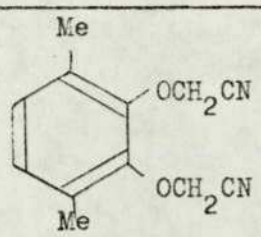
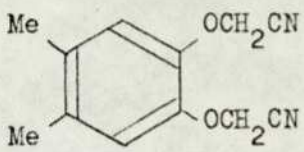
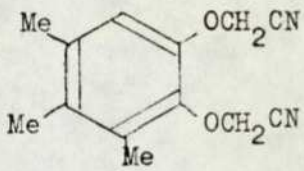
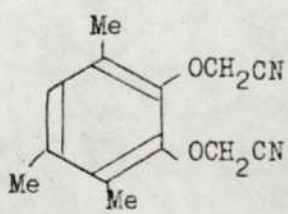
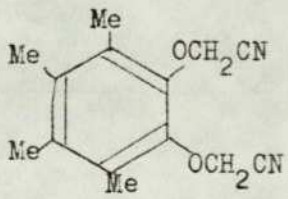
Compound (III)	λ max (nm) (ε)	Change in λ and ε relative to (III a)
 (a)	269* (1440) 273.5 (1380)	0 (0, 0%) - -
 (b)	268* (737) 275 (634)	-1 (-703, -48.7%) - -
 (c)	274* (1665) 277 (1630)	+5 (+225, +15.6%) - -
 (d)	271.5* (943) 275 (943) 279.5 (916)	+2.5 (-497, -34.5%) - - - -
 (e)	270.5* (792) 274 (792) 278.5 (810)	+1.5 (-648, -45%) - - - -

TABLE 28 (Cont.)

Compound (III)	λ max (nm) (ε)	Change in λ and ε relative to (IIIa)
 (f)	266* (342) 271 sh (306) 274 sh (278)	-3 (-1098,-76.3%) - -
 (g)	277.5* (2485) 281.5 (1985)	+8.5 (+1045, +72.5%) -
 (h)	273* (1008) 277.5 (1043) 284 (1020)	+4 (-432,-30%) - -
 (i)	268.5* (373) 273.5 (354)	-0.5 (-1067,-73.9%) -
 (j)	269* (268)	-1 (-1172,-81.5%)

* Taken as principal band.

(a) All spectra were recorded for methanol solutions.

been prepared in a crude state[155] its physical constants have not been recorded. Consequently a precise value for Θ cannot be calculated. However, in view of the similar magnitude of the extinction coefficients of phenoxyacetonitrile (ε 1291) and phenoxyacetic acid (ε 1275) (Table 27) it would not be an unreasonable assumption to expect the extinction coefficient of 2-cyano-2,3-dihydrobenzofuran (XCVII, R = $-CO_2H$) in this region to be similar (ε ca 2700) to that of 2,3-dihydrobenzofuran-2-carboxylic acid (XCVII R = $-CO_2H$) (ε 2670) (see Table 27). When this predicted figure for ε_o was used to evaluate Θ for phenoxyacetonitrile using the $\cos^2\Theta = \varepsilon/\varepsilon_o$ relationship the ratio of the extinction coefficients was 0.478 and the calculated angle of twist 46° which is close to the values similarly obtained for the related aryl ethers in Table 27 by Clarke and Williams[132]. This implies that the small Ph-O- conjugation, unlike the Ph-C = O conjugation in acetophenones[123], is insufficient to produce a large potential energy well for the conformation in which Θ is close to 0° and free rotation can occur about the phenyl-oxygen bond at room temperature.

Electronic absorption data for the substituted o-phenylenedioxydiacetonitriles (III a-j) have been recorded in Table 28 and pronounced variations were observed for the band intensities within the series. Owing to the poor resolution of the absorption bands in most of these compounds (see Figs. 19 and 20) it proved difficult to identify the principal absorption band particularly when two and three peaks of similar intensities were present. Generally the longest wavelength absorption was considered to be a fine structure band and was discounted. In the case of the two lower wavelength bands it was decided to take the extinction coefficient of the shorter wavelength band as a measure of the relative oscillator strength of the $\pi \rightarrow \pi^*$ transition and since these results are discussed mainly from

Figure 19

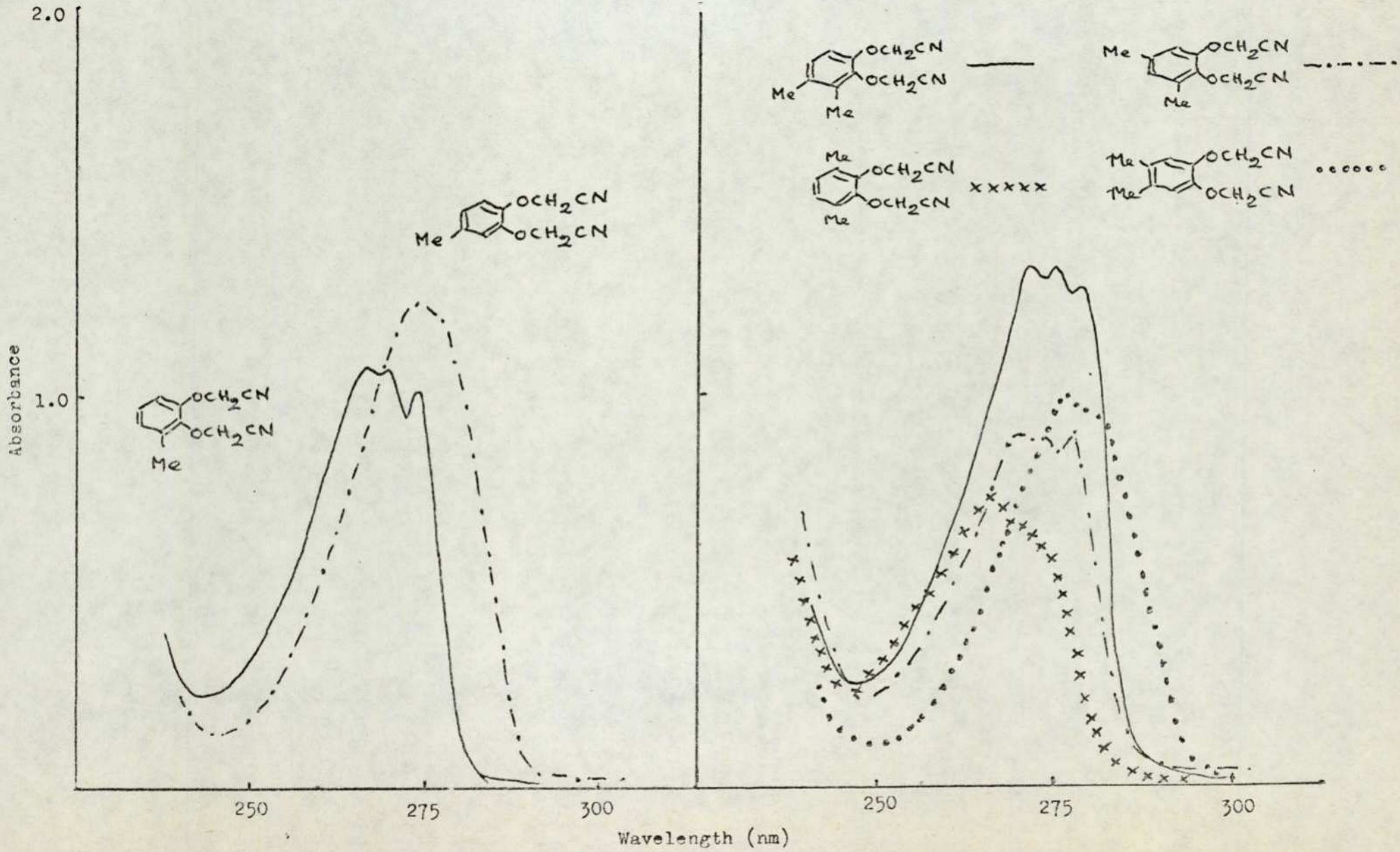
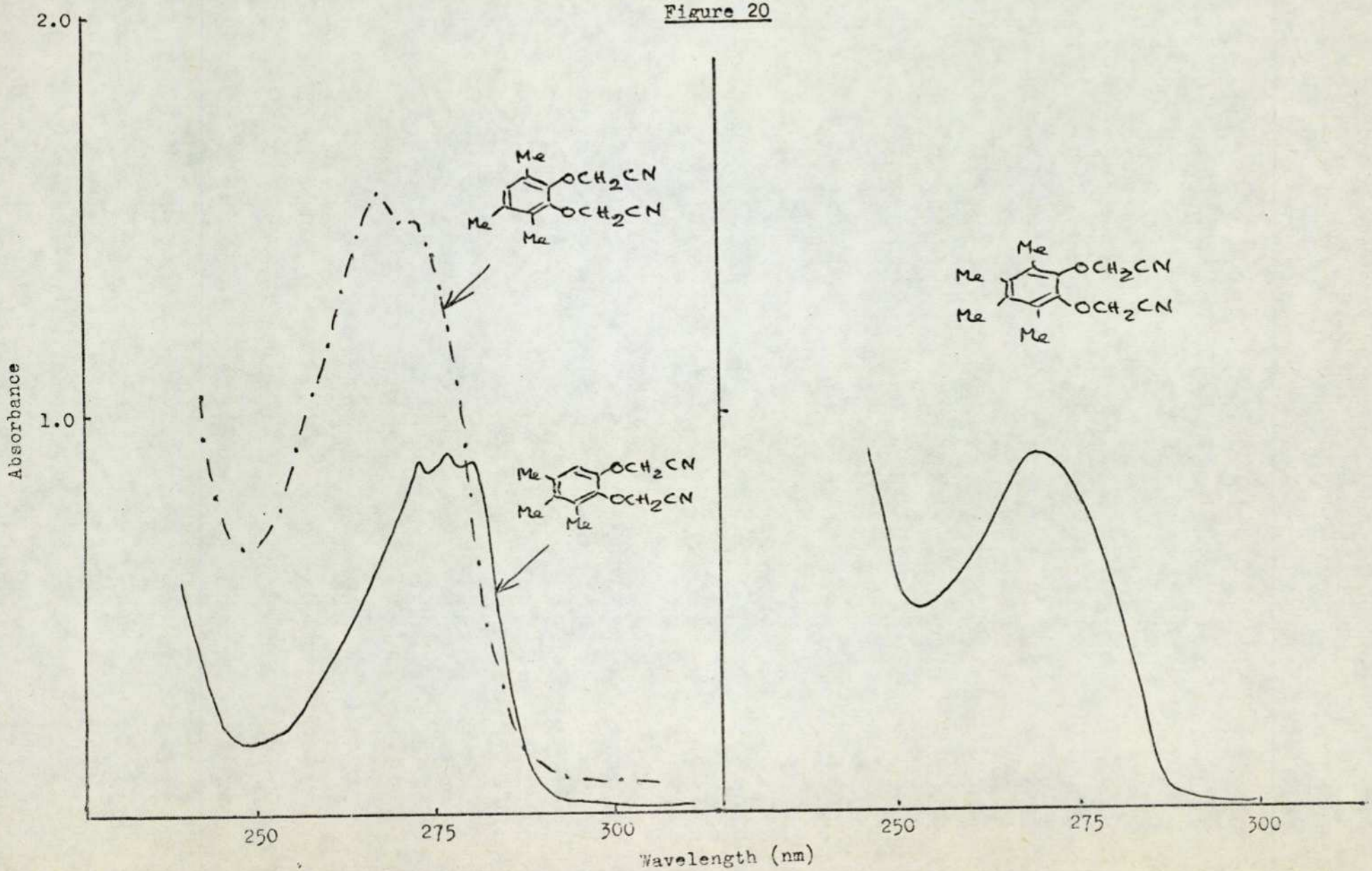


Figure 20


2.0
1.0
Absorbance
250
275
300
Wavelength (nm)
250
275
300
Me
OCH2CN
OCH2CN
Me
Me
Me
OCH2CN
OCH2CN
Me
Me
Me
Me
OCH2CN
OCH2CN
Me
Me
Me

a qualitative aspect an incorrect choice in the absorption band would not lead to serious errors.

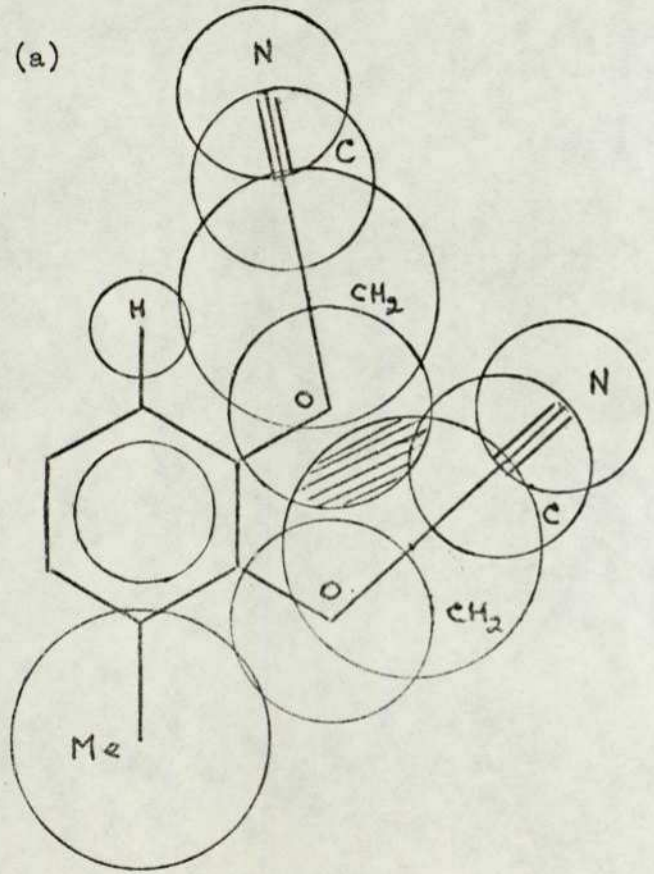
The introduction of a 4-methyl substituent into o-phenylenedioxydiacetonitrile (IIIa) produces a small bathochromic displacement (+5 nm) of the bands and enhances the absorption intensity slightly (+ 225). This value is similar to the hyperchromic effect observed for a para-methyl substituent in anisole[132] and benzaldehyde[123]. The introduction of a second methyl group at position 5 resulted in a further bathochromic shift of the band (+ 3.5 nm) and a marked magnification of its intensity, effects which are both indicative of enhanced conjugation within the molecule. This compound was also the only member of the series where a synergistic effect was observed on further nuclear methylation. The large decrease in the molar extinction coefficient of 3-methyl-o-phenylenedioxydiacetonitrile (IIIb) occasioned by a small hypsochromic wavelength displacement (-1 nm) are both characteristic of the Type (1) electronic spectral effects discussed by Braude and co-workers[122,123] (see Chapter 5.1, page 238). This decrease in intensity is consistent with a steric inhibition of lone-pair conjugation with the aryl ring arising from conformational changes within the molecule. Reasons for this become apparent when scale projections of the compound are examined (Figs. 21 a, b and c). Scale diagrams were made using the appropriate bond lengths[156] and interference radii equal to twice the covalent radii[123]. These parameters were employed by Braude and his associates to demonstrate steric interference in some substituted benzaldehydes[123], acetophenones[123] and related compounds[124-126] and later by Clarke and Williams[132] to depict similar steric effects in ortho-substituted anisoles. The choice of twice the covalent radii, values which are slightly less than the van der Waal's radii, to represent interference radii has been discussed in detail by Braude and Sondheimer[123]. The smaller values were preferred on the

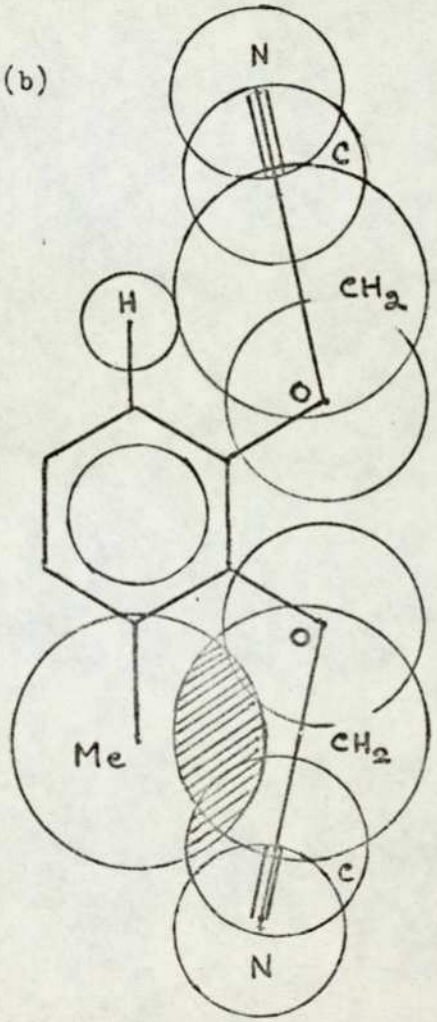
grounds that van der Waal's radii can predict marked steric effects in many compounds whose ultra-violet light absorption properties are normal. It is evident that in the two 'in-plane, in-plane' conformations (Figs. 21a and b) appreciable non-bonded interactions occur as indicated by the shaded portions. This is minimal when the 1-OCH_2CN and 2-OCH_2CN groups assume ('in-plane, out-of-plane' arrangements respectively (Fig. 21c), but even so a slight overlap occurs between the interference spheres of the methyl group and the 2-oxygen atom. On a Dreiding model the distance between the centres of the 3-methyl group and the methylene carbon attached to the oxygen at position 2, when $\Theta = 90^\circ$, is 3.4 Å which is twice the chosen interference radius of a methyl or methylene group and indicates that these interference spheres are in contact. Also, when θ for the 2-OCH_2CN group is 90° the distance between the centre of this methylene carbon and the centre of the oxygen atom of the 1-OCH_2CN group is 3.3Å which is only 0.3Å greater than the sum of their respective interference radii (1.70Å + 1.32Å = 3.02Å). Consequently any deviation by the 2-OCH_2CN group of more than 20° from an orthogonal orientation ($\Theta = 90^\circ$) towards the 1-oxygen would also result in contact of these interference spheres. This combination of steric factors is almost identical with the steric situation existing in some 2,6-dimethyl substituted aryl ethers[132] and would be expected to give rise to compressional energies[122,123,132] of less than ca 3 K cal/mole with the result that at room temperature the 2-OCH_2CN group in the di-ether (IIIb) would be expected to adopt a fairly rigid conformation in which θ is close to 90°. The ultra-violet absorption actually observed for this compound comprises mesomeric contributions from the 1-OCH_2CN group, 'non-steric' effects of the 3-methyl group and some residual absorption of the aryl ring. Other investigators[122,123,132] have assumed that in the absence of a special 'ortho-effect' the

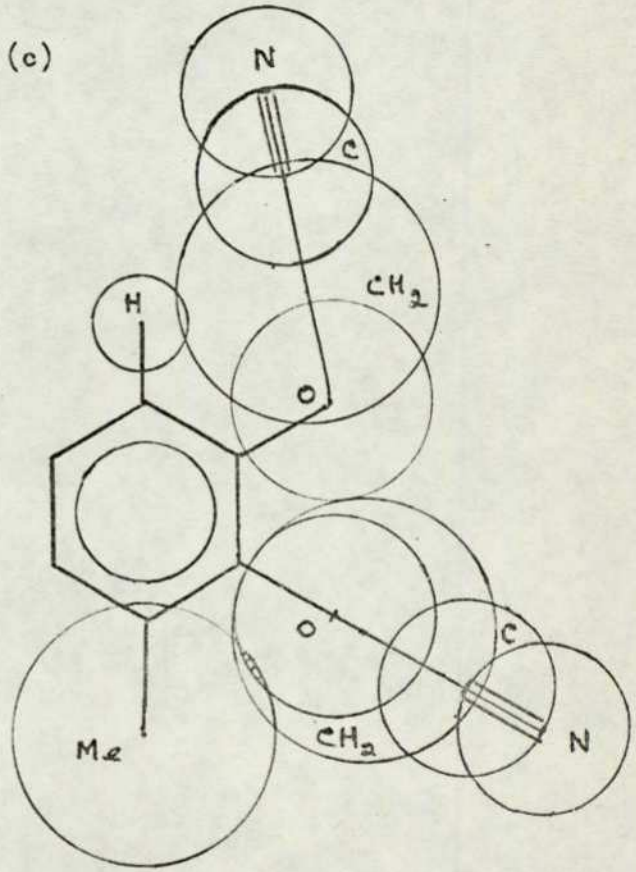
FIGURE 21

Scale drawings of 3-methyl-o-phenylenedioxydiacetonitrile (IIIb)

(a) and (b) represent the two 'in-plane, in-plane' conformations and (c) represents the 'in-plane, out-of-plane' conformation.







Bond lengths[156]:

All aromatic bonds . .	1.39 Å
C-C	1.54 Å
C-H	1.07 Å
C-O	1.43 Å
C≡N	1.16 Å

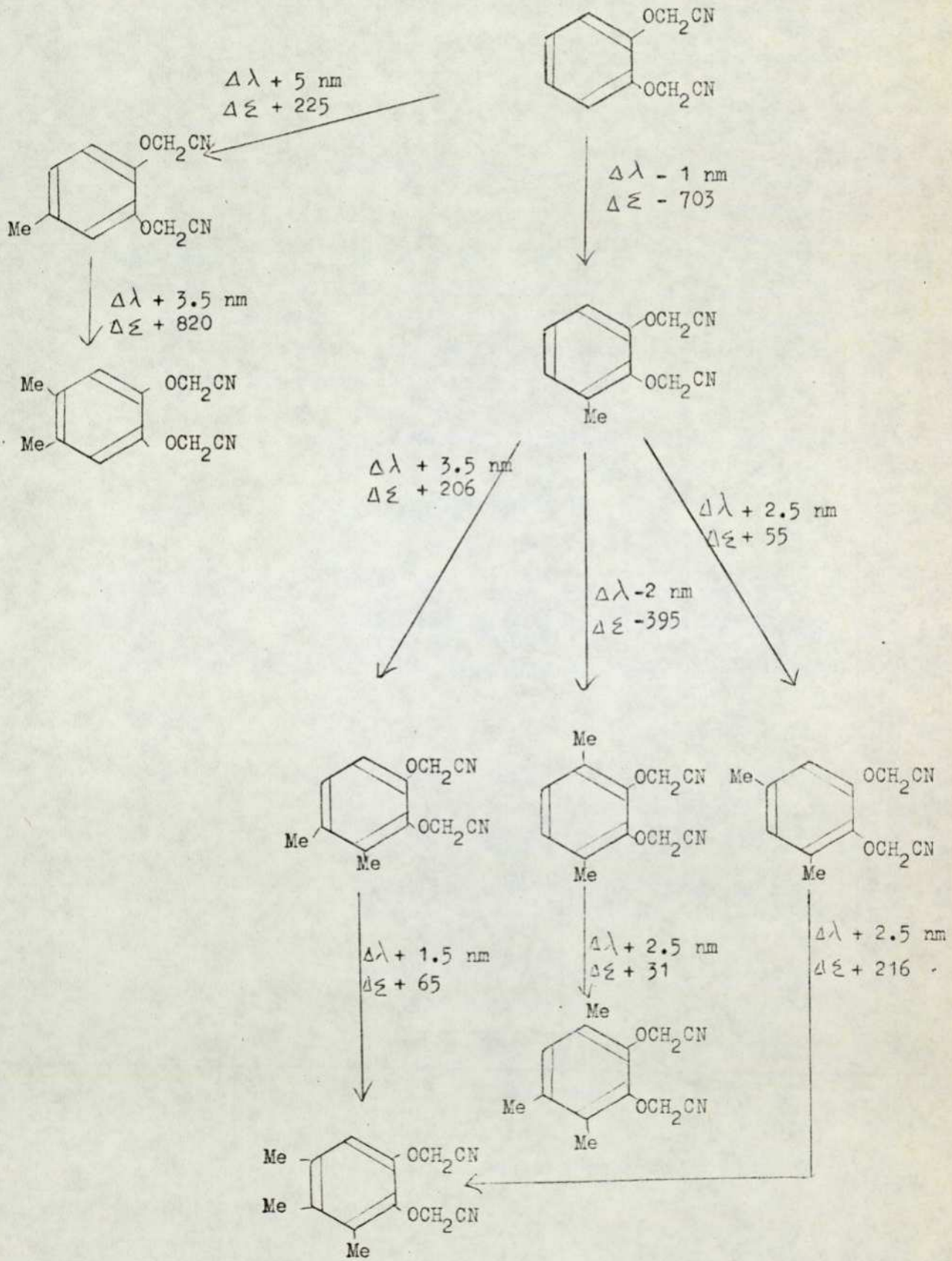
A bond angle of 108° (sp^3 hybridisation) for the O-atom was used

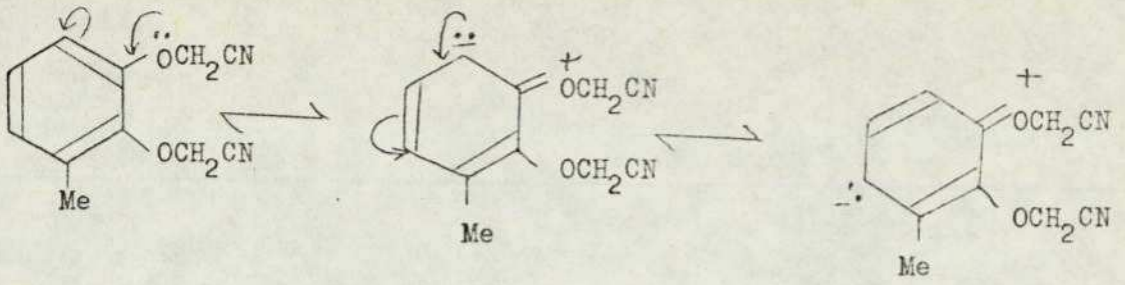
Interaction radii[123]:

Me and CH_2 . .	1.70 Å
C-	1.54 Å
C≡	1.20 Å
H	0.62 Å
O-	1.32 Å
N≡	1.1 Å

FIGURE 22

Changes in λ and ε with successive nuclear methylation





electronic contribution of an ortho-methyl group would be similar to that of a para-methyl substituent but it can be less[132]. It is evident from inspection of the ultra-violet spectral data given in Table 28 that an 'ortho-effect' is operating in all the compounds substituted at the 3 and 3,6-positions with the result that no accurate value for the non-steric effects of a 3-methyl group can be estimated.

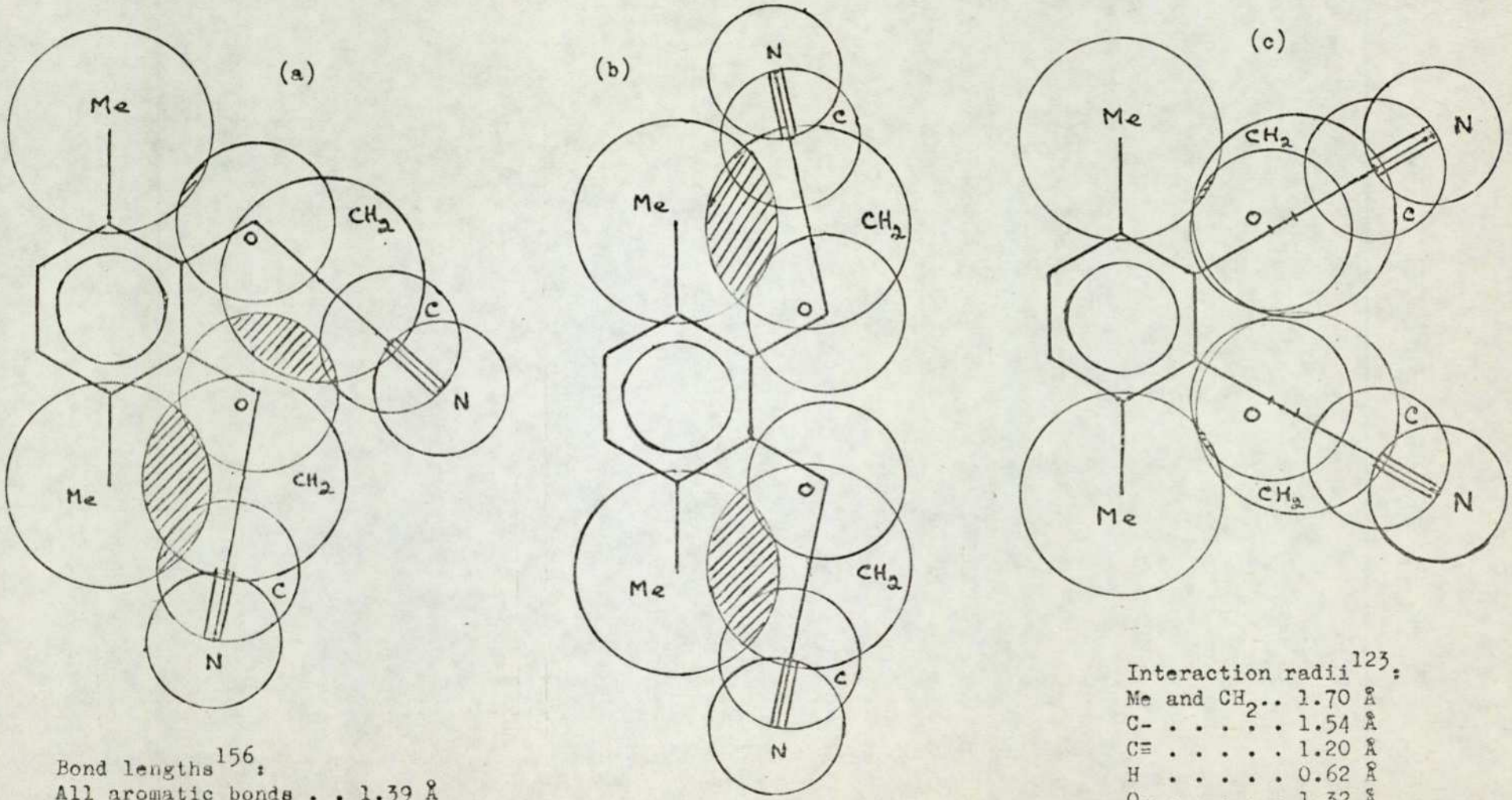
Introduction of a 4-methyl group into 3-methyl-o-phenylenedioxydiacetonitrile (IIIb) was accompanied by a small (+4.5 nm) bathochromic displacement of the band and an increase of 206 in its intensity (see Fig. 22) which is similar to the increase of 225 produced by the single substituent in the 4-methyl isomer (IIIc). In comparison the introduction of a 5-methyl substituent into the 3-methyl compound (IIIb) exerted a similar wavelength shift (+ 3.5 nm) but the intensity enhancement was only 55. (see Fig. 22). Similar trends were also observed on progressing from certain dimethyl to trimethyl analogues. Thus, introduction of a 5-methyl group into 3,4-dimethyl-o-phenylenedioxydiacetonitrile (IIId) and a 4-methyl group into the 3,5-dimethyl analogue (IIIe) increased the molar extinction coefficients by 65 and 216 respectively (see Fig. 22).

It is notable that intensity increases of ca 200 are associated with the introduction of a methyl group para to the 1-OCH_2CN group which is capable of attaining co-planarity with the benzene ring and with which lone-pair conjugation can occur whereas hyperchromic effects of ca 60 appear to be associated with the introduction of an additional methyl substituent para to the orthogonally oriented 2-OCH_2CN group. It is possible that this smaller increase could be attributed to electronic

effects of the 5-methyl group being located meta to the co-planar 1-OCH_2CN group. When allowances are made for the non-steric effects of the methyl groups in 3,4-dimethyl-(IIId), 3,5-dimethyl- (IIIe) and 3,4,5-trimethyl-o-phenylenedioxydiacetonitrile (IIIh) it is evident that a marked 'ortho-effect' is operating in these compounds and their conformations would be expected to be similar to that proposed for 3-methyl-o-phenylenedioxy-diacetonitrile (IIIb) in Fig. 21c. An additional interesting feature of the 3,4,5-trimethyl- compound (IIIh) was the loss of the synergistic effects of the 4,5-dimethyl groups. Flanking of both $-OCH_2CN$ substituents by methyl groups as in 3,6-dimethyl- (IIIf), 3,4,6-trimethyl- (IIIi) and 3,4,5,6-tetramethyl-o-phenylenedioxydiacetonitriles (IIIj) causes only small hypsochromic displacement of the bands relative to the non-methylated parent compound (IIIa) but the hypochromic effect in all three is considerable (-1067 to -1172). The low extinction coefficients of these three di-ethers are similar in magnitude to those reported[138,139] for a series of 2,6-disubstituted anisoles (ε 300-420) (see Table 21) in which the conformation about the Ph-O bond is orthogonal. It is probable that these low molar extinction coefficients are comprised of contributions from the alkyl substituents and some residual benzenoid absorption. The electronic spectral effects observed in these three compounds also correspond to the Type (1) effects proposed by Braude[122,123] (see Chapter 5.1, page 238). When scale diagrams of 3,6-dimethyl-o-phenylenedioxydiacetonitrile (IIIf) are made it can be seen that considerable overlap of the interference spheres occurs, as shown by the shaded portions, with the two 'in-plane, in-plane' arrangements of the ether functions. (Figs. 23a and b) but when they both assume 'out-of-plane' orientations (Fig. 23c) non-bonded interactions are minimised. Nevertheless, methyl $\leftrightarrow$ oxygen, methyl $\leftrightarrow$ methylene and methylene $\leftrightarrow$ methylene interactions still occur. Steric repulsions between the latter groups can be completely avoided without

FIGURE 23

Scale drawings of 3,6-dimethyl-o-phenylenedioxydiacetonitrile (IIIf)
(a) and (b) represent the two 'in-plane, in-plane' conformations and (c)
depicts the 'out-of-plane, out-of-plane' arrangements



Bond lengths[156]:

All aromatic bonds	1.39 Å
C-C	1.54 Å
C-H	1.07 Å
C-O	1.43 Å
C≡N	1.16 Å

A bond angle of 108° (sp^3 hybridisation) for the oxygen atom was used

Interaction radii[123]:

Me and CH_2	1.70 Å
C-	1.54 Å
C≡	1.20 Å
H	0.62 Å
O-	1.32 Å
N≡	1.1 Å

affecting the orthogonal arrangement of the two $-OCH_2CN$ groups by rotating one of them 180° about the axis of the Ph-O bond. Thus θ for one $-OCH_2CN$ group is $\sim 90^\circ$ and for the other $\sim 180^\circ$. It is suggested that similar conformations would be adopted by the two $-OCH_2CN$ groups in both the 3,4,6-trimethyl- (IIIi) and 3,4,5,6-tetramethyl- (IIIj) analogues.

5.3 Discussion of the ultra-violet spectra of the (ar)-substituted -1,3-benzodioxoles (VII a-m)

Ultra-violet spectral data for all the substituted 1,3-benzodioxoles (VII a-m) in the 280 nm region were determined in methanol and the results are recorded in Table 29. The absorption curves for all these cyclic diethers in this region are shown in Figs. 24 and 25 and it is evident that the majority are symmetrical in appearance with the exception of the 4,7-dimethyl- (VIIf) and 4,5,7-trimethyl (VIIi) compounds which exhibit distinct, shorter wavelength, shoulders. Half-band widths for all but one of the compounds were very similar, 24-26 nm; the one exception was the 5,6-dimethyl- analogue (VIIg) which showed a slight increase at 28 nm.

In related conformational studies[132,157] it has been assumed that the five membered ring in 2,3-dihydrobenzofuran is flat and co-planar with the aromatic ring, i.e. $\Theta = 0$, and hence the extinction coefficient, [λ max (hexane) 283 nm, ε 3095][132] must be at its maximum. The introduction of two oxygen atoms into the heterocyclic ring as in 1,3-benzodioxole (VIIa) causes little change in the extinction coefficient [λ max (hexane) 284 nm, ε 3122][140], as only one of the two chromophores may participate in resonance structures during a $\pi \rightarrow \pi^*$ transition.

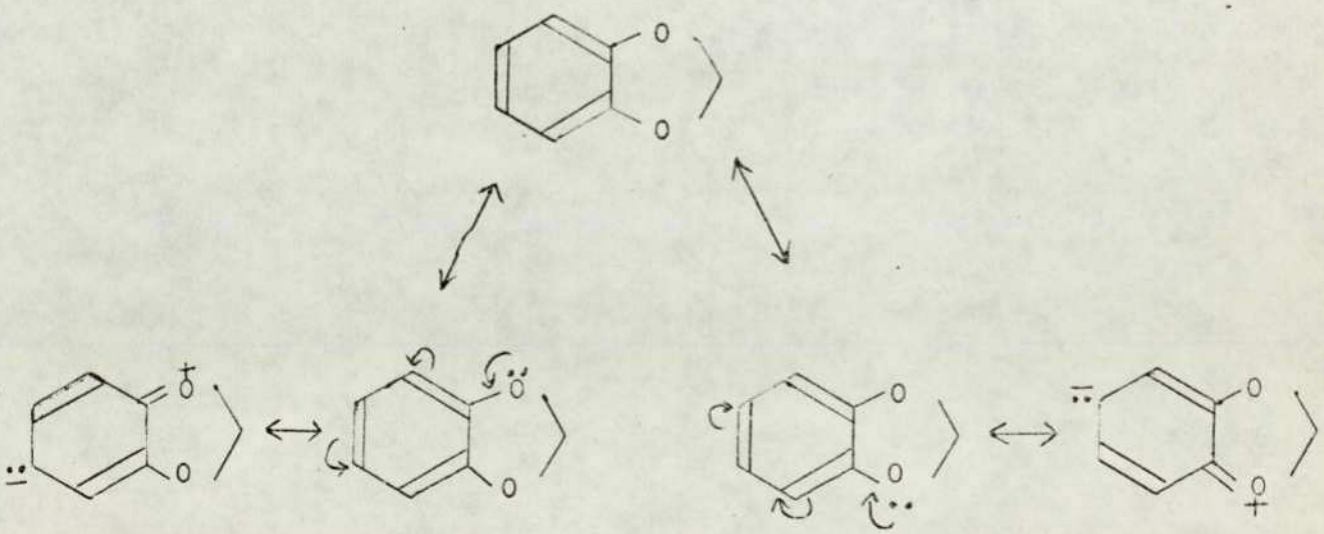


FIGURE 24

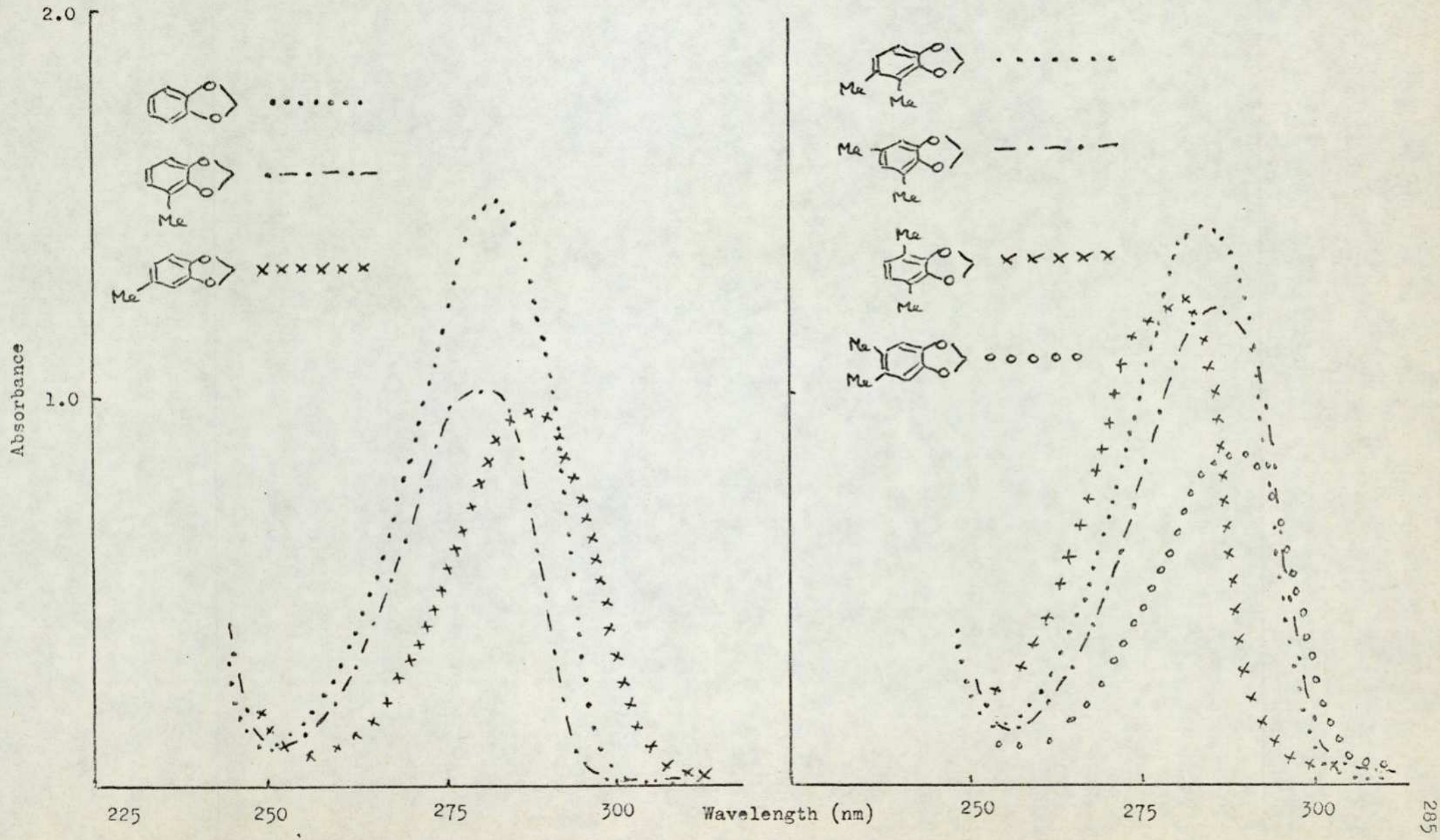

2.0
1.0
Absorbance
225
250
275
300
Wavelength (nm)
250
275
300
Me
Me
Me
Me
Me
Me
Me
Me

FIGURE 25

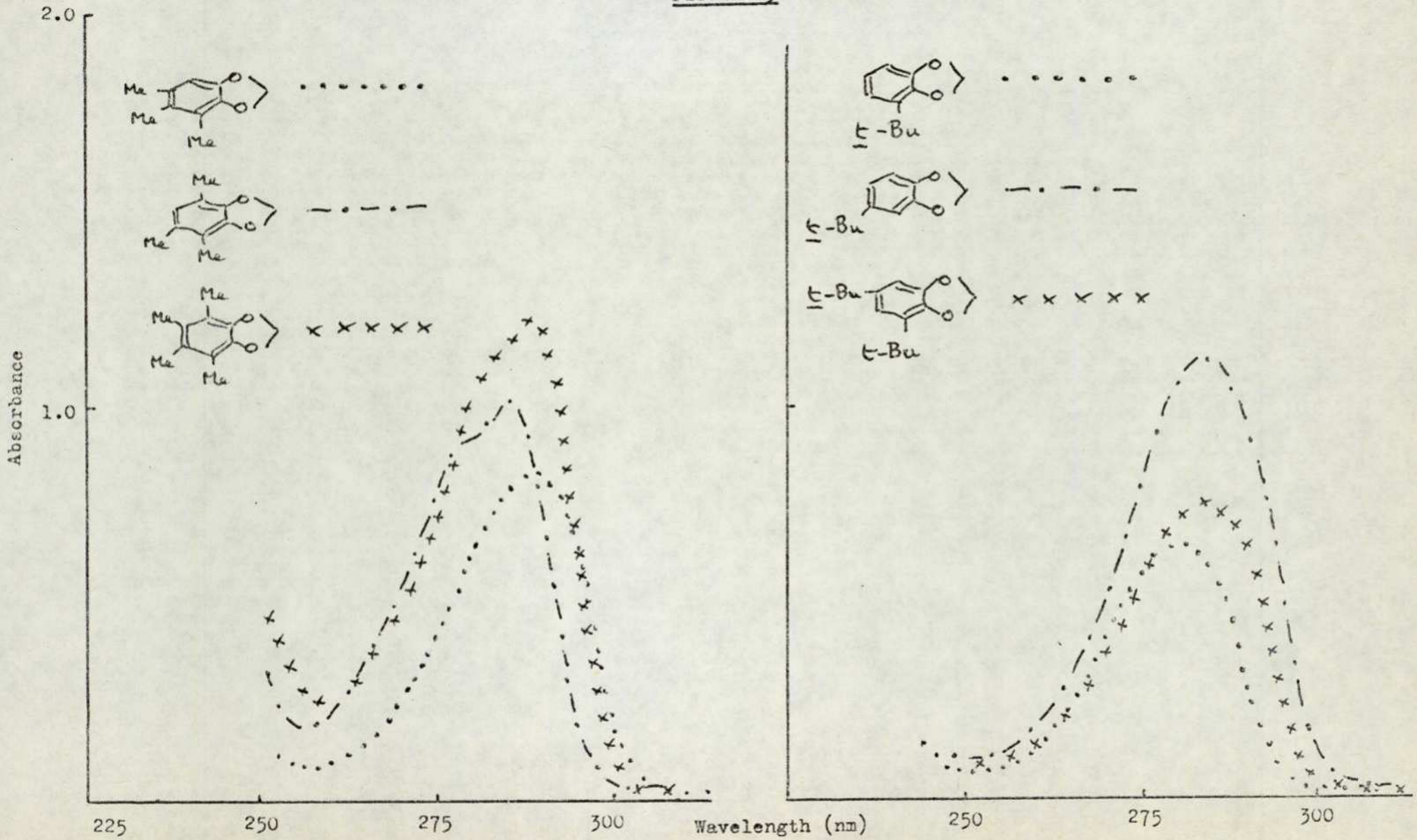

2.0
1.0
Absorbance
Me
Me
Me
Me
Me
Me
Me
Me
Me
t-Bu
t-Bu
t-Bu
t-Bu
225
250
275
300
Wavelength (nm)
250
275
300

TABLE 29

Ultra-violet spectral data for some (ar)- alkyl substituted 1,3-benzodioxoles (VII a-m) in methanol

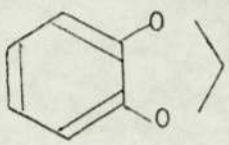
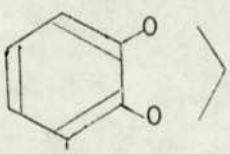
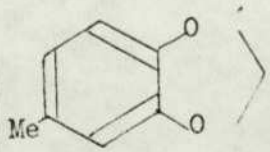
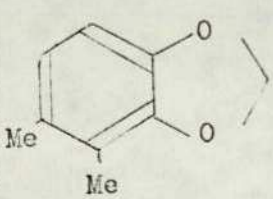
Compound (VII)	λ max (nm) (ε)	Change in λ and apparent change in ε relative to (VIIa)	Loss of Ph-O resonance
 (a)	287 (3180)	0 (0, 0%)	-
 (b)	280.5 (2495)	-6.5 (-685, -21.6%)	30% [a] 32% [a,b]
 (c)	287.5 (3440)	+0.5 (+260, +8.2%)	-
 (d)	284.5 (2622)	-2.5 (-558, -17.6%)	30% [a] 32% [a,b]

TABLE 29 (Cont.)

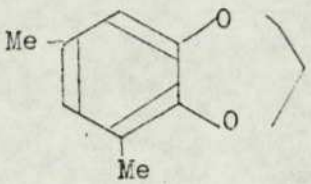
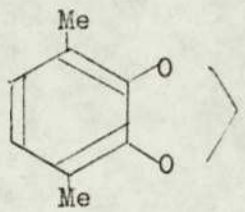
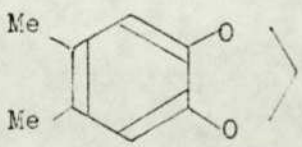
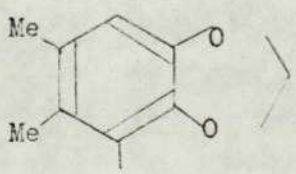
Compound (VII)	λ max (nm) (ε)	Change in λ and apparent change in ε relative to (VIIa)	Loss of Ph-O resonance
 (e)	286.5 (2782)	-0.5 (-398,-12.5%)	30%[a] 32%[a,b]
 (f)	277 sh (1660) 281.5*(1690)	- - -5.5 (-1490,-46.9%)	63%[a] 68.5%[a,b]
 (g)	290.5 (4015)	+3.5 (+835,+26.3%)	-
 (h)	289 (3125)	+2.0 (-55,-1.7%)	30%[a] 32%[a,b]

FIGURE 29 (Cont.)

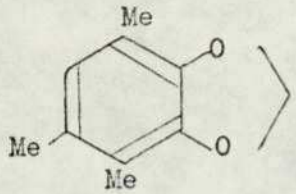
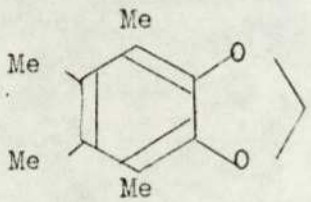
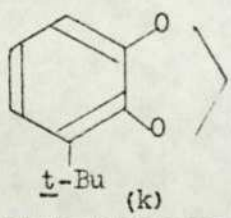
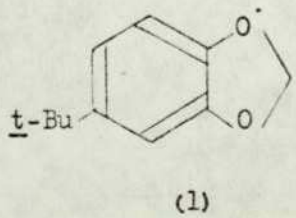
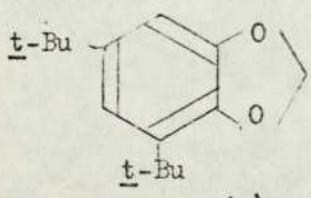
Compound (VII)	λ max (nm) (ε)	Change in λ and apparent change in ε relative to VIIa	Loss in Ph-O resonance
 (i)	280.5 sh (1835) 285* (1945)	- -2.0 (-1235,-39%)	63%[a] 68.5%[a,b]
 (j)	287.5 (2190)	+0.5 (-990,-31.3%)	63%[a] 68.5%[a,b]
 (k)	280.5 (2387)	-6.5 (-793,-25%)	41%[c] 45%[c,b]
 (l)	285 (3697)	-2.0 (+517,+16.3%)	-
 (m)	284.5 (2795)	-2.5 (-385,-12.1%)	41%[c] 45%[c,b]

TABLE 29 (Cont.)

* Taken as the principal band.

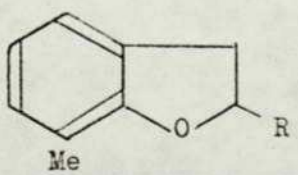
(a) A value of 260/Me was deducted from the calculated extinction coefficient to correct for 'non-steric' effects of the methyl groups.

(b) A value of 250 was subtracted from the extinction coefficient of (VIIa) to compensate for residual absorption of the molecule.

(c) To correct for 'non-steric' effects of the t-butyl groups a value of 517/t-Bu was deducted from the calculated extinction coefficient.

It is therefore reasonable to assume that the 1,3-benzodioxole molecule is planar and that its absorption is also at its maximum.

Of initial interest in this series were the wavelength and intensity changes that occurred as a result of successive nuclear alkylation of the 1,3-benzodioxole molecule. The changes are depicted in Figs. 26 and 27 and are discussed below. Introduction of a 5-methyl group exerted little wavelength displacement (+ 0.5 nm) but increased the extinction coefficient by 260, similar to that of a para-methyl substituent in anisoles[132] and the alkyl group in 4-methyl-o-phenylenedioxydiacetonitrile (IIIc) series (see Chapter 5.2). In comparison a 5-t-butyl group at this position produced a small hypsochromic shift (-2.0 nm) but the absorption was intensified by 16.3% compared with 8.2% for a methyl group. Further methylation at position 6 exerted a bathochromic displacement of 3 nm and increased the absorption 575. The mutual synergistic effect of this methyl substitution pattern was also observed with 4,5-dimethyl-o-phenylenedioxydiacetonitrile (IIIg) (see Chapter 5.2). The presence of either a methyl or t-butyl group at the 4 position effected a 6.5 nm hypsochromic shift with hypochromic effects of 685 and 795 respectively. These results are in contrast to the slight increase in absorption intensity observed[132,139,158] for ortho-alkyl anisoles (Table 30) but are similar to the decrease in absorption intensity (-710) produced by the alkyl group in 7-methyl-2,3-dihydrobenzofuran (XCVIII R=H)[132].



XCVIII

R = H, $-CO_2H$, $-CH_2\overset{+}{N}Me_3\bar{Br}$

FIGURE 26

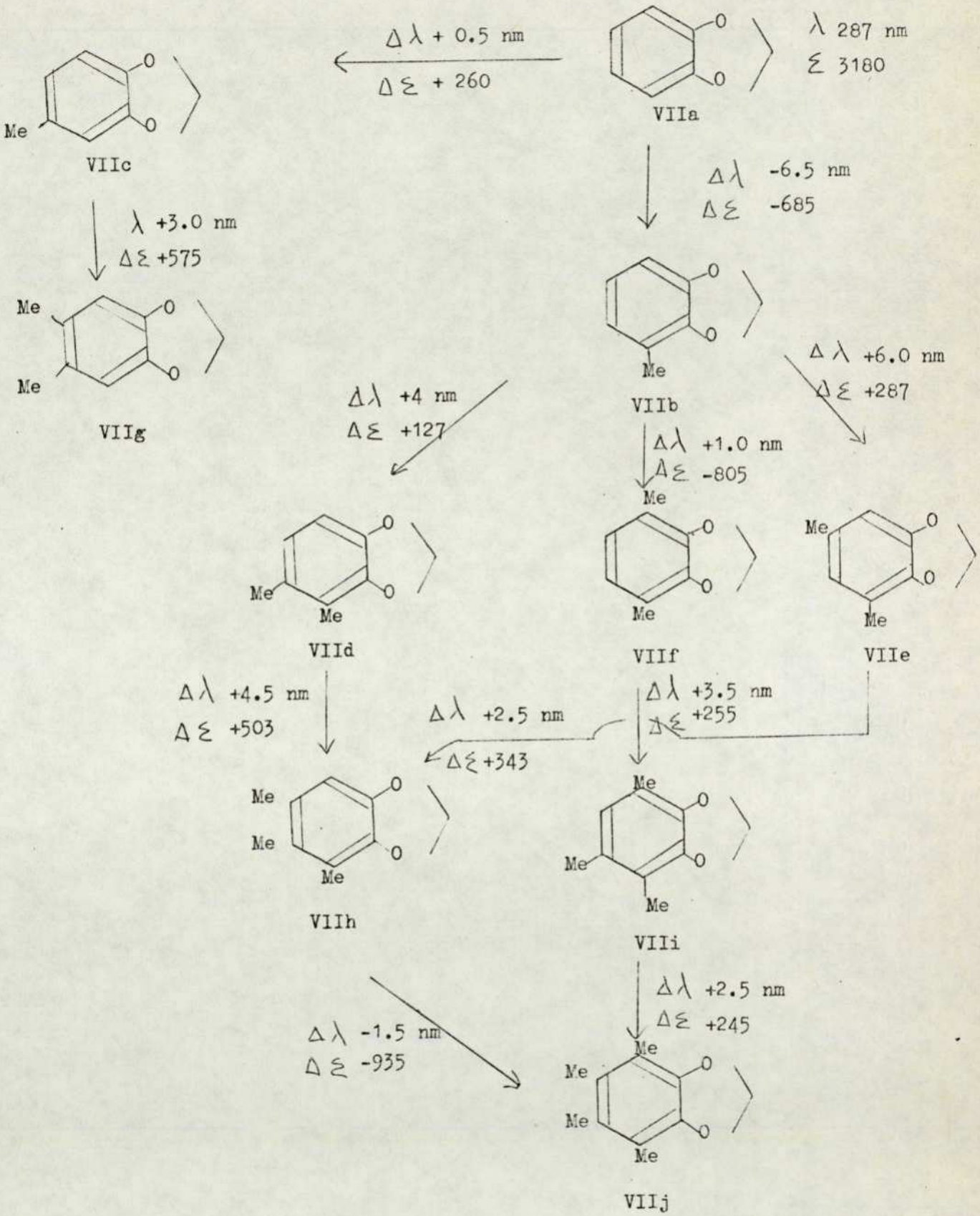

Δλ + 0.5 nm
Δε + 260
λ 287 nm
ε 3180
VIIa
VIIc
Δλ -6.5 nm
Δε -685
λ +3.0 nm
Δε +575
VIIb
Δλ +6.0 nm
Δε +287
Δλ +4 nm
Δε +127
Δλ +1.0 nm
Δε -805
VIIg
VIId
VIIf
VIIe
Δλ +4.5 nm
Δε +503
Δλ +2.5 nm
Δε +343
Δλ +3.5 nm
Δε +255
VIIh
VIIi
Δλ +2.5 nm
Δε +245
Δλ -1.5 nm
Δε -935
VIIj

FIGURE 27

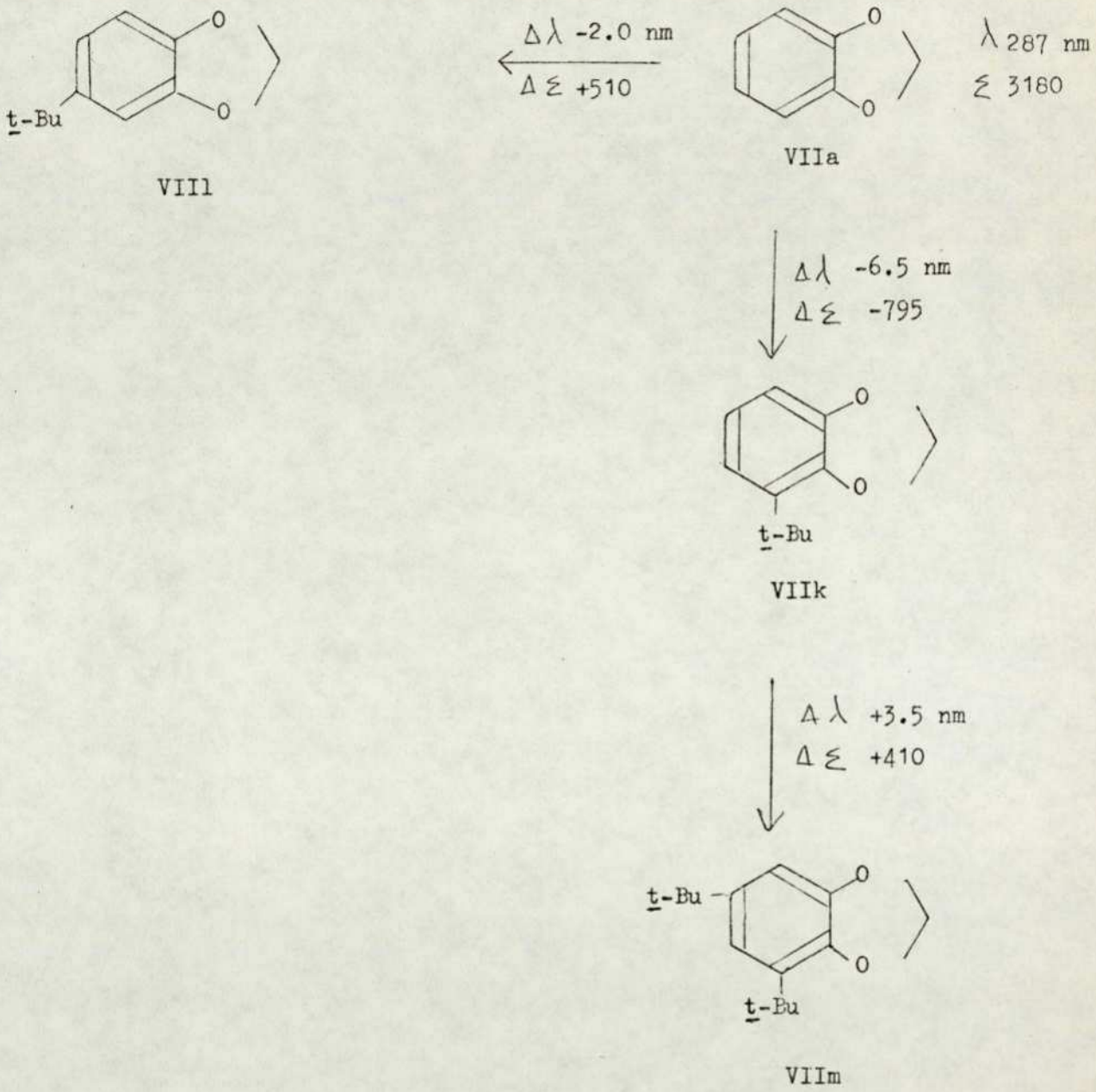
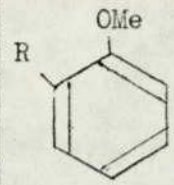

t-Bu
VIIl
Δλ -2.0 nm
Δε +510
VIIa
λ 287 nm
ε 3160
Δλ -6.5 nm
Δε -795
t-Bu
VIIk
Δλ +3.5 nm
Δε +410
t-Bu
t-Bu
VIIm

TABLE 30

Compound	λ max (nm)	ε	Solvent	Reference
				
R = H	271	1579	hexane	139
R = Me	272	1812	"	"
R = i-Pr	269	2089	cyclohexane	158
R = t-Bu	268	1995	"	"

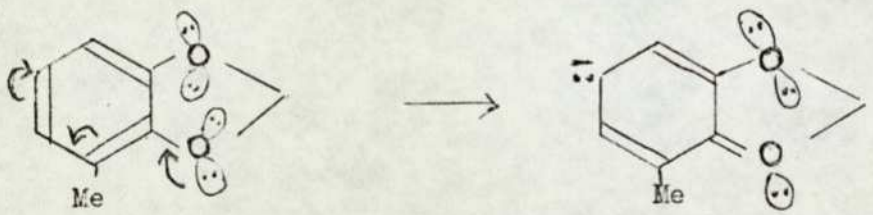
The reasons for these marked hypochromic effects are discussed in more detail on page 296 . In this series bathochromic shifts of 4.0 and 6.0 nm respectively resulted in introducing a 5 or 6-methyl substituent into 4-methyl-1,3-benzodioxole (VIIb) and were accompanied by intensity increases of 127 and 287 respectively. This is a reversal of the trend observed for the methylation of 3-methyl-o-phenylenedioxydiacetonitrile (IIIb) at the corresponding 4 and 5 positions in the ring (see Chapter 5.2). Although the presence of a single 5-t-butyl group caused a small hypsochromic shift (-2.0 nm) the effect of a similarly positioned second t-butyl substituent in the 4-t-butyl compound (VIIk) led to a bathochromic shift of 3.5 nm but the intensity increase was 20% lower than that found for the 5-t-butyl analogue (VIIl). Introduction of a 5-methyl group into 4,6-dimethyl-1,3-benzodioxole (VIIe) and a 6-methyl group into 4,5-dimethyl-1,3-benzodioxole (VIId) caused bathochromic shifts of 2.5 and 4.5 nm with intensity increases of 343 and 503 respectively. It appears that the

level of the synergistic effect of the 5,6-dimethyl groups in compound (VIIg) was not maintained but was reduced by about 20% when a 4-methyl substituent was also present. It was interesting to note that the successive methylation of 4,7-dimethyl-1,3-benzodioxole (VIIf) at the 5 and 6 positions effected small bathochromic shifts of 3.5 and 2.5 nm respectively with absorption enhancements of 255 and 245 per methyl group. These latter values were similar in magnitude to the hyperchromic effect realised by a single 5-methyl group (260) and clearly indicated that the additional 7-methyl substituent had suppressed the synergistic effect exerted by the 5,6-dimethyl groups. The effect was even more pronounced than that observed in the o-phenylenedioxydiacetonitrile (III a-j) series (see Chapter 5.2).

Since nuclear substitution would not be expected to alter the conformation of the 1,3-benzodioxole molecule, wavelength displacements and changes in absorption intensity must be attributed to electronic and/or other factors. Two distinct effects were in fact observed depending upon the position(s) of the substituent(s). Alkyl groups at the 5 and 5,6 position(s) produced slight bathochromic wavelength displacements [the 5-t-butyl compound (VIIi) was an exception] and intensified the absorptions by 8-26% for compounds (VII c,g and l, Table 29) as a result of their inductive and hyperconjugative effects but when these substituents occupy the 4 and 4,7 positions, i.e, 'ortho' to the ether functions, hypsochromic shifts and marked hypochromic effects are evident particularly when 5 or 5,6-substituents are absent (see compounds VII b, f and k, Table 29). The effects are less pronounced when 5 or 5,6-substituents are also present (compounds VII d, e and h, Table 29) but when an allowance is made for their 'non-steric' contributions an 'ortho-effect' of similar magnitude to that observed for the 4-methyl- and

4,7-dimethyl- analogues (VII b and f) became apparent. This substantial drop in the absorption intensity, 22% for VII b, 25% for VII k and 47% for VII f (Table 29, column 3) is attributed to steric inhibition of resonance by the 'ortho' groups. A similar decrease in mesomerism (21.5 - 31.5%) has been observed[132,144] for three 7-methyl substituted 2,3-dihydrobenzofurans (XCVIII).

The inhibition of resonance observed in the 1,3-benzodioxoles bearing 4-alkyl and 4,7-dialkyl substituents (VII b,d,e,f,h,i,j,k,m) can be explained if the processes that occur during the absorption of ultraviolet light are considered. In the ground state of 4-methyl-1,3-benzodioxole (VIIb) the lone-pairs of the 3-oxygen atom will straddle the 4-methyl group (the same will be true of the lone-pairs of the 1-oxygen and 7-methyl group) and interact minimally with it but during a



transition, when the hybridisation of the oxygen atom changes essentially from sp^3 to sp^2, the newly created lone-pair will be in the plane of the benzene ring and its spacial requirements must be such that interaction with the ortho-methyl group must occur with the consequential loss of Ph-O resonance. This is not unexpected since scale projection drawings of o-methylanisole[132], 3-methyl- (IIIb) and 3,6-dimethyl-o-phenylenedioxydiacetonitrile (IIIf) (see Chapter 5.2, Fig. 21) using interference radii

equal to twice the covalent radii[123] in place of the slightly greater Van der Waal's radii generally employed, clearly indicate slight overlap of the interference spheres of the sp^3 hybridised oxygen atoms and the adjacent methyl groups. This would indicate that in 4-methyl-1,3-benzodioxole (VIIb) the overall steric dimensions of the 3-oxygen after sp^2 hybridisation are at least as great and may in fact exceed its volume in the ground state. An alternative interpretation is that the lone-pair makes a significant steric contribution in its own right. Barton and Cookson[159] suggested that a nitrogen lone-pair is bulkier than an attached proton and evidence has been presented[160-164] that lone-pairs are sufficiently large to produce observable steric effects. As a result of dipole moment studies, Aroney and Le Fevre[161,162] considered that the volume requirements of a lone electron pair exceed that of a covalently bound hydrogen atom and in N-methyl piperidine approach that of a methyl group but these findings have been questioned by other investigators[164]. It follows that steric interactions between the t-butyl group and the adjacent ether function are responsible for the loss of resonance in the 4-t-butyl (VIIk) and 4,6-di-t-butyl-1,3-benzodioxole (VII m).

The usual effect of a single ortho-methyl substituent in non-rigid molecules, such as anisoles[132,157] etc., is to cause a small enhancement in the absorption intensity similar in value to that of a para-methyl group[132,157]. Unfortunately, when an 'ortho-effect' is operating no precise value for the inductive effects of the 4 and 7 alkyl groups can be determined. Other investigators[122,123,132] have assumed that the 'non-steric' contributions of ortho-substituents in related systems, where an 'ortho-effect' occurs, is comparable[128,132] with that produced by a para-substituent. Since the methyl group at position 5 in this series exerts 'non-steric' effects similar to those produced by a para-methyl function

in other series[132,139] and as the 4-methyl group behaves essentially as an ortho substituent in 2,6-dimethylanisole[132,139,157] and 7-methyl-2,3-dihydrobenzofuran (XCVIII, R=H)[132] there is some justification for this. A value of 260 for the 'non-steric' contribution of a 4-methyl group has therefore been used in subsequent calculations but it must be emphasised that this value is a speculative one. When the extinction coefficients for all the 4-methyl-1,3-benzodioxoles (VII b, d, e and h) were corrected for 'non-steric' effects of each substituent but without compensation for any residual absorption of the aromatic ring, which would be expected[120b] to have a value of 200-300 in this region, the calculated loss in mesomerism for each compound amounted to 30%. Using a value of 250 to correct for residual absorption the loss was 32%. These values are similar to the 31.4% loss of resonance reported[132] for 7-methyl-2,3-dihydrobenzofuran (XCVIII, R=H) (no correction for residual benzenoid absorption used). When similar corrections (517 per t-butyl group) were applied to the two t-butyl analogues (VII k and m) the drop in mesomerism for each compound as a result of the 4-substituent was calculated to be 41% (45% after correction for residual absorption). For the 4,7-dimethyl-1,3-benzodioxoles (VII f, i and j) the loss in resonance in each compound after a non-steric allowance of 260 per methyl group was made, but without any adjustment for residual benzenoid absorption, amounted to 63%; 67% if a figure of 250 was used to correct for residual absorption. The allowance of 260 per methyl group for non-steric contributions of the 4 and 7 methyl groups appears to be too high since the extinction coefficient of 3,6-dimethyl-o-phenylenedioxydiacetonitrile (IIIf) (see Chapter 5.2, Table 28), in which both $-OCH_2CN$ groups are considered to be orthogonally oriented, is only 342 and comprises 'non-steric' contributions from both methyl groups and residual benzenoid absorption.

5.4 The conformations of some 3-substituted-3,4-dihydro-2H-1,5-benzodioxepins as determined from their ultra-violet spectra

5.4.1 Discussion of the ultra-violet spectra of the ar-substituted 3-keto- (I a-m), 3-hydroxy- (XV a-m) and 3-oximino-3,4-dihydro-2H-1,5-benzodioxepins (XXVIII a-m, R=OH).

Ultra-violet spectral curves in the 270 nm region for the series of ketones (I a-m), alcohols (XV a-k) and oximes (XXVIII a-k, R=OH) have been recorded in Figures 28-34. Generally in this region, the spectra of the ketones (I a-m) and alcohols (XV a-k) consisted of a single principal peak which was attended by a slightly longer wavelength shoulder of reduced intensity. The curves of the ketones (I a-c) and alcohols (XV a-c) strongly resembled those of the correspondingly substituted parent 3,4-dihydro-2H-1,5-benzodioxepins (VIII a-c) (cf. Figures 28-30). Peak widths at half-height for the ketones (I a-m) and alcohols (XV a-k) were in the range 22-27 nm, similar to the range of 24-26 nm observed for the series of substituted 1,3-benzodioxoles (VII a-m) but in the four series of 1,5-benzodioxepins (I, VIII, XV, and XXVIII, R=OH) the presence of 6 or 6,9-substituents tended to broaden half-height widths by about 2 nm and 3-4 nm respectively. Despite these slight variations, the half-height widths of the 1,3-dioxoles (VII) and 1,5-benzodioxepins (I, VIII, XV, XXVIII, R=OH) remained consistently within the range 22-27 nm and the use of ε max to calculate the extinction coefficients in each series was considered justified. In contrast, the principal peak observed for the oximes (XXVIII, R=OH) in this region was usually accompanied by a narrower, longer wavelength band of similar intensity. Half-height widths for the principal peaks in this series were also in the range 23-27 nm

FIGURE 28

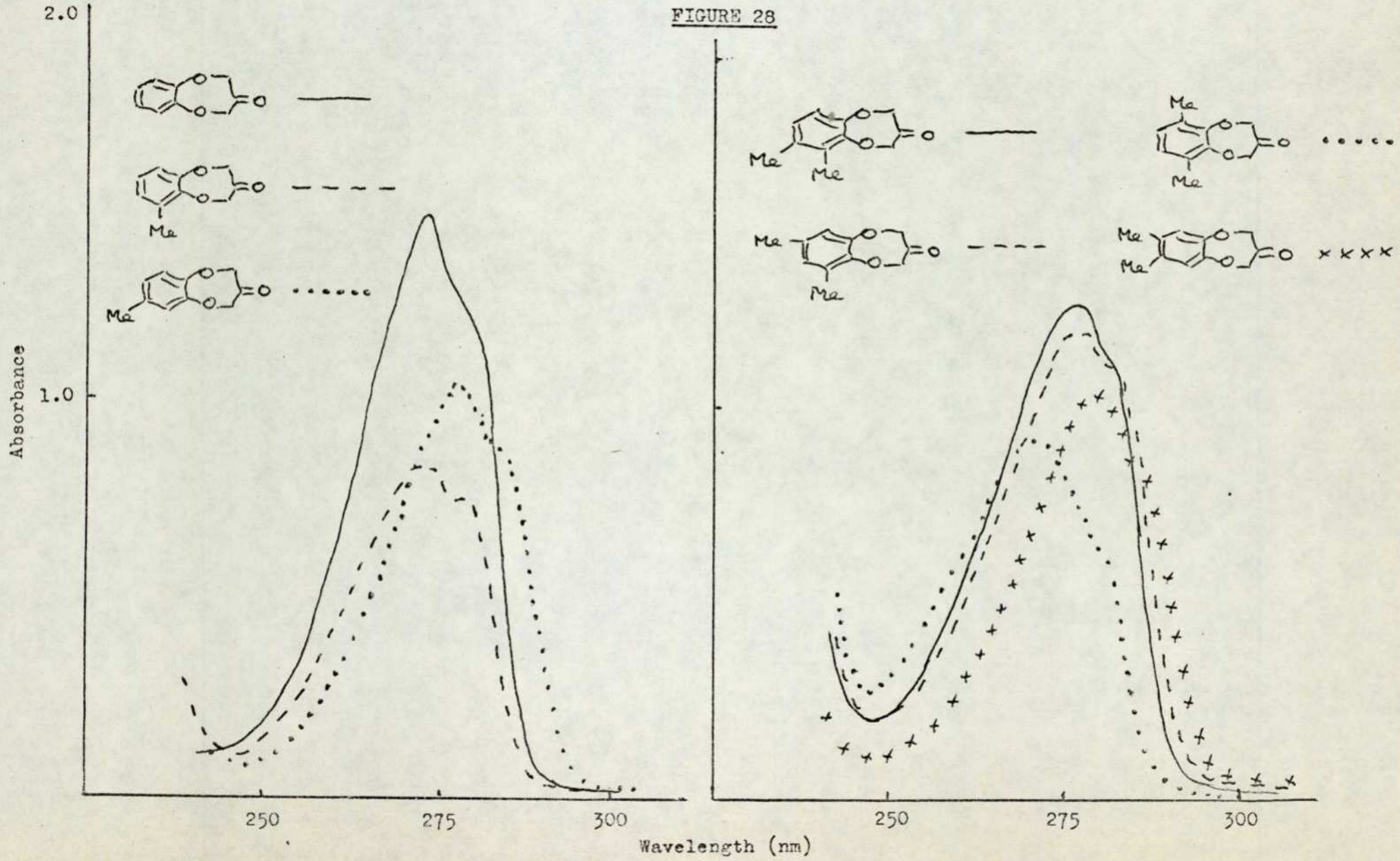

2.0
1.0
Absorbance
Me
Me
Me
Me
Me
Me
Me
250
275
300
250
275
300
Wavelength (nm)

FIGURE 29

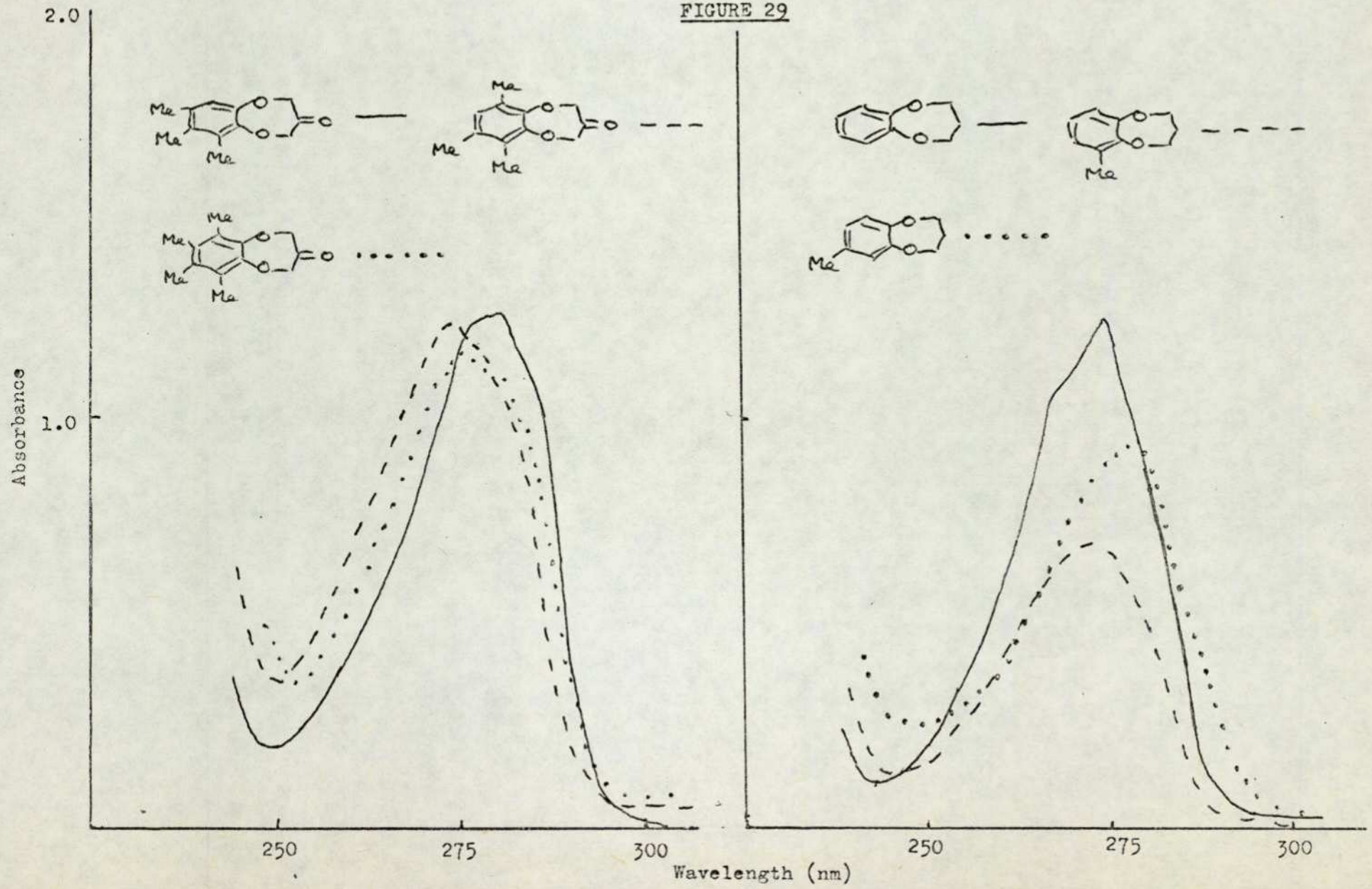

2.0
1.0
Absorbance
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
250
275
300
Wavelength (nm)
250
275
300

FIGURE 30

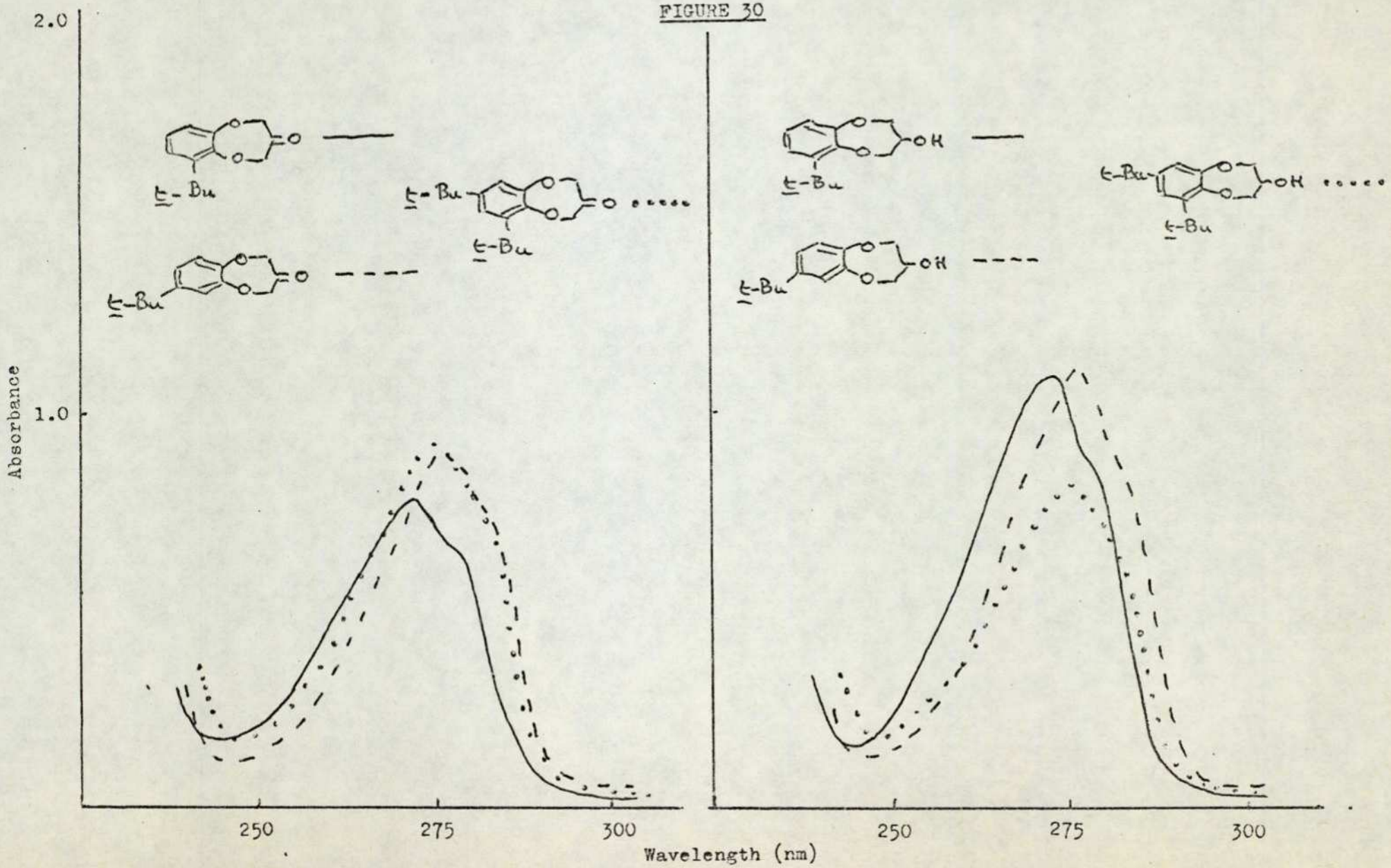

2.0
1.0
Absorbance
t-Bu
t-Bu
t-Bu
t-Bu
t-Bu
OH
t-Bu
t-Bu
OH
t-Bu
OH
250
275
300
250
275
300
Wavelength (nm)

FIGURE 31

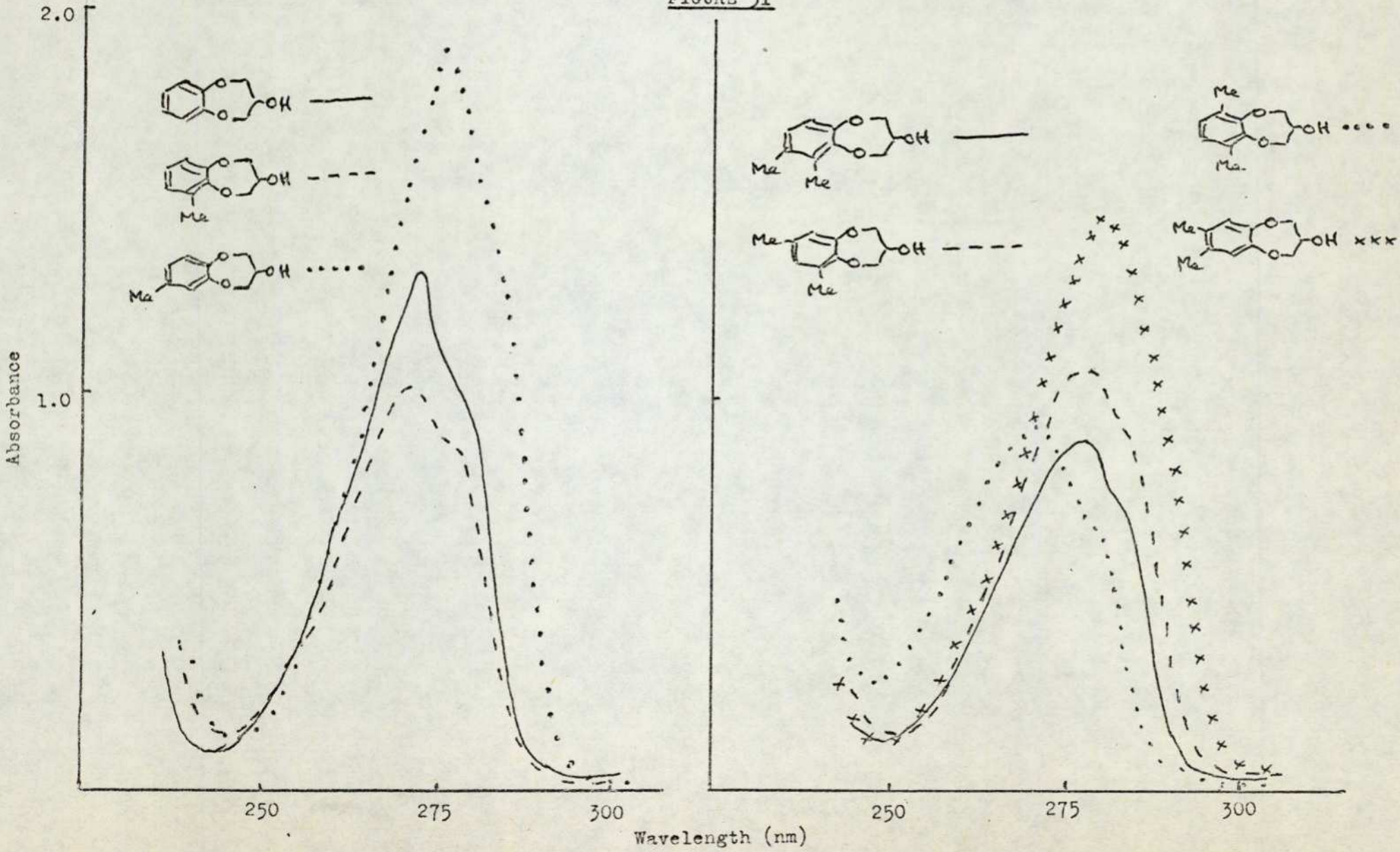


FIGURE 32

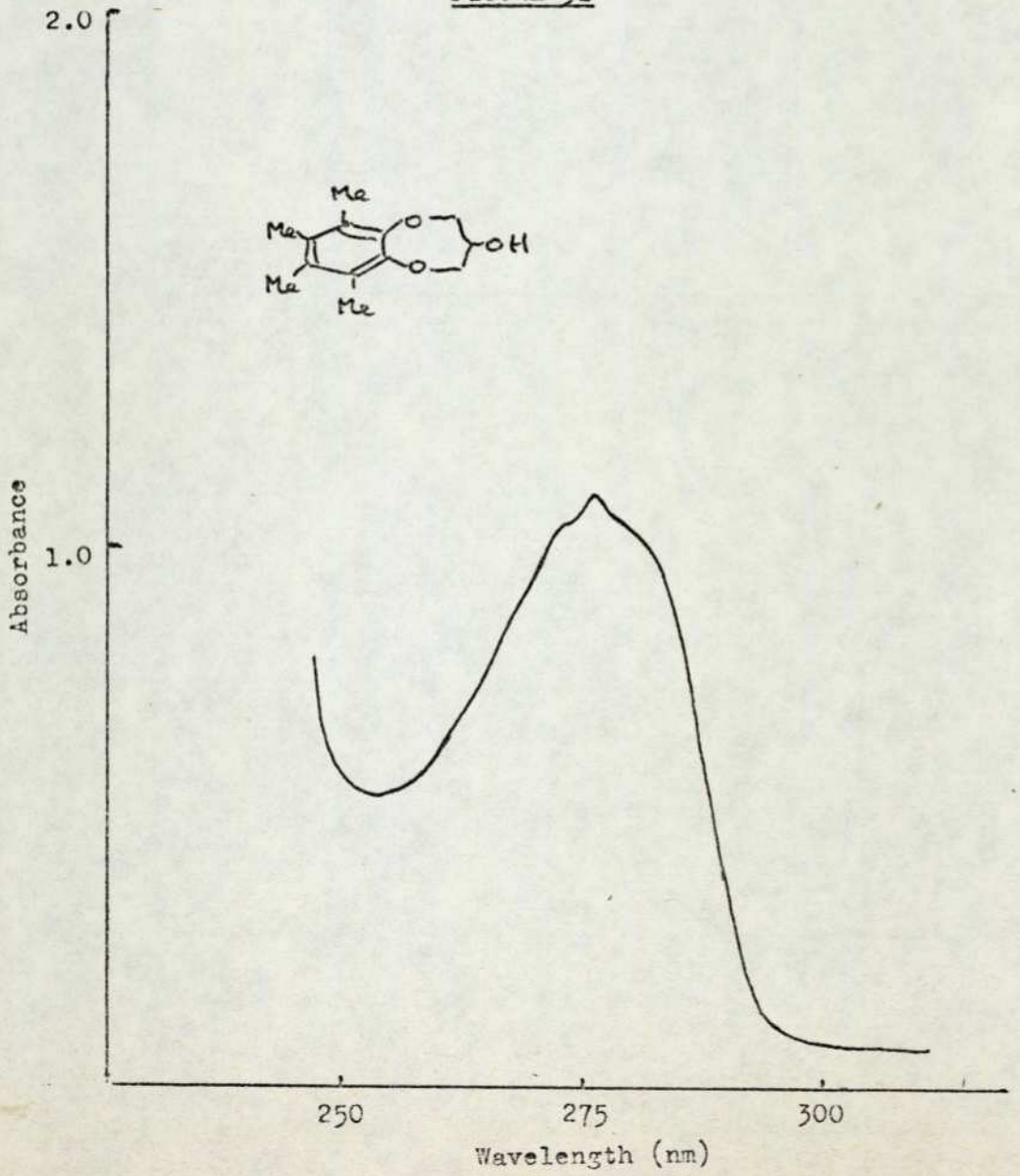


FIGURE 33

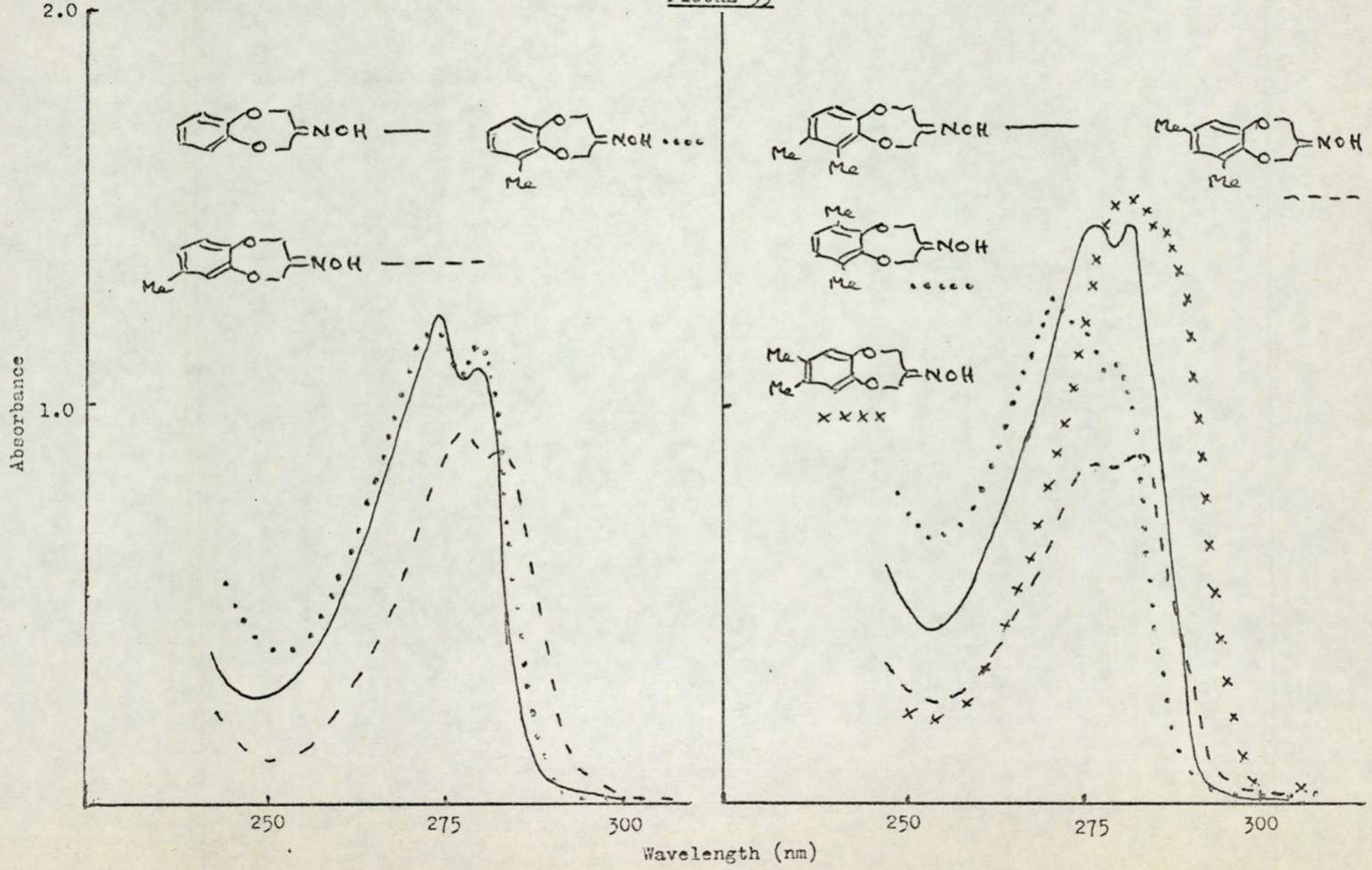
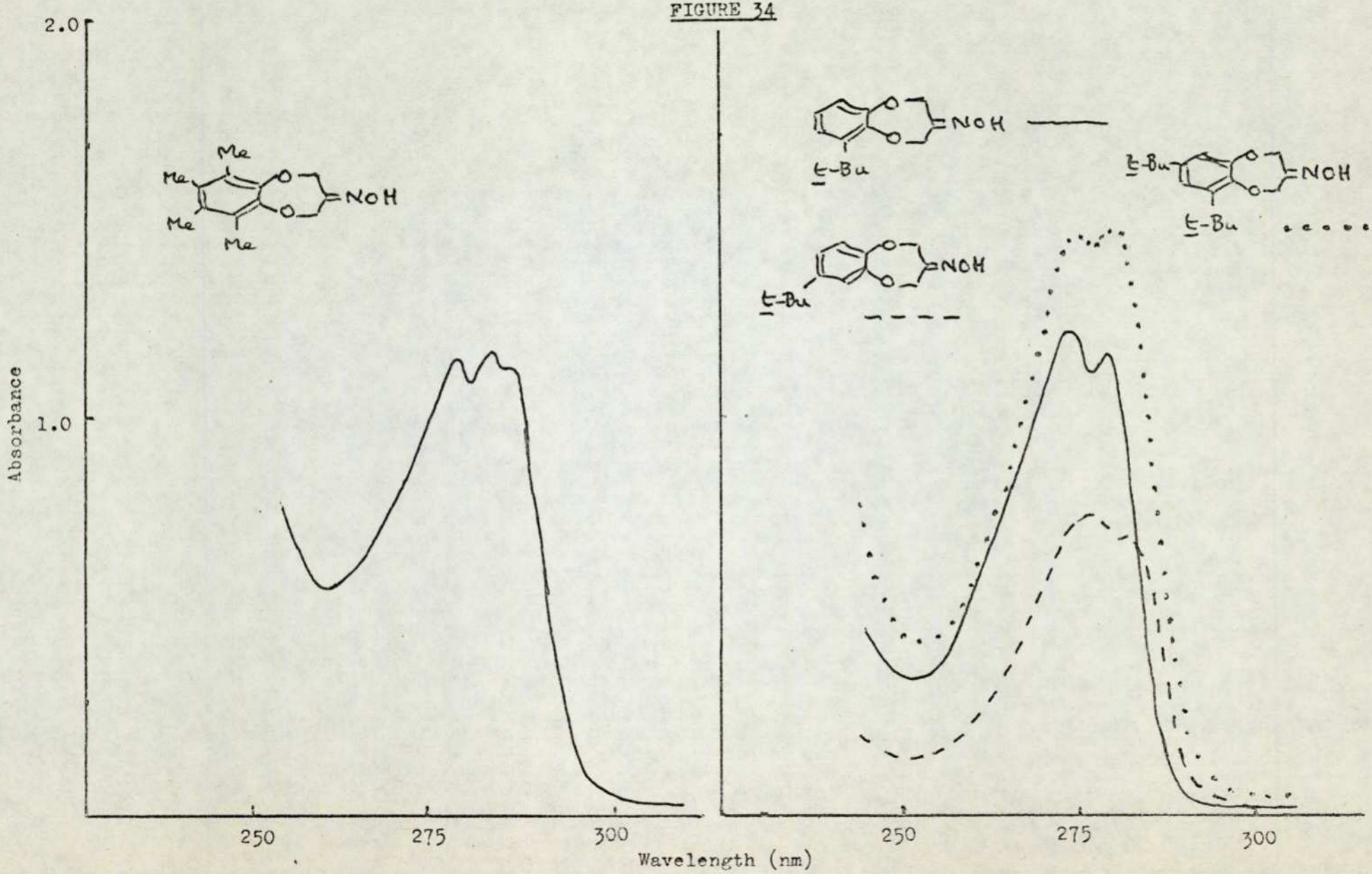
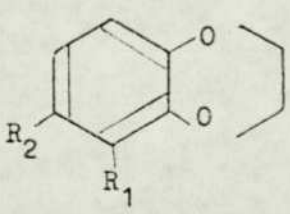


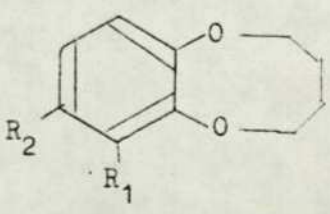
FIGURE 34


2.0
1.0
Absorbance
Me
Me
Me
Me
NOH
t-Bu
NOH
t-Bu
t-Bu
NOH
t-Bu
250
275
300
250
275
300
Wavelength (nm)

but in three instances (XXVIII f, h and k, R=OH) their measurement was not possible owing to the unusually high position of ε min in the 250 nm region. However, the use of ε max to calculate the molar extinction coefficients in these compounds did not appear to incur any serious errors. Spectral data for the series of ketones (I a-m), alcohols (XV a-m) and oximes (XXVIII a-m, R=OH) have been recorded in Tables 32, 33 and 34 respectively. Wavelength shifts and intensity changes exerted by the nuclear substituents on the principal band relative to the unsubstituted parent compounds (VIIIa), (Ia), (XV a) and (XXVIII a, R=OH) of each series are given in columns three of Tables 31-34 respectively. It is clear from these results that the wavelength shifts and percentage changes in absorption intensities relative to the parent compounds are similar for the correspondingly substituted members of each series. The trends observed for the variations in wavelength position and absorption intensity with the location of the nuclear substituent for the three series of 1,5-benzodioxepins (I a-m), (XV a-k) and (XXVIII a-k, R=OH) together with those for the series of 1,3-benzodioxoles (VII a-m) and the few reported[18] members of the six (XCIX a-c), seven (VIII a-c) and eight (C a-c) membered ring analogues are recorded in Figures 35-38.



XCIX



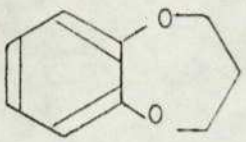
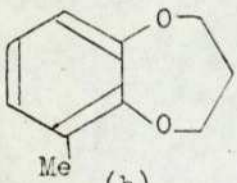
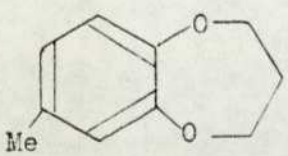
C

(a) $R_1 = R_2 = H$

(b) $R_1 = Me$, $R_2 = H$

(c) $R_1 = H$, $R_2 = Me$

TABLE 31

Compound (VIII)	λ max(nm), ε	Change in λ max (nm) and relative ε to VIIIa			Decrease in absorption intensity relative to corresponding	
					planar compound (VIIa)	parent compound (VIIIa)
 (a)	270 sh 1175 274* 1285	- 0	- 0	- (0%)	- 65%(i)	/
 (b)	273* 739 279 sh 578	-1.0 -	-546 -	(-42.5%) -	"	74%(ii) 63.5%(iii)
 (c)	274 sh 1308 278.5* 1504	- +4.5	- +219	- (+17%)	"	/

* Principal band.

(i) A value of 250 was used to correct for ε min.

(ii) Values of 250 and 220 were used to compensate for ε min and the contribution of the alkyl group respectively.

(iii) As in (ii) but a value of 110 was employed for the alkyl substituent.

TABLE 32

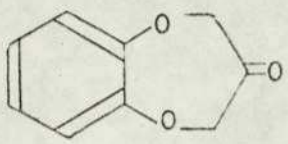
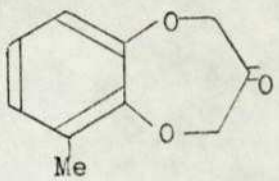
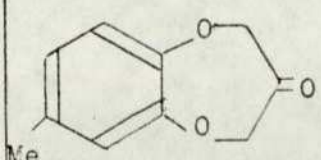
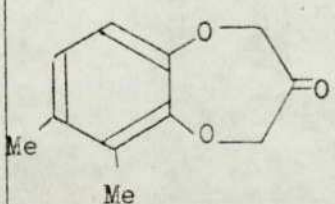
Compound (I)	λ max (nm) ε	Change in λ max (nm) and ε relative to (Ia)	Decrease in absorption intensity relative to corresponding planar compound (VIIa)	Decrease in absorption intensity relative to corresponding parent compound (Ia)
 (a)	273 * 1554 278 sh 1310	0 0 (0%) - - -	55.5%(i)	/
 (b)	272.5* 862 278.5 sh 778	-0.5 -692 (-44.6%) - - -	"	71.5%(ii) 62.3%(ii)
 (c)	278* 1792 283 sh 1650	+5.0 +238 (+15.3%) - - -	"	/
 (d)	276.5* 963 281.5 sh 862	+3.5 -591 (-38%) - - -	"	71.5%(ii) 62.3%(iii)

TABLE 32 (Cont.)

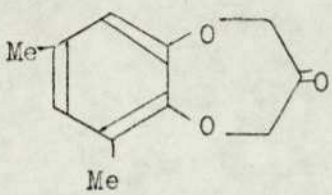
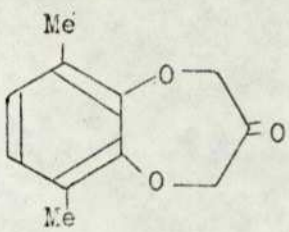
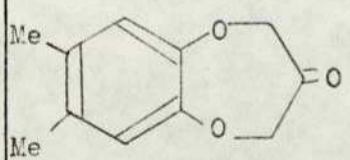
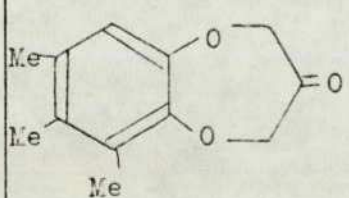
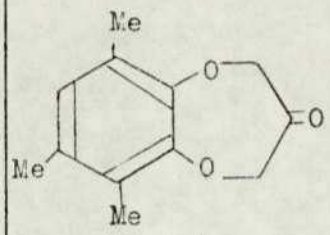
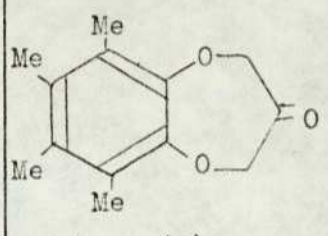
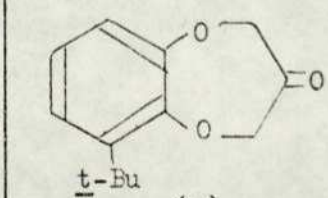
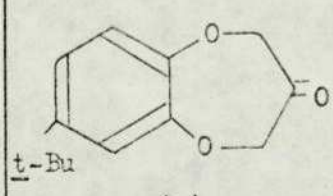
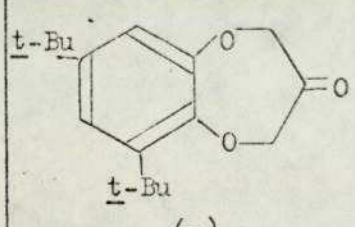
Compound (I)	λ max (nm) ε	Change in λ max (nm) and ε relative to (Ia)	Decrease in absorption relative to corresponding planar compound (VIIa)	Decrease in absorption relative to corresponding parent compound (Ia)
 (e)	277* 1059 282 sh 982	+4.0 -495 (-31.9%) - - -	55.5%(i)	71.5%(ii) 62.3%(iii)
 (f)	270.5* 445 279 sh 322	-2.5 -1109 (-71.3%) - - -	"	ca 100%
 (g)	280.5 2085 286 sh 1750	+7.5 +531 (+34.3%) - - -	"	/
 (h)	280* 1210 283 sh 1050	+7.0 -344 (-22.1%) - - -	"	71.5%(ii) 62.3%(iii)

TABLE 32 (Cont.)

Compound	λ max (nm) ε	Change in λ max (nm) and ε relative to (Ia)	Decrease in absorption intensity relative to corresponding planar compound (VIIa)	Decrease in absorption intensity relative to corresponding parent compound (VIIIa)
 (i)	273.5* 545 277.5 sh 525 280.5 sh 470	+0.5 -1009 (-65%) - - - - - -	55.5%(i)	ca 100%
 (j)	276* 530 281 sh 505 284 sh 440	+3.0 -1004 (-65.2%) - - - - - -	"	"
 (k)	272.5* 915 277 sh 810	-0.5 -639 (-41.1%) - - -	"	75%(iv) 62%(v) -
 (l)	276* 1890 281 1620	+3.0 +336 (+21.6%) - - -	"	/
 (m)	275* 1147 279.5 sh 1020	+2.0 -407 (-26.2%) - - -	"	75%(iv) 62%(v) -

* Absorption taken as principal band.

(i) Σ min taken as 250

(ii) " " " " and a value of 238 deducted for contribution of 6-methyl group.

(iii) As for (ii) but 119 used for contribution of 6-methyl group.

(iv) Σ min taken as 250 and a value of 336 deducted for contribution of 6-t-butyl substituent.

(v) As for (iv) but 168 used for 6-t-butyl group contribution.

TABLE 33

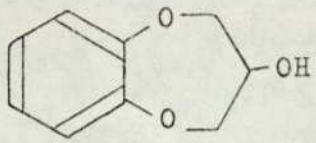
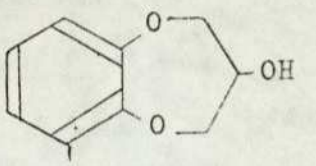
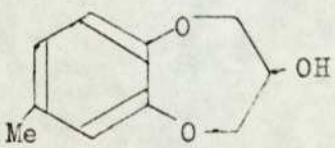
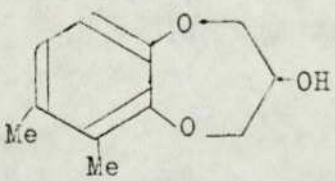
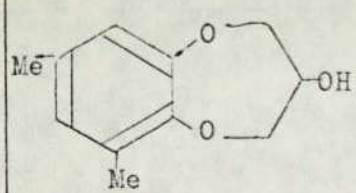
Compound XV	λ max (nm) ε	Change in λ max (nm) and ε relative to (XVa)	Decrease in absorption intensity relative to corresponding planar compound (VIIa)	Decrease in absorption intensity relative to corresponding parent compound (XVa)
 (a)	273.5* 1475 278.5 1215	0 0 (0%) - - -	58.2%(i)	/
 (b)	273* 821 278.5 sh 720	-0.5 -654 (44.3%) - - -	"	74%(ii) 63.8%(iii)
	278.5* 1727 284 sh 1400	+5.0 +252 (+17.1%) - - -	"	/
	277* 905 282 778	+3.5 -570 (-38.7%) - - -	"	74%(i) 63.8%(iii)
	277.5* 993 283 sh 858	+4.0 -482 (-32.7%) - - -	"	"

TABLE 33 (Cont.)

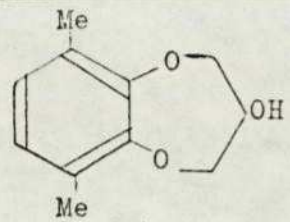
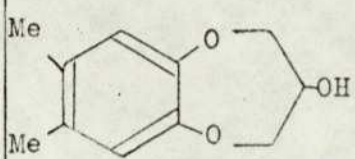
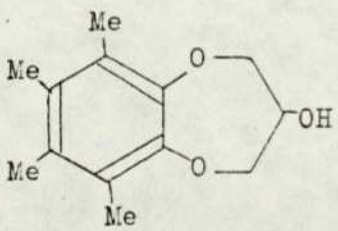
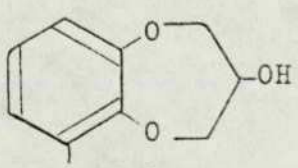
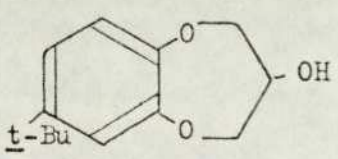
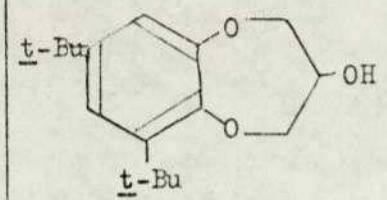
Compound XV	λ max (nm) ε	Change in λ max (nm) and ε relative to (XVa)	Decrease in absorption intensity relative to corresponding planar compound (VIIa)	Decrease in absorption intensity relative to corresponding parent compound (XVa)
 (f)	271* 424 278 310	-2.5 -1051 (-71.2%) - - -	58.2%(i)	ca 100%
 (g)	280.5 2100	+7.0 +625 (42.5%)	"	/
 (h)	273.5 505 276.5* 532 280.5 sh 505	- - - - - -	"	ca 100%
 t-Bu (i)	273* 835 277 sh 705	-0.5 -640 (-43.5%) - - -	"	87.6%(iv) 65.8%(v)
 (j)	276 1810 281 sh 1480	+3.0 +335 (+22.7%) - - -	"	/

TABLE 33 (Cont.)

Compound XV	λ max (nm) ε	Change in λ max (nm) and ε relative to (XVa)	Decrease in absorption intensity relative to corresponding	
			planar compound (VIIa)	parent compound (XVa)
	276 1090	+3.0 -385 (-26.1%)	58.2%	87.6%(iv) 65.8%(v)

* Principal absorption

(i) ε min taken as 250

(ii) " " " " and a value of 252 deducted for effect of 6-methyl group.

(iii) As for (ii) but value of 126 used for effect of 6-methyl group.

(iv) ε min taken as 250 and a value of 335 deducted for effect of t-butyl substituent.

(v) As for (iv) but value for effect of t-butyl group reduced to 167.

TABLE 34

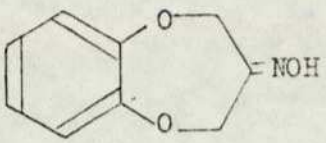
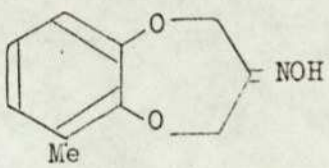
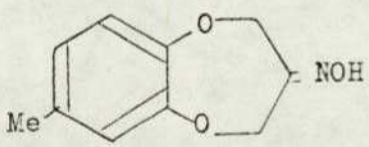
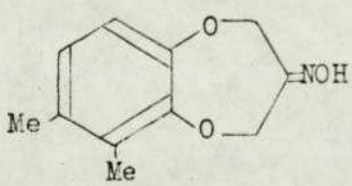
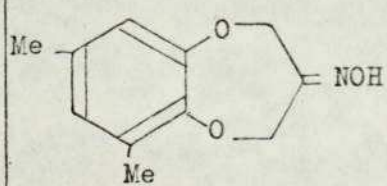
Compound (XXVIII a, R=OH)	λ max (nm) ε	Change in λ max (nm) and ε relative to (XXVIII a, R=OH)	Decrease in absorption intensity relative to corresponding planar compound (VIIa)	Decrease in absorption intensity relative to corresponding parent compound (XXVIII a, R=OH)
 (a)	274* 1855 280 1675	0 0 (0%) - - -	45.3%(i)	/
 (b)	273.5* 1120 279.5 1085	-0.5 -735 (-39.7%) - - -	"	58.5%(ii) 52%(iii)
 (c)	278.5 2057 284 1950	+4.5 +202 (+10.9%) - - -	"	/
 (d)	278* 1243 282 1243	+4.0 -612 (-33%) - - -	"	58.5%(ii) 52%(iii)
 (e)	278.5* 1285 283 1345	+4.5 -510 (-27.6%) - - -	"	"

TABLE 34 (Cont.)

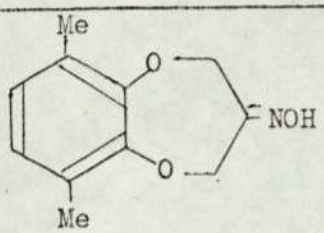
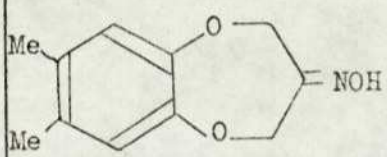
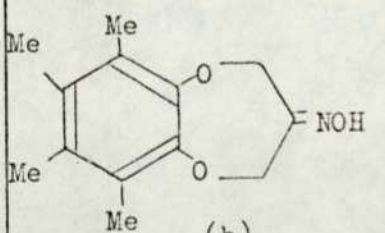
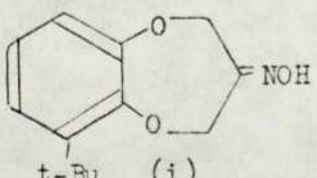
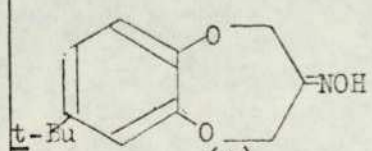
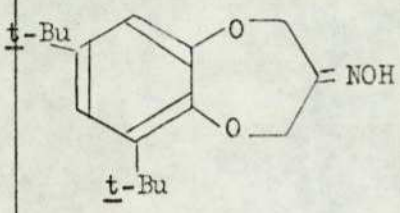
Compound (XXVIII a, R=OH)	λ max (nm) ε	Change in λ max (nm) and ε relative to (XXVIII a, R=OH)	Decrease in absorption intensity relative to corresponding planar compound (VIIa)	Decrease in absorption intensity relative to corresponding parent compound (XXVIII a, R=OH)
 (f)	271.5* 687 274.5 sh 665 279.5 608	-2.5 -1168 (-63%) - - - - - -	45.3%(i)	ca 100%
 (g)	282.5* 2445 286.5 sh 2325	+8.5 +590 (+31.9%) - - -	"	/
 (h)	277* 846 282.5 866	+3.0 -1009 (-54.3%) - - -	"	ca 100%
 t-Bu (i)	273* 1244 284 1200	-1.0 -611 (-33%) - - -	"	52.5%(iv) 45.2%(v)
 t-Bu (j)	277* 2085 282.5 1945	+3.0 +230 (+12.4%) - - -	"	/

TABLE 34 (Cont.)

Compound (XXVIII a, R=OH)	λ max (nm) ε	Change in λ max (nm) and ε relative to (XXVIII a, R=OH)	Decrease in absorption intensity relative to corresponding	
			planar compound (VIIa)	parent compound (XXVIII a, R=OH)
	275.5* 1475 281.5 1500	+1.5 -380 (-20.5%) - - -	"	52.5%(iv) 45.2%(v)

* Principal band.

(i) ε min taken as 250.

(ii) " " " " and a value of 202 subtracted for contribution of 6-methyl substituent.

(iii) As for (ii) but using a value of 101 for effect of 6-methyl group.

(iv) ε min taken as 250 and a value of 230 deducted for 6-t-butyl group.

(v) As for (iv) but using 115 for effect of t-butyl group.

This method of presenting the data is particularly informative since it allows any serious anomalies in λ and ε to be detected and furthermore enables values of λ and ε to be predicted for missing members of each series with reasonable accuracy. Thus, values of λ and ε for the unprepared 6,7,8- and 6,7,9-trimethyl alcohols and the correspondingly substituted oximes have been included in the curves in Figs. 35 and 37. Tentative values of λ and ε for some di-t-butyl members of the series are also given in Figs. 36 and 38 and are based on trends observed for the similarly substituted dimethyl analogues in Figs. 35 and 37. However, values for compounds possessing o-di-t-butyl groups should be treated with caution since the effects of two adjacent bulky ortho-alkyl substituents on λ and ε are unknown in these series and may cause anomalies.

The calculated loss in Ph-O resonance (i.e. the decrease in absorption intensity after correcting for the electronic contributions of the alkyl substituents and residual benzenoid absorption) on ascending from the planar 1,3-benzodioxoles (VII a-m) to the non-planar 1,5-benzodioxepins amounted to 56, 58 and 45% for the ketones (I a-m), alcohols (XV a-k) and oximes (XXVIII a-k, R=OH) respectively (see Tables 32-34, columns four).

Losses in mesomerism from the parent compounds in each series (VIII, I, XV and XXVIII, R=OH), arising from the introduction of a 6-methyl or 6-t-butyl substituent were also calculated for each series (Tables 31-34, columns five). In computing these losses it was assumed that residual benzenoid absorption in each series would be about 250 and initially it was assumed that in the absence of an ortho effect enhancement of the absorption intensity by a 6-alkyl group would be similar to that produced by the same group at the 7 position (cf. Chapter 5.3. p 297).

FIGURE 35

The numberings of the nuclear substituents are relative to the parent pyrocatechols

FIGURE 36

Series

* =

△ =

⊙ =

⊡ =

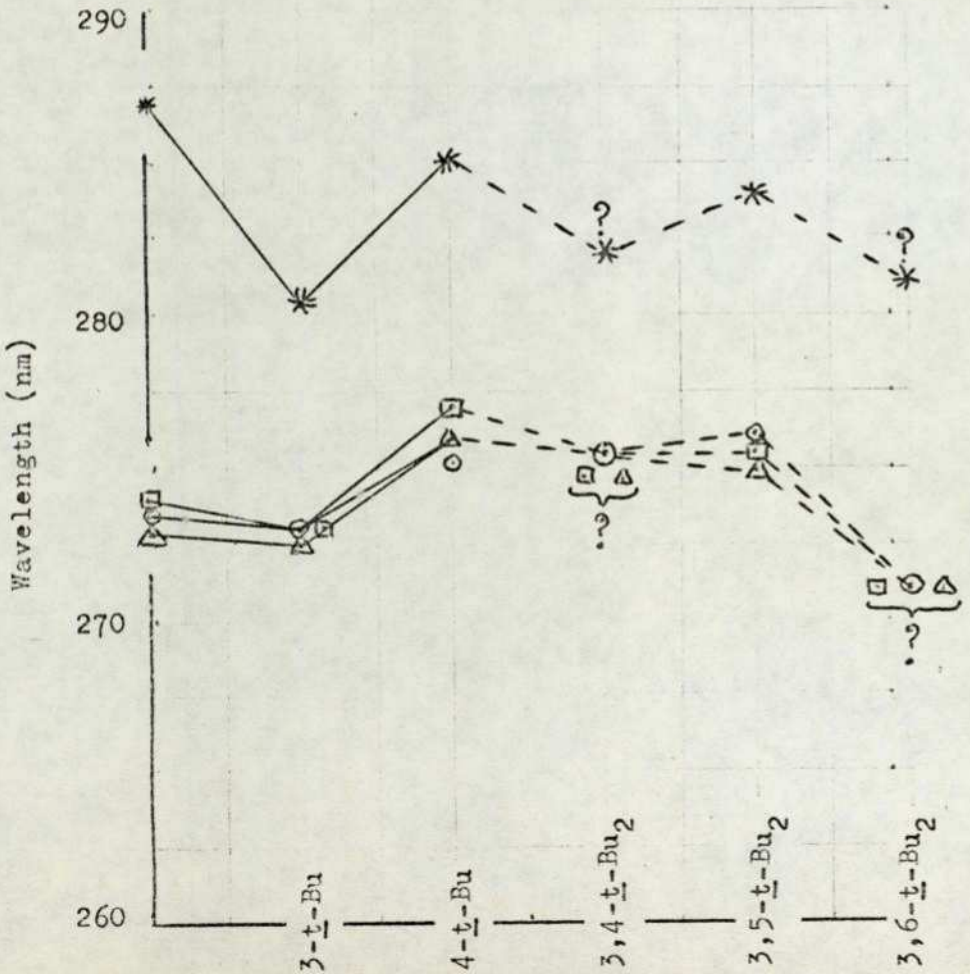
? = Predicted values

The numberings of the nuclear substituents are relative to the parent pyrocatechols

FIGURE 37

Wavelength (nm)
290
280
270
260
3-Me
4-Me
3,4-Me2
3,5-Me2
3,6-Me2
4,5-Me2
3,4,5-Me3
3,4,6-Me3
3,4,5,6-Me4
The numberings of the nuclear substituents are relative to the parent pyrocatechols
Series
OH
=NOH
Predicted values

FIGURE 38



Series

* =

△ =

○ =

⊡ =

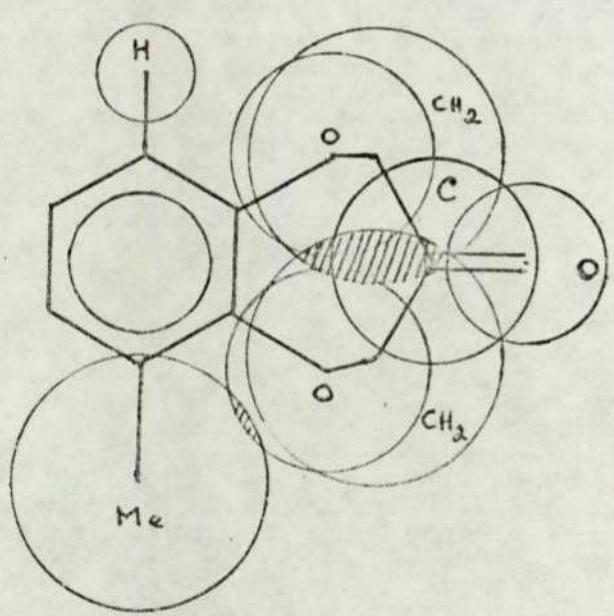
? = Predicted values

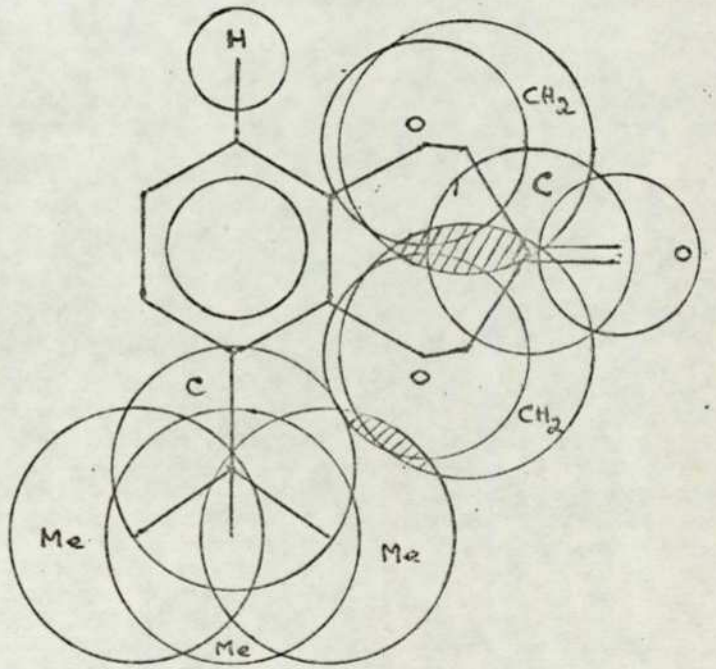
The numberings of the nuclear substituents are relative to the parent pyrocatechols

FIGURE 39

Scale drawings of 3-keto-6-methyl-3,4-dihydro-2H-1,5-benzodioxepin (Ib) and

6-t-butyl-3-keto-3,4-dihydro-2H-1,5-benzodioxepin (Ik)





Bond lengths[156]:

All aromatic bonds	1.39 Å
C-C	1.54 Å
C-H	1.07 Å
C-O	1.43 Å
C=O	1.22 Å

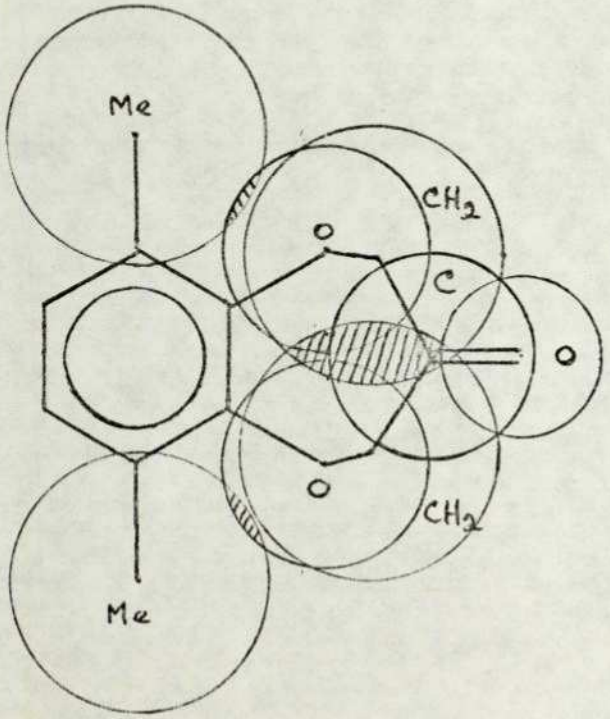
A bond angle of 108° (sp^3 hybridisation) for the oxygen atom was used

Interaction radii[123]:

Me and CH_2	1.70 Å
C-	1.54 Å
H-	0.62 Å
O-	1.32 Å
O=	1.10 Å

FIGURE 40

Scale drawing of 3,6-dimethyl-3-keto-3,4-dihydro-2H-1,5-benzodioxepin (If)



Bond lengths[156]:

All aromatic bonds	1.39 Å
C-C	1.54 Å
C-H	1.07 Å
C-O	1.43 Å
C=O	1.22 Å

A bond angle of 108° (sp^3 hybridisation) for the oxygen atom was used

Interaction radii[123]:

Me and CH_2	1.70 Å
C-	1.54 Å
H-	0.62 Å
O-	1.32 Å
O=	1.10 Å

Using these corrections the calculated losses in resonance for these compounds amounted to 71-88%, compared with the decrease of 32-44.5% produced by the corresponding 4-alkyl substituents in the 1,3-benzodioxole series (VII a-m). It seems unlikely that a single alkyl group would cause a loss in resonance much greater than 50% since mesomerism was still possible from the 1-oxygen. Thus, it would appear that compensation for the inductive and conjugative effects of 6-alkyl substituents in the series of 1,5-benzodioxepins (VIII, I, XV and XXVIII, R=OH) may be too high and should in fact be reduced by about half. Percentage losses in absorption intensity employing these lower values for the electronic contributions of the alkyl groups are 45-66% and have also been included in the Tables.

The use of scale projection diagrams to explain the loss of Ph-O resonance in the 3-methyl-o-phenylenedioxydiacetonitriles (IIIb, d, e, h) was discussed in 5.2. When scale drawings of the 6-methyl- and 6-t-butyl-ketones (Ib and k) were similarly constructed (Fig. 39) overlap of the interference spheres of the 6-alkyl group and the adjacent ether oxygen was again clearly evident. The low absorption intensities observed for compounds substituted at both the 6 and 9 positions are similarly attributed to non-bonded interactions of these groups with the neighbouring oxygen atoms as depicted in Fig. 40. It is probable that the actual absorbance observed for these compounds comprises the residual benzenoid absorption and electronic contributions from the alkyl groups; little if any is considered to originate from the Ph-O chromophore.

5.4.2 Conformations of the ar-substituted 3-keto- (I a-m), 3-hydroxy- (XV a-m) and 3-oximino-3,4-dihydro-2H-1,5-benzodioxepins (XXVIII a-m, R=OH) and miscellaneous derivatives as deduced from their ultra-violet spectra.

The construction of Dreiding stereomodels of 3,4-dihydro-2H-1,5-benzodioxepin (VIIIa) in the rigid 'chair' and flexible 'skew' forms enables θ for the two conformations to be measured. When these measured angles are substituted into the $\cos\theta = \varepsilon/\varepsilon_0$ and $\cos^2\theta = \varepsilon/\varepsilon_0$ equations, together with the appropriate value for ε_0, the extinction coefficients for the two extreme conformations may be calculated and compared with values of ε observed for 1,5-benzodioxepins variously substituted in the heterocyclic ring. Admirably suited for this purpose were the miscellaneous 1,5-benzodioxepin derivatives prepared in Chapter 3 whose absorption intensities were uncomplicated by additional aromatic substituents. Ultra-violet spectral data for these compounds have been recorded in Table 35.

In this investigation Dreiding models of the two conformers were assembled from units whose bond angles were carefully prechecked to prevent the use of distorted components. The models were then placed on a horizontal surface and viewed along the axis of the Ph-O bond from where θ was measured directly from a protractor. The values of θ thus obtained for the 'skew' and 'chair' forms were 45° and 73° respectively. Previously twist angles of 44° and 64° were reported[18] for the two conformations. These were measured directly from photographs of Dreiding models taken from a point in the plane of the benzene ring along the axis of the Ph-O bond. However, the value of 64° is now considered to be incorrect. It is interesting to note that the angle of twist reported by Clarke and Williams[132] for homochroman (CI) in the

TABLE 35

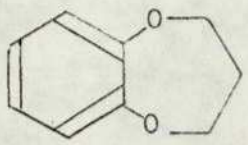
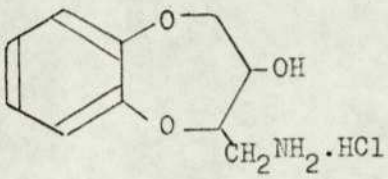
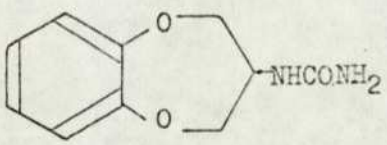
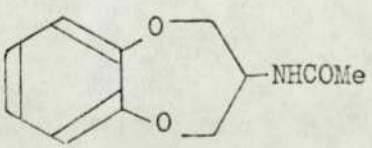
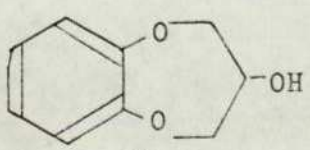
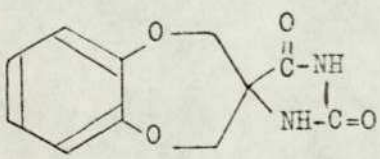
Compound	λ max (nm) (ε)	θ calculated from: $\cos\theta = \varepsilon/\varepsilon_0$ (i)	(ii)	$\cos^2\theta = \varepsilon/\varepsilon_0$ (i)	(ii)	θ measured from model skew	chair
 VIIIa	274(iv) (1285)	66	69½	50½	53½	45°	73°
 LVIII; HCl salt	272(v) (1290)	66	69	50	53½	"	"
 LVIIa	273(v) (1370)	64½	67½	49	52	"	"
 LVIIb	273.5(v) 1470	62½	67½	47	52	"	"
 XVa	273.5(iv) (1475)	62½	65½	47	49½	"	"
 XXXXIX	272(v) (1490)	62	65	47	49½	"	"

TABLE 35 (Cont.)

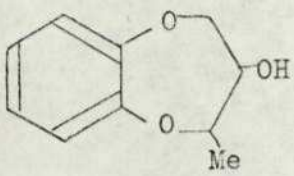
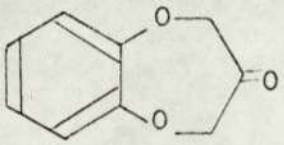
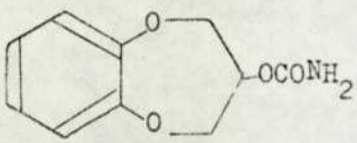
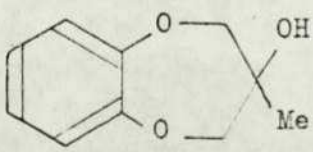
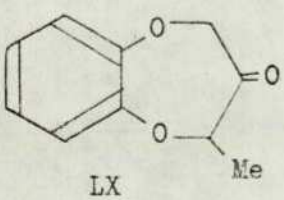
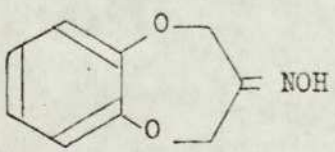
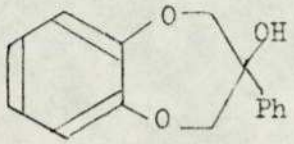
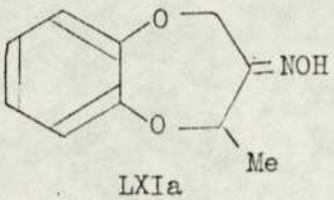
Compound	λ max (nm) (ε)	Θ calculated from: $\cos\Theta = \varepsilon/\varepsilon_0$ (i)	(ii)	$\cos^2\Theta = \varepsilon/\varepsilon_0$ (i)	(ii)	Θ measured from model: skew	chair
 LXII	274(iv) (1530)	61	64	46	48½	45°	73°
 Ia	273(iv) (1554)	60½	63½	45½	48	"	"
 LII	273(v) (1570)	60½	63	45	48	"	"
 LVa	274(v) (1530)	61	63	46	47½	"	"
 LX	274(v) (1760)	56½	59	42	44	"	"
 XXVIIIa	274(iv) (1855)	54½	57	40	42	"	"

TABLE 35 (Cont.)

Compound	λ max (nm) (ε)	θ calculated from: $\cos\theta = \varepsilon/\varepsilon_o$ (i)	(ii)	$\cos^2\theta = \varepsilon/\varepsilon_o$ (i)	(ii)	θ measured from model: skew	Chair
 LVb	273.5(v) (1900)(iii)	57½	61½c	43	46½c	45	73
 LXIa	275(v) (2030)	50	51½	37	38	"	"

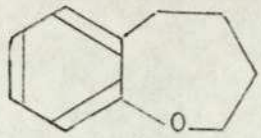
(i) No corrections applied.

(ii) A correction of 250 was applied for ε min.

(iii) A value of 250 was deducted for the contribution of the 3-phenyl group.

(iv) See reference 29b.

(v) " " 29a.



CI

chair conformation was also 73° which is not unexpected since the oxygen at position 5 (bond angle 110°) in 3,4-dihydro-2H-1,5-benzodioxepin (VIIIa) has merely been replaced by a $-CH_2-$ group of bond angle 109° 28'. Values of ε for the two extreme conformations of the dihydrobenzodioxepin ring were then calculated from the equations:-

$$\text{Cos } \theta \text{ or } \text{Cos}^2 \theta = \frac{(\varepsilon - \varepsilon \text{ min})}{(\varepsilon_o - \varepsilon \text{ min})}$$

using the revised values of 45° and 73° and a value of 3180 for ε_o [i.e., ε for 1,3-benzodioxole (VIIa), Table 29)], together with a correction of 250 for ε min. The values of ε calculated by the Cos θ expression for the 'chair' and 'skew' forms were, after readjustment for ε min, 1105 and 2320 respectively; using the $\text{Cos}^2 \theta$ equation the respective values were 500 and 1715. From the results in Table 35 it can be seen that the spectroscopically determined extinction coefficients occur in the range 1285-2030 which suggests that the Cos θ equation gives a more accurate indication of the conformation of the seven-membered heterocyclic ring than the $\text{Cos}^2 \theta$ equation. Furthermore the value of θ calculated for the parent 3,4-dihydro-2H-1,5-benzodioxepin (VIIIa) from spectroscopic data (see Table 35) agreed satisfactorily with the revised value of θ measured from a stereomodel in the 'chair' conformation, particularly when corrections for ε min were applied. Agreement between θ calculated from the $\text{Cos}^2 \theta$ equations and the value measured for the 'skew' conformation is not unreasonable but the extinction coefficient range (500-1715)

calculated for the two extreme conformations does not accommodate all the observed values in Table 35. In addition the 'skew' effect produced by the $Cos^2 \theta$ function tends to decrease the spectroscopic estimate of θ by 10-15° in this range. The results for the limited but varied assortment of compounds in Table 35 are consistent with those found previously by Archer[18]. Thus, compounds with extinction coefficients 1300 ~ 1400 would appear to exist in a 'chair' conformation similar to those found[142,143, 146,147,148] and calculated[149] for carbocyclic and heterocyclic analogues whereas compounds with extinction coefficients > 2000 would probably exist with the heterocyclic ring in a 'skew' conformation. Most of the compounds in Table 35 have extinction coefficients in the range 1400-1800 and are considered, in agreement with previous findings[18], to exist as an equilibrium mixture of the 'chair' and 'skew' forms. The ratio of these two conformations at equilibrium would depend mainly upon the conformational preference of the substituents in the heterocyclic ring.

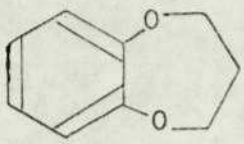
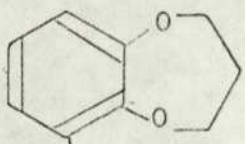
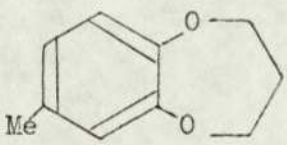
The introduction of substituents into the aromatic ring of the 1,5-benzodioxepins would not be expected to affect the conformation of the heterocyclic ring. To confirm this, attempts were made to calculate values of θ for the series of 1,5-benzodioxepins (VIII a-c), (Ia-m), (XV a-k) and (XXVIII a-k, R=OH) using the spectroscopic data in Tables 31-34, together with data for the correspondingly substituted planar 1,3-benzodioxoles (VII a-m) in Table 29.

From the discussions concerning the electronic absorption data of these compounds (5.4.1) it was evident that accurate $\varepsilon/\varepsilon_o$ ratios could only be calculated from the appropriate unsubstituted heterocycles (VIII a, Ia, XVa and XXVIIIa, R=OH) or from 1,5-benzodioxepins possessing 7- or 7,8-dialkyl groups (VIIIc, Ic, g, XV c, g and XXVIII c, g, R=OH) and the appropriate 5- or 5,6-dialkyl-1,3-benzodioxoles (VII c,g) where the absorption enhancements

produced by the alkyl substituent(s) are similar in each series (Tables 31-34) and would tend to cancel out. Values of Θ for these compounds are given in Tables 36-39 and were calculated from the $\text{Cos}\ \Theta = \varepsilon/\varepsilon_o$ and $\text{Cos}^2\ \Theta = \varepsilon/\varepsilon_o$ equations and from the modified expressions incorporating the correction for ε min proposed by Clarke and Williams[132], i.e., $\text{Cos}\ \Theta$ or $\text{Cos}^2\ \Theta = \dfrac{\varepsilon_{corr} - \varepsilon_{min}}{\varepsilon_o - \varepsilon_{min}}$

Appreciable errors occur when calculating $\varepsilon/\varepsilon_o$ ratios, and hence Θ, from the requisite 1,3-benzodioxoles and 1,5-benzodioxepins having one alkyl substituent ortho to an ether function (i.e., compounds VIIb, d, e, h, k, m; VIIIb; Ib, d, e, h, k, m, XVb, d, e, i. k and XXVIII b, d, e, i, k, R=OH) for two reasons. Firstly, no precise value can be estimated for the contribution to the absorption intensity by an ortho-alkyl substituent in either series although it is probable that in calculating $\varepsilon/\varepsilon_o$ ratios they would tend to cancel out. The second source of error arises because the loss of resonance from the ether chromophore adjacent to the ortho-alkyl group differs considerably on passing from the planar 4-alkyl-1, 3-benzodioxoles (VII b, d, e, h), where the fall amounted to 64.5% to the non-planar 6-methyl-1,5-benzodioxepins (VIII b , I b, d, e, h, XV b, d, e and XXVIII b , d,e, R=OH) where the fall was ca 100%. Consequently values of θ calculated from the available data by the $\text{Cos}\ \Theta = \varepsilon/\varepsilon_o$ and $\text{Cos}^2\theta = \varepsilon/\varepsilon_o$ equations have not been included in the Tables. However, an approximate value for Θ may be calculated as follows. If it is assumed that the observed absorption in 6-alkyl-1,5-benzodioxepins originates mainly from the oxygen chromophore at the 1-position then, after correcting for the electronic contribution of the 6-alkyl group (a value equal to half that observed for the electronic contribution of the 7-alkyl substituent was used) a value for $\varepsilon/\varepsilon_o$ may be calculated based on half the absorption coefficient of the planar reference compound:-

TABLE 36

Compound VIII	θ calculated from: Cos θ (i)	Cos θ (ii)	Cos² θ (i)	Cos² θ (ii)	θ measured from Dreiding model: skew	chair
 a	66	69½	50½	53½	45	73
 b	/	75(iii)	/	59½(iii)	"	"
 c	64	69½	48½	53½	"	"

(i) No correction applied for ∠ min.

(ii) A correction of 250 for ∠ min was used.

(iii) An allowance of 110 was made for the effect of the 6-methyl group (cf. Table 31).

TABLE 37

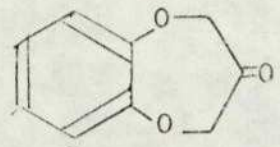
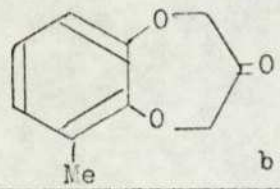
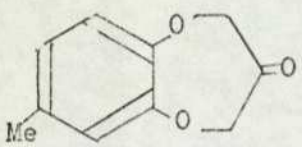
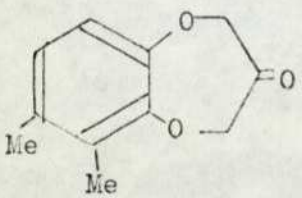
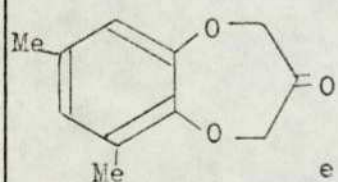
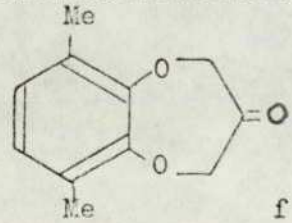
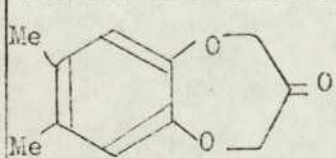
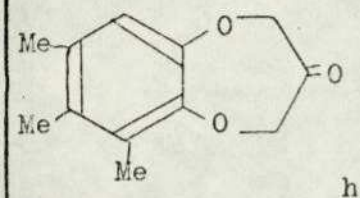
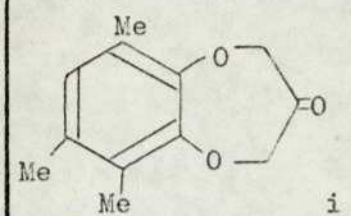
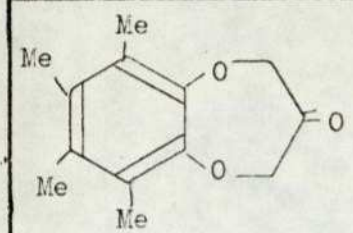
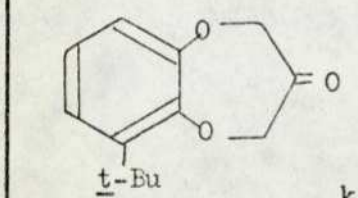
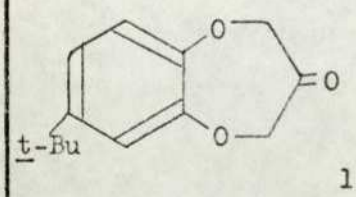
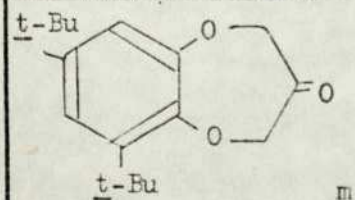
Compound (I)	θ calculated from: Cos θ (i)	Cos θ (ii)	Cos² θ (i)	Cos² θ (ii)	θ measured from Dreiding model: skew	chair
 a	60½	63½	45½	48	45	73
 b	/	(iii) 70½	/	(iii) 54½	"	"
 c	58½	63½	44	48	"	"
 d	/	70½ (iv)	/	54½	"	"
 e	/	70½ (iv)	/	54½	"	"
 f	/	/	/	/	"	"
	58½	63½	44	48	"	"

TABLE 37 (Cont.)

Compound (I)	θ calculated from: Cos θ (i)	Cos θ (ii)	Cos² θ (i)	Cos² θ (ii)	θ measured from Dreiding model: skew	chair
 h	/	70½ (iv)	/	54½	45	73
 i	/	/	/	/	"	"
	/	/	/	/	"	"
 k	/	70½ (iv)	/	54	"	"
 l	59½	63½	44½	48	"	"
 m	/	70	/	54	"	"

(i) No corrections applied.

(ii) A correction of 250 for ε min used.

(iii) An allowance of 119 was made for effect of 6-methyl group (cf. Table 32).

(iv) An allowance of 168 was made for the effect of the 6-t-butyl group (cf. Table 32).

TABLE 38

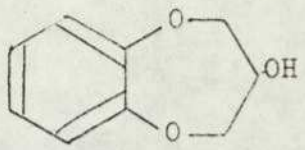
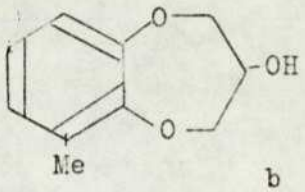
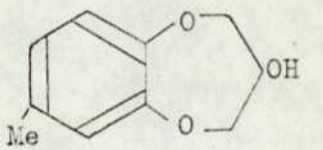
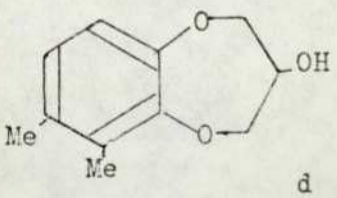
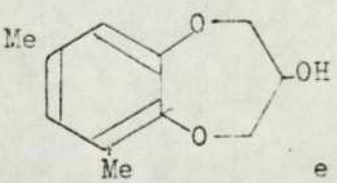
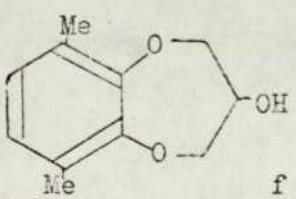
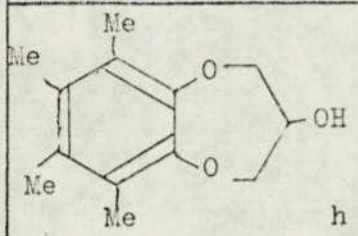
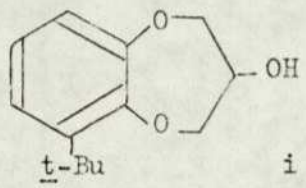
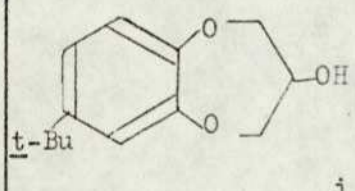
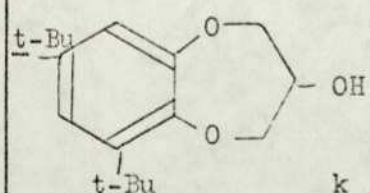
Compound (XV)	θ calculated from: Cos θ (i)	Cos θ (ii)	Cos² θ (i)	Cos² θ (ii)	θ measured from Dreiding model: skew	chair
 a	62½	65½	47	49½	45	73
 b	/	72½	/	56½	"	"
 c	60	65½	45	49½	"	"
 d	/	72½	/	56½	"	"
 e	/	/	/	/	"	"
 f	58½	65½	43½	49½	"	"

TABLE 38 (Cont.)

Compound XV	θ calculated from: $\cos\theta$ (i)	$\cos\theta$ (ii)	$\cos^2\theta$ (i)	$\cos^2\theta$ (ii)	θ measured from Dreiding model: skew	chair
 h	/	/	/	/	45	73
 i	/	73½	/	58	"	"
 j	61	65½	45½	49½	"	"
 k	/	73½	/	58	"	"

(i) No correction applied for Σ min.

(ii) A correction of 250 for Σ min was applied.

(iii) An allowance of 126 was made for the effect of the 6-methyl group (cf. Table 33).

(iv) A correction of 167 was applied for the effect of the 6-t-butyl group (cf. Table 33).

TABLE 39

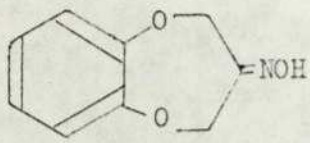
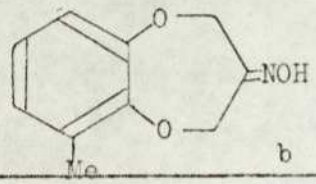
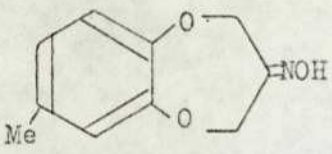
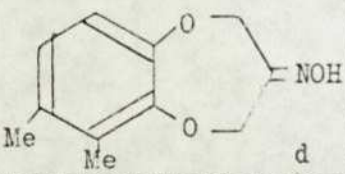
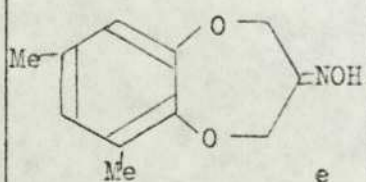
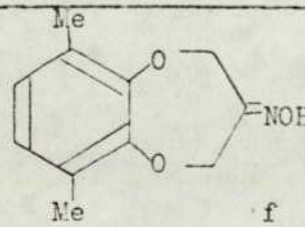
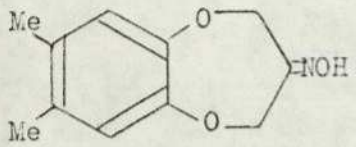
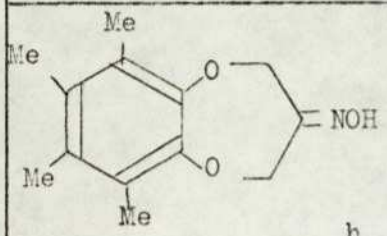
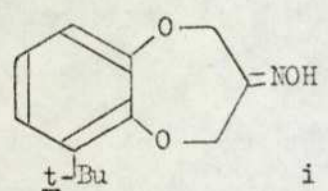
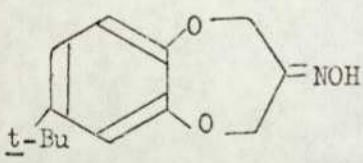
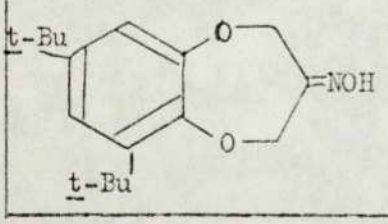
Compound (XXVIII, R=OH)	Θ calculated from: $\cos\Theta$ (i)	$\cos\Theta$ (ii)	$\cos^2\Theta$ (i)	$\cos^2\Theta$ (ii)	Θ measured from Dreiding model. skew	chair
 a	54½	57	40	42	45	73
 b	/	58½	/	43½	"	"
 c	53	57	39	42	"	"
 d	/	58½	/	43½	"	"
 e	/	58½	/	43½	"	"
 f	/	/	/	/	"	"

TABLE 39 (Cont.)

Compound (XXVIII, R=OH)	θ calculated from:				θ measured from Dreiding model	
	$\cos\theta$		$\cos^2\theta$			
	(i)	(ii)	(i)	(ii)	skew	chair
 g	52½	57	38½	42	45	73
 h	/	/	/	/	"	"
 i	/	53	/	39	"	"
 j	55½	57	41½	42	"	"
	/	53	/	39	"	"

(i) No correction for Σ min used.

(ii) An allowance of 250 was used for Σ min.

(iii) An allowance of 101 was applied for the effect of the 6-methyl group (cf. Table 34).

(iv) A value of 115 was deducted for the effect of the 6-t-butyl group (cf. Table 34).

$$\varepsilon/\varepsilon_o = \frac{\varepsilon_{corr} - \varepsilon_{min}}{\frac{1}{2}(\varepsilon_o - \varepsilon_{min})}$$

Values of Θ calculated in this way are given in the Tables.

No value for Θ can be calculated for the 3,6-dimethyl-3,4-dihydro-2H-1,5-benzodioxepins (If, i, j, XVf, h and XXVIII f, h, R=OH) because, as discussed earlier, little if any of their observed absorption can be considered to originate from the Ph-O chromophore.

From the results recorded in Tables 36-39 it is apparent that values of Θ calculated for the nuclear substituted compounds are very similar to those calculated for the parent compounds. The small discrepancies observed between Θ calculated for the latter compounds and those with 6-alkyl substituents merely reflect the difficulties encountered in correcting for the size of the conjugative contribution of the 6-alkyl substituent rather than any direct steric effect that the 6-alkyl group has on the conformation. It is therefore unlikely that substituents at the 6 and 9 positions would exert any severe conformational change on the heterocyclic ring.

A recent X-ray crystallographic study in this University by Steward and co-workers[152] has demonstrated that the crystal structure of 3,4-dihydro-2H-1,5-benzodioxepin-2,4-dicarboxylic acid (compound 8, Table 24) has a 'skew' conformation, as its crystalline dihydrate, with a twist angle of approximately 40°. Previously, this acid was considered[3,18] to exist in the 'chair' conformation on the basis of its molar extinction coefficient (1320 l $mol^{-1}cm^{-1}$) determined in solution in methanol in the 270 nm region of its ultra-violet spectrum. Although the two results do not agree it does not necessarily follow that the conformation deduced from ultra-violet studies is incorrect since in the solid state the conformation may not be the same as it is in solution. On the other hand it must be emphasised that whereas X-ray crystallography is a direct

method for determining the crystal structure the method proposed for the deduction of conformation from ultra-violet absorption data is based upon certain empirical and intuitive relationships (see Chapter 5.1). In the earlier ultra-violet spectral investigation[3,18] it was found that the majority of molar extinction coefficients measured for a variety of dihydrobenzodioxepin derivatives correlated better with the range 1360 - 2230 $1\ mol^{-1}cm^{-1}$, which would be expected on the basis of Dreiding models and calculations using the $Cos\theta = \varepsilon/\varepsilon_o$ relationship, than with the range 595 - 1604 $1\ mol^{-1}cm^{-1}$ calculated in a similar way using the $Cos^2\theta = \varepsilon/\varepsilon_o$ expression and it was considered that the value of 1320 $1\ mol^{-1}cm^{-1}$ measured for 3,4-dihydro-2H-1,5-benzodioxepin-2,4-dicarboxylic acid in methanol was indicative of the 'chair' conformation. Steward and co-workers[152] pointed out that the use of the $Cos^2\theta = \varepsilon/\varepsilon_o$ relationship for this particular compound (ε = 1320 $1\ mol^{-1}\ cm^{-1}$) would have indicated that in solution the structure was time-averaging about the 'skew' conformation, in agreement with their X-ray analysis of the crystalline form. If this suggestion were applied generally to the other dihydrobenzodioxepins, and if the angles of twist (θ) predicted by Dreiding stereomodels are approximately correct, then the maximum extinction coefficient to be expected for compounds in the 'skew' conformation ($\theta = 45°$) would be about 1600 $1\ mol^{-1}cm^{-1}$. The many compounds having extinction coefficients between 1600 and 2400 $1\ mol^{-1}cm^{-1}$ would then have to be assigned conformations in which the mean angle of twist (θ) lies between about $45°$ and $28°$ respectively. If this were the case, then these compounds would possess a higher energy content owing to the steric strain experienced by the heterocyclic ring which would have to be relieved by some other advantage such as enhanced conjugation of the oxygen lone-pair electrons with the aromatic ring. An X-ray analysis of one of the compounds having a high extinction coefficient might provide useful information on this point if it can be assumed that the structure in the solid state is close to the mean structure in solution.

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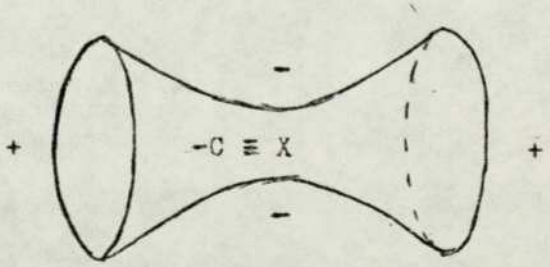
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72

76

118

119 A + B?

126

179 of/

218 last line but one out favourably

280 last line but one O-CH_2-CN ⇒

pp 104/5 interchanged
175/176

239 → 236
240 → 237
236 → 238
237 → 239
238 → 240