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SOME CHEMISTRY OF 2-DIAZOCARBONYL COMPOUNDS.

A thesis submitted in fulfilment
of the Conditions for the
Degree of Doctor of Philosophy.

by

David Malcolm Hamilton Abram.

Department of Chemistry

The City University

LONDON.

February 1984.

For my Parents.

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Abstract.

The object of these studies is to contribute to the continuing development of the use of the diazo group in synthesis. 2-Diazocarbonyl compounds were chosen owing to their relative ease of synthesis, their stability and because the carbonyl group is excellent for further bond building.

Literature reviews of the chemistry of 2-diazo-1,3-dicarbonyl compounds and of cyclopropanones are presented. An efficient synthesis of 3-diazopentane-2,4-dione has been developed and the chemistry of this compound has been examined. It has proved to be very sluggish in carbenoid reactions and gives poor yields of cyclopropanation products with olefins. Attempts to oxidise the resulting 1,1-diacetylcyclopropanes and similar compounds in order to furnish cyclopropanone equivalents were unsuccessful.

The reported reactions of diazo compounds with thiophenes are reviewed in detail and possible mechanisms for product formation are discussed. The reactions of 3-diazopentane-2,4-dione and related diazo compounds with thiophenes have been examined and it has been shown that in special cases, 2H-thiopyran can be formed. A feasible mechanism for their formation is demonstrated to be via the cyclization of intermediate 2Z-dienethials. The latter compounds are potentially useful intermediates in a general route to 2H-thiopyrans, but owing to their difficulty of synthesis it did not prove possible to develop such a route.

Following a review of asymmetric induction reactions, it is shown that copper complexes of 3-trifluoroacetyl-d-camphor (facam) and some of its derivatives are efficient chiral catalysts for cyclopropanation with a high degree of asymmetric induction. The copper complex of an immobilized, silica bonded version of facam was also shown to be very efficient for this purpose, offering the prospect for easy recovering and recycling of the catalyst.

The chemistry of 2-diazoamides is reviewed and attempts to improve the synthesis of 2-diazo-3-phenylpropanoic acid N,N-dimethylamide are described. This 2-diazoamide failed to give a 2H-thiopyran on reaction with thiophene. A review is then presented of the synthesis of benzothiophenes. The acetylation and cyclisation of 2-thienyl-1,3-dicarbonyl compounds (formed by condensation of thiophene with 2-diazo-1,3-dicarbonyl compounds) is shown to lead, in some cases, to benzothiophenes, but yields were too low to make the route of much practical value.

CHAPTER ONE.

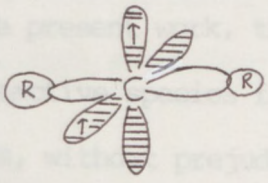
STUDIES WITH 3-DIAZOPENTANE-2,4-DIONE.

"By faith we understand that the world was created by the word of God, so that what is seen was made out of things which do not appear." (Hebrews 11:3).

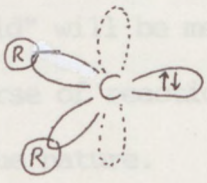
1.1. Literature Review of 2-Diazo-1,3-dicarbonyl Compounds.

1.1.1. Introduction.

The chemistry of diazo compounds has been very extensively studied and has been reviewed in a number of books [1-3]. Diazoalkanes lose nitrogen under the action of heat, light or metal catalysts to give highly reactive unstable intermediates which readily combine with a variety of functional groups and therefore have proved to be extremely useful in synthetic organic chemistry. The nature of the intermediates formed in such reactions are often a matter of speculation rather than proof. There is good evidence that photolysis of diazoalkanes can give rise to "free" carbenes: i.e. divalent carbon species which have either (i) an sp hybridisation and unpaired electrons in two of the orbitals (1a) giving a triplet state or (ii) an sp^2 hybridisation and paired electrons in plane (1b) giving a singlet state [4].



(1a)



(1b)

Methylene itself has a triplet ground state [5]. However many substituted carbenes seem to favour a singlet ground state, as revealed by the application of Skell´s hypothesis [6]. This states that a singlet carbene will add concertedly and stereospecifically to an olefin to form a cyclopropane, whereas a triplet carbene will necessarily add by a non-concerted process via a triplet biradical in which free rotation will occur leading to non-stereospecific cyclopropanation. Thus, the degree of stereoselectivity observed in a cyclopropanation provides evidence for the character of the

intermediate carbene.

Thermal decomposition of diazoalkanes in the presence of substrates generally produce the same types of reactions as their photochemical counterparts, although often with marked differences in product distribution. It is often unclear whether the thermal reactions are producing carbenes of relatively low energy , or whether competing reactions are involved in which nitrogen loss is not the first step but occurs at an intermediate stage.

Metal catalysed reactions provide a further level of complication to the mechanistic picture. Compared with purely thermal processes, metal catalysed reactions are generally characterised by increases in reaction rates and changes in the nature and distribution of products. Although the intermediacy of metal-carbene complexes (metallocarbenoids) is often referred to in such cases, the evidence in their favour is rarely present, and alternatives such as metal-diazo complexes need also to be considered.

In the present work, the term "carbenoid" will be meant to refer to any reactive species formed in the course of reactions of diazo compounds, without prejudice as to its true nature.

α-Diazoketones are readily prepared (scheme 1) by (i) condensation of terminal diazoalkanes with an acid chloride with loss of hydrogen chloride [7], (ii) by conversion of an α-amino carbonyl compound to the corresponding diazocarbonyl analogue: this may involve diazotisation under acidic conditions [8], or elimination from an N-nitroso-N-acyl derivative under alkaline conditions [9], (iii) diazo group transfer from a sulphonyl azide to an α-methylene group carbonyl compound [10,11].

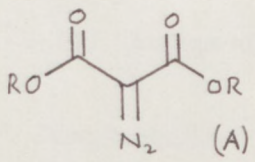
The chemistry of α-diazocarbonyl compounds is often similar to that of simple diazoalkanes. Thus the action of heat, light or

metal catalysts affords carbenoid intermediates, which may undergo bond insertion reactions (e.g. into C-H or C-O bonds) or cyclopropanation of olefins (e.g. the intramolecular addition in scheme 2, which allows construction of the highly strained tricyclo[2.1.0.$0^{3,5}$]pentan-2-one) (2) [12].

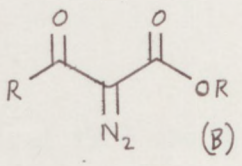
A reaction unique to α-diazocarbonyl compounds is the Wolff rearrangement (scheme 3), a key step in the Arndt-Eistert homologation of carboxylic acids [13]. In this process the intermediate ketocarbene (or "carbenoid") undergoes a 1,2-shift of the substituent from the carbonyl group to the electron deficient carbenoid carbon atom, leading to a ketene which can be isolated or trapped in situ with nucleophiles such as water, alcohols, amines and thiols. In addition to heat and light, a number of metals can be used to catalyse the reaction (silver oxide, colloidal platinum and certain copper compounds are effective). However many copper compounds inhibit Wolff rearrangement, apparently by forming stabilised ketocarbene-metal complexes that tend to favour other reactions such as cyclopropanation and intramolecular C-H insertion [14].

2-Diazo-1,3-dicarbonyl compounds are in many respects different from the simple 2-diazocarbonyl compounds. The second carbonyl group evidently affords extra stabilisation; both to the parent compounds, which tend to decompose more slowly, and to the intermediate carbenoid.

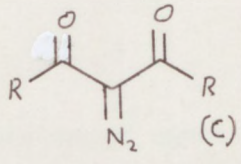
Three classes of 2-diazo-1,3-dicarbonyl compound have been studied in the literature namely (A) diazomalonate esters, (B) 2-diazo-3-keto-esters and (C) 2-diazo-1,3-diketones.



(A)

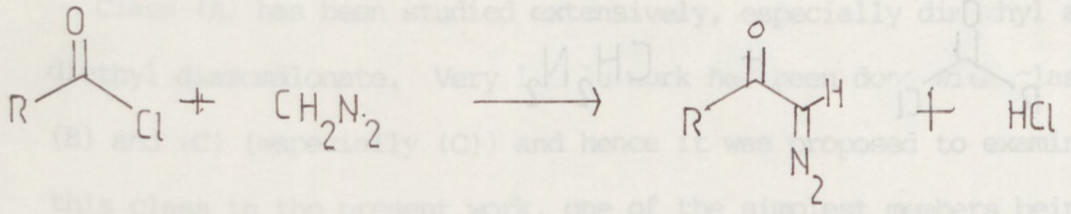


(B)

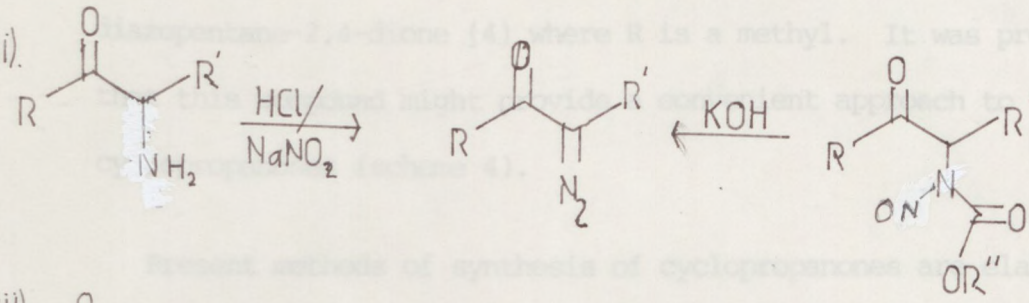


(C)

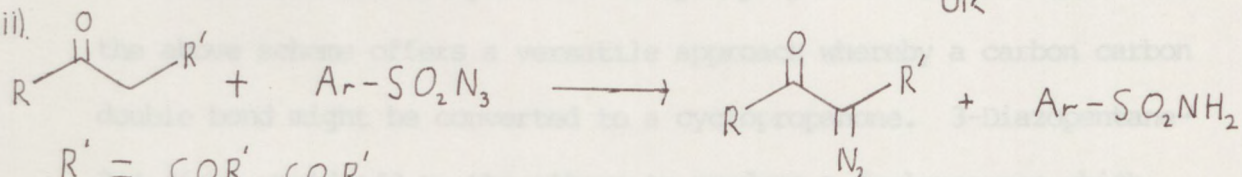
i).



ii).

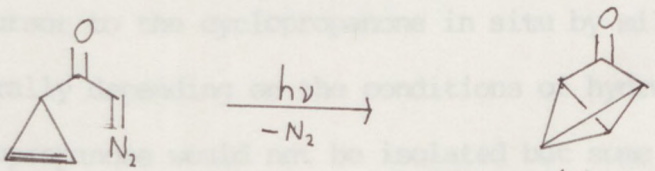


iii).



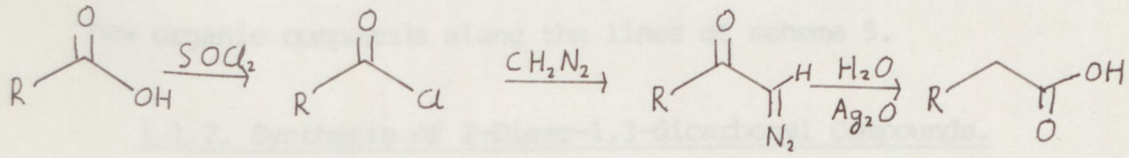
$R' = COR', CO_2R'$.

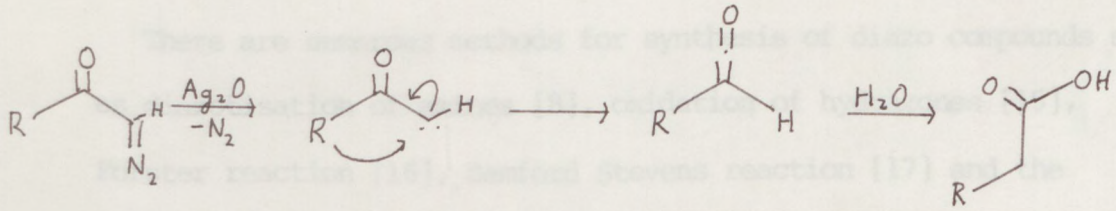
Scheme 1.



(2)

Scheme 2.





Scheme 3

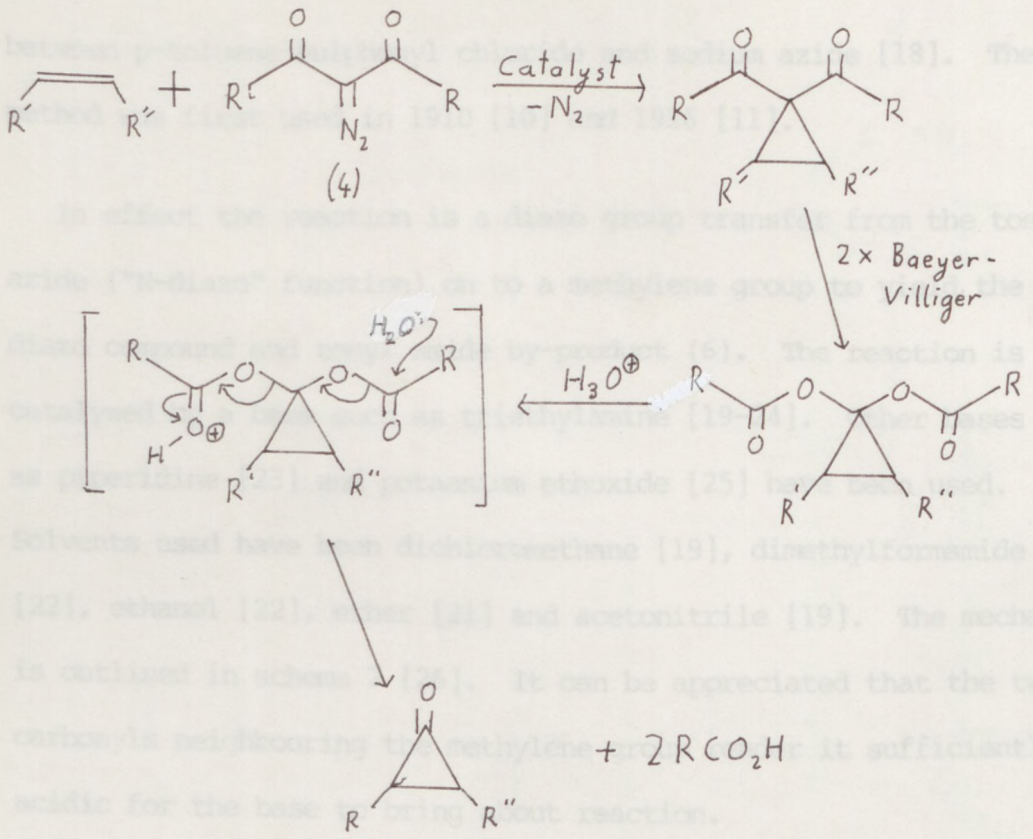
Class (A) has been studied extensively, especially dimethyl and diethyl diazomalonate. Very little work has been done with classes (B) and (C) (especially (C)) and hence it was proposed to examine this class in the present work, one of the simplest members being 3-diazopentane-2,4-dione (4) where R is a methyl. It was proposed that this compound might provide a convenient approach to cyclopropanones (scheme 4).

Present methods of synthesis of cyclopropanones are elaborate and the above scheme offers a versatile approach whereby a carbon carbon double bond might be converted to a cyclopropanone. 3-Diazopentane-2,4-dione would add to the alkene to produce a cyclopropane which would then be converted to a cyclopropane-1,1-diacetate by two Baeyer-Villiger oxidations. Such a diacetate would be a stable precursor to the cyclopropanone in situ by mild hydrolysis. Naturally depending on the conditions of hydrolysis the cyclopropanone would not be isolated but some adduct typical of a reaction of a cyclopropanone (scheme 5). The scheme not only offers insights into the chemistry of 3-diazo-pentane-2,4-dione but an approach whereby a carbon-carbon double bond can be used to produce new organic compounds along the lines of scheme 5.

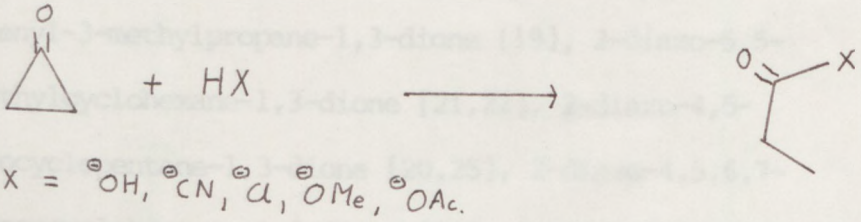
1.1.2. Synthesis of 2-Diazo-1,3-dicarbonyl Compounds.

There are numerous methods for synthesis of diazo compounds such as diazotisation of amines [8], oxidation of hydrazones [15], Forster reaction [16], Bamford Stevens reaction [17] and the cleavage of N-nitroso-carboxamides [9]. A method especially suitable for 2-diazo-1,3-dicarbonyl compounds is the action of an active azide such as tosyl azide on a 1,3-dicarbonyl compound [10,11] (scheme 6).

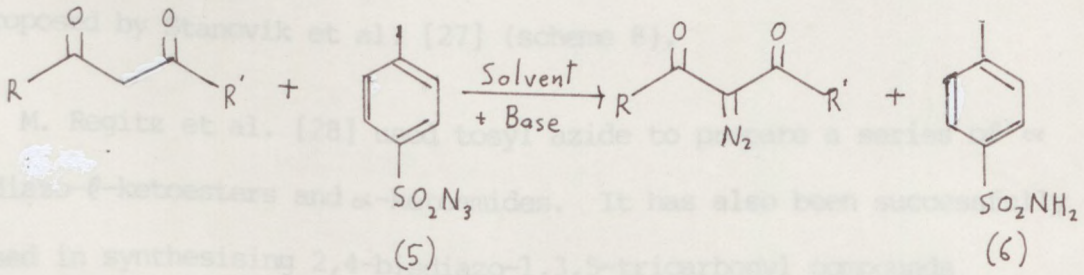
Tosyl azide (5) is prepared from the double displacement reaction



Scheme 4.



Scheme 5.



Scheme 6.

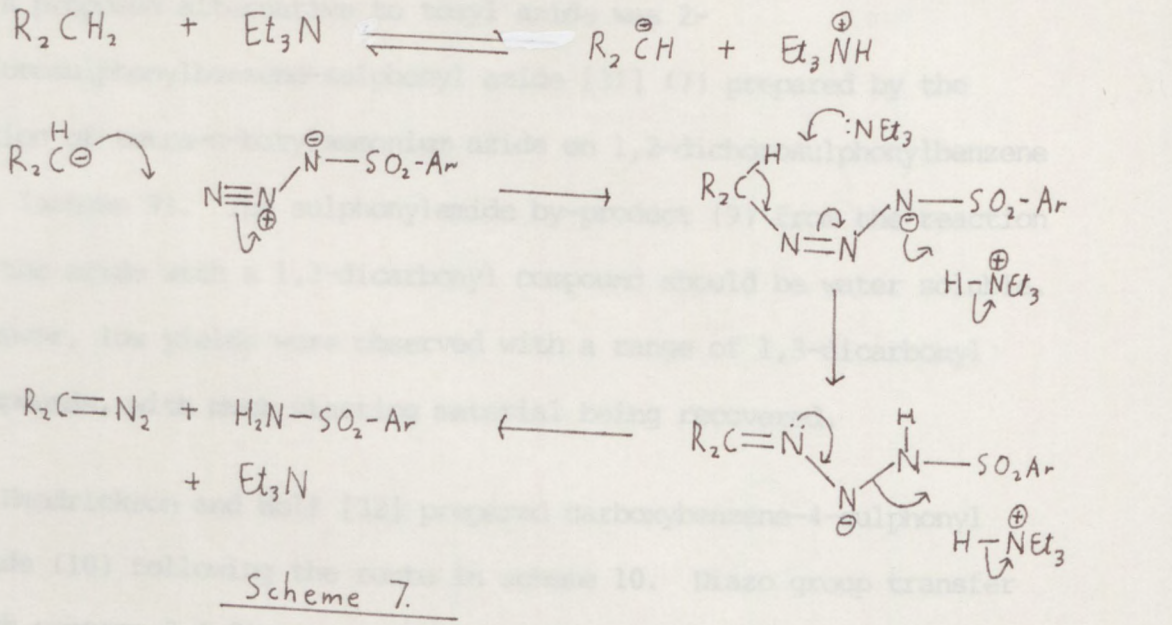
between p-toluene-sulphonyl chloride and sodium azide [18]. The method was first used in 1910 [10] and 1926 [11].

In effect the reaction is a diazo group transfer from the tosyl azide ("N-diazo" function) on to a methylene group to yield the diazo compound and tosyl amide by-product (6). The reaction is catalysed by a base such as triethylamine [19-24]. Other bases such as piperidine [23] and potassium ethoxide [25] have been used. Solvents used have been dichloromethane [19], dimethylformamide [22], ethanol [22], ether [21] and acetonitrile [19]. The mechanism is outlined in scheme 7 [26]. It can be appreciated that the two carbonyls neighbouring the methylene group render it sufficiently acidic for the base to bring about reaction.

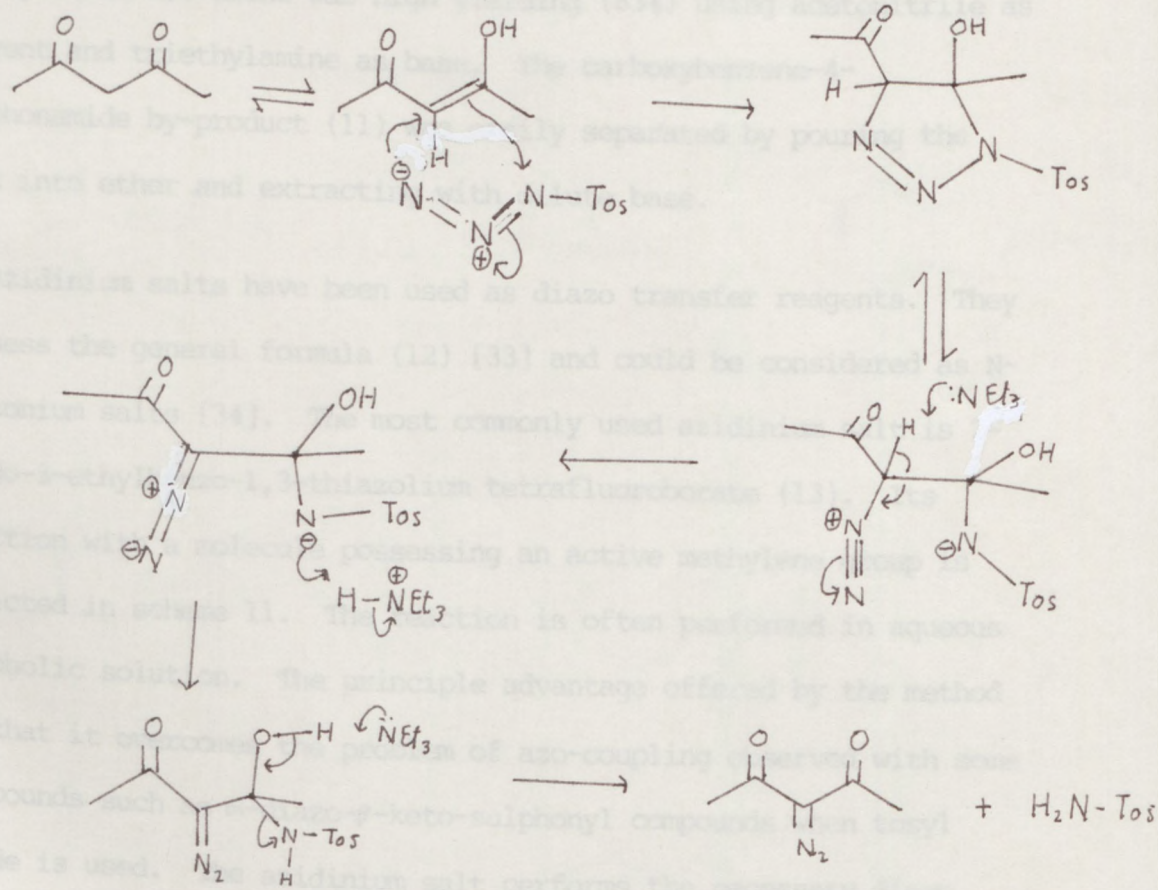
Examples of diazo compounds that have successfully been made with tosyl azide are 2-diazo-1,3-diphenylpropane-1,3-dione [19], 2-diazo-1-phenyl-3-methylpropane-1,3-dione [19], 2-diazo-5,5-dimethylcyclohexane-1,3-dione [21,22], 2-diazo-4,5-benzocyclopentane-1,3-dione [20,25], 2-diazo-4,5,6,7-dibenzocycloheptane-1,3-dione [23], 2-diazo-5,6-benzo-4,4-dimethylcyclohexane-1,3-dione [24], ethyl diazoacetoacetate [19,21] and diethyl diazomalonate [19].

An alternative mechanism for the diazo group transfer was later proposed by Stanovik et al. [27] (scheme 8).

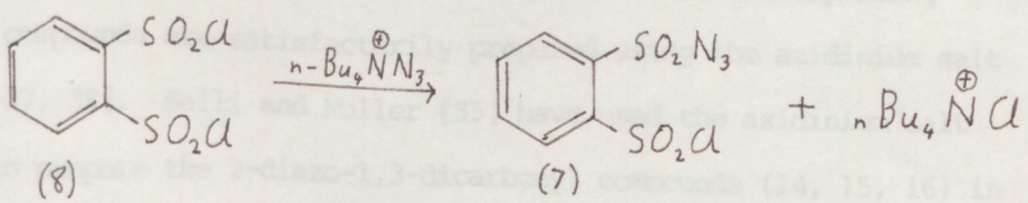
M. Regitz et al. [28] used tosyl azide to prepare a series of α-diazo-β-ketoesters and α-ketoamides. It has also been successfully used in synthesising 2,4-bisdiazo-1,3,5-tricarbonyl compounds [29,30]. A problem in the use of tosyl azide is the removal of the tosyl amide by-product. A common procedure is to obtain maximun precipitation of the amide by freezing [21].



Scheme 7.



Scheme 8.

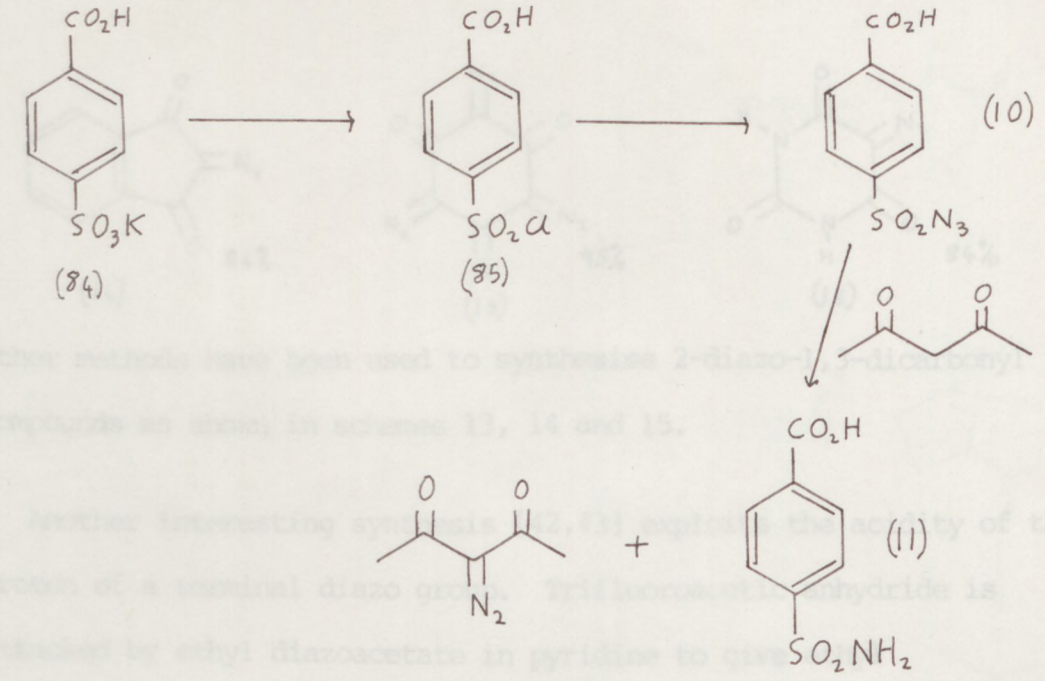


Scheme 9.

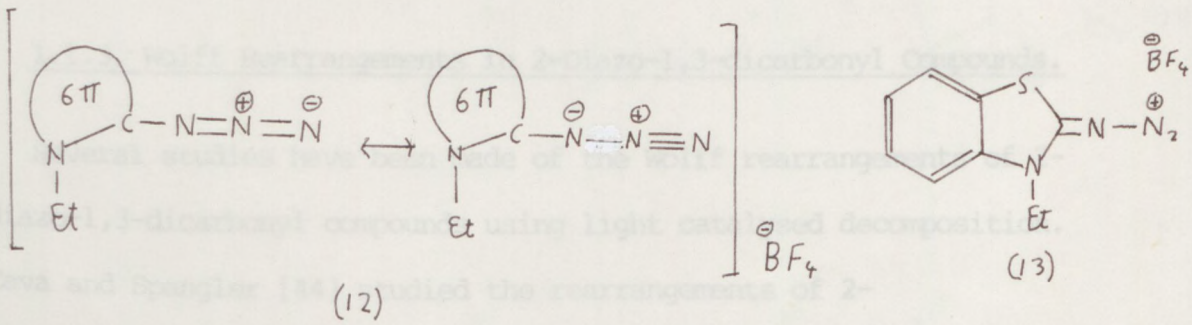
A proposed alternative to tosyl azide was 2-chlorosulphonylbenzene-sulphonyl azide [31] (7) prepared by the action of tetra-n-butylammonium azide on 1,2-dichorosulphonylbenzene (8) (scheme 9). The sulphonylamide by-product (9) from the reaction of the azide with a 1,3-dicarbonyl compound should be water soluble. However, low yields were observed with a range of 1,3-dicarbonyl compounds, with much starting material being recovered.

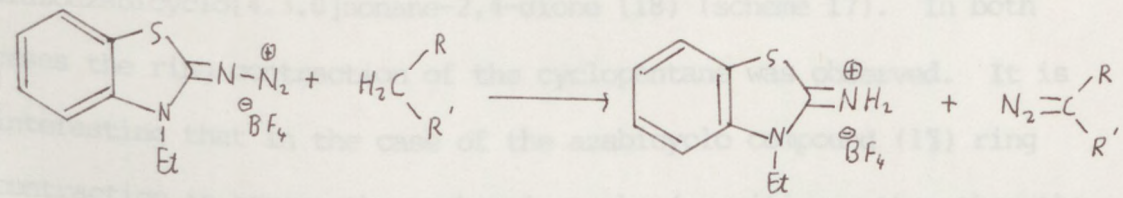
Hendrickson and Wolf [32] prepared carboxybenzene-4-sulphonyl azide (10) following the route in scheme 10. Diazo group transfer with pentane-2,4-dione was high yielding (83%) using acetonitrile as solvent and triethylamine as base. The carboxybenzene-4-sulphonamide by-product (11) was easily separated by pouring the bulk into ether and extracting with dilute base.

Azidinium salts have been used as diazo transfer reagents. They possess the general formula (12) [33] and could be considered as N-diazonium salts [34]. The most commonly used azidinium salt is 2-azido-3-ethylbenzo-1,3-thiazolium tetrafluoroborate (13). Its reaction with a molecule possessing an active methylene group is depicted in scheme 11. The reaction is often performed in aqueous alcoholic solution. The principle advantage offered by the method is that it overcomes the problem of azo-coupling observed with some compounds such as α-diazo-β-keto-sulphonyl compounds when tosyl azide is used. The azidinium salt performs the necessary diazo transfer [35] as illustrated in scheme 12. Other examples of compounds which undergo azo coupling with tosyl azide are nitromethanes and cyanomethanes [36]. However the corresponding diazo compounds are satisfactorily prepared using the azidinium salt (13) [37, 38]. Balli and Muller [35] have used the azidinium salt (13) to prepare the 2-diazo-1,3-dicarbonyl compounds (14, 15, 16) in high yield.

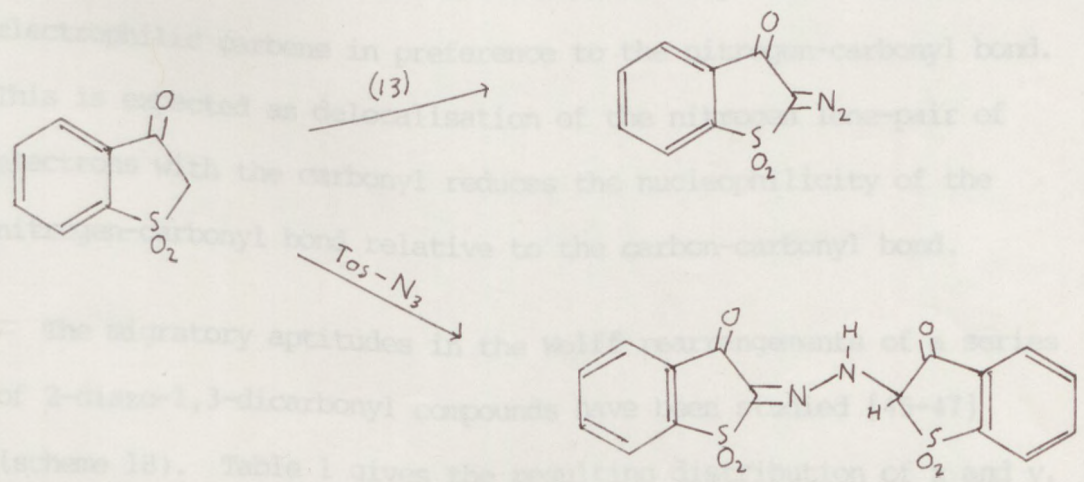


Scheme 10.

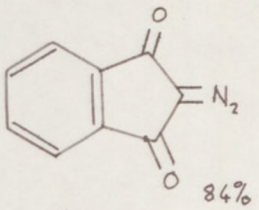




Scheme 11.

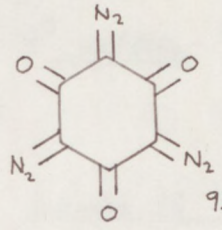


Scheme 12.



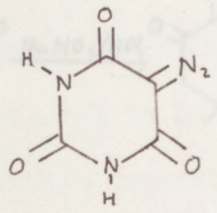
84%

(14)



95%

(15)



84%

(16)

Other methods have been used to synthesise 2-diazo-1,3-dicarbonyl compounds as shown in schemes 13, 14 and 15.

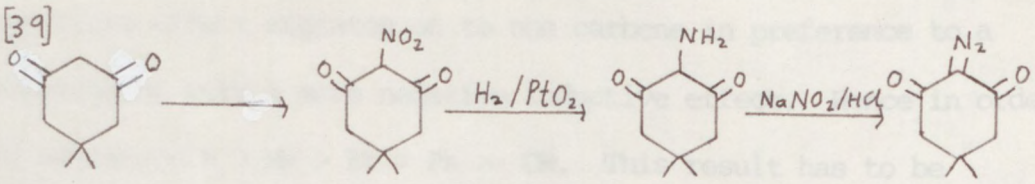
Another interesting synthesis [42,43] exploits the acidity of the proton of a terminal diazo group. Trifluoroacetic anhydride is attacked by ethyl diazoacetate in pyridine to give ethyl diazotrifluoroacetoacetate (scheme 16).

1.1.3. Wolff Rearrangements in 2-Diazo-1,3-dicarbonyl Compounds.

Several studies have been made of the Wolff rearrangements of 2-diazo-1,3-dicarbonyl compounds using light catalysed decomposition. Cava and Spangler [44] studied the rearrangements of 2-diazobenzo(a)cyclopentane-1,3-dione (17) and 2-diazoazabicyclo[4.3.0]nonane-2,4-dione (18) (scheme 17). In both cases the ring contraction of the cyclopentane was observed. It is interesting that in the case of the azabicyclo compound (18) ring contraction is across the carbonyl at the 4-position rather than the 2-position. In other words the carbon-carbonyl bond migrates to the electrophilic carbene in preference to the nitrogen-carbonyl bond. This is expected as delocalisation of the nitrogen lone-pair of electrons with the carbonyl reduces the nucleophilicity of the nitrogen-carbonyl bond relative to the carbon-carbonyl bond.

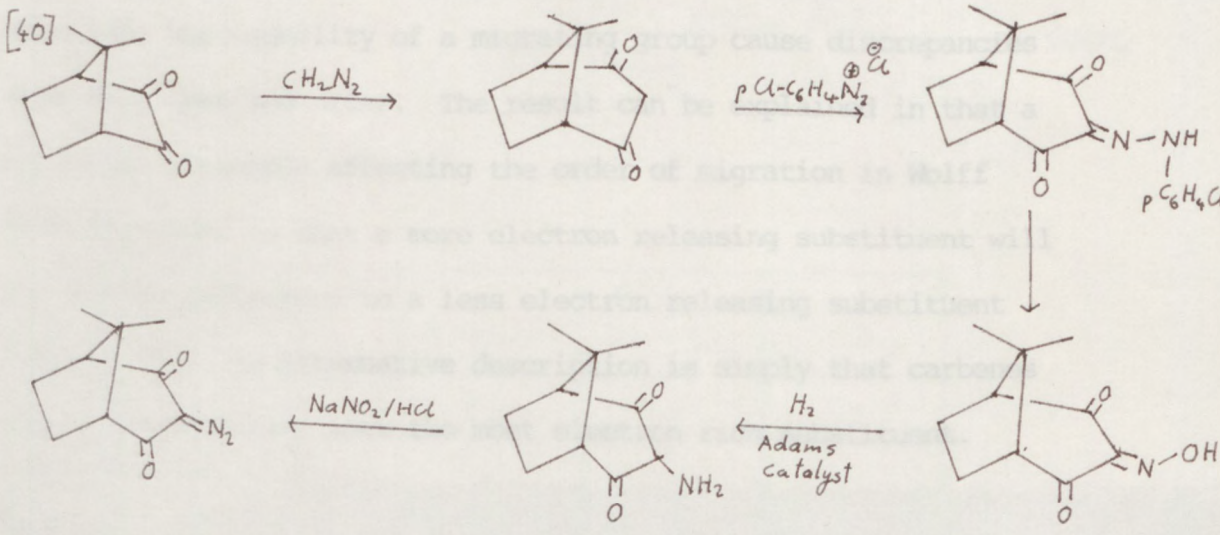
The migratory aptitudes in the Wolff rearrangements of a series of 2-diazo-1,3-dicarbonyl compounds have been studied [45-47] (scheme 18). Table 1 gives the resulting distribution of x and y. The table demonstrates that a substituent with a more positive

[39]



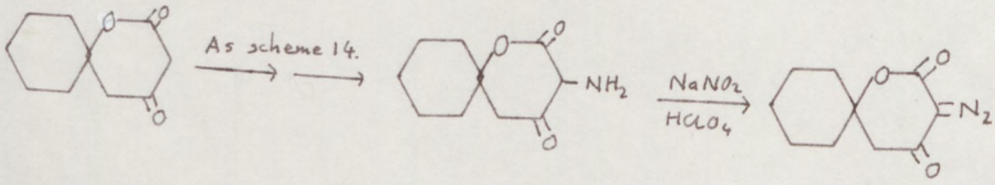
Scheme 13

[40]

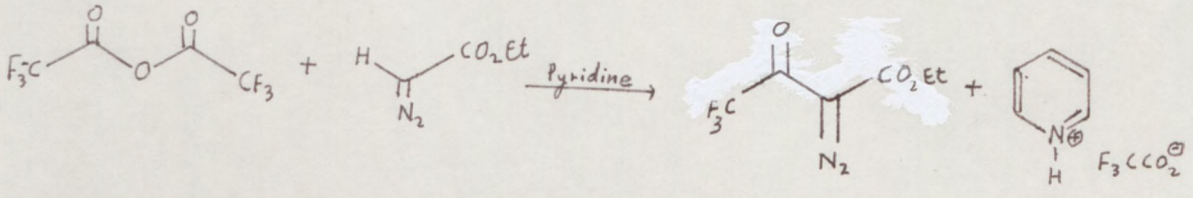


Scheme 14

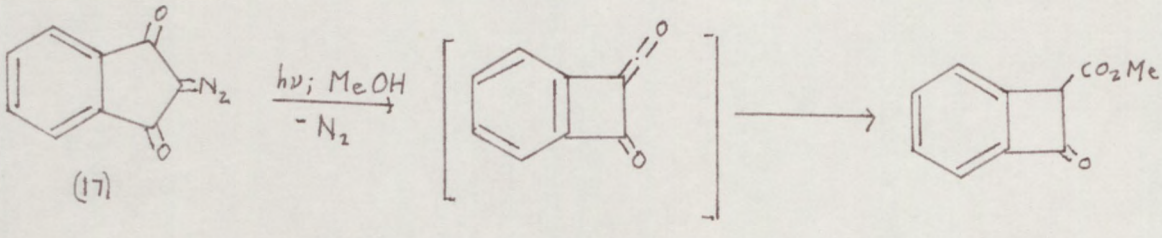
[41]

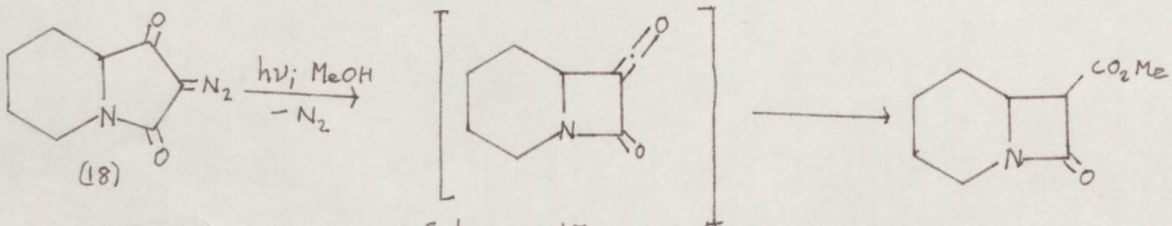


Scheme 15.



Scheme 16.

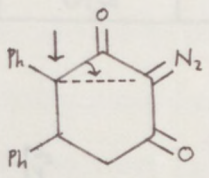




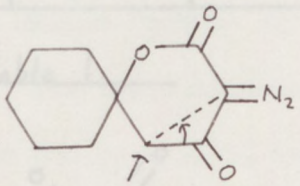
Scheme 17.

inductive effect migrates on to the carbene in preference to a substituent with a more negative inductive effect. Hence in order of migration H > Me > Et > Ph >> OR. This result has to be qualified by comparison with Wolff rearrangements in general where factors such as steric inaccessibilty or other functionalities affecting nucleophility of a migrating group cause discrepancies from this observed order. The result can be explained in that a governing principle affecting the order of migration in Wolff rearrangements is that a more electron releasing substituent will migrate in preference to a less electron releasing substituent (scheme 18). An alternative description is simply that carbenes being electrophilic seek the most electron rich substituent.

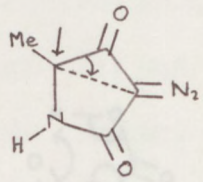
The argument accounts for the migrations observed in the following compounds [48-50].



[48]



[49]



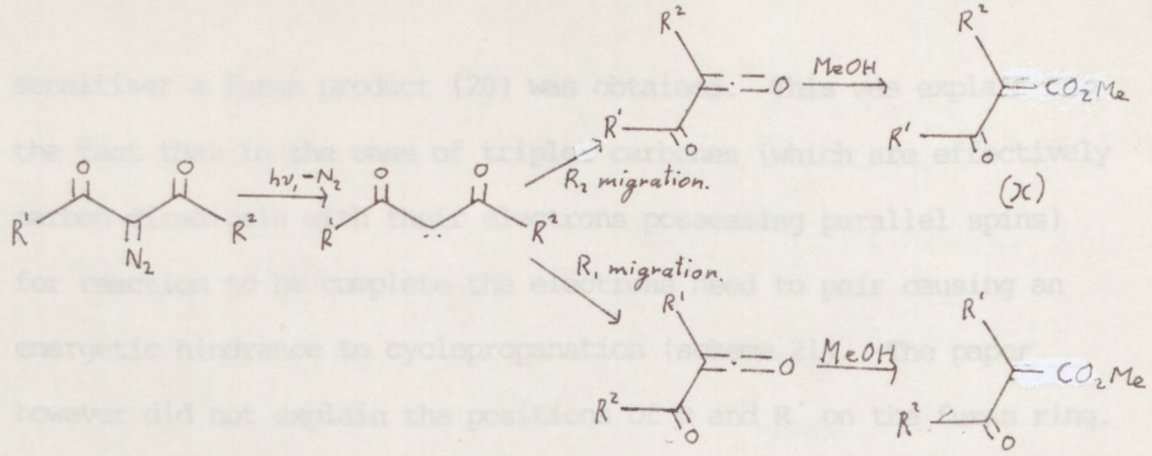
[50]

Korobitsyna and Nikolaev [51] observed Wolff rearrangements with 2-diazo-dimedone (19) and 3-diazopentane-2,4-dione (4) in aqueous solution (scheme 19). They obtained the ring contracted ketone (19a) and butanone via decarboxylation of the β-ketoacid which in turn was derived from the ketene intermediate.

1.1.4. Chemistry of Diazomalonate Esters.

1.1.4a. Additions Forming Cyclopropanes.

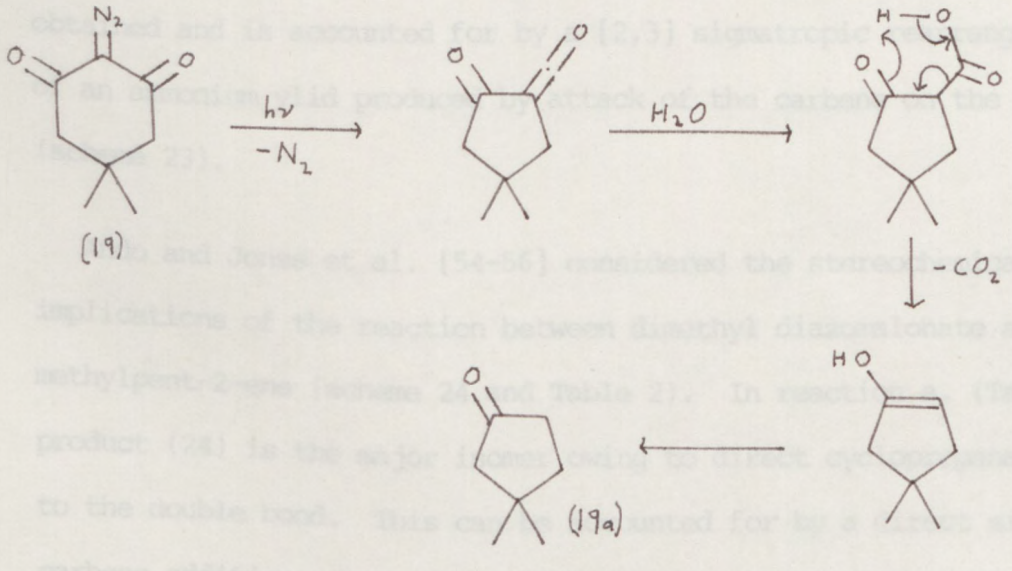
Hendrick [52] studied the photochemical reaction of dimethyl diazomalonate with alkynes (scheme 20). Without the triplet sensitiser the cyclopropene was formed in every case. With triplet

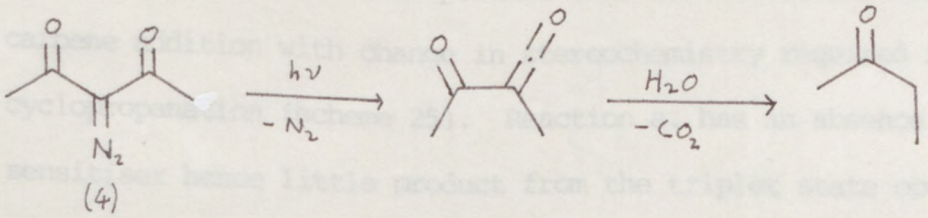


Scheme 18.

R'	R²	% Yield	Product Ratio % x	% y
Et	Me	84	51	49
Ph	H	90	100	0
Ph	Me	64	96	4
OEt	Me	78	100	0
OMe	Ph	88	100	0

Table 1.



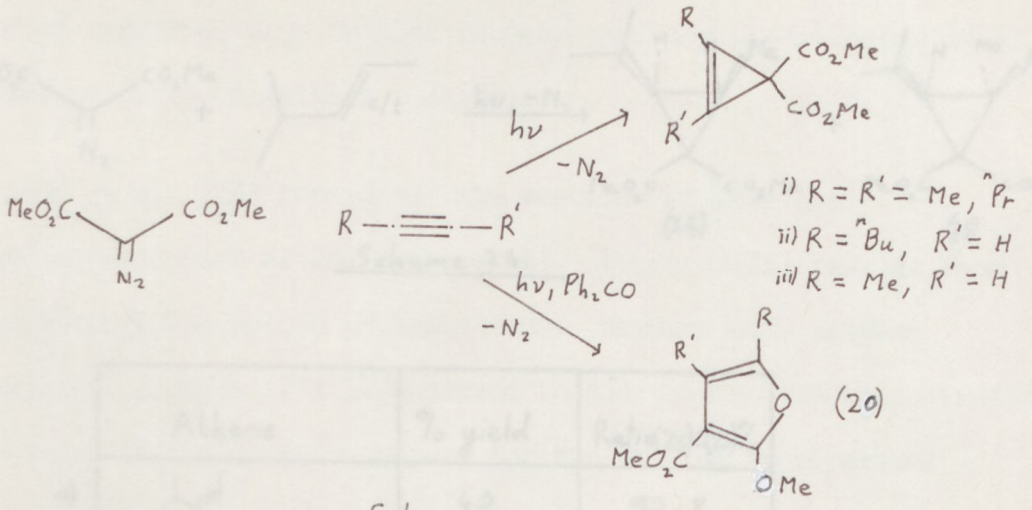


Scheme 19.

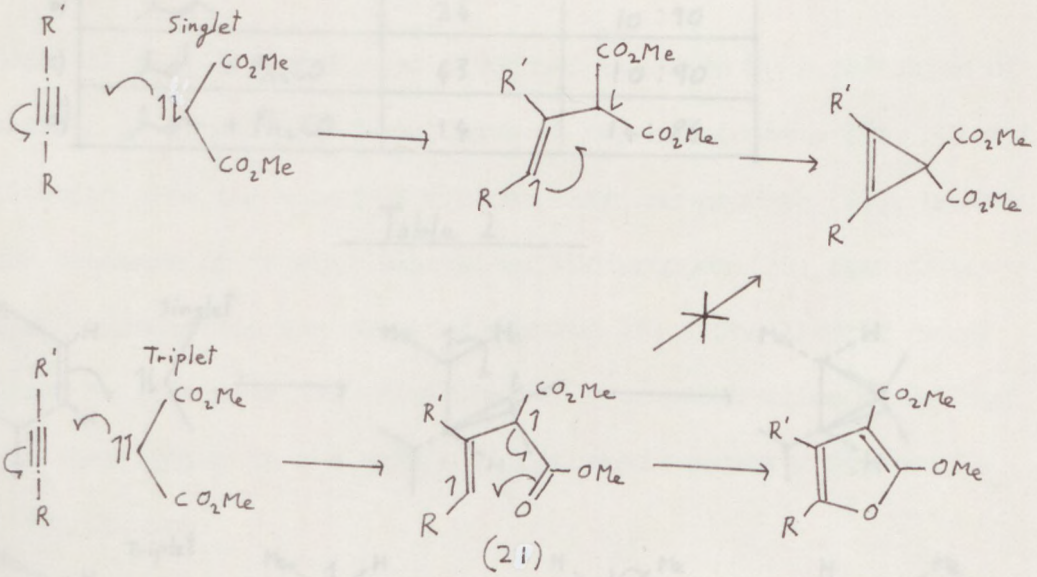
sensitiser a furan product (20) was obtained. This was explained by the fact that in the case of triplet carbenes (which are effectively carbon diradicals with their electrons possessing parallel spins) for reaction to be complete the electrons need to pair causing an energetic hindrance to cyclopropanation (scheme 21). The paper however did not explain the positions of R and R´ on the furan ring. In the two cases of the unsymmetrical alkyne, which were terminal alkynes, the substituent neighboured the oxygen in the furan ring. This can be accounted for by the fact that the addition of the triplet carbene to the alkyne would place the resulting alkenyl radical in the more substituted position as shown in intermediate (21), as in this case t-butyl and methyl groups stabilise a radical centre.

Ando et al. [53] considered the reaction of dimethyl diazomalonate with allyl amines (scheme 22). In addition to the cyclopropanation product (22) the rearranged product (23) was obtained and is accounted for by a [2,3] sigmatropic rearrangement of an ammonium ylid produced by attack of the carbene on the amine (scheme 23).

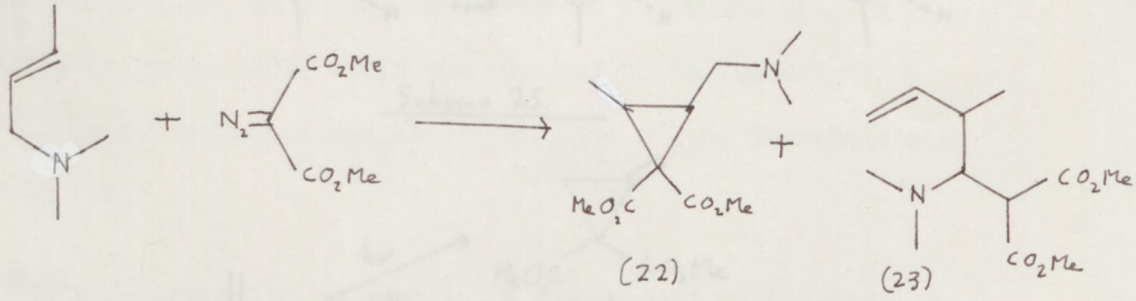
Ando and Jones et al. [54-56] considered the stereochemical implications of the reaction between dimethyl diazomalonate and 4-methylpent-2-ene (scheme 24 and Table 2). In reaction a. (Table 2) product (24) is the major isomer owing to direct cyclopropanation on to the double bond. This can be accounted for by a direct singlet carbene addition. However product (25) results from a triplet carbene addition with change in stereochemistry required for cyclopropanation (scheme 25). Reaction a. has an absence of triplet sensitiser hence little product from the triplet state occurs. The same result is obtained in reaction b. where the stereochemistry of the alkene substrate is reversed. In reactions c. and d. the



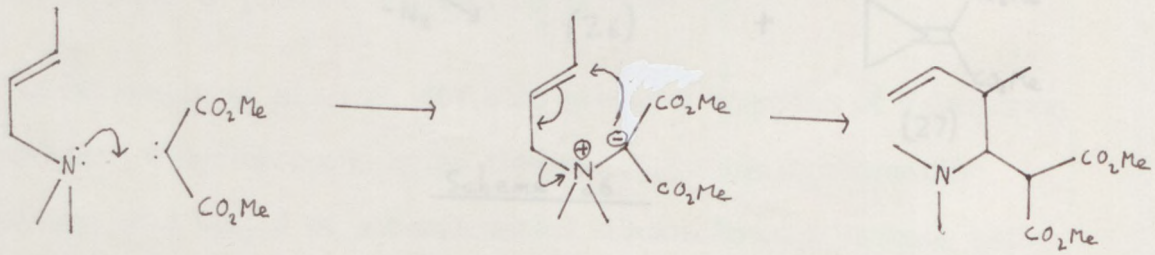
Scheme 20.



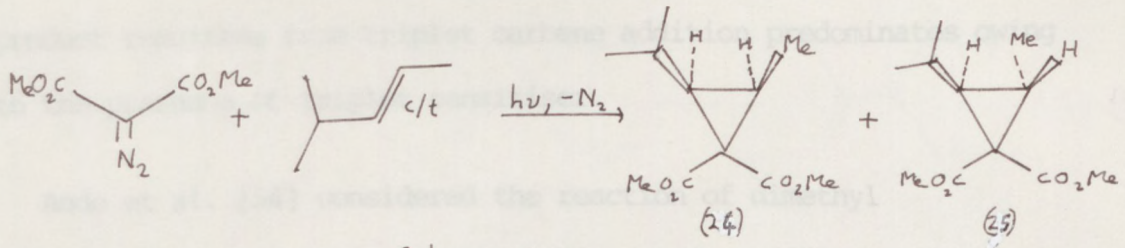
Scheme 21.



Scheme 22.



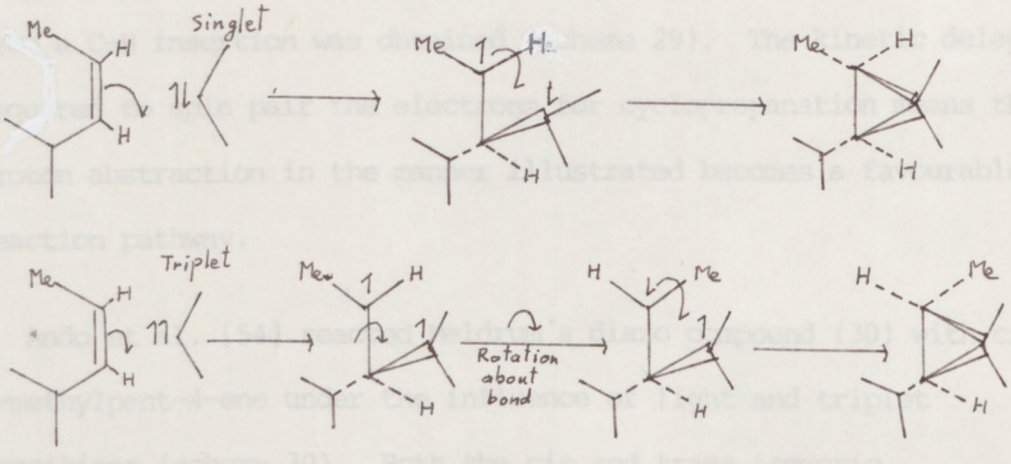
Scheme 23.



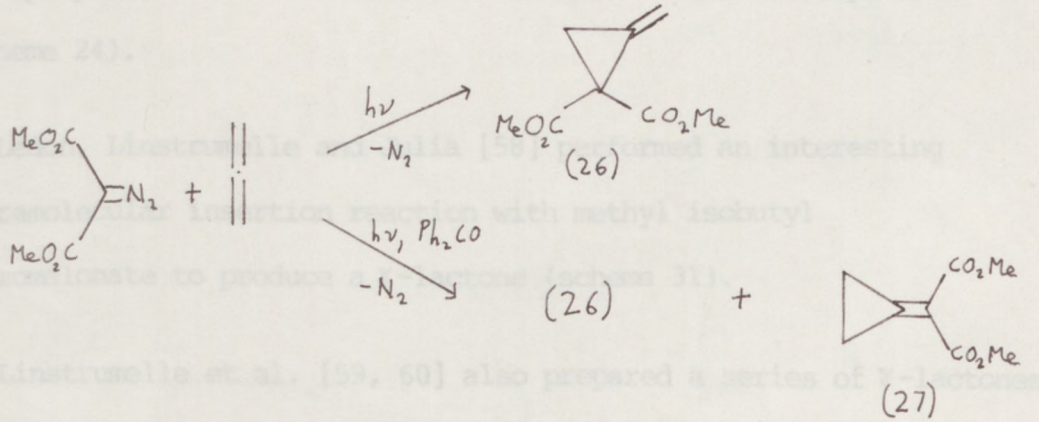
Scheme 24.

	Alkene	% yield	Ratio (24):(25) %
a)		40	92:8
b)		24	10:90
c)	 + Ph_2CO	43	10:90
d)	 + Ph_2CO	14	14:86

Table 2.



Scheme 25.



Scheme 26.

product resulting from triplet carbene addition predominates owing to the presence of triplet sensitiser.

Ando et al. [54] considered the reaction of dimethyl diazomalonate with allene (scheme 26). Product (26) results from direct cyclopropanation of the allene. However with triplet sensitiser product (27) is observed in addition to (26) illustrating the delay in the kinetic pathway for the pairing of electrons (scheme 27).

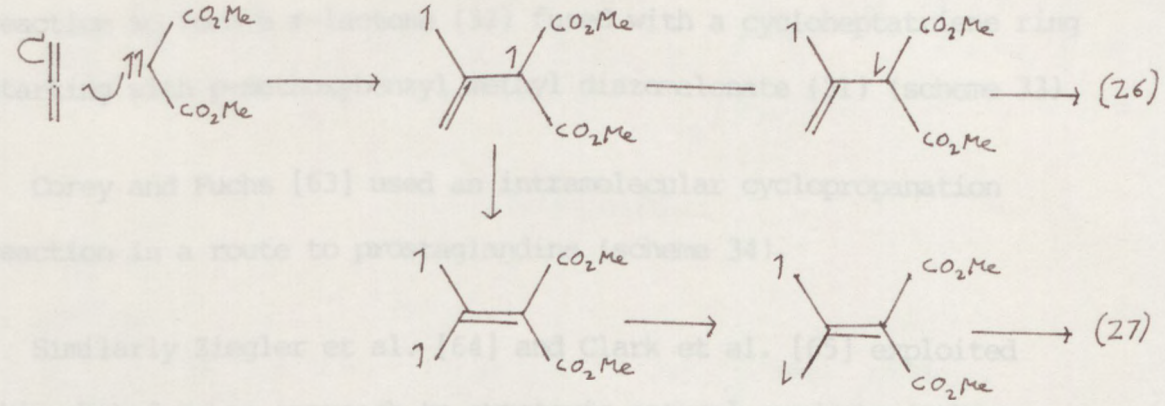
Ledon et al. [57] performed a Buchner reaction by irradiation of a solution of dimethyl diazomalonate in benzene (scheme 28). Direct irradiation gave the expected cycloheptatriene product (28), however in the presence of triplet sensitiser the product (29) resulting from a C-H insertion was obtained (scheme 29). The kinetic delay required to spin pair the electrons for cyclopropanation means that proton abstraction in the manner illustrated becomes a favourable reaction pathway.

Ando et al. [54] reacted Meldrum´s diazo compound (30) with cis-2-methylpent-4-ene under the influence of light and triplet sensitiser (scheme 30). Both the cis and trans isomeric cyclopropanes were obtained as in the case of the dimethyl ester (scheme 24).

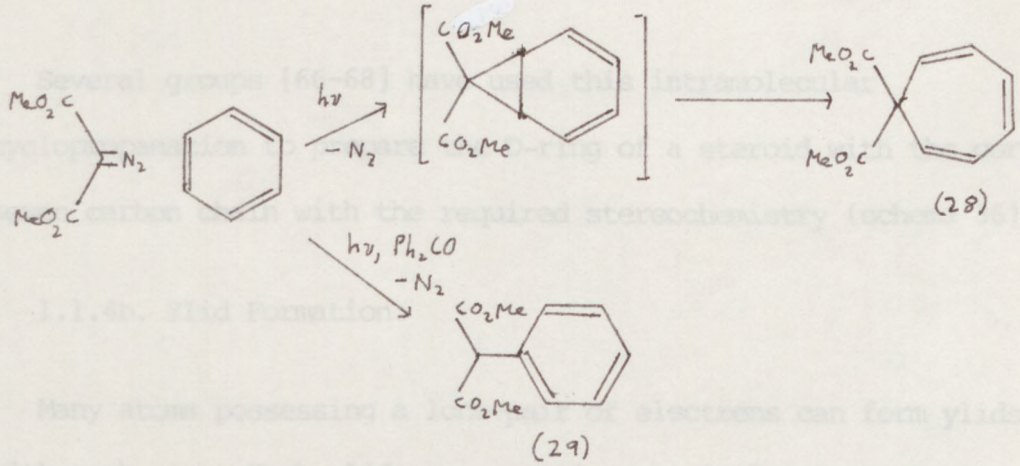
Ledon, Linstrumelle and Julia [58] performed an interesting intramolecular insertion reaction with methyl isobutyl diazomalonate to produce a γ-lactone (scheme 31).

Linstrumelle et al. [59, 60] also prepared a series of γ-lactones fused with a cyclopropane by an intramolecular cyclopropanation reaction of a series of alkenyl methyl diazomalonates (scheme 32).

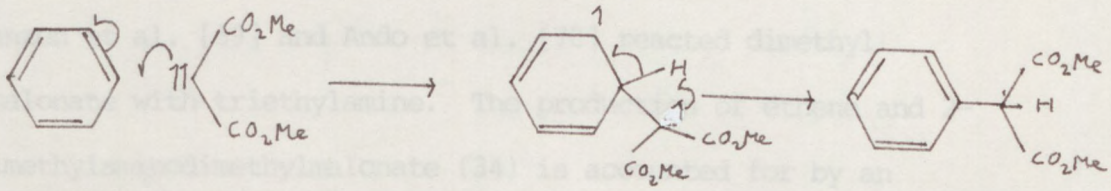
Linstrumelle et al. [61, 62] exploited an intramolecular Buchner



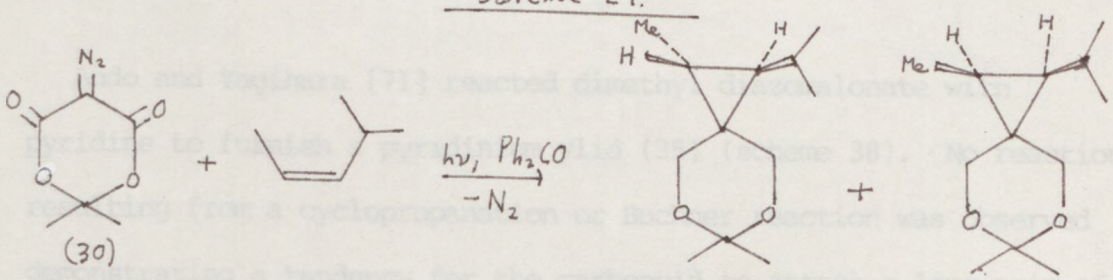
Scheme 27.



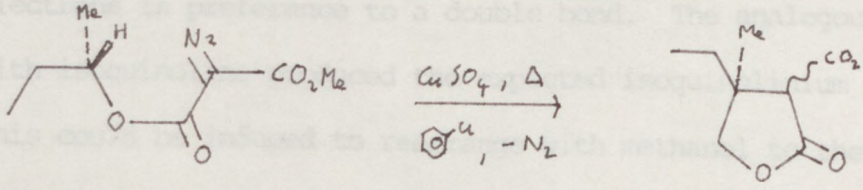
Scheme 28.



Scheme 29.



Scheme 30.



Scheme 31.

reaction to form a γ-lactone (32) fused with a cycloheptatriene ring starting with p-methoxybenzyl methyl diazomalonate (31) (scheme 33).

Corey and Fuchs [63] used an intramolecular cyclopropanation reaction in a route to prostaglandins (scheme 34).

Similarly Ziegler et al. [64] and Clark et al. [65] exploited this method as an approach to cytotoxic natural products (scheme 35).

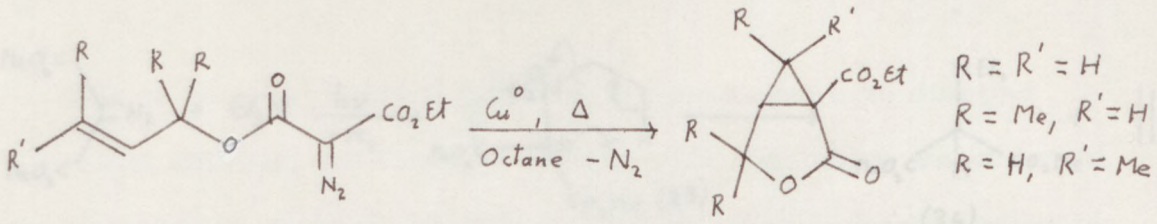
Several groups [66-68] have used this intramolecular cyclopropanation to prepare the D-ring of a steroid with the correct seven carbon chain with the required stereochemistry (scheme 36).

1.1.4b. Ylid Formation.

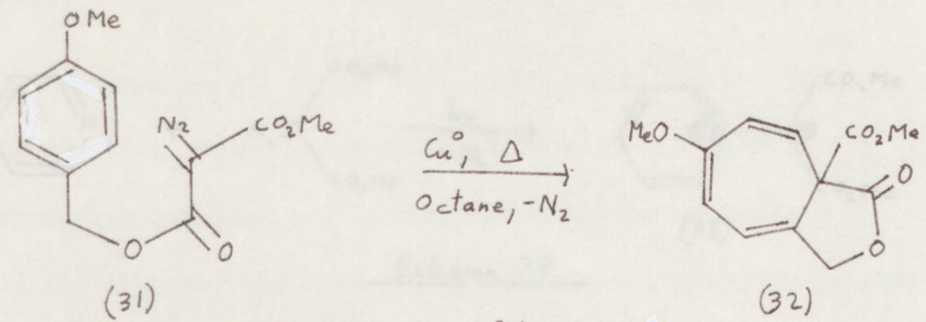
Many atoms possessing a lone-pair of electrons can form ylids with carbenes. Such ylids can sometimes be isolated as stable compounds but frequently they rearrange to other compounds.

Franzen et al. [69] and Ando et al. [70] reacted dimethyl diazomalonate with triethylamine. The production of ethene and 2-N,N-dimethylaminodimethylmalonate (34) is accounted for by an ammonium ylid (33) (scheme 37)

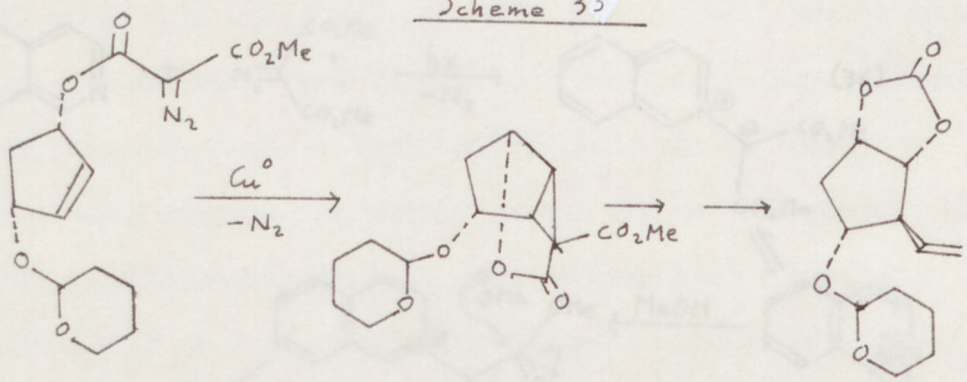
Ando and Yagihara [71] reacted dimethyl diazomalonate with pyridine to furnish a pyridinium ylid (35) (scheme 38). No reaction resulting from a cyclopropanation or Buchner reaction was observed demonstrating a tendency for the carbenoid to attack a lone-pair of electrons in preference to a double bond. The analogous reaction with isoquinoline produced the expected isoquinolinium ylid (36) but this could be induced to rearrange with methanol to the polycyclic aromatic compound (37) as described in scheme 39 with accompanying elimination of dimethyl carbonate.



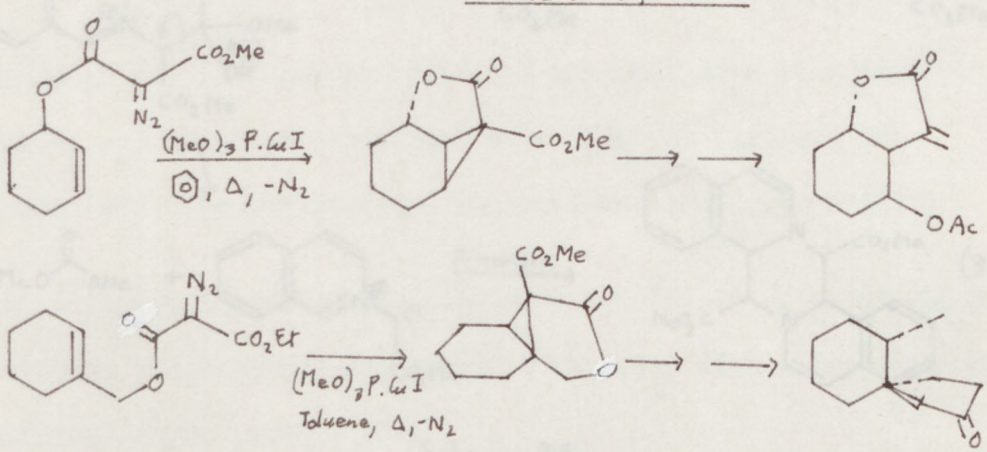
Scheme 32



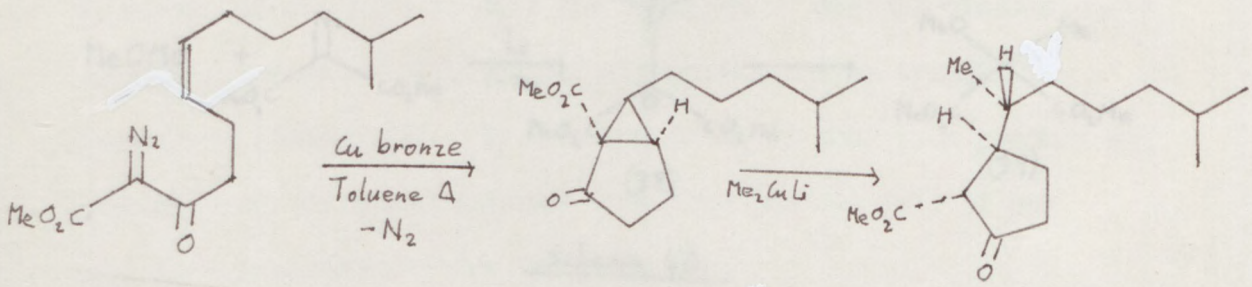
Scheme 33



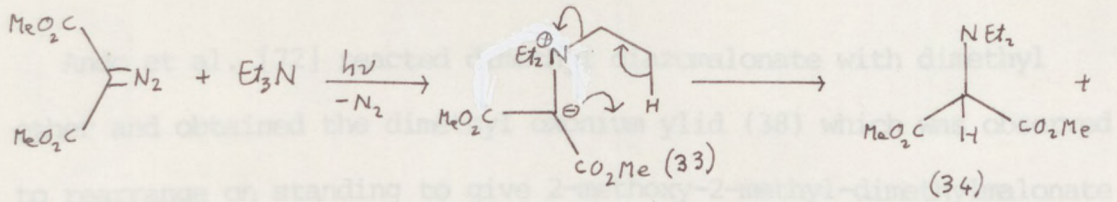
Scheme 34



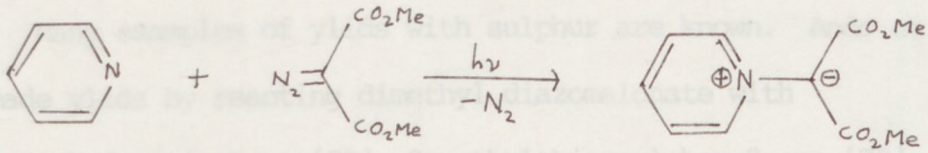
Scheme 35.



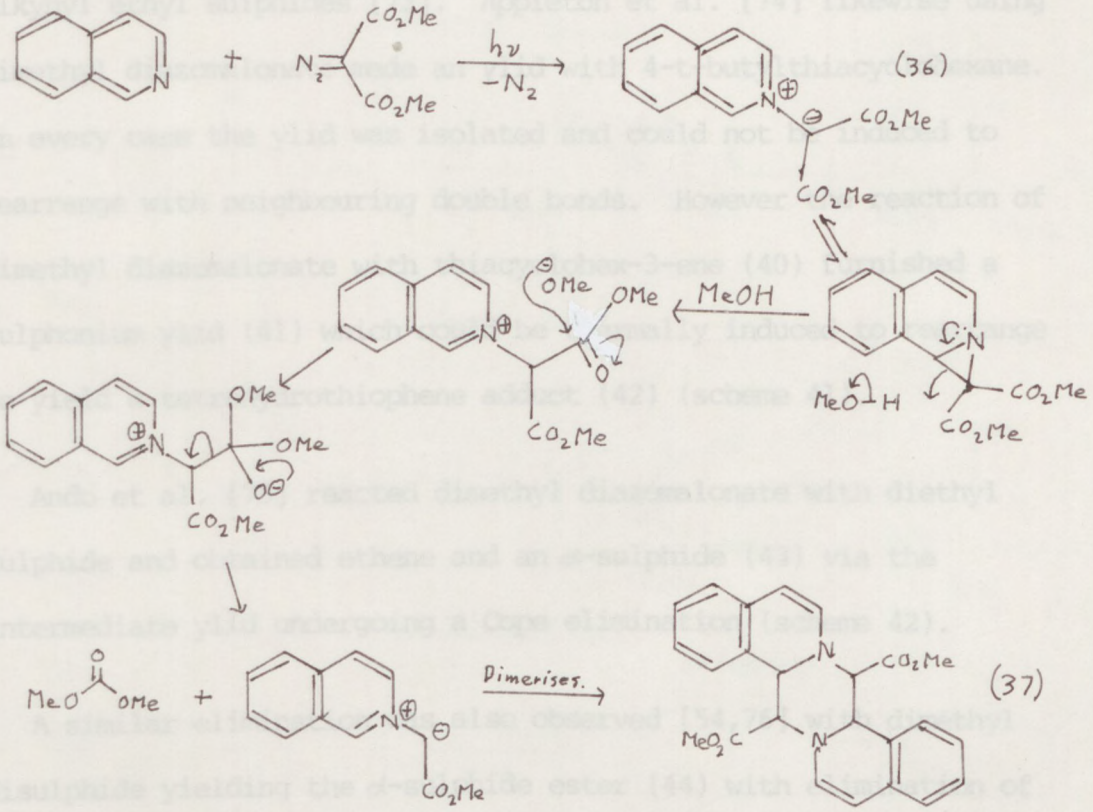
Scheme 36.



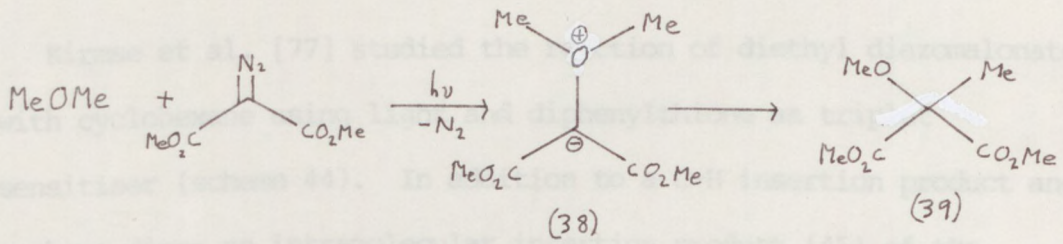
Scheme 37.



Scheme 38.



Scheme 39.



Scheme 40.

Ando et al. [72] reacted dimethyl diazomalonate with dimethyl ether and obtained the dimethyl oxonium ylid (38) which was observed to rearrange on standing to give 2-methoxy-2-methyl-dimethylmalonate (39) by the methyl migrating on to the carbanion (scheme 40).

Many examples of ylids with sulphur are known. Ando et al. have made ylids by reacting dimethyl diazomalonate with tetrahydrothiophene [72], 2-methylthiacyclohex-2-ene [72], thiophene [72] and dibenzothiophene [72]; also vinyl alkyl sulphides [73] and alkynyl ethyl sulphides [73]. Appleton et al. [74] likewise using dimethyl diazomalonate made an ylid with 4-t-butylthiacyclohexane. In every case the ylid was isolated and could not be induced to rearrange with neighbouring double bonds. However the reaction of dimethyl diazomalonate with thiacyclohex-3-ene (40) furnished a sulphonium ylid (41) which could be thermally induced to rearrange to yield a tetrahydrothiophene adduct (42) (scheme 41).

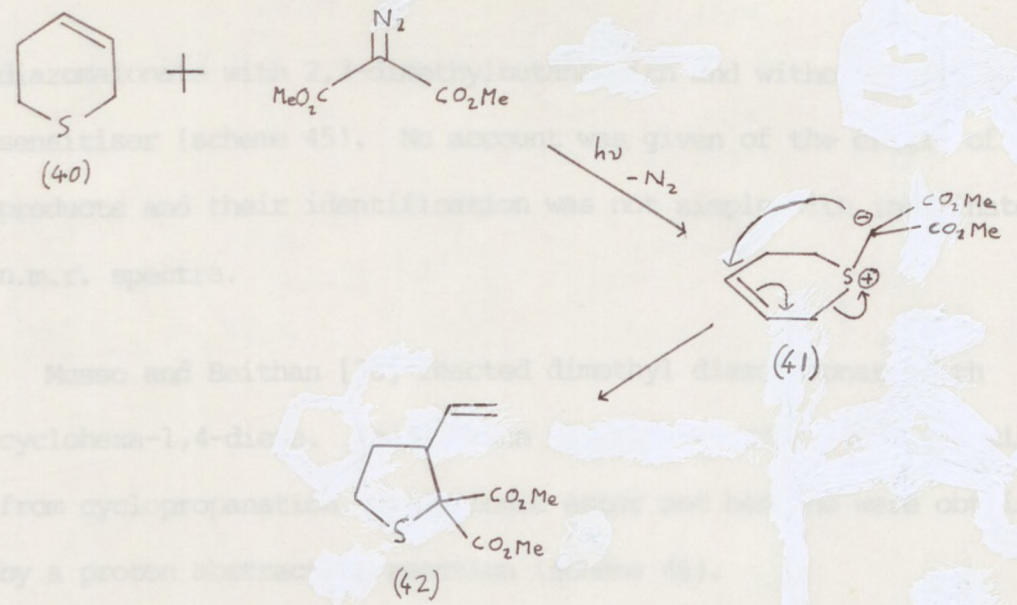
Ando et al. [75] reacted dimethyl diazomalonate with diethyl sulphide and obtained ethene and an α-sulphide (43) via the intermediate ylid undergoing a Cope elimination (scheme 42).

A similar elimination was also observed [54,76] with dimethyl disulphide yielding the α-sulphide ester (44) with elimination of thioformaldehyde (scheme 43).

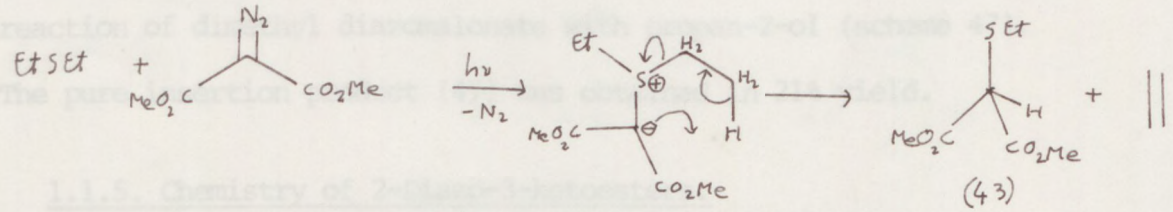
1.1.4c. Insertion Reactions.

Kirmse et al. [77] studied the reaction of diethyl diazomalonate with cyclohexane using light and diphenylthione as triplet sensitiser (scheme 44). In addition to a C-H insertion product and carbene dimer an intramolecular insertion product (45) of the carbenoid intermediate was obtained.

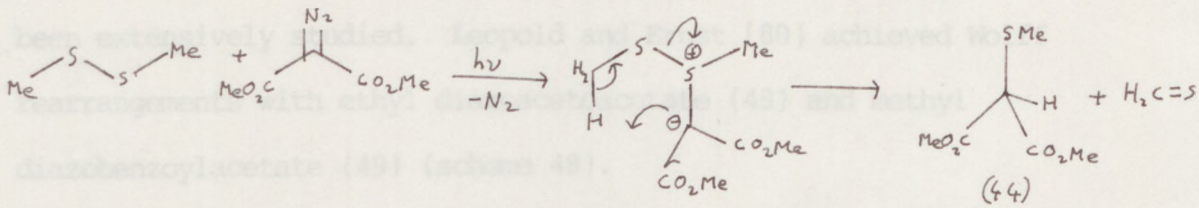
Maitland Jones Jr. et al. [55] studied the reaction of dimethyl



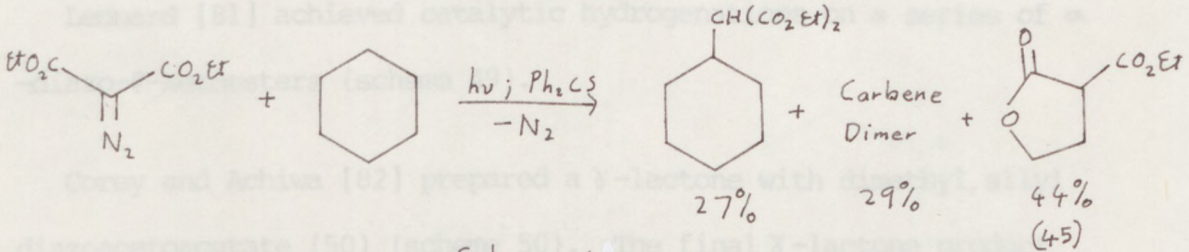
Scheme 41.



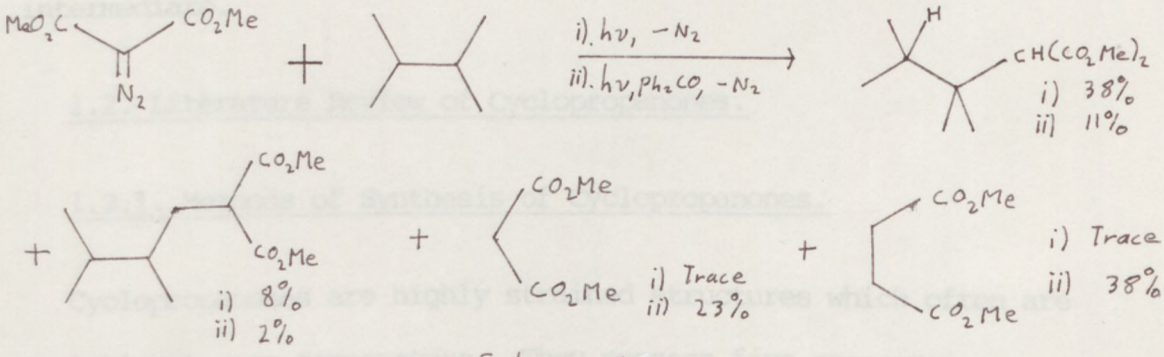
Scheme 42.



Scheme 43.



Scheme 44



Scheme 45.

diazomalonate with 2,3-dimethylbutane with and without triplet sensitiser (scheme 45). No account was given of the origin of the products and their identification was not simple with indefinate n.m.r. spectra.

Musso and Beithan [78] reacted dimethyl diazomalonate with cyclohexa-1,4-diene. In addition to the norcarene (46) resulting from cyclopropanation, the malonic ester and benzene were obtained by a proton abstraction reaction (scheme 46).

Ando et al. [79] have reported the photochemical O-H insertion reaction of dimethyl diazomalonate with propan-2-ol (scheme 47). The pure insertion product (47) was obtained in 21% yield.

1.1.5. Chemistry of 2-Diazo-3-ketoesters.

In contrast to diazomalonates this group of compounds have not been extensively studied. Leopold and Ernst [80] achieved Wolff rearrangements with ethyl diazoacetoacetate (48) and methyl diazobenzoylacetate (49) (scheme 48).

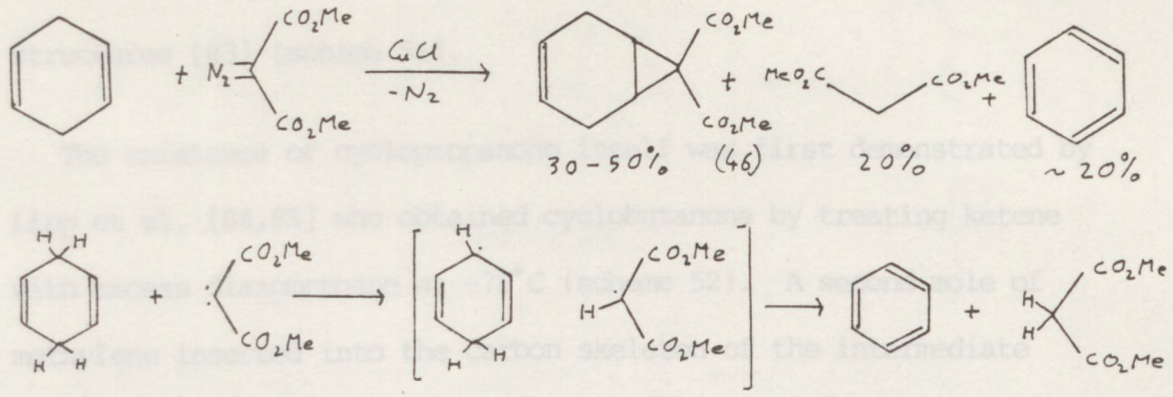
Leonard [81] achieved catalytic hydrogenations on a series of α-diazo-β-ketoesters (scheme 49).

Corey and Achiwa [82] prepared a γ-lactone with dimethyl allyl diazoacetoacetate (50) (scheme 50). The final γ-lactone product (51) results from rearrangement of a fused cyclopropane intermediate.

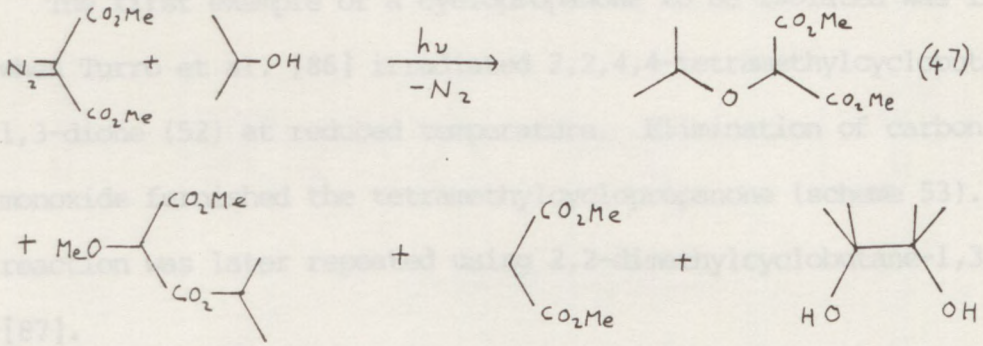
1.2. Literature Review of Cyclopropanones.

1.2.1. Methods of Synthesis of Cyclopropanones.

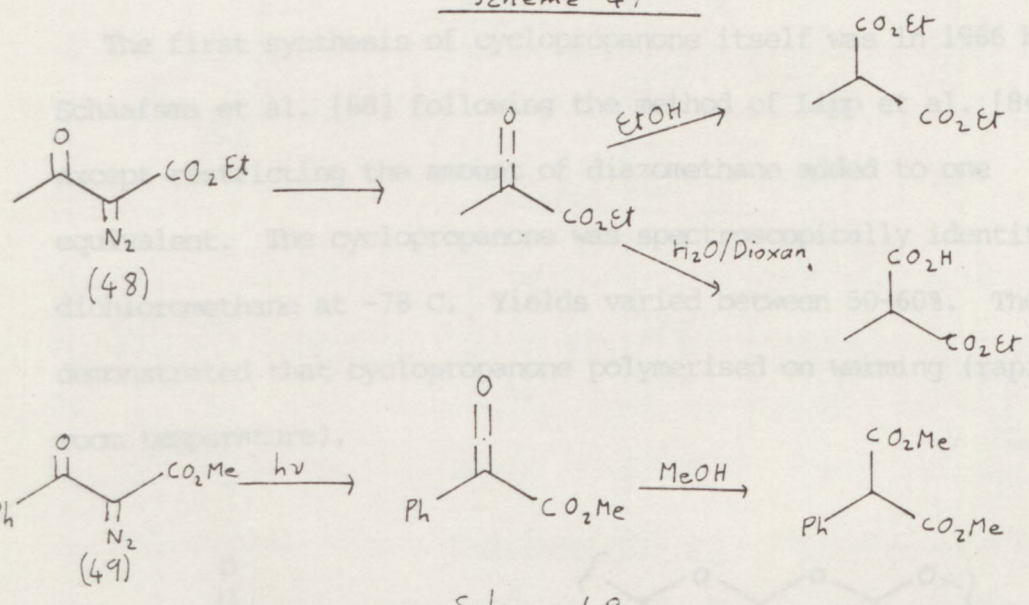
Cyclopropanones are highly strained structures which often are unstable at room temperature. They possess five resonance



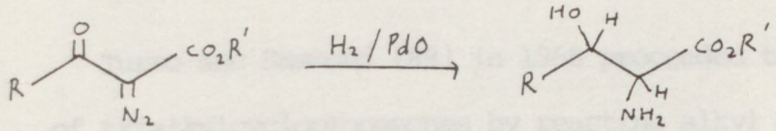
Scheme 46.



Scheme 47



Scheme 48



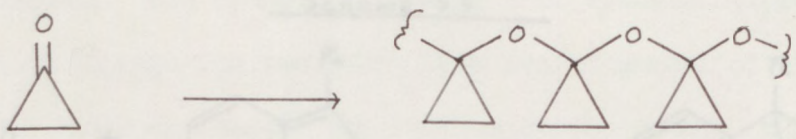
Scheme 49

structures [83] (scheme 51).

The existance of cyclopropanone itself was first demonstrated by Lipp et al. [84,85] who obtained cyclobutanone by treating ketene with excess diazomethane at -78°C (scheme 52). A second mole of methylene inserted into the carbon skeleton of the intermediate cyclopropanone.

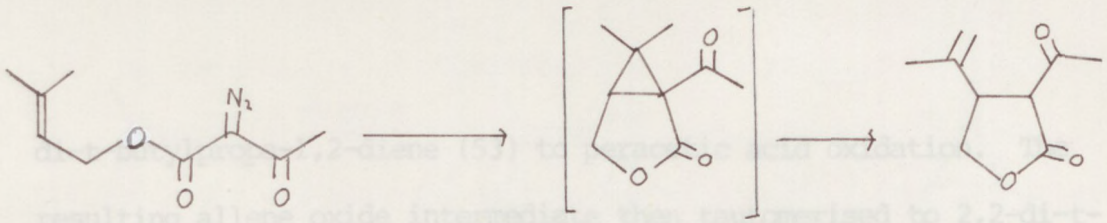
The first example of a cyclopropanone to be isolated was in 1965 when Turro et al. [86] irradiated 2,2,4,4-tetramethylcyclobutane-1,3-dione (52) at reduced temperature. Elimination of carbon monoxide furnished the tetramethylcyclopropanone (scheme 53). The reaction was later repeated using 2,2-dimethylcyclobutane-1,3-dione [87].

The first synthesis of cyclopropanone itself was in 1966 by Schaafsma et al. [88] following the method of Lipp et al. [84] except restricting the amount of diazomethane added to one equivalent. The cyclopropanone was spectroscopically identified in dichloromethane at -78 C. Yields varied between 50-60%. They demonstrated that cyclopropanone polymerised on warming (rapidly at room temperature).



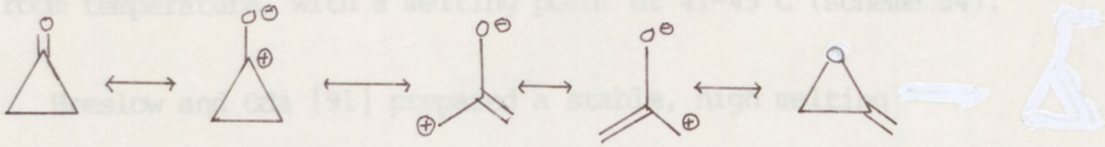
Turro and Hammond [89] in 1968 proceeded to synthesise a series of trialkylcyclopropanones by reacting alkyl diazomethanes with dialkylketenes.

An alternative method of synthesising cyclopropanones is by epoxidation of an allene. Gandall and Machleder [90] subjected 1,1-

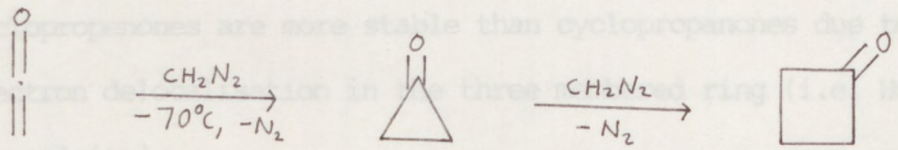


(50) (51)

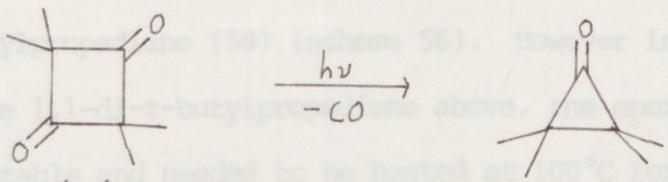
Scheme 50



Scheme 51

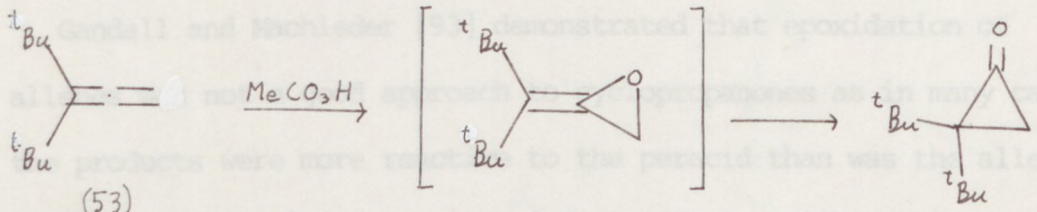


Scheme 52



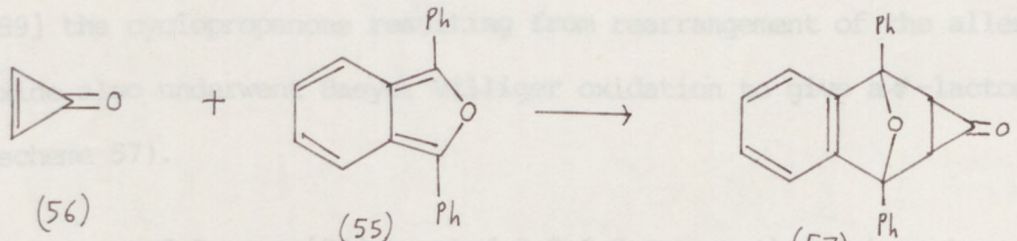
(52)

Scheme 53



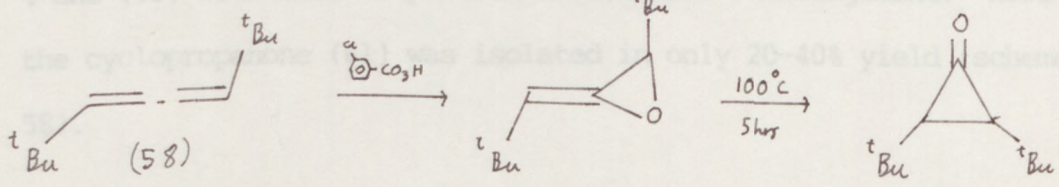
(53) (54)

Scheme 54



(56) (55) (57)

Scheme 55



(58) 59

Scheme 56

di-t-butylpropa-1,2-diene (53) to peracetic acid oxidation. The resulting allene oxide intermediate then tautomerised to 2,2-di-t-butylcyclopropanone (54) which was isolated as a solid, stable at room temperature, with a melting point of 41-43°C (scheme 54).

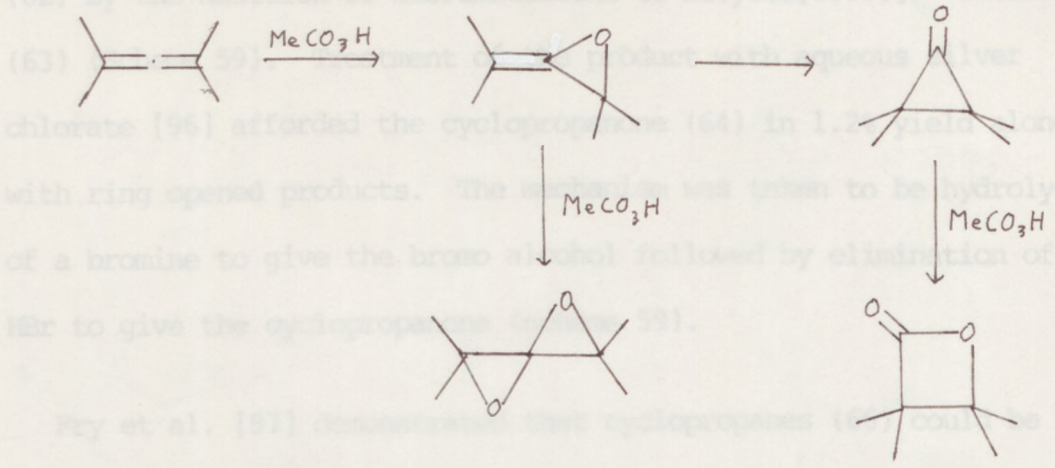
Breslow and Oda [91] prepared a stable, high melting cyclopropanone (57) by performing a Diels Alder reaction between a furan derivative (55) and cyclopropenone (56) (scheme 55). Cyclopropenones are more stable than cyclopropanones due to a 2π electron delocalisation in the three membered ring (i.e. Huckel aromaticity).

Camp and Greene [92] performed an epoxidation reaction of 1,3-di-t-butylpropadiene (58) (scheme 56). However in contrast to the case of the 1,1-di-t-butylpropadiene above, the epoxide of the 1,3-isomer was stable and needed to be heated at 100°C for five hours to induce 50% conversion to the 1,2-di-t-butylcyclopropanone (59).

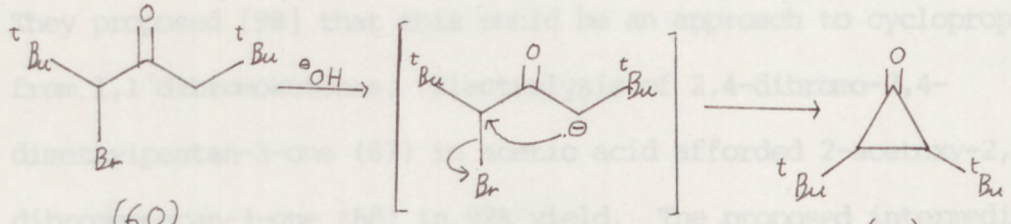
Gandall and Machleder [93] demonstrated that epoxidation of allenes was not a good approach to cyclopropanones as in many cases the products were more reactive to the peracid than was the allene, leading to extensive formation of diepoxide in addition to cyclopropanone. For example in the case of tetramethylpropadiene [89] the cyclopropanone resulting from rearrangement of the allene oxide also underwent Baeyer Villiger oxidation to give a β-lactone (scheme 57).

Pazos and Greene [94] treated 2,2,6,6-tetramethyl-3-bromoheptan-4-one (60) with base to perform a Favorskii rearrangement. However the cyclopropanone (61) was isolated in only 20-40% yield (scheme 58).

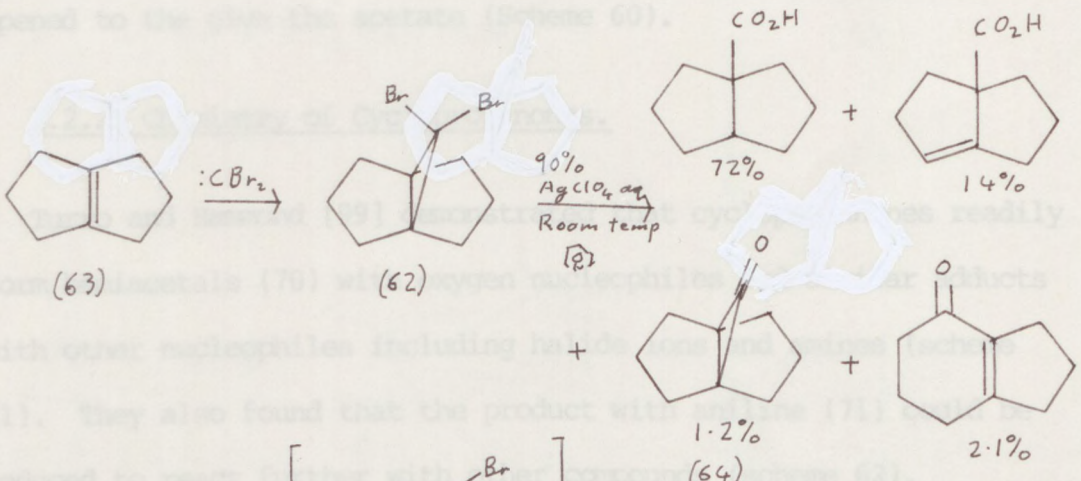
Warner et al. [95] prepared 9,9-dibromotricyclo[3.3.1.$0^{1,5}$]nonane

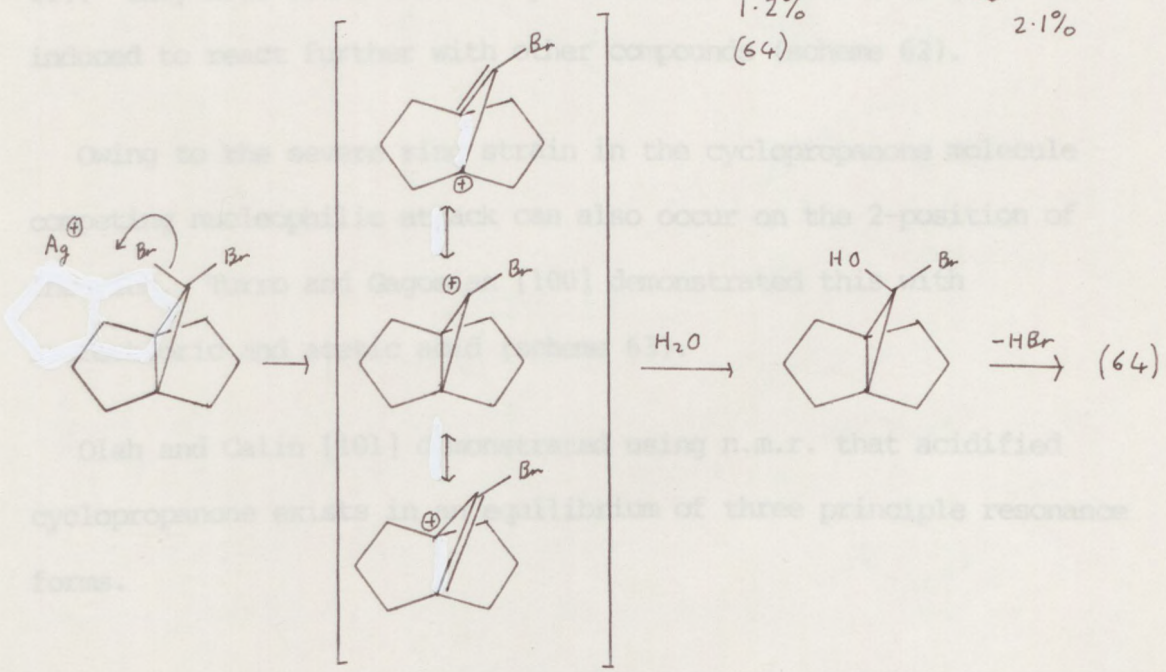


Scheme 57.



Scheme 58.





Scheme 59

(62) by the addition of dibromocarbene to bicyclo[3.3.0]$\Delta^{1,5}$-octene (63) (Scheme 59). Treatment of the product with aqueous silver chlorate [96] afforded the cyclopropanone (64) in 1.2% yield along with ring opened products. The mechanism was taken to be hydrolysis of a bromine to give the bromo alcohol followed by elimination of HBr to give the cyclopropanone (scheme 59).

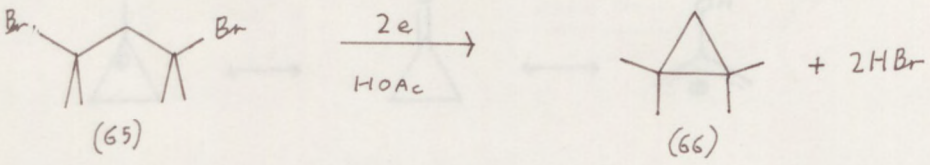
Fry et al. [97] demonstrated that cyclopropanes (66) could be formed from 1,3-dibromoalkanes (65) by electrolysis (scheme 60). They proposed [98] that this could be an approach to cyclopropanones from 1,1´dibromoketones. Electrolysis of 2,4-dibromo-2,4-dimethylpentan-3-one (67) in acetic acid afforded 2-acetoxy-2,4-dibromopentan-3-one (68) in 92% yield. The proposed intermediate was a cyclopropanone (69) which under the reaction conditions ring opened to the give the acetate (Scheme 60).

1.2.2. Chemistry of Cyclopropanones.

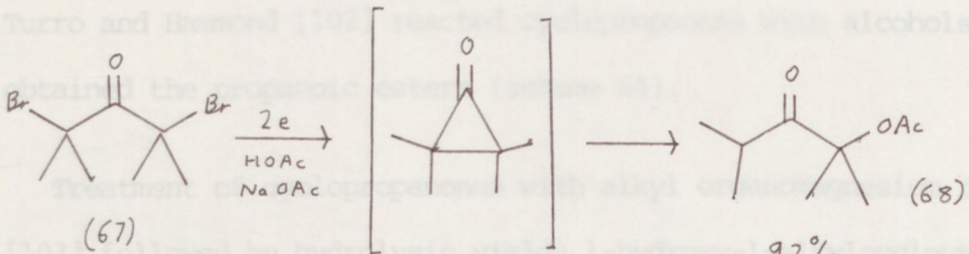
Turro and Hammond [99] demonstrated that cyclopropanones readily form hemiacetals (70) with oxygen nucleophiles and similar adducts with other nucleophiles including halide ions and amines (scheme 61). They also found that the product with aniline (71) could be induced to react further with other compounds (scheme 62).

Owing to the severe ring strain in the cyclopropanone molecule competing nucleophilic attack can also occur on the 2-position of the ring. Turro and Gagosian [100] demonstrated this with hydrochloric and acetic acid (scheme 63).

Olah and Calin [101] demonstrated using n.m.r. that acidified cyclopropanone exists in an equilibrium of three principle resonance forms.



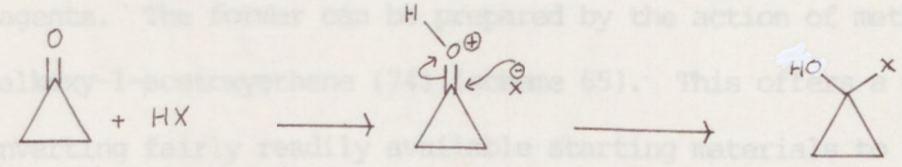
(65) (66)



(67) (69) (68)

92%

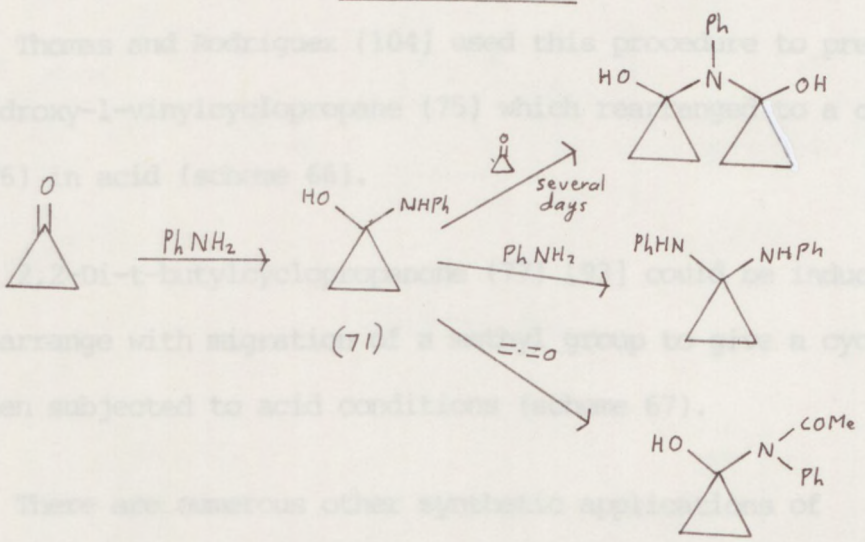
Scheme 60



X = $^{\ominus}OH$, $^{\ominus}CN$, $^{\ominus}Cl$, $^{\ominus}OMe$, $^{\ominus}OAc$, $PhN^{\ominus}Me$

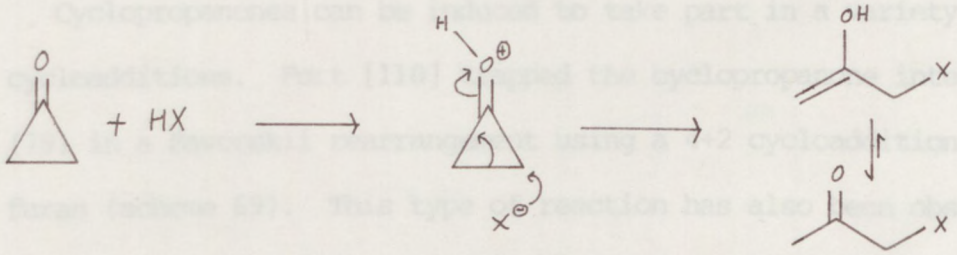
(70)

Scheme 61.

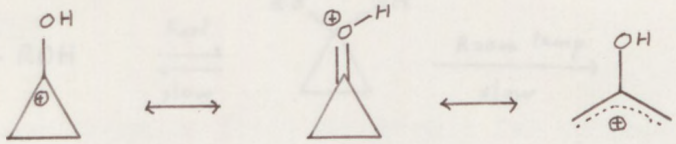


(71)

Scheme 62.



Scheme 63.



Turro and Hammond [102] reacted cyclopropanone with alcohols and obtained the propanoic esters (scheme 64).

Treatment of cyclopropanones with alkyl organomagnesium reagents [103] followed by hydrolysis yields 1-hydroxy-1-alkylcyclopropanes (72). Indeed 1-alkoxy-1-acetoxycyclopropanes (73) are themselves a source of cyclopropanones when treated with organomagnesium reagents. The former can be prepared by the action of methylene on 1-alkoxy-1-acetoxyethene (74) (scheme 65). This offers a means of converting fairly readily available starting materials to cyclopropanones.

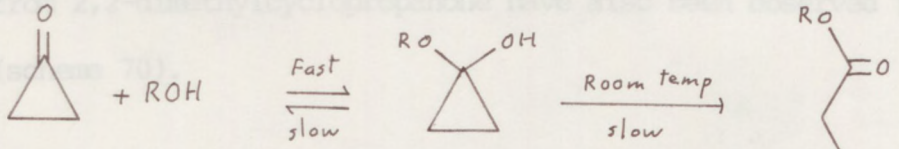
Thomas and Rodriguez [104] used this procedure to prepare 1-hydroxy-1-vinylcyclopropane (75) which rearranged to a cyclobutanone (76) in acid (scheme 66).

2,2-Di-t-butylcyclopropanone (77) [93] could be induced to rearrange with migration of a methyl group to give a cyclobutanone when subjected to acid conditions (scheme 67).

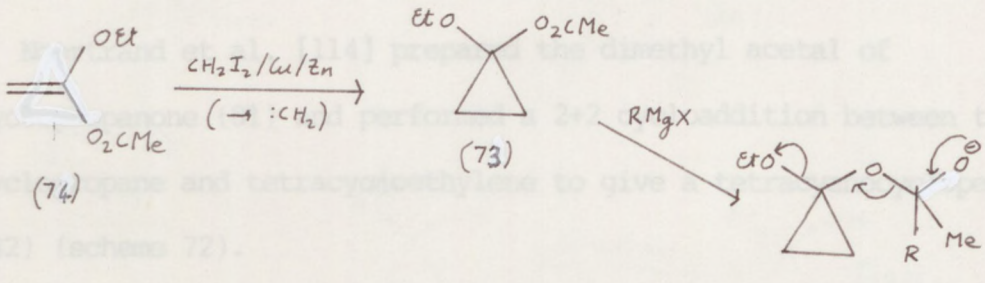
There are numerous other synthetic applications of cyclopropanones, a number of which are illustrated in scheme 68.

Cyclopropanones can be induced to take part in a variety of cycloadditions. Fort [110] trapped the cyclopropanone intermediate (79) in a Favorskii rearrangement using a 4+2 cycloaddition with furan (scheme 69). This type of reaction has also been observed with cyclopenta-1,3-diene [111] and N-methylpyrrole [112].

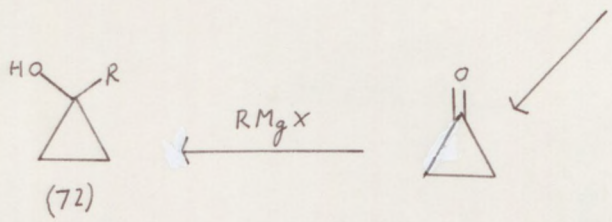
1,3-Dipolar cycloadditions of the oxy-allyl system (80) derived



Scheme 64

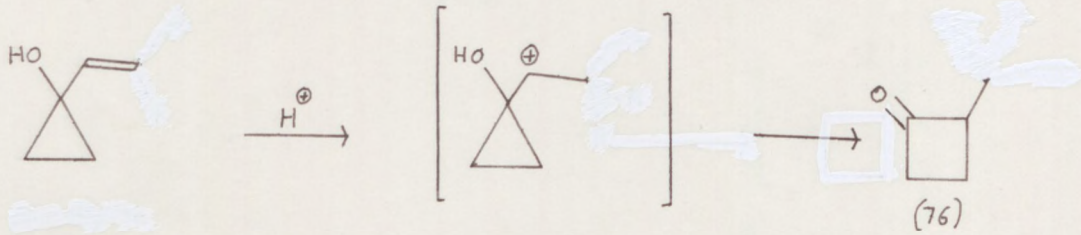


(74) (73)



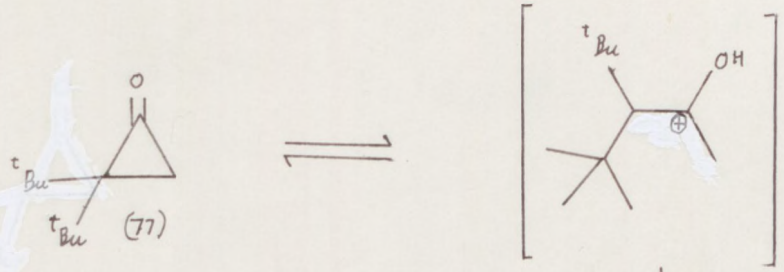
(72)

Scheme 65

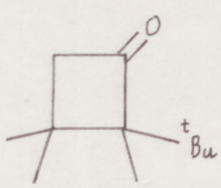


(75) (76)

Scheme 66.



(77)



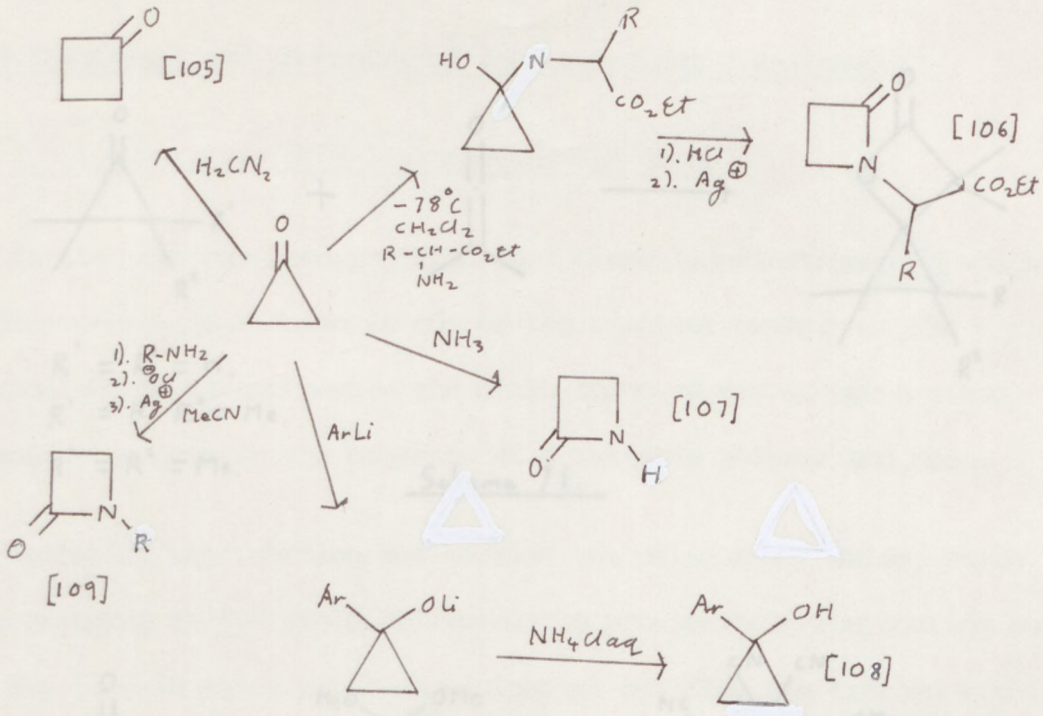
(78)

Scheme 67.

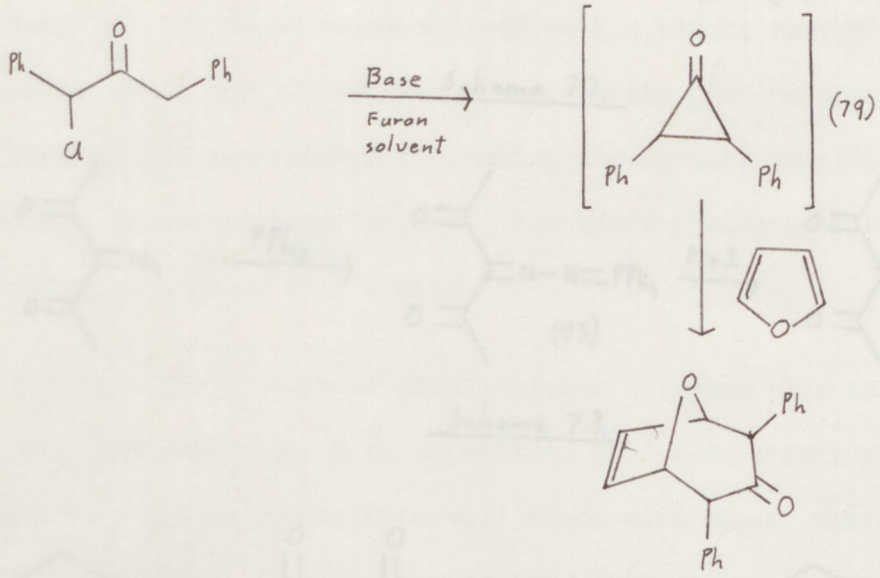
from 2,2-dimethylcyclopropanone have also been observed [109] (scheme 70).

Turro and Gagosian [113] reported a 2+2 cycloaddition involving the carbonyl and the carbon-carbon double bond of a ketene (scheme 71).

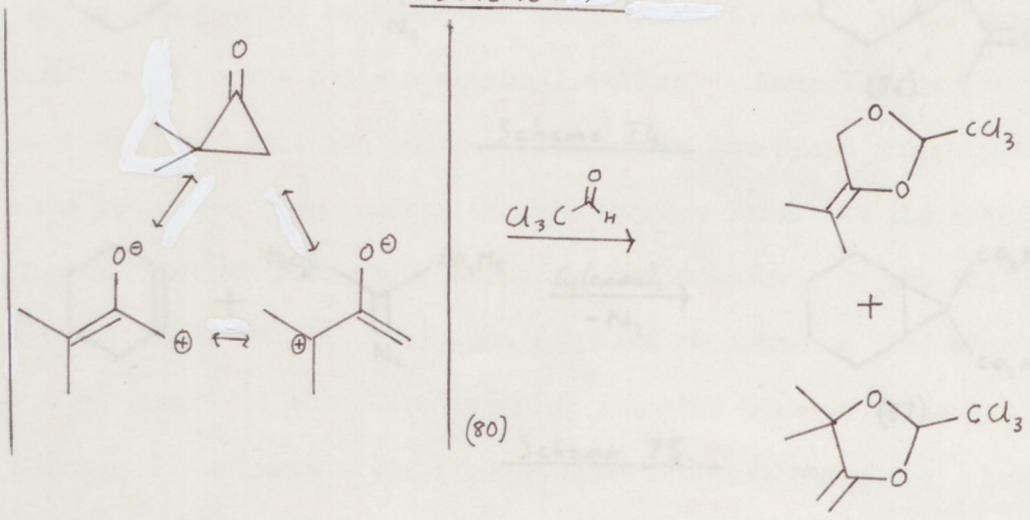
Noortrand et al. [114] prepared the dimethyl acetal of cyclopropanone (81) and performed a 2+2 cycloaddition between the cyclopropane and tetracyanoethylene to give a tetracyanocyclopentane (82) (scheme 72).



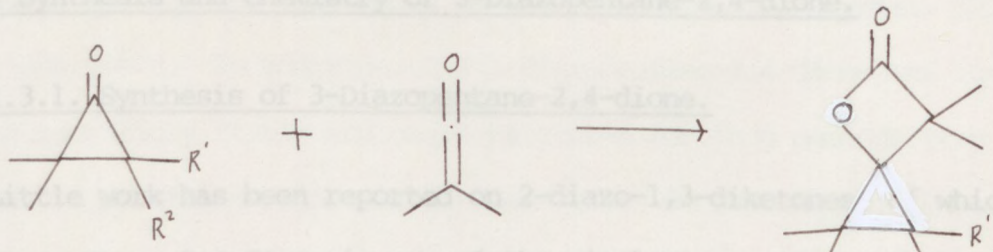
Scheme 68.



Scheme 69.

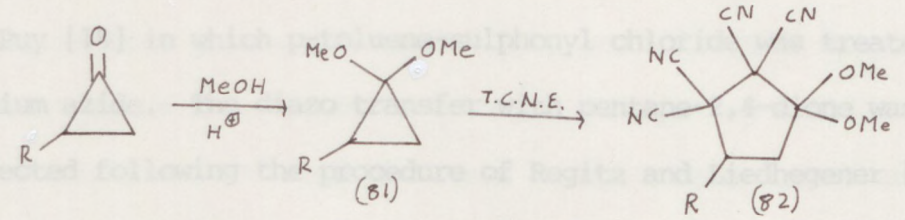


Scheme 70.

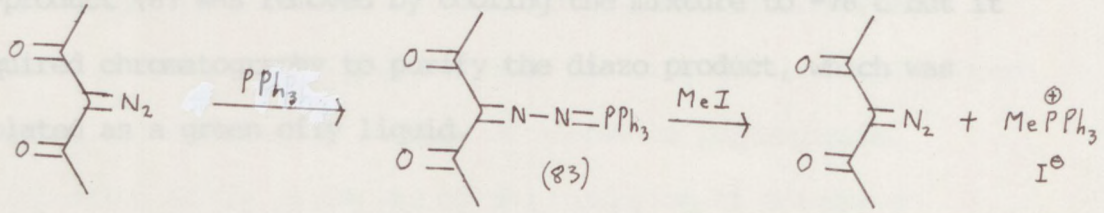


$R^1 = R^2 = H.$
$R^1 = H,\ R^2 = Me.$
$R^1 = R^2 = Me.$

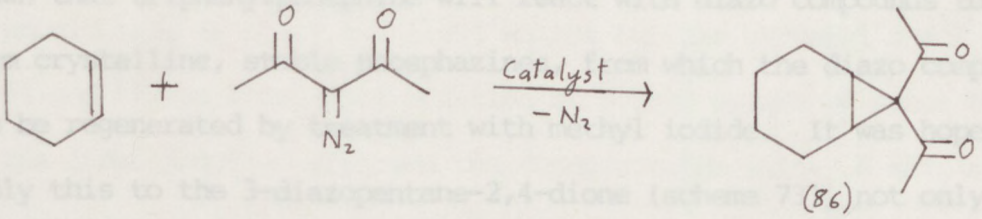
Scheme 71.



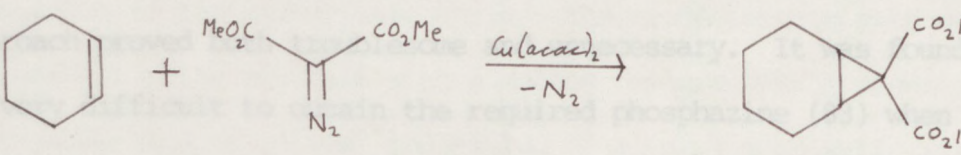
Scheme 72.



Scheme 73.



Scheme 74.



Scheme 75.

1.3. Synthesis and Chemistry of 3-Diazopentane-2,4-dione.

1.3.1. Synthesis of 3-Diazopentane-2,4-dione.

Little work has been reported on 2-diazo-1,3-diketones, of which 3-diazopentane-2,4-dione is one of the simplest examples. The method chosen to synthesise the diazo compound was to use a diazo transfer reagent in the presence of a suitable solvent and base.

Initially the reaction was carried out using tosyl azide, which was prepared in 82% yield following the procedure of Von Doering and De Puy [18] in which p-toluene-sulphonyl chloride was treated with sodium azide. The diazo transfer with pentane-2,4-dione was then effected following the procedure of Regitz and Liedhegener [19] (scheme 6), the dione being stirred with a slight excess of the azide in ether for 100 minutes. Some of the p-toluene-sulphonamide by-product (6) was removed by cooling the mixture to -78°C but it required chromatography to purify the diazo product, which was isolated as a green oily liquid.

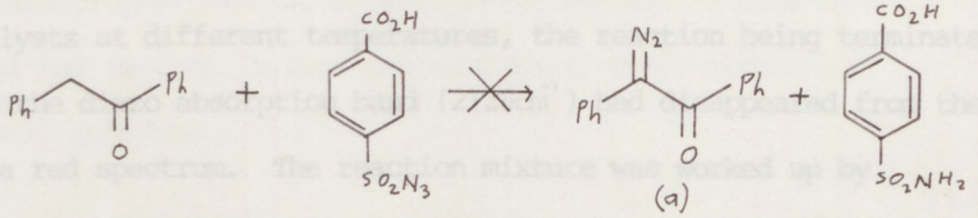
Owing to the problem of purification, attempts were made to develop a chemical means of separating the diazo compound. It is known that triphenylphosphine will react with diazo compounds to form crystalline, stable phosphazines, from which the diazo compound can be regenerated by treatment with methyl iodide. It was hoped to apply this to the 3-diazopentane-2,4-dione (scheme 73), not only facilitating isolation and purification of the diazo compound but also providing a convenient, stable storage form. In the event this approach proved both troublesome and unnecessary. It was found to be very difficult to obtain the required phosphazine (83) when the crude product of the diazo transfer reaction between pentane-2,4-dione and tosyl azide was treated with triphenylphosphine. Later studies revealed that even with pure 3-diazopentane-2,4-dione, the

required phosphazine (83) could be obtained as yellow crystals in only 20% yield. In addition, the 3-diazopentane-2,4-dione was found to be remarkably stable and could be stored for long periods (two years) in a refridgerator without detectable decomposition. On one occasion it was distilled unchanged at 120°C (15mm Hg). The problem of obtaining pure 3-diazopentane-2,4-dione was solved by using an alternative diazo transfer reagent.

Carboxybenzene-4-sulphonyl azide (10) (scheme 10), first described by Hendrickson and Wolf [32], has the advantage of producing more polar, water soluble by-products which simplifies the work-up procedure. The carboxybenzene-4-sulphonic acid (84) (scheme 10) which Hendrickson and Wolf used as starting material has ceased to be commercially available and therefore had to be synthesised by oxidation of p-toluene-sulphonic acid. Several papers referred to the oxidation of p-toluene-sulphonic acid, some involved high pressure techniques [115,116] or even bacteria [117]. Only a Czech patent [118] referred to the use of potassium permanganate. Modification of the procedure of the oxidation of toluene-o-sulphonamide [119] afforded the carboxybenzene-4-sulphonic acid monopotassium salt quantitatively. The approximate pKa for the sulphonic acid is about 0.7 [120] whilst for the carboxyl about 4.7 [120] and it was found that addition of slight excess of conc. HCl to the final solution afforded the monopotassium salt. A sample of the dipotassium salt was prepared which was a white crystalline solid giving a strong absorption peak at 1610cm^{-1} in the i.r. indicative of the carboxylate anion. The monopotassium salt was obtained as white crystals with a softer texture with a carboxyl absorption band at 1710cm^{-1} indicative of an aryl carboxylic acid. The presence of potassium was indicated by the lilac colour observed in a flame test.

The conversion of the monopotassium salt to the sulphonyl chloride (85) (scheme 10) proceeded as described in the literature. However, for the final azide transfer step between the sulphonyl chloride and sodium azide it was found that drying the chloride improved yields. Washing the final azide product (10) in a little cold ethanol gave satisfactorily pure product without the recommended recrystallisation. Overall 200g of p-toluene-sulphonic acid afforded about 70g of carboxybenzene-4-sulphonyl azide which showed no decomposition on prolonged storage in a refridgerator.

Carboxybenzene-4-sulphonyl azide was used extensively throughout this study for preparing 2-diazo-1,3-dicarbonyl compounds. However there is evidence that it is not as active as tosyl azide. A standard procedure to convert benzyl phenyl ketone to the α-diazo compound, azibenzil (a) is to use tosyl azide. However after stirring the ketone in dichloromethane with carboxybenzene-4-sulphonyl azide and two equivalents of base no diazo transfer was observed.



The diazo transfer reaction with pentane-2,4-dione was examined using a variety of solvents in addition to the literature use of acetonitrile [32]. The transfer proceeded very slowly in ether, dichloromethane and ethyl acetate, but methanol and ethanol gave complete transfer in a short period. After evaporation of the methanol, the residue was taken up in dichloromethane and the mixture filtered, which removed much of the carboxybenzene-4-sulphonamide by-product (11) (scheme 10). Complete removal was

ensured by giving the dichloromethane solution an aqueous base wash. Drying and evaporation of the dichloromethane afforded pure 3-diazopentane-2,4-dione.

1.3.2. Chemistry of 3-Diazopentane-2,4-dione.

It was proposed (scheme 4) that 2-diazo-1,3-diketone compounds might provide a convenient approach to cyclopropanones and that 3-diazopentane-2,4-dione would be the simplest choice of diazo compound for the scheme.

Initially, the reaction of 3-diazopentane-2,4-dione with cyclohexene was investigated in order to obtain 7,7-di acetylnorcarane (7,7-diacetylbicyclo[4.1.0]heptane) (86) (scheme 74). It was already known that dimethyl diazomalonate afforded the 7,7-dicarbomethoxynorcarane (87) in good yield [121,122] (scheme 75) and hence success in this reaction was expected.

Several reactions were performed in which the diazodiketone was dissolved in cyclohexene and the solution treated with various catalysts at different temperatures, the reaction being terminated when the diazo absorption band ($2120 cm^{-1}$) had disappeared from the infra red spectrum. The reaction mixture was worked up by preparative thin layer chromatography. The results (Table 3) indicated that a complex reaction was occuring since each reaction gave several initial product bands and many of these proved to be mixtures on further examination.

With copper acetyl acetonate and copper bronze the reaction needed to be heated at reflux temperature for about three days for the reaction to be complete. From the table it can be seen that prolonged reflux and short periods of reflux conditions were used but neither gave any indication of the required product. Rhodium

Catalyst.	Reaction time.	Temperature.	No. bands.
1. $Cu(acac)_2$.	11hrs.	Reflux (93°C).	Six.
2. $Cu(acac)_2$.	3hrs.	Reflux.	Seven.
3. $Cu(acac)_2$.	4days.	Reflux.	Nine.
4. $Cu(acac)_2$.	60hrs.	Reflux.	Six.
5. Cu bronze.	60hrs.	Reflux.	Six.
6. Cu bronze.	72hrs.	60°C.	Five.
7. Rh acetate.	36hrs.	Room temp.	Five.

Table 3.

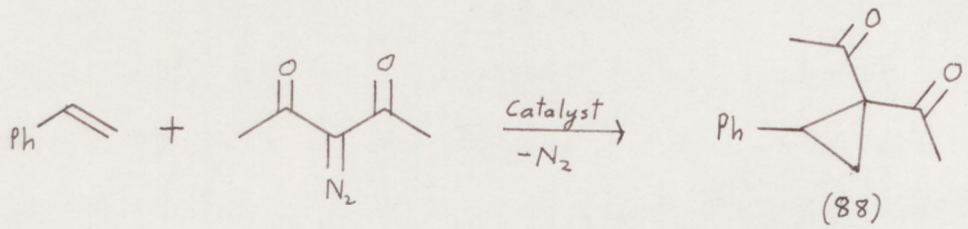
All reactions used about 1.5% equivalent of catalyst. All reactions were worked up on prep. t.l.c. with the exception of 7. which was submitted to column chromatography. The five bands from reaction 7. were then submitted to prep. t.l.c. and were found to be mixtures of several products.

acetate was considerably more efficient, bringing about decomposition within two days at room temperature, but again no identifiable product was observed.

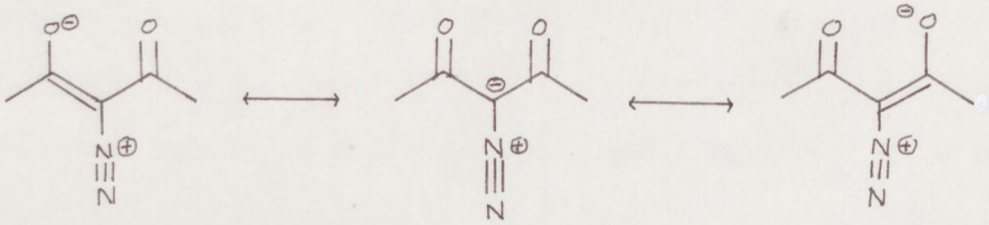
The reaction was also attempted using styrene as the alkene (scheme 76), since this is generally a good substrate for cyclopropanation. However reflux of styrene with 3-diazopentane-2,4-dione in the presence of copper acetylacetonate led to the formation of considerable amounts of polystyrene, hindering work-up. Use of rhodium acetate as the catalyst at room temperature caused less polymerisation but only a very low yield could be obtained of a product which showed two methyl singlets in the H'n.m.r. (1.82 and 2.28ppm) as expected for the diacetylcyclopropane (88) and this reaction was not pursued further.

3-Diazopentane-2,4-dione has proved to be a remarkably stable compound and to be unexpectedly reluctant to enter into cyclopropanation reactions with alkenes. The reasons for this stability and poor reactivity towards double bonds may be partly electronic. Thus, delocalisation involving the two carbonyl groups probably explains the increased stability of the diazo function and altered reactivity of the carbenoid (scheme 77).

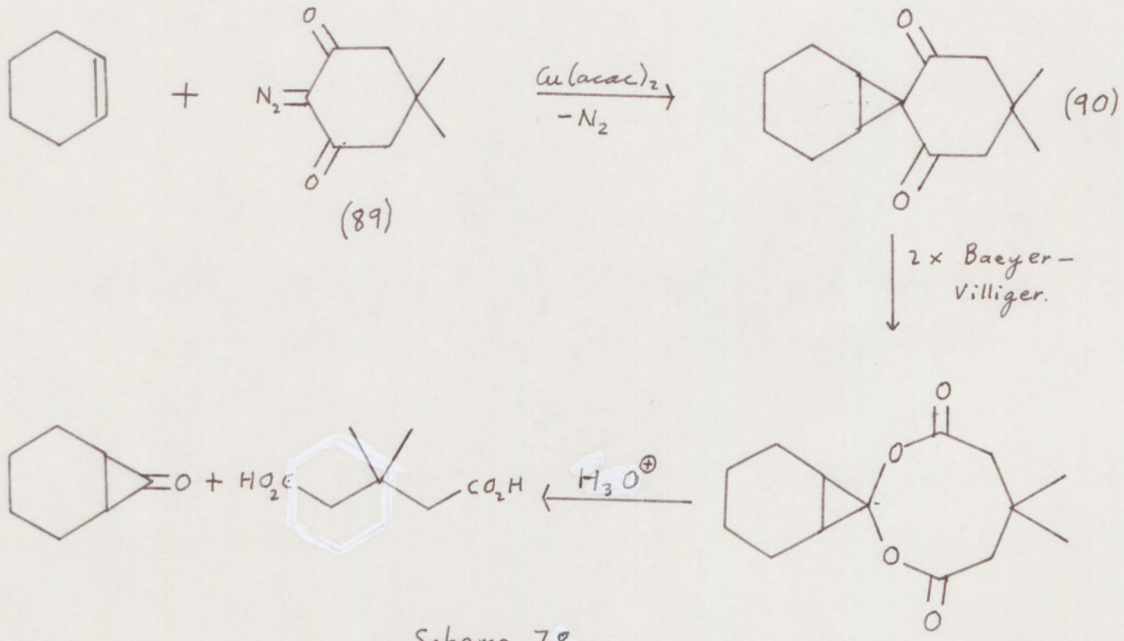
It was of interest to react the diazo compound in an inert solvent to see if there were any identifiable products of decomposition. A sample was refluxed in benzene taking sixteen hours for the diazo compound to completely decompose. However there was no identifiable decomposition product after work-up with prep. t.l.c. The reaction was repeated using about 0.5% equivalent copper acetate taking thirty hours to decompose the diazo compound. In fact benzene as an "inert" solvent was an unreasonable choice because the C-H insertion product, 3-phenylpentane-2,4-dione (88b) (scheme 79), was obtained in 3% yield, with no other identifiable



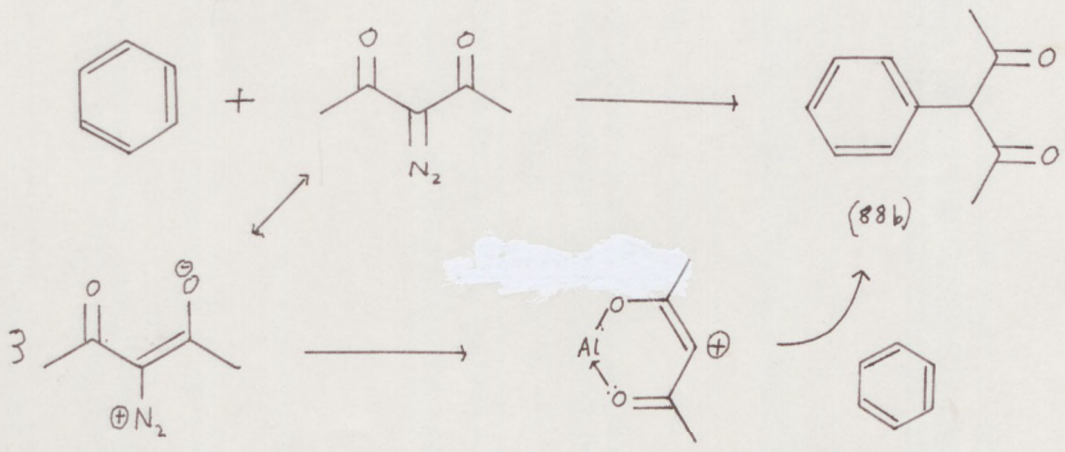
Scheme 76.



Scheme 77.



Scheme 78.



Scheme 79.

product. The reaction was repeated in dichloromethane with complete decomposition achieved after three days at room temperature in the presence of copper acetate. The resulting polymeric product gave no identifiable product after submission to chromatography. However the result with benzene suggested that the yield could be optimised with a Lewis acid which would coordinate with the β-diketone and encourage a Friedel Craft's type acylation of the benzene (scheme 79). Using aluminium trichloride as a suitable Lewis acid in about 70% equivalent gave a yield of 5% which is only a slight increase on the first reaction.

It has been shown by the use of n.m.r. and dipole data [123] that simple 2-diazo-1,3-dicarbonyl compounds exist exclusively, between -50°C and 60°C, in a s-cis, s-cis conformation; i.e. with both of the carbonyl oxygens anti to the diazo group as illustrated (scheme 77). Since the conformation would be of importance in determining reaction course (as in the case for Wolff rearrangement, where a syn orientation is required), it was decided to examine a case in which a syn conformation of carbonyl and diazo groups would be present. 2-Diazodimedone (89) was selected as a model in which both carbonyls are syn to the diazo function and in which the substituents on the carbonyl groups are tied into a ring around the back of the diazo carbon, offering the minimun of steric hindrance to reaction at the carbenoid centre. Scheme 78 demonstrates the proposed route to a cyclopropanone by reacting 2-diazodimedone with cyclohexene.

2-Diazodimedone was prepared by treatment of dimedone with carboxybenezene-4-sulphonyl azide following an analogous procedure with pentane-2,4-dione. The yield of 89% offers an improvement on previous methods [39,51]. The required norcarane (3,3-dimethylspiro[5.6.$0^{6,11}$]dodecane-1,5-dione (90) was obtained as a white solid in 22% yield. However when the norcarane was treated with m-

chloroperbenzoic acid in dichloromethane no oxygen insertion adduct in accordance with a Baeyer Villiger oxidation was isolated. The n.m.r. spectra of chromatographic fractions isolated were complex.

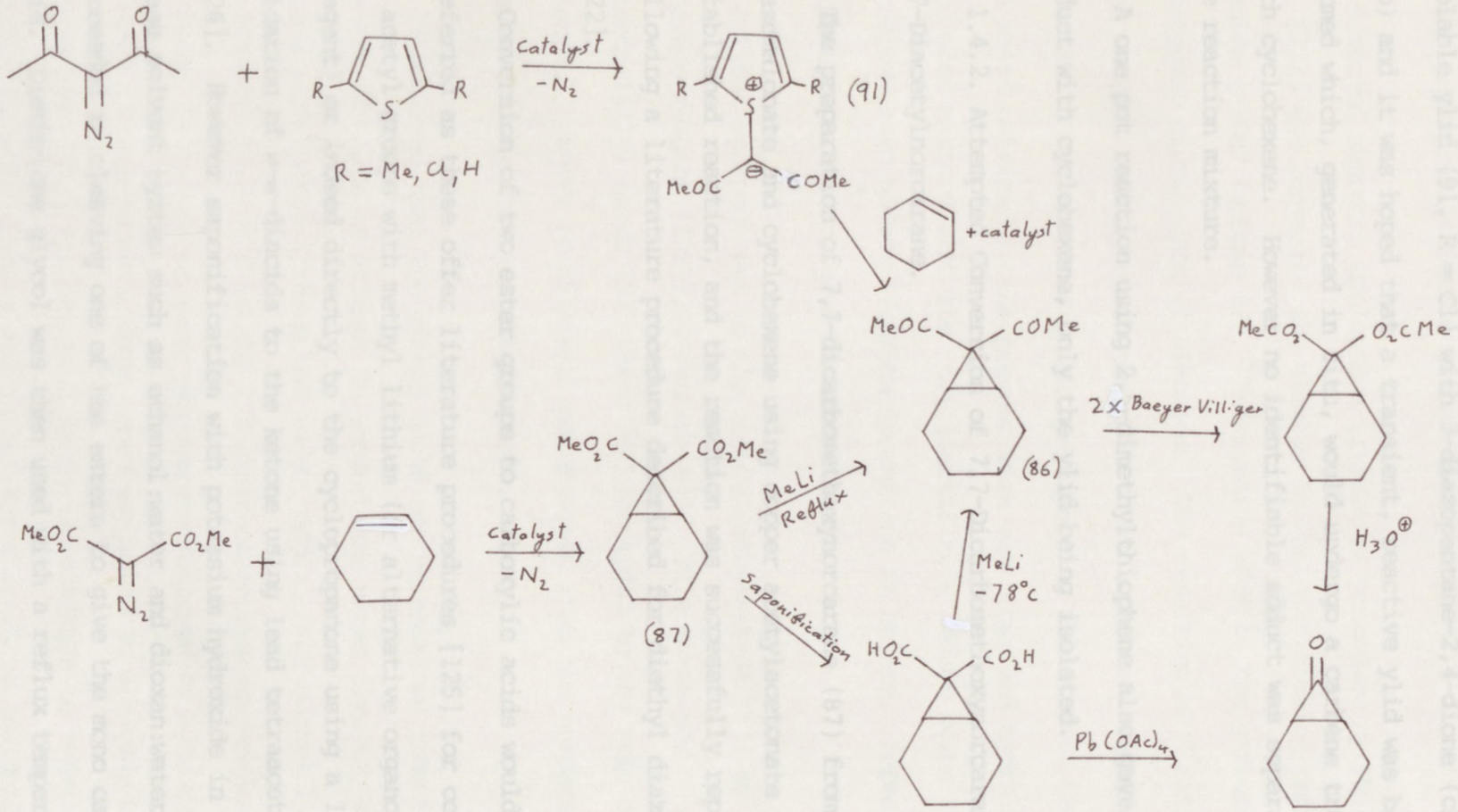
1.4. Other Attmpted Routes to 7,7-Diacetylnorcarane.

Following the failure of a direct cyclopropanation reaction between 3-diazopentane-2,4-dione and cyclohexene, alternative approaches to the 7,7-diacetylnorcarane (86) were proposed as summarised in scheme 80. Essentially two approaches were available. Firstly, a thiophenium ylid (91) [124] could be used in a carbene transfer reaction with cyclohexene to produce the 7,7-diacetylnorcarane. Secondly, the two ester groups of 7,7-dicarbomethoxynorcarane (87) might be converted to ketone groups, either directly or via the carboxylic acid.

1.4.1. Reaction of Thiophenium Ylids with Cyclohexene.

Chapter two deals with the preparation of these ylids. When 2,5-dimethylthiophenium-bisacetylmethylide (91, R = Me) was stirred and refluxed with cyclohexene in the presence of copper acetylacetonate, decomposition of the ylid was very slow and no norcarane was isolated from the crude reaction material, which gave no identifiable products. The reaction was also attempted with cyclooctene and vinyl acetate with a higher reflux temperature. Complete dissociation of the ylid was obtained but no characterisable material indicative of a cyclopropanated product was obtained upon work-up of the crude reaction mixture.

One pot reactions were attempted in which thiophene, diazo compound and cyclohexene were refluxed together. It was hoped that the ylid (91, R = H) produced in situ would react with the alkene solvent. Thiophene itself gave only the 2-thienyl adduct in 18%


R = Me, Cl, H
Catalyst
$-N_2$
(91)
+catalyst
(86)
2x Baeyer Villiger
MeLi
Reflux
MeLi
$-78°C$
Saponification
$H_3O^{\oplus}$
$Pb(OAc)_4$
Catalyst
$-N_2$
(87)

Scheme 80.

yield (2-(2´-thienyl)-pentane-2,4-dione, described in chapter two) with no observed adduct with cyclohexene.

2,5-Dichlorothiophene was then examined. It failed to give an isolable ylid (91, R = Cl) with 3-diazopentane-2,4-dione (chapter two) and it was hoped that a transient, reactive ylid was being formed which, generated in situ, would undergo a carbene transfer with cyclohexene. However no identifiable adduct was separated from the reaction mixture.

A one pot reaction using 2,5-dimethylthiophene also gave no adduct with cyclohexene, only the ylid being isolated.

1.4.2. Attempted Conversion of 7,7-Dicarbomethoxynorcarane to 7,7-Diacetylnorcarane.

The preparation of 7,7-dicarbomethoxynorcarane (87) from dimethyl diazomalonate and cyclohexene using copper acetylacetonate is an established reaction, and the reaction was successfully repeated following a literature procedure described for diethyl diazomalonate [122].

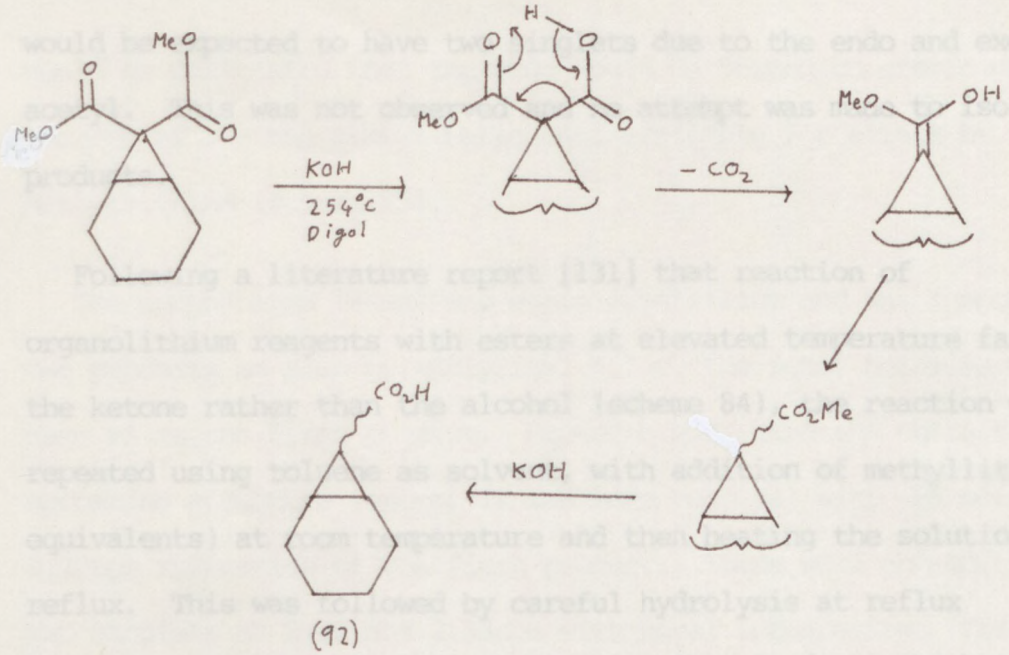
Conversion of two ester groups to carboxylic acids would be preferred as these offer literature procedures [125] for conversion to acetyl groups with methyl lithium (or alternative organometallic reagent) or indeed directly to the cyclopropanone using a literature oxidation of α-α-diacids to the ketone using lead tetraacetate [126]. However saponification with potassium hydroxide in a one phase solvent system such as ethanol:water and dioxan:water only succeeded in cleaving one of the esters to give the mono carboxylic acid. Diethylene glycol was then used with a reflux temperature of 254°C. Potassium hydroxide readily dissolves in this solvent above 80°C and the solution can be used to cleave diesters such as phthalic acid esters [127] which are notoriously difficult to

completely saponify. However 7-carboxylnorcarane (92) was obtained indicating that one of the carboxylic acid functions had decarboxylated at the elevated temperature, presumably via a β-keto acid elimination mechanism (scheme 81).

A second approach employed a literature procedure by Wulfman et al. [122] who converted the diester to the diacid using potassium cyanide in DMF (scheme 82). The cyanide adds to the carbonyl with subsequent elimination of alkoxide. The resulting acyl nitrile is then readily hydrolysed to the acid. The literature reported that a white solid was obtained which hydrolysed to the diacid. However the solid obtained in the present work was brown and hydrolysis gave a complex mixture with the only identifiable adduct being the decarboxylated adduct 7-carboxylnorcarane as before. Repeating the literature procedure gave the same result.

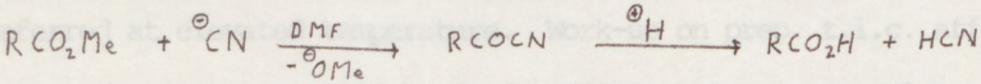
A final approach was to use iodotrimethylsilane (93) as the ester cleavage reagent [128-130] (scheme 83). This gives the trimethylsilyl ester (94) which is hydrolysed to the acid and silanol. However no cleavage was observed when the norcarane diester was treated with the reagent.

It appeared that the diacid could not be obtained from the diester and thus an attempt to convert the ester directly to the ketone with methyl lithium was made. Addition of methyl lithium (4 equivalents) at -78°C to the 7,7-dicarbomethoxynorcarane and allowing it to warm to room temperature followed by hydrolysis yielded a crude product which, when subjected to analysis by n.m.r, gave a new methyl singlet at 1.80ppm (in addition to substantial starting material peaks) and an infra red spectrum indicative of a tertiary alcohol (95) (OH stretch at 3600cm^{-1}) (scheme 84). The diacetylnorcarane product, in analogy to dicarbomethoxynorcarane,

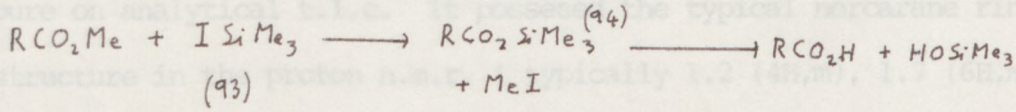


(92)

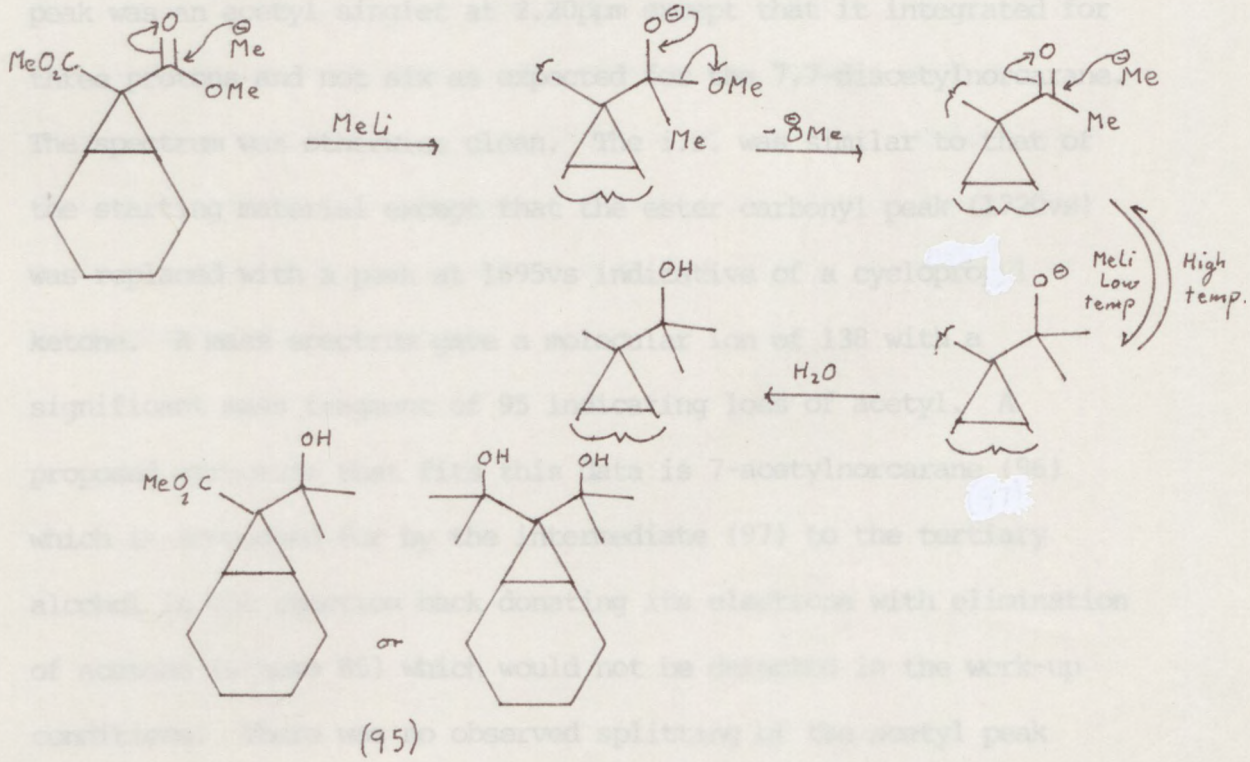
Scheme 81.



Scheme 82.



Scheme 83.



(95)

Scheme 84.

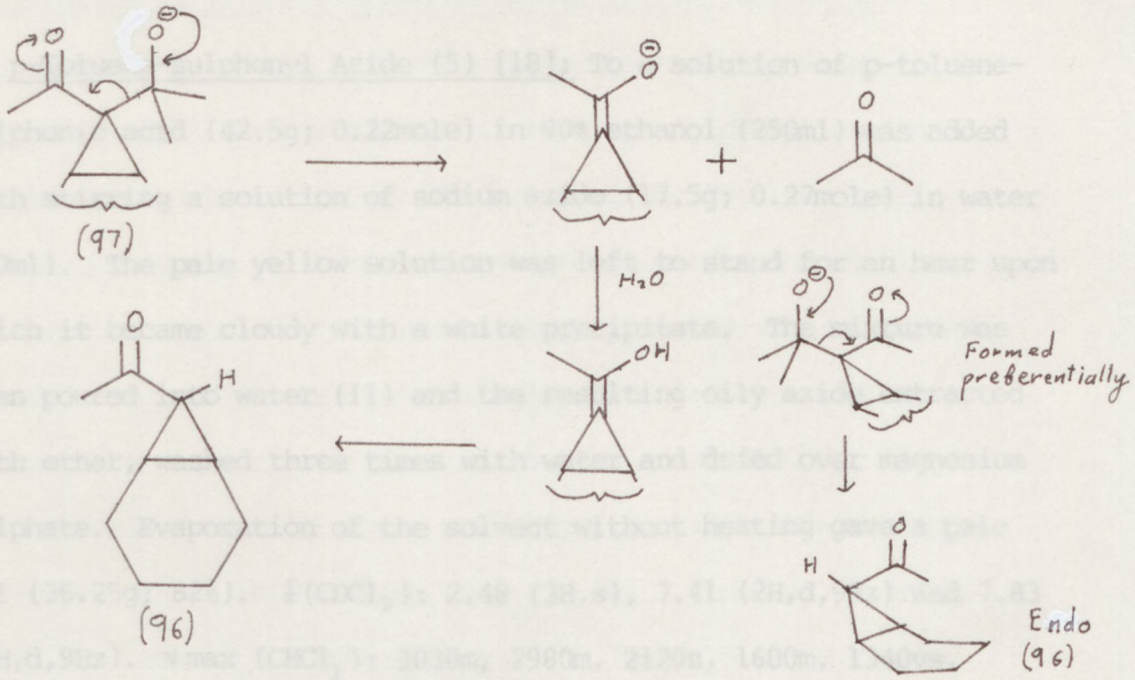
would be expected to have two singlets due to the endo and exo acetyl. This was not observed and no attempt was made to isolate products.

Following a literature report [131] that reaction of organolithium reagents with esters at elevated temperature favours the the ketone rather than the alcohol (scheme 84), the reaction was repeated using toluene as solvent, with addition of methyllithium (6 equivalents) at room temperature and then heating the solution to reflux. This was followed by careful hydrolysis at reflux temperature, thus hydrolysing the anion that leads to the ketone and not that which leads to the tertiary alcohol, as the former is preferred at elevated temperature. Work-up on prep. t.l.c. afforded two interesting, low yield bands in addition to a large polar polymeric residue. The first product (32mg) was an oil which was pure on analytical t.l.c. It possesed the typical norcarane ring structure in the proton n.m.r. (typically 1.2 (4H,m), 1.7 (6H,m)) except that the lower field multiplet had a broader shape and integrated for seven protons instead of six. However the only other peak was an acetyl singlet at 2.20ppm except that it integrated for three protons and not six as expected for the 7,7-diacetylnorcarane. The spectrum was otherwise clean. The i.r. was similar to that of the starting material except that the ester carbonyl peak (1720vs) was replaced with a peak at 1695vs indicative of a cyclopropyl ketone. A mass spectrum gave a molecular ion of 138 with a significant mass fragment of 95 indicating loss of acetyl. A proposed structure that fits this data is 7-acetylnorcarane (96) which is accounted for by the intermediate (97) to the tertiary alcohol in the reaction back donating its electrons with elimination of acetone (scheme 85) which would not be detected in the work-up conditions. There was no observed splitting of the acetyl peak suggesting that the product is either a pure exo or endo isomer. It

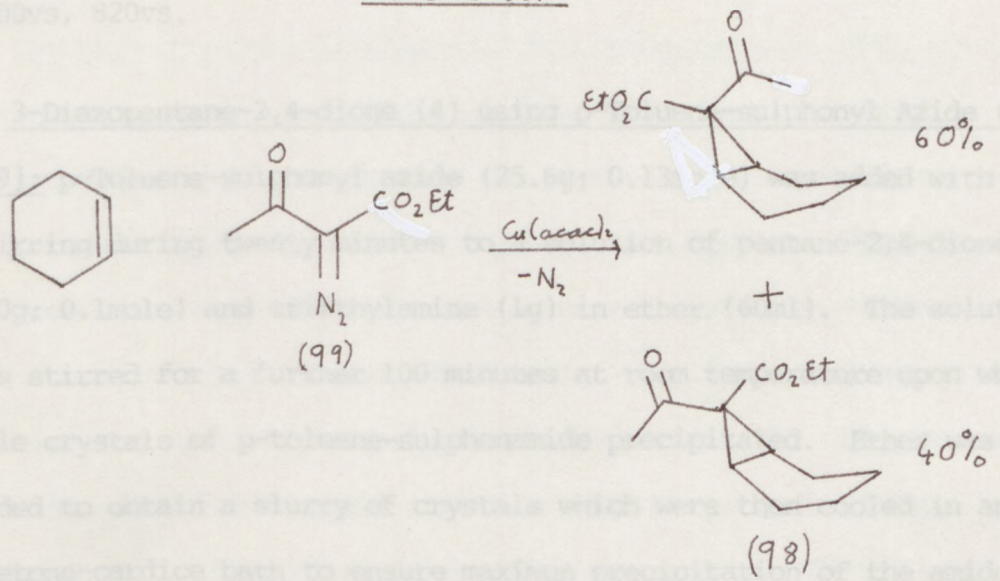
would be postulated that the endo would be formed on steric grounds, because of the exo acetyl being more available for attack by the methyllithium (scheme 85).

The second band (64mg) was again crystalline and was composed of two products as seen by analytical t.l.c. the least polar having the same rf as the first product. Proton n.m.r. gave the characteristic norcarane structure (except it was more complex) with the singlet at 2.20ppm indicative of the first product. There were an additional two singlets at 2.10 and 2.32ppm with equal integration. This is presumed to be due to the desired 7,7-diacetylnorcarane but no attempt was made to isolate it, owing to the low yield.

An alternative approach to the 7,7-diacetylnorcarane is via 7-carboethoxy-7-acetylnorcarane (98) which has only one ester function to transform. The product was prepared in 6% yield by addition of ethyl diazoacetoacetate (99) with cyclohexene (scheme 86). The proton n.m.r. of the product showed a mixture of exo and endo isomers in respective 60% and 40% yields assuming the acetyl of the exo isomer to be upfield of the endo isomer´s acetyl (being above the plane of the norcarane ring). However no further work was pursued on the molecule. Saponification of the ester would almost certainly lead to decarboxylation, whereas the already low product yield would probably be decreased significantly by the methods of ester conversion to a ketone.



Scheme 85.



Scheme 86.

1.5. Experimental.

p-Toluene-sulphonyl Azide (5) [18]: To a solution of p-toluene-sulphonic acid (42.5g; 0.22mole) in 90% ethanol (250ml) was added with stirring a solution of sodium azide (17.5g; 0.27mole) in water (50ml). The pale yellow solution was left to stand for an hour upon which it became cloudy with a white precipitate. The mixture was then poured into water (1l) and the resulting oily azide extracted with ether, washed three times with water and dried over magnesium sulphate. Evaporation of the solvent without heating gave a pale oil (36.25g; 82%). $\delta(CDCl_3)$: 2.48 (3H,s), 7.41 (2H,d,9Hz) and 7.83 (2H,d,9Hz). νmax ($CHCl_3$): 3030m, 2980m, 2120s, 1600m, 1340vs, 1300vs, 820vs.

3-Diazopentane-2,4-dione (4) using p-Toluene-sulphonyl Azide (5) [19]: p-Toluene-sulphonyl azide (25.6g; 0.13mole) was added with stirring during twenty minutes to a solution of pentane-2,4-dione (10g; 0.1mole) and triethylamine (1g) in ether (60ml). The solution was stirred for a further 100 minutes at room temperature upon which pale crystals of p-toluene-sulphonamide precipitated. Ether was added to obtain a slurry of crystals which were then cooled in an acetone-cardice bath to ensure maximun precipitation of the amide. The solution was filtered and washed with a little cold acetone removing the green of the residue to leave white crystals of the amide. The combined filtrate and acetone washings were evaporated to constant weight without heating to give a brown impure oil (16.9g) which n.m.r. showed to be the product with substantial amide impurity. 1g of this was submitted to prep. t.l.c. eluting with dichloromethane. The first band extracted was the pure product, 0.44g. $\delta(CDCl_3)$: 2.46 (s). νmax ($CHCl_3$): 3000w, 2930w, 2120vs, 1660vs, 1365s, 1405s, 1240s, 1020m, 960m, 930m.

Preparation of Triphenylphosphazine Derivative (83) of 3-Diazopentane-2,4-dione (4): Pure 3-Diazopentane-2,4-dione (1.38g; 11.5mmole) was added to a solution of triphenylphosphine (3g; 11.5mmole) in ether (20ml). The solution was left to stand overnight, during which time orange yellow needle shaped crystals of the product appeared which were filtered, washed with ether and dried (0.95g; 20%). Recrystallisation from 1:1 ether:chloroform decreased the quality of the crystals. m.p. 98-98.5°C. $\delta(CDCl_3)$: 2.45 (6H,s), 7.44 (15H, bs). νmax ($CHCl_3$): 2120s, 1660s, 1360s, 800-860m. λmax (MeOH): 210nm (log ϵ 4.31). Found C, 71.39; H, 5.80; N, 7.94%; $C_{23}H_{21}N_2O_2P$ requires C, 71.31; H, 5.88; N, 7.84%.

Carboxybenzene-4-sulphonic acid Monopotassium salt (84): Potassium permanganate (340g; 2.15mole) was added with rapid stirring during four hours to a solution of p-toluenesulphonic acid monohydrate (200g; 1.12mole) and potassium hydroxide (100g; 1.79mole) in water (4l). The solution was stirred for a further four hours and left to stand overnight. The black manganese dioxide precipitate was filtered and washed with water. The filtrate and washings were decolourised with slow addition of hydroxylamine after which conc. HCl was added to slight excess (pH 1). The bulk was reduced to one sixth of its original volume by distillation of the water and then cooled to give a slurry of crystals which were filtered, washed in ether and dried overnight at 60°C under vacuum (275g; 100%). m.p. >325°C. $\delta(CF_3CO_2H)$: 7.8 (dd). νmax (nujol mull): 1720s.

Carboxybenzene-4-Sulphonyl Chloride (85): Freshly distilled chlorosulphonic acid (180g; 1.55mole) was added to carboxybenzene-4-sulphonic acid monopotassium salt (79g; 0.329mole). The mixture was stirred at 100°C for two hours. The final clear solution was then cooled and slowly poured on to ice with rapid stirring to give a thick white creamy solid with rapid evolution of HCl gas. The creamy solid was then filtered, washed with water and dried under vacuum overnight at 50°C to give white crystals (26.3g; 36%), m.p. 213-216° C.

Carboxybenzene-4-sulphonyl Azide (10) [32]: To a solution of carboxybenzene-4-sulphonyl chloride (26.3g; 0.119mole) in acetone (500ml) was added with stirring a solution of sodium azide (21.5g; 0.331mole) in water (50ml). Extra water was then added until the bulk was one phase. The solution was stirred for a further two hours and then poured into water (4l) precipitating a mass of white crystals which were filtered, washed with a little cold ethanol and dried under vacuum (26.1g; 96%). m.p. 177-179°C (lit. 182-183 C). δ (CD_3COCD_3): 8.44 (dd). ν max (nujol mull): 3050w, 2980vs, 2960vs, 2930vs,2150m, 1690s, 1460s, 1380s, 1120m, 1095s, 1170s, 935w, 780m, 770m, 690m.

3-Diazopentane-2,4-dione (4) using Carboxybenzene-4-sulphonyl Azide (10): To a stirred suspension of carboxybenzene-4-sulphonyl azide (18.05g; 79.5mmole) in methanol (100ml) was added pentane-2,4-dione (5g; 53mmole). This was followed by triethylamine (16.06g; 159mmole) causing the azide to dissolve leaving a clear green solution. The solution was stirred at room temperature overnight, protected from light, and then evaporated down without heating to an oily mass of white crystals. These were taken up in dichloromethane (400ml) and filtered, removing the carboxybenzene-4-sulphonamide residue. The filtrate was washed with 0.05M sodium hydroxide and

then water. The aqueous washings were then further extracted with dichloromethane which were combined with the filtrate, dried over anhydrous sodium sulphate, and evaporated to dryness to give a green oil (5.82g; 91%) which gave spectra identical to the previously purified product.

Ethyl Diazoacetoacetate (99): An identical procedure was adopted as with 3-diazopentane-2,4-dione. Ethyl acetoacetate (4g; 31mmole), carboxybenzene-4-sulphonyl azide (10.44g; 46mmole) and triethylamine (9.3g; 92mmole) were used. The product was a pale green oil (3.15g; 66%). $\delta(CDCl_3)$: 1.35 (3H,t), 2.49 (3H,s), 4.30 (2H,q). νmax ($CHCl_3$): 2140s, 1720vs, 1645s, 1360s, 1315vs, 1150s, 960w.

2-Diazo-dimedone (89): An identical procedure was adopted as with 3-diazopentane-2,4-dione. Dimedone (5g; 35.7mmole), carboxybenzene-4-sulphonyl azide (12.2g; 53.6mmole) and triethylamine (10.8g; 107mmole) were used. The product was pale yellow crystals (5.30g; 89%). m.p. 109°C, (lit [132] 108 C, dec). $\delta(CDCl_3)$: 1.18 (6H,s), 2.48 (4H,s). νmax ($CHCl_3$): 3010w, 2960m, 2880w, 2190m, 2140s, 1645vs, 1305vs, 1280vs.

Addition of 3-Diazopentane-2,4-dione (4) to Cyclohexene: 3-Diazopentane-2,4-dione was added dropwise to a stirred mixture of catalyst (0.5% equivalent) in cyclohexene (about tenfold excess). The solution was stirred at room temperature then reflux if needed until the diazo absorption band (2120cm^{-1}) had disappeared in the infra red. The solvent was evaporated off and the product submitted to prep. t.l.c. eluting with dichloromethane and extracting the bands with dichloromethane and ethyl acetate which were evaporated down and the residues submitted to spectral analysis. The discussion has an account of catalysts used, specific reaction conditions and analysis of products.

Addition of 3-Diazopentane-2,4-dione (4) to Styrene: Copper acetylacetonate (40mg) was added to a solution of 3-diazopentane-2,4-dione (2g; 16.7mmole) in styrene (17g; 163mmole). The solution was stirred at 80°C for seven hours after which the diazo absorption band had disappeared in the infra red. The styrene was evaporated off to leave a brown polymeric solid (6g), which was submitted to prep. t.l.c. It was found that the t.l.c. plate had to be added immediately to the eluting solution after applying the compound, otherwise the applied band would dry and peel off. Four bands were obtained but only revealed polystyrene in the n.m.r. The reaction was repeated with 100mg (0.794mmole) of diazo compound in styrene (3ml) using rhodium acetate hydrate (3mg) as catalyst. The diazo absorption band had disappeared after stirring at room temperature overnight. The n.m.r. of the residue after evaporation of solvent was largely composed of polystyrene with two strong singlets at 1.82 and 2.28ppm indicative of the required product. The product was submitted to prep. t.l.c. eluting with dichloromethane. The required product was separated in low yield but with substantial impurities.

3,3-Dimethylspiro[5.6.$0^{6,11}$]dodecane-1,5-dione (90): A solution of 2-diazodimedone (500mg; 3.01mmole) in cyclohexene (20ml) was stirred under reflux with copper acetylacetonate (5mg) for thirty eight hours after which the diazo absorption band (2140cm^{-1}) had disappeared in the infra red. The excess cyclohexene was evaporated off to leave a brown oil which was submitted to prep. t.l.c. eluting with dichloromethane. Following an initial impurity band the second band was the cyclopropane, 3,3-dimethylspiro[5.6.$0^{6,11}$]dodecane-1,5-dione which was a white solid (146mg; 22%). m.p. 75-76.5°C. δ ($CDCl_3$): 1.08 (6H,s), 1.76 (6H,m), 2.27 (10H,m and s). νmax ($CHCl_3$): 3030w, 3000w, 2960s, 2870s, 1710vs, 1570s, 1365m, 1060m. m/e: 220

(58.9%, M+), 216 (8.2%), 206 (5.4%), 197 (15.3%), 190 (27.7%), 188 (49.0%), 158 (26.9%). λmax (MeOH): 285nm (log ε 1.20). Found C, 76.46; H, 8.91%; $C_{14}H_{20}O_2$ requires C, 76.36%; H, 9.09%. The reaction was repeated using rhodium acetate furnishing the cyclopropane in 30% yield (199mg).

3,3-Dimethylspiro[5.6.$0^{6,11}$]dodecane-1,5-dione (90) with m-Chloroperbenzoic acid: A solution of 80% m-chloroperbenzoic acid (200mg; 1.16mmole) and 3,3-dimethylspiro[5.6.$0^{6,11}$]dodecane-1,5-dione (100mg; 0.455mmole) in dichloromethane (6ml) was stirred slowly overnight upon which white crystals of m-chlorobenzoic acid appeared. The crystals were filtered and the filtrate evaporated to dryness to leave a brown crystalline solid which was submitted to prep. t.l.c. eluting with dichloromethane. Four bands were eluted which gave complex spectra with no evidence of a mono or diester product.

Decomposition of 3-Diazopentane-2,4-dione (4): A solution of 3-diazopentane-2,4-dione (500mg; 4.17mmole) in benzene (10ml) was refluxed for sixteen hours after which the diazo absorption band (2120cm^{-1}) had disappeared in the infra red. The excess benzene was evaporated off to leave a black polymeric residue (360mg), which was extracted with dichloromethane and evaporated to dryness to leave a black oil (122mg). The oil was submitted to prep. t.l.c. eluting with 10% methanol in dichloromethane. Three bands were separated (11, 56 and 7mg) in addition to much polar material. The n.m.r. gave complex multiplets, whilst the infra red possessed hydrocarbon stretches with a complex carbonyl region but no definate assignment was made.

The reaction was repeated using copper acetate (7mg) as catalyst. Decomposition was complete after stirring at room temperature for thirty hours. The benzene was evaporated off to leave a black oil

(358mg) which was submitted to prep. t.l.c. eluting with dichloromethane. Six bands were eluted, some of which had similar spectra as before. The third band was 3-phenylpentane-2,4-dione (21mg; 3%) obtained as a white solid. m.p. 63-64.5°C. $\delta(CDCl_3)$: 1.86 (6H,s), 7.08m and 7.12m (both 5H), 16.82 (1H,s). The molecule is about 100% enolised. νmax ($CHCl_3$): 3680m, 3605m, 3010s, 1720m, 1600s, 1520s, 1420s, 1210vs, 1150s, 790-720vs, 670vs. m/e: 176 (73.9%, M+), 169 (4.0%), 162 (6.9%), 161 (60.4%), 158 (8.2%), 149 (6.6%), 134 (41.0%), 133 (30.2%), 115 (33.4%), 105 (58.7%), 99 (25.1%), 43 (100%).

The reaction was repeated using copper acetate (7.6mg; 0.021mmole) stirred in dichloromethane (15ml). The diazo absorption band had disappeared after 80 hours at room temperature. The excess dichloromethane was evaporated off to leave a brown liquid (444mg) which was submitted to prep. t.l.c. eluting with 5% ethyl acetate in dichloromethane. In addition to polar residue, three low yielding bands were eluted, all giving complex spectra.

The procedure was repeated with benzene as solvent with aluminium trichloride (150mg; 2.38mmole) as catalyst. The diazo absorption band disappeared after four hours reflux. The mixture was washed with dil. HCl, water and then dried over anhydrous sodium sulphate. Evaporation of solvent gave a brown oil which was submitted to prep. t.l.c. eluting with dichloromethane. The only identifiable band was the first, 3-phenylpentane-2,4-dione (20mg; 5%).

7,7-Dicarbomethoxynorcarane (87) [122]: Dimethyl diazomalonate (3g; 18.99mmole) was added dropwise over an hour to a stirred refluxing solution of copper acetylacetonate (35mg; 0.135mmole) in cyclohexene (25ml). The solution was stirred under reflux for a further thirty six hours before the diazo absorption band had

disappeared in the infra red. The cyclohexene layer was then decanted off (from a dark brown residue) and evaporated to dryness to give yellow crystals (2.26g) which were submitted to column chromatography eluting firstly with dichloromethane, and then dichloromethane with increasing amounts of ethyl acetate. The first band eluted gave 7,7-dicarbomethoxynorcarane (1.43g; 35%) m.p. 77-78° C, the literature reference quoted the preparation of dimethyl diazomalonate but gave only the product data for the diethyl ester; the same author describes a preparation of the dimethyl ester in another paper [133] and obtained it as an impure oil. $\delta(CDCl_3)$: 0.8-1.5 (4H,m), 1.8-2.1 (6H,m), 3.75 (3H,s), 3.85 (3H,s). νmax ($CHCl_3$): 3030w, 2940m, 1720vs, 1440m, 1330m, 1280s, 1160m, 1110m, 1000w, 960w, 920w. C^{13} n.m.r. $\delta(CDCl_3)$: 19.73t, 20.70t, 25.59d, 35.48s, 52.34q, 52.73q, 168.29s, 172.06s. The second band eluted was the carbene dimer (tetracarbomethoxyethene) (0.82g; 33%). $\delta(CDCl_3)$: 3.90 (s). The third band gave a pale yellow oil (90mg) which gave a complex multiplet at 3.83ppm.

7-Carboethoxy-7-acetylnorcarane (98): Ethyl diazoacetoacetate (2.61g; 16.7mmole) was added to a stirred suspension of copper acetylacetonate (5mg) in cyclohexene (50ml). The solution was heated under reflux for twenty hours after which the diazo absorption band had disappeared in the infra red. The excess cyclohexene was evaporated off to leave a black gum which was submitted to column chromatography eluting with dichloromethane. Six bands were eluted, the second being the only one identified as 7-carboethoxy-7-acetylnorcarane which was a green liquid giving no crystals (209g; 6%). $\delta(CDCl_3)$: 1.20 (4H,m), 1.36(3H,s) 4.29 (2H,q). The ethyl and acetyl peaks are doubled with a difference of 2Hz due to the presence of exo and endo isomers. Assuming the endo's acetyl (being above the plane of the norcarane ring) to be slightly upfield of the exo's acetyl, then from the ratio of the integral the product

is 60% exo and 40% endo. νmax ($CHCl_3$): 3045w, 2980m, 2940w, 1720vs, 1690vs, 1440m, 1360s, 1275m, 1280s, 1160m, 990w, 925w. m/e: 210 (20.6M+), 205 (4.2%), 181 (13.2%), 168 (16.0%), 167 (89.9%), 165 (18.7%), 156 (8.8%), 153 (3.4%), 149 (10.3%), 139 (43.2%), 136 (72.9%), 121 (75.7%), 79 (100%).

Reaction of 2,5-Dimethylthiophenium Bisacetylmethylide (91) with (a) Cyclohexene, (b) Cyclooctene and (c) Vinyl Acetate: (a). 2,5-Dimethylthiophenium bisacetylmethylide (1g; 4.76mmole) was added to a stirred suspension of copper acetylacetonate (10mg) in cyclohexene (15ml). The mixture was stirred under reflux, upon which the ylid went into solution, and stirring was continued for sixteen hours after which no further change was observed on analytical t.l.c. The excess cyclohexene was evaporated off to leave a solid residue (715mg) which was submitted to prep. t.l.c. eluting with dichloromethane. Five bands were eluted which all gave complex spectra with the exception of the fifth one, which was undissociated ylid (286mg).

(b). An identical procedure using cyclooctene with 600mg (2.86mmole) of the ylid was used. After stirring for twelve hours complete dissociation of the ylid had occured but workup gave no identifiable product.

(c). 2,5-Dimethylthiophenium bisacetylmethylide (1g; 4.76mmole) was added to vinyl acetate (10ml) followed by copper acetylacetonate (15mg). The mixture was stirred under reflux for two days after which analytical t.l.c. showed no change. The excess vinyl acetate was evaporated off to leave a brown residue which was submitted to prep. t.l.c. eluting with dichloromethane. Five bands were eluted of which the fifth was undissociated ylid (117mg). The third band showed signs of being a cyclopropanated adduct of the vinyl acetate

(67.8mg) with a large number of methylene peaks in the n.m.r., but the spectra were not simplified upon resubmission to prep. t.l.c.

Reaction of 3-Diazopentane-2,4-dione with Cyclohexene in the presence of Thiophenes: 3-Diazopentane-2,4-dione (420mg; 3.5mmole) was added dropwise to a solution of rhodium acetate hydrate (5mg) in thiophene (2.5ml) and cyclohexene (15ml). The solution was stirred at room temperature for one hour after which the diazo absorption band ($2120cm^{-1}$) had disappeared in the infra red. The excess thiophene and cyclohexene were evaporated off to leave a green oil (676mg) which was submitted to prep. t.l.c. eluting with dichloromethane. The only identifiable band was the first band being the 2-thienyl adduct (2-(2´-thienyl)-pentane-2,4-dione) (112mg, 18%) which is described in chapter two. No adduct with cyclohexene was observed.

The reaction was repeated using 2,5-dichlorothiophene under reflux but no adduct was separated.

The reaction was repeated using 2,5-dimethylthiophene stirring at room temperature for five hours in the presence of rhodium acetate. The only observed adduct was the ylid in high yield as observed in the n.m.r. of the crude product.

Saponification of 7,7-Dicarbomethoxynorcarane (87). Four procedures were attempted: I). With potassium hydroxide in dioxan and in ethanol. II). With potassium cycnide [122], III). With iodotrimethylsilane and IV). Potassium hydroxide and diethylene glycol.

I). A solution of 7,7-dicarbomethoxynorcarane (1g; 4.72mmole) in 1,4-dioxan (5ml) was added dropwise with stirring to a solution of potassium hydroxide (2.53g; 45.2mmole) in water (16ml) and dioxan (15ml). The reaction was followed using analytical t.l.c. and after

stirring at room temperature for fourteen hours there was no further change. The solution was then poured into excess water and acidified (pH 3) with HCl. The product was extracted with ether, dried over anhydrous sodium sulphate and then evaporated down removing the ether and dioxan to leave a colourless oil 7-carbomethoxy-7-carboxylnorcarane [122] (0.92g; 86%). $\delta(CDCl_3)$: 0.91-1.34 (4H,m), 1.80-2.00 (6H,m), 3.77 (3H,s split due to endo and exo isomers), 9.96 (1H,s). ν max ($CHCl_3$): 1715vs, 1710vs, 1440m, 1280s, 1105m, 995w.

The reaction was repeated using potassium hydroxide in refluxing aqueous ethanol. The same product was obtained.

II). A solution of 7,7-dicarbomethoxynorcarane (1.2g; 5.66mmole) and potassium cyanide (0.8g; 11.6mmole) in dry DMF (20ml) was refluxed overnight upon which a brown solid appeared. The excess DMF was evaporated off and the brown residue taken up in ether to give a suspension which was filtered and washed in ether. The residue was dissolved in water (20ml) and neutralised with dilute HCl. (pH 3). The mixture was extracted with dichloromethane, dried over anhydrous sodium sulphate, and evaporated to dryness to give a brown oil which was submitted to prep. t.l.c. eluting with 20% ethyl acetate in dichloromethane. Five bands were eluted which gave complex spectra. The fourth one (186mg) was impure mono carboxylic acid as described in IV).

III). 7,7-Dicarbomethoxynorcarane (250mg; 1.4mmole) in carbon tetrachloride (8ml) was added to a stirred solution of iodotrimethylsilane (0.56g; 2.82mmole) in carbon tetrachloride (4ml). The solution was refluxed under nitrogen overnight with only a small change observed on analytical t.l.c. The excess solvent was evaporated off to leave a brown oil which was submitted to prep.

t.l.c. eluting with dichloromethane. Four bands were eluted, the third of which was starting material (44mg) whilst the rest gave complex spectra.

IV). 7,7-Dicarbomethoxynorcarane (1g; 4.72mmole) was added to a hot solution of potassium hydroxide (1g; 17.9mmole) in diethylene glycol (20ml). The solution was then refluxed for eight hours after which no further change was observed on analytical t.l.c. The solution was allowed to cool, poured into excess dil. HCl and extracted with dichloromethane which was dried over anhydrous sodium sulphate and evaporated to dryness to leave a white crystalline solid which was submitted to prep. t.l.c., eluting with 1:1 dichloromethane and ethyl acetate. The major band was 7-carboxylnorcarane (293mg; 44%) a white crystalline solid. m.p. 81-82°C. δ ($CDCl_3$): 1.05-1.50 (4H,m), 1.60-2.10 (6H,m), 11.71 (1H, bs, exchanges with D_2O). ν max ($CHCl_3$): 3550-2450m, 2980m, 2870m, 1690vs, 1450m, 1310m, 1130m, 910vs. Found C, 68.59; H, 8.57%; $C_8H_{12}O_2$ requires C, 68.57; H, 8.57. The other bands gave complex spectra with no carboxylic proton resonance in the n.m.r.

7,7-Dicarbomethoxynorcarane with Methyllithium. 1.15M methyllithium in ether (3ml; 3.4mmole) was added dropwise under nitrogen with stirring to a solution of 7,7-dicarbomethoxynorcarane (250mg; 1.18mmole) in sodium dry ether (10ml) at -78°C. The solution was allowed to warm to room temperature and then stirred overnight after which excess water was added and the product extracted with ether. The ether was dried over anhydrous sodium sulphate and evaporated to dryness to give a pale grey oil. A n.m.r. of the crude product was similar to the starting material with a new singlet at 1.80ppm. Infra red demonstrated O-H stretch (3600cm^{-1}) with an additional carbonyl peak at 1690cm^{-1}. Analytical t.l.c. demonstrated that there was substantial starting material.

The reaction was repeated using 60mg norcarane and a sixfold excess of methyllithium. A similar result was obtained except the new methyl singlet was smaller.

The reaction was repeated using a sixfold excess of methyllithium with 1g of norcarane in sodium dry toluene (20ml). Addition of the methyllithium was at room temperature. The solution was heated, evaporating of the ether (from the methyl lithium solution), until it was refluxing at the boiling point of toluene (112°C). The solution was refluxed for one hour, and excess water (30ml) was then added slowly, maintaining the reflux temperature. The mixture was cooled and extracted with dichloromethane, dried over anhydrous sodium sulphate and evaporated to dryness to leave a pale yellow oil which was submitted to prep. t.l.c. eluting with dichloromethane. Four bands were eluted. The first two (4 and 43mg) were close together and gave complex spectra. The third (32mg) was a pale green oil (one spot analytical t.l.c). δ ($CDCl_3$): 1.05-1.40 (4H,m), 1.45-1.90(7H,m), 2.15 (3H,s). ν max ($CHCl_3$): 3040m, 3005m, 2940s, 2860m, 1695vs, 1460m, 1450m, 1410s, 1355m, 1210w, 1170s, 970m, 850w. m/e: 138 (68.2%, M+), 123 (8.4%), 115 (7.9%), 111 (5.5%), 102 (18.2%), 95 (47.2%), 82 (12.6%), 79 (8.0%). The fourth band was a pale green oil (64mg) which by analytical t.l.c. was seen to be contaminated with the third product. δ ($CDCl_3$): 1.05-1.40 (9H,m), 1.50-2.00 (12H,m), 2.10 (3H,s), 2.19 (3H,s), 2.34 (3H,s).

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CHAPTER TWO.

THE REACTIONS OF DIAZO COMPOUNDS WITH THIOPHENES.

"Ask, and it shall be given to you; seek, and you shall find; knock, and it shall be opened to you. For every one who asks receives, and he who seeks finds, and to him who knocks it shall be opened." (Matthew 7:7-8).

2.1. Literature Review on the Reactions of Diazo Compounds with Thiophenes.

Reactions with Diazomethane.

In 1963 Muller et al. [1] reported that diazomethane added to thiophene to give the cyclopropane (1) in the presence of copper bromide (22% yield) or light (17% yield; the duration of irradiation was not given) (scheme 1).

A more extensive treatment was reported in a thesis by L.L. Jackson [2] in 1968 though the work has since not been published. Diazomethane added to 2-methylthiophene to give both the 2,3 and 4,5 cyclopropanes (scheme 2) although no attempt was made to separate them. The ratio of products being 1:1 demonstrated that there is no discrimination between the two double bonds in adding to the methylene. The mechanism was reported as being a direct interaction between the methylene and the thiophene double bond.

With 2,5-dimethylthiophene the cyclopropane was obtained as expected. However, with 2-t-butylthiophene addition was only observed in the 4,5-position (scheme 3). The explanation was that the t-butyl group offered a steric constraint to the approach of the carbenoid intermediate.

2-Chlorothiophene not only furnished the cyclopropane (2) but also a C-Cl insertion product (3). Cyclopropanation thus occured at the unsubstituted double bond, with steric constraint again being offered as the explanation (chlorine being more bulky than a methyl group), in addition to the deactivation of the double bond due to the negative inductive effect of the chlorine. It was reported that this adduct (2) on standing in a refridgerator for one month showed signs of rearrangement to a 2H-thiopyran (4) indicated by the

appearance of new vinyl signals in the n.m.r. However no attempt was made to isolate the adduct and no mechanism for the rearrangement was offered (scheme 4).

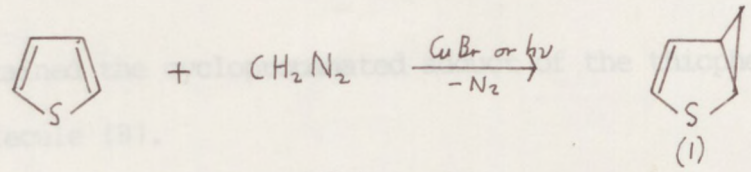
The reaction of diazomethane with 2-methoxythiophene and 2-carbomethoxythiophene afforded the 4,5-cyclopropanated adduct (scheme 5).

Reactions with 2-Diazo-1-carbonyl Compounds.

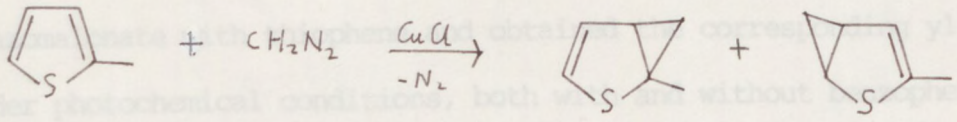
The earliest report of a reaction between thiophene and a diazo compound was by Steinkopf and Augestad-Jenson in 1922 [3]. The reaction between thiophene and ethyl diazoacetate afforded the cyclopropane (5) with no details of endo and exo isomerism being given (scheme 6). Photolysis was shown to give the same result by Schenck and Steinmetz many years later [4].

Pettit [5] repeated the reaction though no details of reaction were given. The structure of the product was confirmed and its conversion to a thiapyrylium cation was effected. This was achieved by conversion of the ethoxycarbonyl group to an isocyanate by treatment with hydrazine followed by nitrous acid and this in turn was converted to the thiapyrylium bromide (6) with hydrogen bromide (scheme 7).

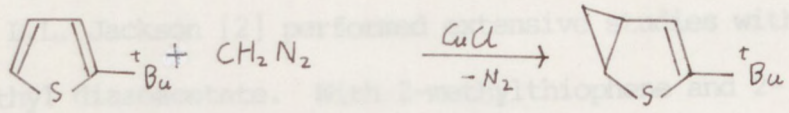
Later Pettit and Sullivan [6] examined the reaction of ethyl diazoacetate with benzothiophene. However the diazo compound added to the benzene ring (scheme 8). The carboethoxy group was treated as before to give the thienotropylium cation (7). Again no experimental details for the addition of the diazo compound was given, nor any discussion of why the carbene or carbenoid intermediate prefered the 3,4 positions on the benzene ring. This result was different to the previously observed result when Badger et al. [7] reacted ethyl diazoacetate with thionaphthene and



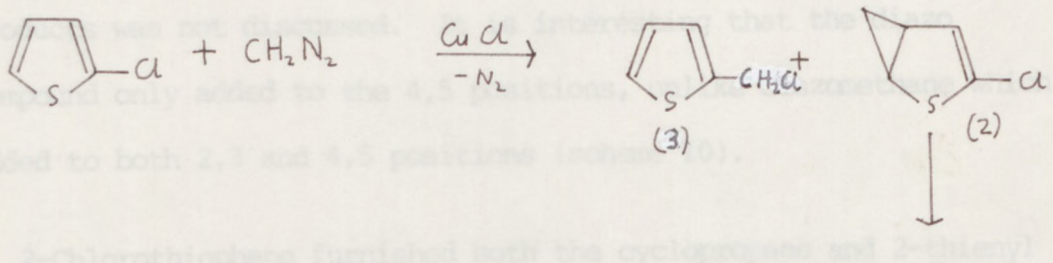
Scheme 1.



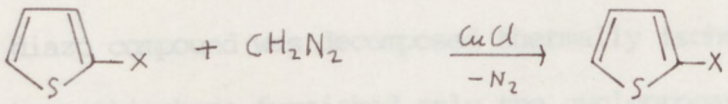
Scheme 2.



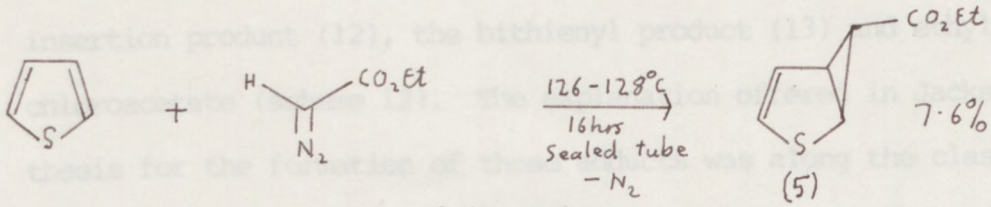
Scheme 3.



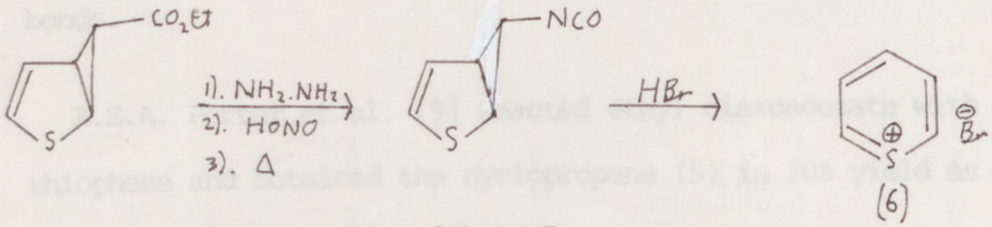
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

obtained the cyclopropanated adduct of the thiophene part of the molecule (8).

Ando et al. [8] reacted ethyl diazoacetate and dimethyl diazomalonate with thiophene and obtained the corresponding ylids under photochemical conditions, both with and without benzophenone triplet sensitiser (scheme 9).

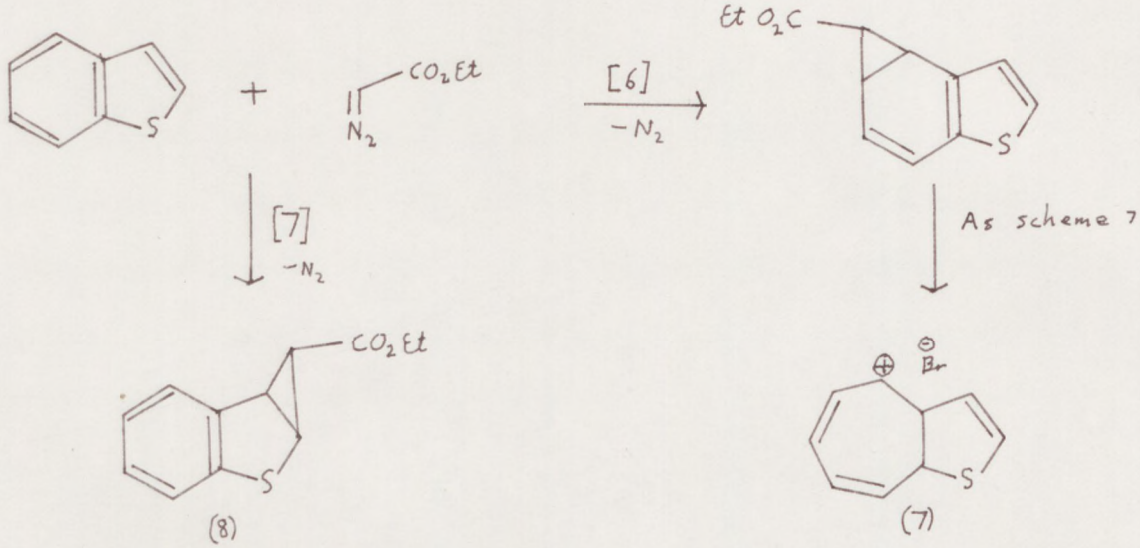
L.L. Jackson [2] performed extensive studies with ethyl and methyl diazoacetate. With 2-methylthiophene and 2-carbomethoxythiophene, the cyclopropane (10) was obtained by attack on the unsubstituted side of the ring. The stereochemistry of the products was not discussed. It is interesting that the diazo compound only added to the 4,5 positions, unlike diazomethane which added to both 2,3 and 4,5 positions (scheme 10).

2-Chlorothiophene furnished both the cyclopropane and 2-thienyl product (11) from a proposed C-Cl insertion along with ethyl chloroacetate whose formation was not explained. This time the diazo compound was decomposed thermally (scheme 11). However 2-bromothiophene furnished only the cyclopropane.

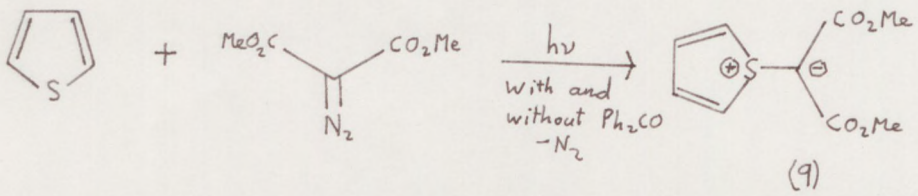
2,5-Dichlorothiophene and tetrachlorothiophene gave the C-Cl insertion product (12), the bithienyl product (13) and ethyl chloroacetate (scheme 12). The explanation offered in Jackson´s thesis for the formation of these adducts was along the classical lines of carbene insertion into double bonds and carbon-halogen bonds.

A.E.A. Porter et al. [9] reacted ethyl diazoacetate with thiophene and obtained the cyclopropane (5) in 20% yield as an unseparated mixture of endo and exo isomers.

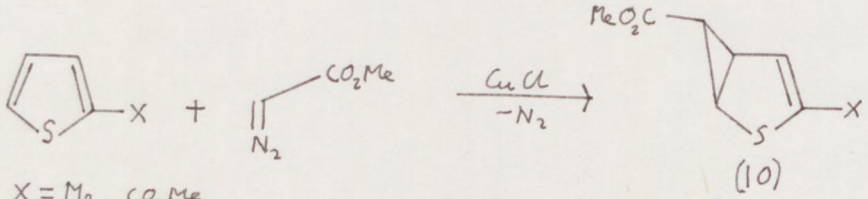
Similarly butyl diazoacetate [9] afforded the cyclopropane (14)



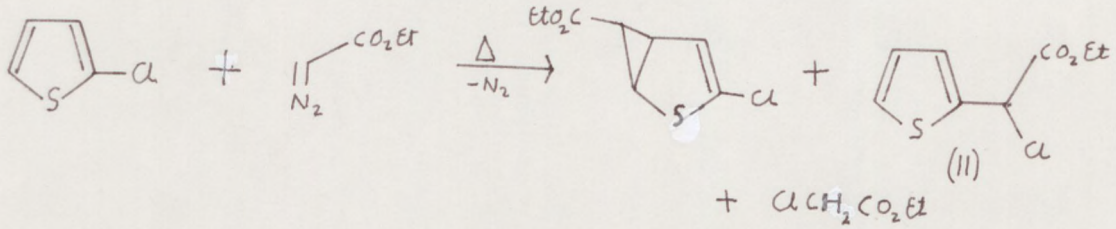
Scheme 8.



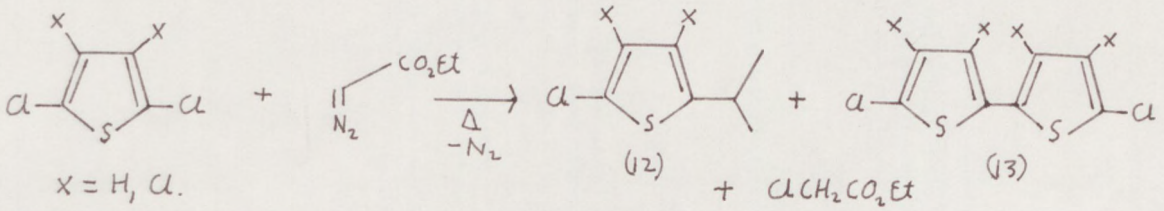
Scheme 9.



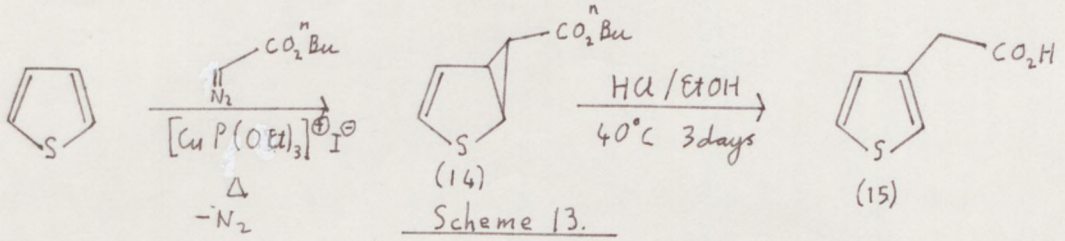
Scheme 10.



Scheme 11



Scheme 12



Scheme 13.

which was converted in low yield to the 3-thienyl acetic acid (15) on prolonged exposure to an acidic medium (scheme 13). A decomposition study was made on this reaction. It was found that the worst yield of 17% was obtained using copper at reflux for fifteen minutes, whereas the optimum yield of 71% was obtained with rhodium acetate at 85°C for fifteen minutes.

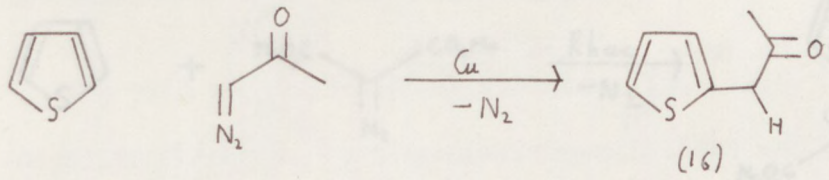
Novak et al. [10] reacted diazoacetone with thiophene in the presence of copper. The resulting 2-thienyl adduct (16) (scheme 14) was unexpected. A cyclopropane was expected, in analogy with the reaction between benzofuran and diazoacetone as described in the same paper.

Reactions with 2-Diazo-1,3-dicarbonyl Compounds.

Bird et al. [11] reacted 2,5-bisdiazo-3,4-dioxoadipate (17) with thiophene and obtained a 2-thienyl adduct (18) and a benzothiophene (19) (scheme 15). The mechanism for the formation of (18) was assumed to be by a C-H insertion on the 2-position of the thiophene followed by a Wolff rearrangement and cyclisation. Compound (19) is also generated by a cyclisation reaction of the ketene intermediate (20) (scheme 15).

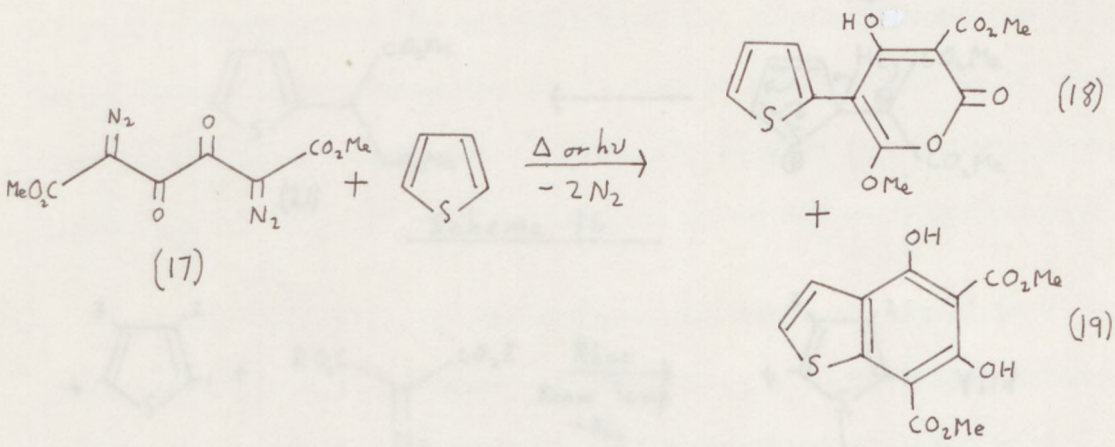
A.E.A. Porter et al. [9] found that dimethyl diazomalonate added to thiophene in the presence of rhodium acetate to give the ylid (9) in 93% yield (scheme 16). The product could be induced to thermally rearrange to the 2-thienyl adduct (21) in reduced yield. The mechanism they proposed was by an intramolecular rearrangement [12] (scheme 16).

Porter et al. [13] then prepared a large number of thiophenium ylids as illustrated in Table 1. In all cases the diazo compound was stirred in the thiophene at room temperature with rhodium



(16)

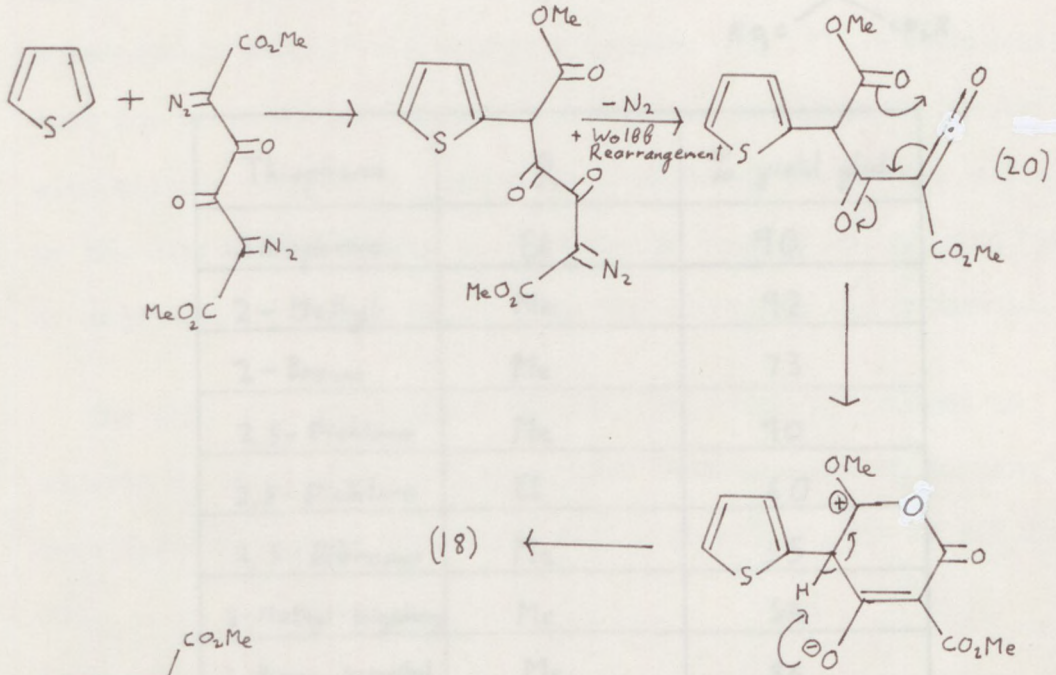
Scheme 14.



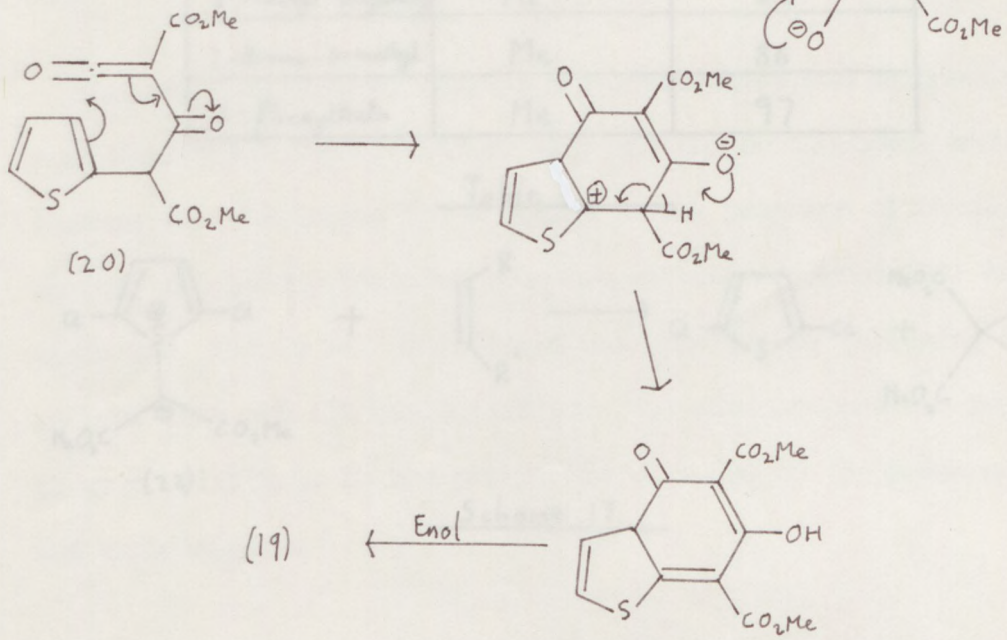
(17)

(18)

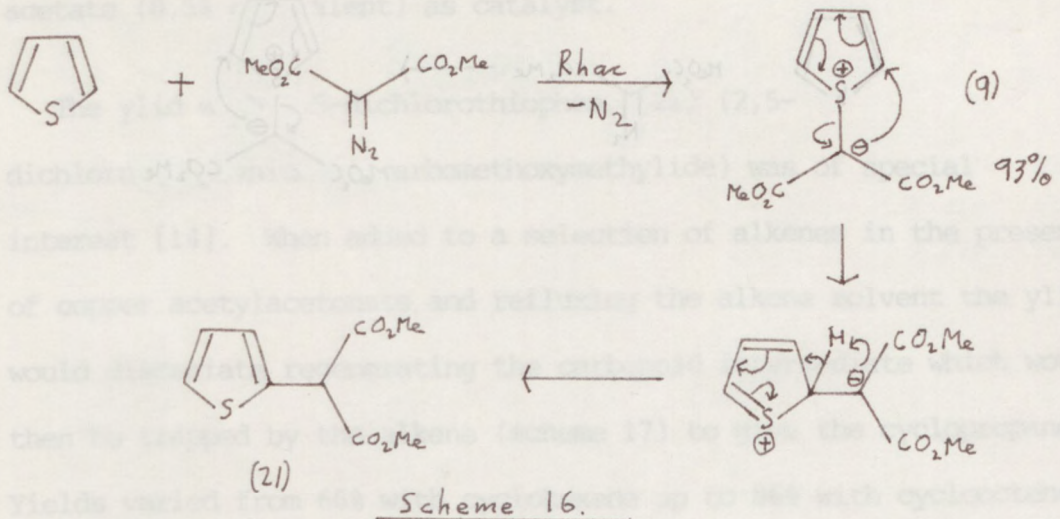
(19)



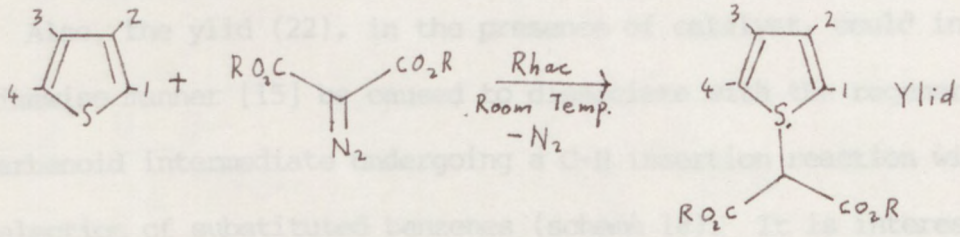
(20)



Scheme 15.

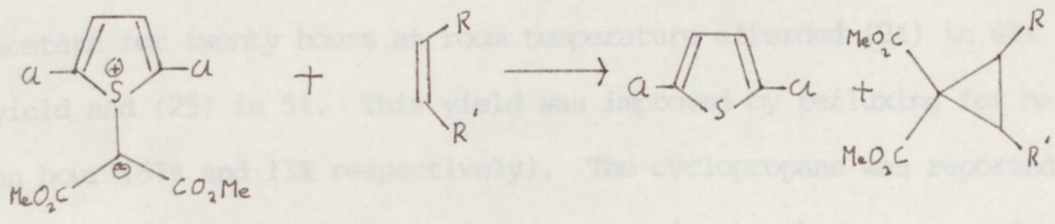


Scheme 16.



Thiophene	R	% yield ylid.
Thiophene	Et	90
2-Methyl	Me	92
2-Bromo	Me	73
2,5-Dichloro	Me	90
2,5-Dichloro	Et	60
2,5-Dibromo	Me	55
2-Methyl-5-hydroxy	Me	54
2-Bromo-3-methyl	Me	86
2-Phenylketo	Me	97

Table 1.



Scheme 17.

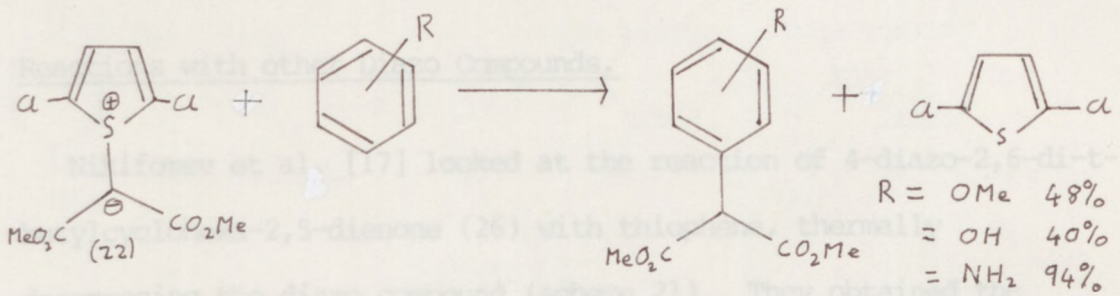
acetate (0.5% equivalent) as catalyst.

The ylid with 2,5-dichlorothiophene (22) (2,5-dichlorothiophenium-biscarbomethoxymethylide) was of special interest [14]. When added to a selection of alkenes in the presence of copper acetylacetonate and refluxing the alkene solvent the ylid would dissociate regenerating the carbenoid intermediate which would then be trapped by the alkene (scheme 17) to give the cyclopropane. Yields varied from 66% with cyclohexene up to 86% with cyclooctene.

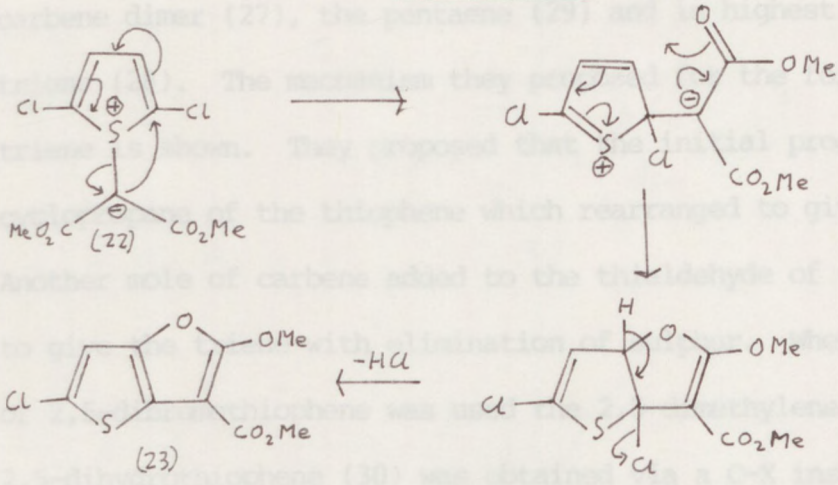
Also, the ylid (22), in the presence of catalyst, could in a likewise manner [15] be caused to dissociate with the regenerated carbenoid intermediate undergoing a C-H insertion reaction with a selection of substituted benzenes (scheme 18). It is interesting that the yield of product with aniline was considerably greater than with anisole or phenol, presumably because of the greater efficiency of the nitrogen lone pair to lend charge density to the ring making it more susceptible to attack from the electrophilic carbenoid.

The ylid (22) in an inert solvent [16] could be induced to undergo an interesting intramolecular rearrangement to furnish a fura(3,2-b)thiophene derivative (23) with elimination of HCl (scheme 19).

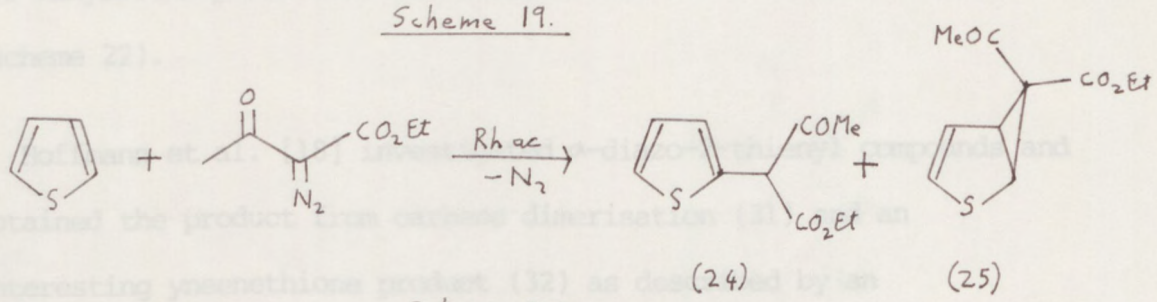
The reaction between ethyl diazoacetoacetate and thiophene furnished the 2-thienyl adduct (24) and the cyclopropane adduct (25) (scheme 20). Stirring the solution in the presence of rhodium acetate for twenty hours at room temperature afforded (24) in 61% yield and (25) in 5%. This yield was improved by refluxing for half an hour (67% and 13% respectively). The cyclopropane was reported to give splittings in the proton n.m.r. owing to the presence of exo and endo isomers.



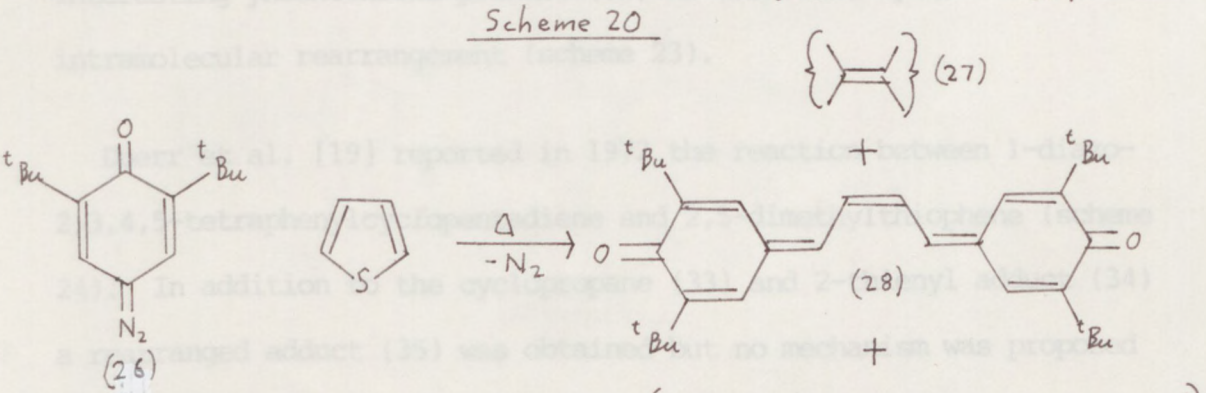
Scheme 18.

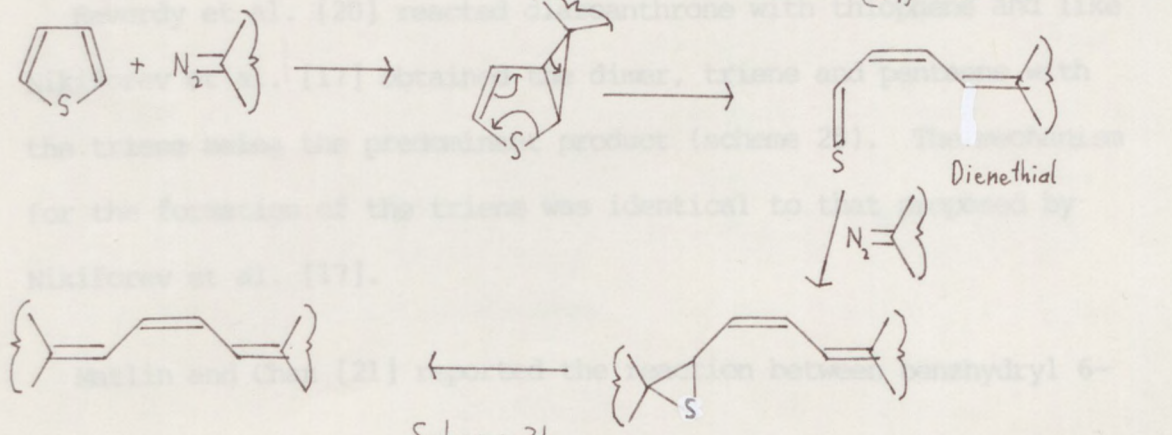


Scheme 19.



Scheme 20





Scheme 21

Reactions with other Diazo Compounds.

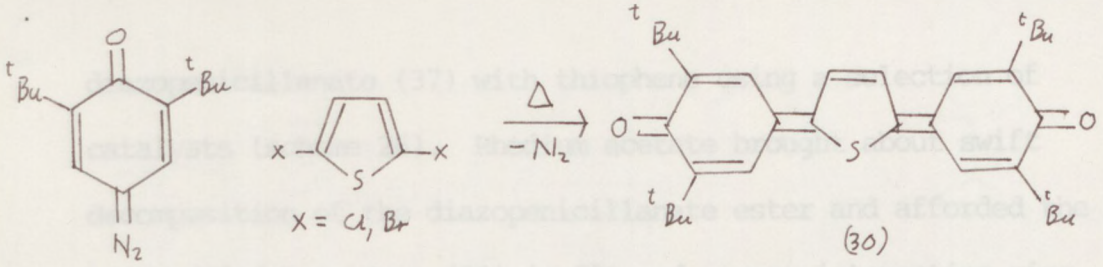
Nikiforev et al. [17] looked at the reaction of 4-diazo-2,6-di-t-butylcyclohexa-2,5-dienone (26) with thiophene, thermally decomposing the diazo compound (scheme 21). They obtained the carbene dimer (27), the pentaene (29) and in highest yield the triene (28). The mechanism they proposed for the formation of the triene is shown. They proposed that the initial product was a cyclopropane of the thiophene which rearranged to give a dienethial. Another mole of carbene added to the thialdehyde of the dienethial to give the triene with elimination of sulphur. Where 2,5-dichloro or 2,5-dibromothiophene was used the 2,5-dimethylene substituted 2,5-dihydrothiophene (30) was obtained via a C-X insertion reaction (scheme 22).

Hoffmann et al. [18] investigated α-diazo-2-thienyl compounds and obtained the product from carbene dimerisation (31) and an interesting yneenethione product (32) as described by an intramolecular rearrangement (scheme 23).

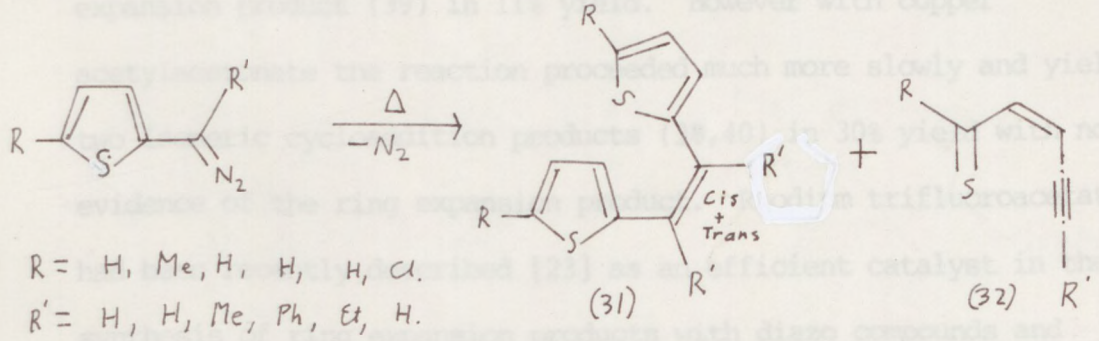
Duerr et al. [19] reported in 1972 the reaction between 1-diazo-2,3,4,5-tetraphenylcyclopentadiene and 2,5-dimethylthiophene (scheme 24). In addition to the cyclopropane (33) and 2-thienyl adduct (34) a rearranged adduct (35) was obtained but no mechanism was proposed for its formation.

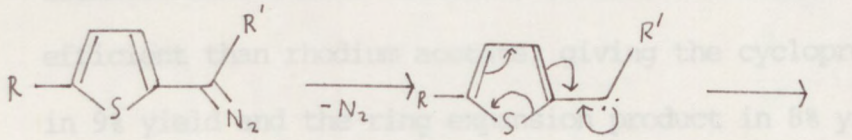
Reverdy et al. [20] reacted diazoanthrone with thiophene and like Nikiforev et al. [17] obtained the dimer, triene and pentaene with the triene being the predominant product (scheme 25). The mechanism for the formation of the triene was identical to that proposed by Nikiforev et al. [17].

Matlin and Chan [21] reported the reaction between benzhydryl 6-

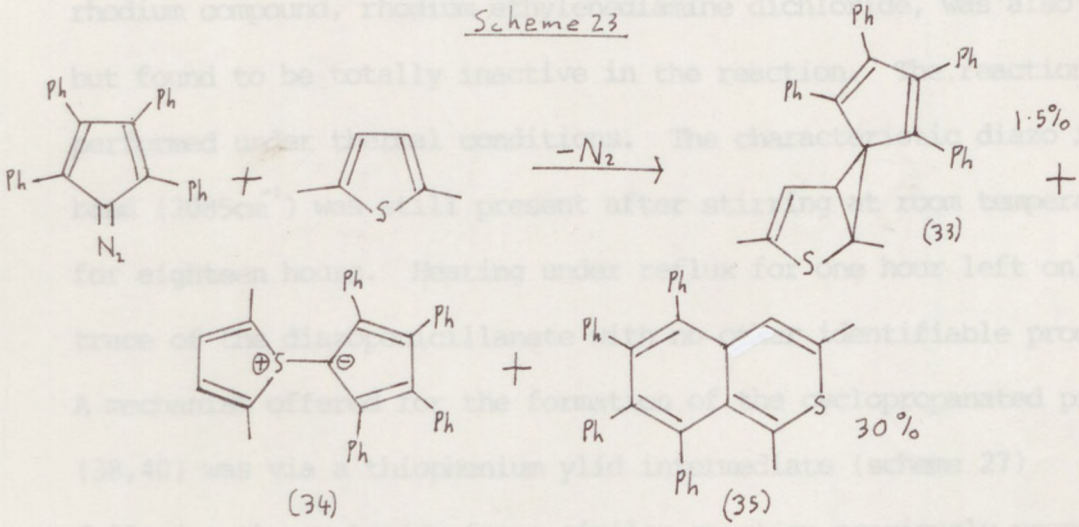


Scheme 22.

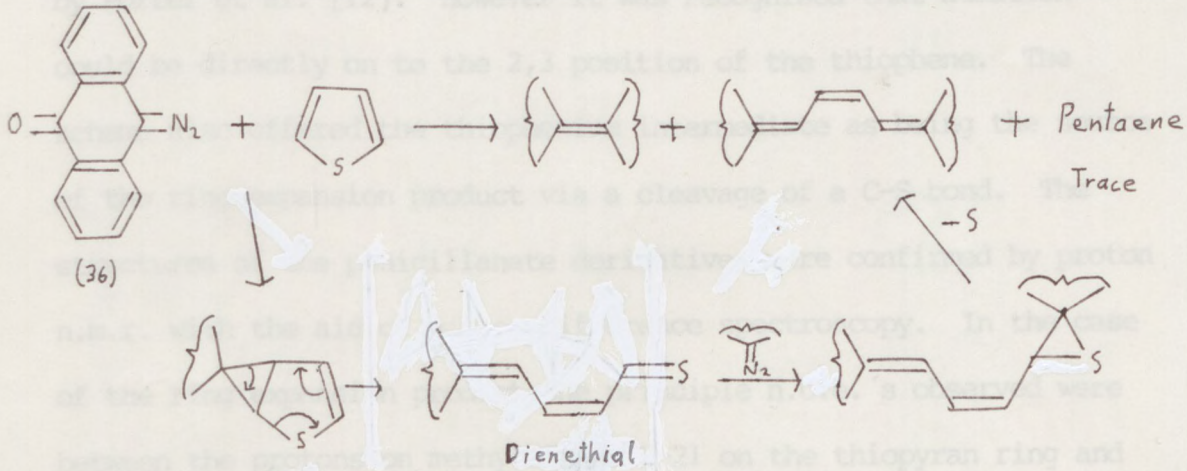




Scheme 23

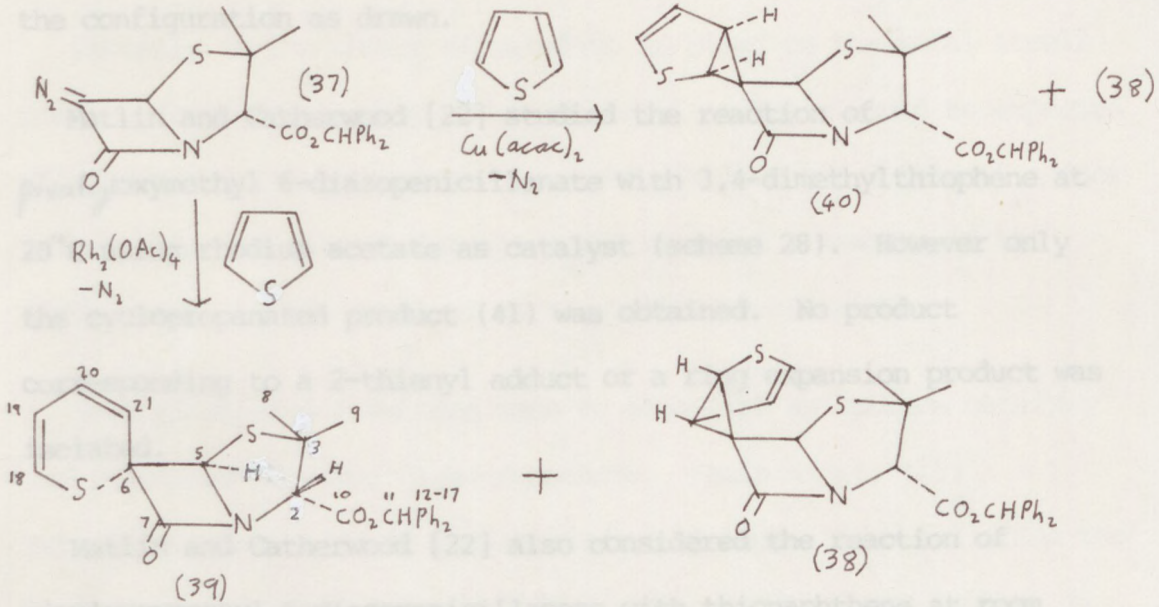


Scheme 24.

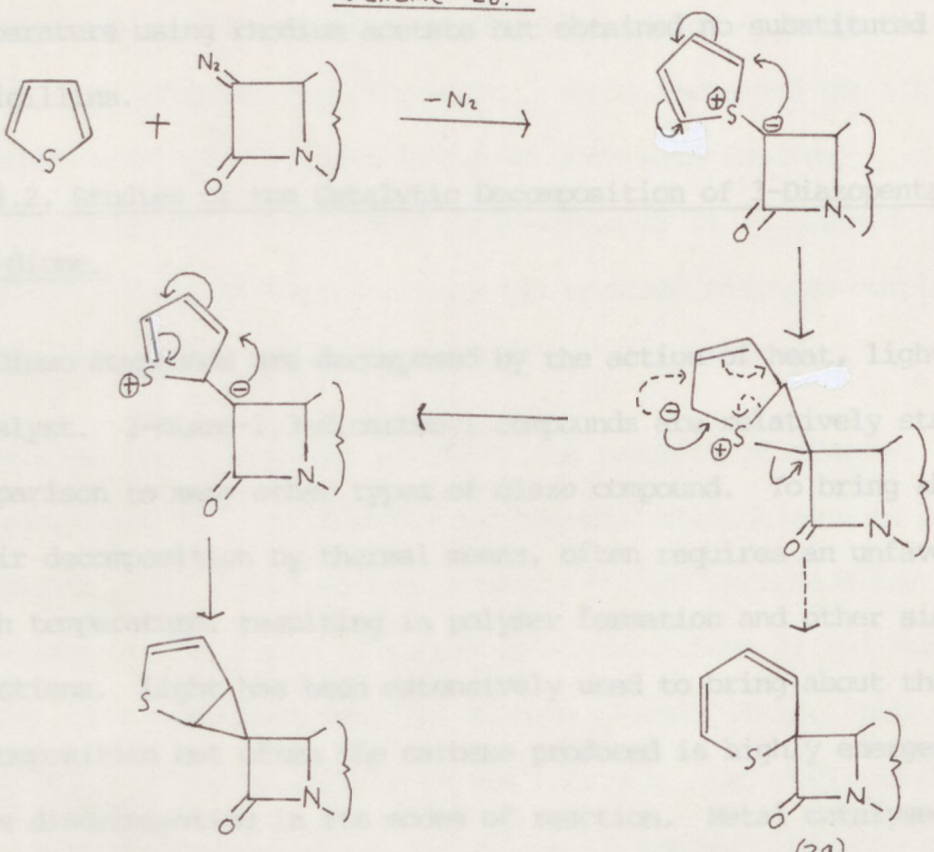


Scheme 25.

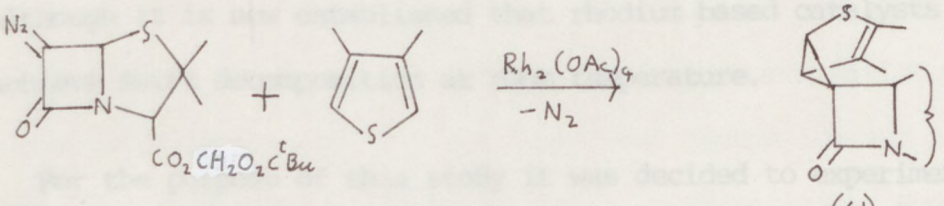
diazopenicillanate (37) with thiophene using a selection of catalysts (scheme 26). Rhodium acetate brought about swift decomposition of the diazopenicillanate ester and afforded the cycloaddition product (38) in 22% and a very interesting ring expansion product (39) in 11% yield. However with copper acetylacetonate the reaction proceeded much more slowly and yielded two isomeric cycloaddition products (38,40) in 30% yield with no evidence of the ring expansion product. Rhodium trifluoroacetate had been recently described [23] as an efficient catalyst in the synthesis of ring expansion products with diazo compounds and aromatic substrates. However, in this reaction it proved to be less efficient than rhodium acetate, giving the cyclopropanated product in 9% yield and the ring expansion product in 8% yield. Another rhodium compound, rhodium ethylenediamine dichloride, was also used but found to be totally inactive in the reaction. The reaction was performed under thermal conditions. The characteristic diazo i.r. band ($2085cm^{-1}$) was still present after stirring at room temperature for eighteen hours. Heating under reflux for one hour left only a trace of the diazopenicillanate with no other identifiable product. A mechanism offered for the formation of the cyclopropanated product (38,40) was via a thiophenium ylid intermediate (scheme 27) following the mechanism for a similar reaction previously proposed by Porter et al. [12]. However it was recognised that addition could be directly on to the 2,3 position of the thiophene. The scheme also offered the thiophenium intermediate as being the source of the ring expansion product via a cleavage of a C-S bond. The structures of the penicillanate derivatives were confirmed by proton n.m.r. with the aid of n.O.e. difference spectroscopy. In the case of the ring expansion product the principle n.O.e.'s observed were between the protons on methyl 8 and H-21 on the thiopyran ring and between H-5 and H-2. These in addition to other n.O.e.'s confirmed



Scheme 26.



Scheme 27.



Scheme 28

the configuration as drawn.

Matlin and Catherwood [22] studied the reaction of pivaloyloxymethyl 6-diazopenicillanate with 3,4-dimethylthiophene at 20°C using rhodium acetate as catalyst (scheme 28). However only the cyclopropanated product (41) was obtained. No product corresponding to a 2-thienyl adduct or a ring expansion product was isolated.

Matlin and Catherwood [22] also considered the reaction of pivolyoxymethyl 6-diazopenicillanate with thionaphthene at room temperature using rhodium acetate but obtained no substituted penicillins.

2.2. Studies of the Catalytic Decomposition of 3-Diazopentane-2,4-dione.

Diazo compounds are decomposed by the action of heat, light or catalyst. 2-Diazo-1,3-dicarbonyl compounds are relatively stable in comparison to many other types of diazo compound. To bring about their decomposition by thermal means, often requires an unfavourably high temperature, resulting in polymer formation and other side reactions. Light has been extensively used to bring about their decomposition but often the carbene produced is highly energetic and less discriminating in its modes of reaction. Metal catalysed decompositions are often more discriminating, affecting the diazo group only. Despite this, elevated temperatures are often needed, although it is now established that rhodium based catalysts often achieve swift decomposition at room temperature.

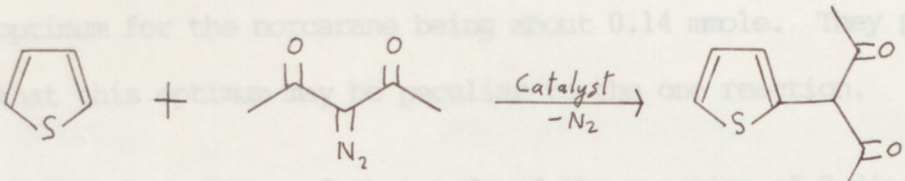
For the purpose of this study it was decided to experiment with the reaction of 3-diazopentane-2,4-dione with thiophene, varying the metal catalysts to optimise the yield of the 2-thienyl adduct (42) (scheme 29).

Emphasis in the choice of catalyst is based on the metal itself and the functionalisation about the metal as these would be expected to affect the catalytic activity. The yield of the 2-thienyl adduct rather than its rate of formation was taken as a measure of the "efficiency" of the catalyst at a specified temperature.

Several studies have been made to establish an optimum catalyst for reactions of other diazo compounds. Noels et al. [23] considered the yields of 1-carboethoxycycloheptatriene (43) from the Buchner reaction between ethyl diazoacetate and benzene (scheme 30 and Table 2). The work demonstrated that increase in the electron withdrawing properties of the metal ligands increased the yield of product, with optimum yield being obtained with rhodium trifluoroacetate. This result is expected if it is assumed that the catalyst effects decomposition by the terminal nitrogen complexing to the metal, thus weakening the carbon-nitrogen bond.

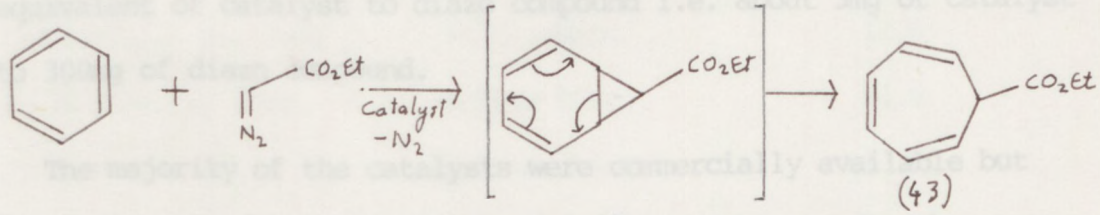
Wulfman and Peace [24] looked at the reaction of dimethyl diazomalonate with cyclohexene and obtained varying amounts of norcarane (44), C-H insertion product (45) and carbene dimer (46) depending on the choice of copper catalyst (scheme 31 and Table 3.). Copper acetylacetonate gave the highest overall yield. This is a reflection of the solubility of the catalyst. Cu, CuCl and $CuSO_4$ have similar yields and are insoluble. Trimethoxyphosphite cuprous chloride is more soluble but it favoured the carbene dimer rather than the norcarane.

They also considered the optimum catalyst concentration using copper acetylacetonate. It was found that both a low and high catalyst concentration decreased yields substantially. However a large range of 0.07 to 0.56 mmole of catalyst to 1 mole of diazo compound (i.e around 1% equivalent) gave similar yields with an



(42)

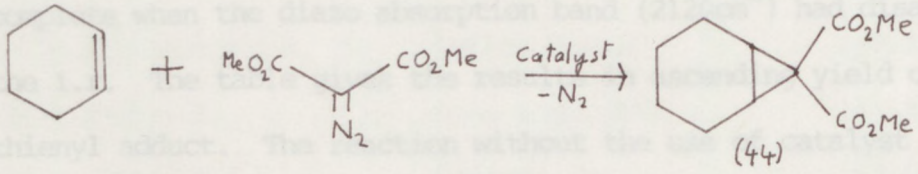
Scheme 29.



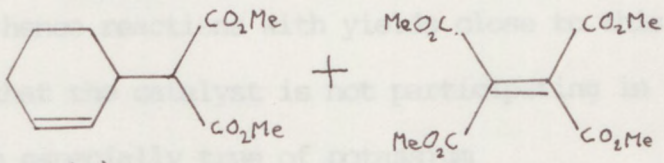
(43)

Catalyst	pKa of free acid	% yield.
$(CF_3CO_2)_4Rh_2$	0·23	100
$(C_6F_5CO_2)_4Rh_2$	1·48	89
$(MeOCH_2CO_2)_4Rh_2$	3·57	30
$(MeCO_2)_4Rh_2$	4·76	7
$(^tBuCO_2)_4Rh_2$	5·03	5

Scheme 30 and Table 2.



(44)



(45) (46)

Catalyst:	Cu	CuCl	$CuSO_4$	$(MeO)_3P.CuCl$	$Cu(acac)_2$
Yield (44) %:	38·0	42·8	45·3	63·7	78·1
Yield (45) %:	1·71	2·18	2·08	4·67	12·4
Yield (46) %:	8·05	8·38	9·07	18·4	5·92

Scheme 31 and Table 3.

optimum for the norcarane being about 0.14 mmole. They pointed out that this optimum may be peculiar to the one reaction.

For the purpose of the study of the reaction of 3-diazopentane-2,4-dione with thiophene it was decided to use about 1.5% wt. equivalent of catalyst to diazo compound i.e. about 5mg of catalyst to 300mg of diazo compound.

The majority of the catalysts were commercially available but some of the copper and rhodium catalysts were prepared. The copper catalysts were prepared by either the action of copper sulphate or copper carbonate on the appropriate carboxylic acid, following literature procedures. The rhodium catalysts were prepared by an exchange reaction of rhodium acetate in an excess of the carboxylic acid.

The results of the reaction between 3-diazopentane-2,4-dione and thiophene are given in Table 4. The reaction was taken to be complete when the diazo absorption band ($2120cm^{-1}$) had disappeared in the i.r. The table gives the results in ascending yield of the 2-thienyl adduct. The reaction without the use of catalyst gave a yield of about 34%, and hence reactions with yields close to this could be an indication that the catalyst is not participating in the reaction. This could be especially true of potassium tetrachloroplatinate, rhodium oxide, molybdenum trioxide and palladium (II) chloride which were insoluble.

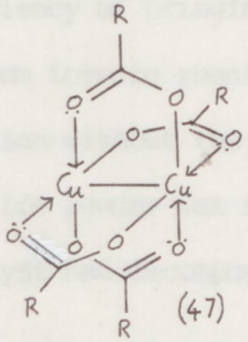
An interesting result is that the copper catalysts appear to decrease yields as compared to the degredation without catalyst. A postulation accounting for this is that the copper carbenoid species generated from the copper catalyst is less discriminating than the carbene from the thermal process and leads to more resinous by-products. For the copper carboxylates an obvious trend is observed

Catalyst.	Reaction Conditions.	Yield %.
Cu butanoate. SS.	70°C. 20hrs.	7.5
Cu acetate. SS. 50mg.	Reflux. 8hrs.	9.6
$Cu(acac)_2$. SS. 10mg.	70°C. 20hrs.	12.8
Cu bronze. I. 10mg.	Reflux 20hrs.	14.0
Cu acetate. SS.	Reflux. 16hrs.	17.5
Rh pivalate. S.	Room temp. 6hrs.	21.0
$PdCl_2$. I.	Reflux. 8hrs.	31.0
Cu trifluoroacetate. SS.	Reflux 7hrs.	33.0
No catalyst.	Reflux 8hrs.	33.0
No catalyst.	Reflux 8hrs.	34.0
MoO_3. I.	Reflux 6hrs.	34.0
Rh_2O_3. I.	Reflux 8hrs.	34.0
Rh formate. S.	Reflux 8hrs.	34.0
K_2PtCl_4. I.	Reflux 8hrs.	36.0
Rh trifluoroacetate. S.	Reflux 7hrs.	39.0
Rh acetate. S.	Room temp. 60hrs.	41.0
Rh acetate. S.	Reflux. 1hr.	60.0

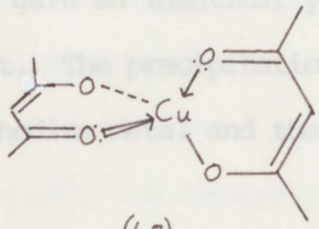
I = insoluble catalyst. SS = sparingly soluble catalyst. S = soluble catalyst. Unless stated amount of catalyst added was 5mg. The amount of diazo compound used was 300mg in 5ml thiophene.

Table 4.

in that the more electron withdrawing is the ligand the higher is the yield, with the trifluoroacetate giving the highest yield. Copper acetate gave a reduced yield when used in 50mg quantity. There is no obvious link with geometry. The copper (and rhodium) carboxylates assume a bridged dimeric structure (47) [25] whereas copper acetylacetonate is te trahedral (48).



(47)



(48)

It can be envisaged that the metal in the carboxylate is more sterically accessible than in the acetylacetonate but the low yield with copper butanoate does not reflect that this is benefitting the approach of the diazo group.

A similar trend was expected for the rhodium carboxylates to that reported in the work of Noels et al. [23]. However the trifluoroacetate required reflux temperature to bring about decomposition and gave a reduced yield compared with the acetate. The acetate gave a better yield under reflux conditions rather than at room temperature, however in many reactions described later, room temperature gave improved yields. The activity of the trifluoroacetate was tested by repeating the literature reaction between ethyl diazoacetate and benzene [23]. This gave, as reported, quantitative yield of the cycloheptatriene, confirming its activity.

It was thought that, for the rhodium carboxylates, an optimum value of pKa of the acid might be required for the greatest yield of 2-thienyl adduct. Hence the reaction was also performed with rhodium pivalate and with rhodium formate, these having

respectively, slightly lower and higher pKa values than the acetate. The pivalate brought about fairly swift decomposition of the diazo compound at room temperature in one tenth of the time required by the acetate. However the considerably lower yield of 21% of 2-thienyl adduct as opposed to 41% with the acetate, demonstrates that efficiency of bringing about decomposition is not related to yield. Rhodium formate required reflux and gave an identical yield to the reaction without the use of catalyst. The precipitation of a metallic powder was indicative of rhodium metal and that the catalyst had decomposed.

A conclusion from these studies is that the acetate is closest to the optimum in electron withdrawing properties. It is also evident that there is no simple, general relationship, with a specific reaction having its own optimum catalyst. For convenience, it was decided to adopt rhodium acetate as the catalyst in the subsequent studies since this is commercially available and had proved highly active in our preliminary study. However, it may not be the optimum catalyst in terms of speed or product yield for each of the different reactions to be described.

2.3. Reactions of Diazo Compounds with Thiophenes.

It has already been established that the reaction of 3-diazopentane-2,4-dione with thiophene furnished 3-(2´-thienyl)-pentane-2,4-dione (42) as a white crystalline solid. The yield of product was an optimum using rhodium acetate as catalyst under reflux conditions. The product gave a vinylic pattern in the n.m.r., characteristic of 2-substituted thiophenes. The presence of a low field singlet at 17.2ppm with little evidence of a methine group resonance suggested that the molecule was virtually 100% enolised. No other thiophene adduct was observed in the reaction.

The behaviour of 3-diazopentane-2,4-dione is thus distinctly different to that of dimethyl diazomalonate in giving a C-H insertion product with thiophene rather than the thiophenium ylid.

A further example of a 2-diazo-1,3-dicarbonyl compound is 2-diazodimedone (49). The molecule has its carbonyls fixed in a conformation cis to the diazo group rather than the trans conformation seen in 3-diazopentane-2,4-dione, which may influence the reactivity of the compound. 2-Diazodimedone was stirred in thiophene at room temperature using rhodium acetate as catalyst until the diazo absorption band ($2140cm^{-1}$) had disappeared in the infra red. The 2-thienyl adduct, 2-(2´-thienyl)-5,5-dimethylcyclohexane-1,3-dione (50), was isolated quantitatively as orange crystals which were white when recrystallised from chloroform (scheme 32). Again a 2-diazo-1,3-dicarbonyl compound preferred to give a C-H insertion product rather than a thiophenium ylid.

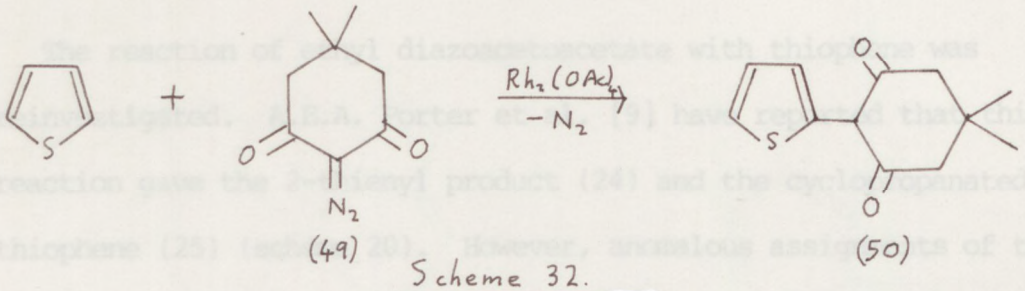
This result prompted the use of 2,5-dimethylthiophene in which the 2,5 positions on the thiophene ring are effectively "blocked" to carbene attack, posing the question whether a C-H insertion product at the 3 position or a thiophenium ylid would be obtained. The 2,5-dimethylthiophene was prepared using the method of mixing hexane-2,5-dione with phosphorus pentasulphide. However contrary to the literature procedure [26] (initial warming and reflux required) a vigorous reaction was obtained and gradual stepwise addition of the hexane-2,5-dione was found to give better results. When 3-diazopentane-2,4-dione was stirred in 2,5-dimethylthiophene at room temperature using rhodium acetate, the thiophenium ylid, 2,5-dimethylthiophenium-bisacetylmethylide (51), was obtained quantitatively as deep red crystals (scheme 33).

The formation of this product indicates that the carbene or carbenoid intermediate suffers attack by the sulphur lone-pair to

give the ylid rather than inserting at the 3 position on the ring. The ylid was heated in refluxing cyclohexene using varying catalysts to promote dissociation of the ylid (as described in chapter one). It was hoped that any regenerated carbenoid species from the dissociation of the ylid would be captured by the cyclohexene to give a norcarane. However only polymeric residues were obtained. When the reaction between 3-diazopentane-2,4-dione and 2,5-dimethylthiophene was performed under reflux, only a trace of the ylid was obtained with no other observed thiophene adducts upon work-up. This result demonstrated that the ylid is thermally labile and a sample of the ylid (51) stored at room temperature, sealed from the atmosphere and light, deteriorated from red crystals to a viscous liquid giving complex peaks in its proton n.m.r.

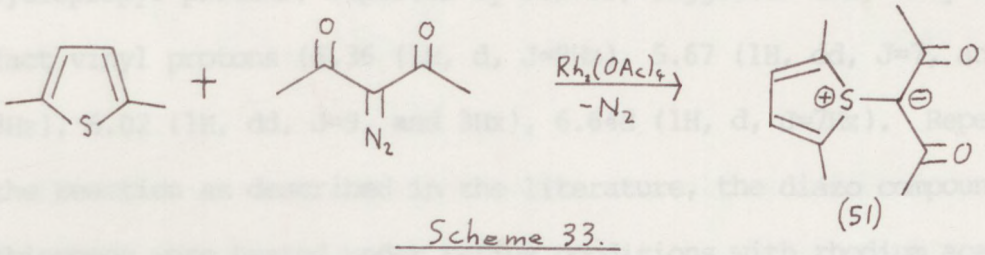
A further point of interest is whether a 3,4 substituted thiophene would effectively "block" a C-H insertion at the 2 position. 3,4-Dimethylthiophene was prepared by the action of sulphur dichloride on 2,3-dimethylbuta-1,3-diene. This was following an analogous literature procedure [27] whereby the first example of 2,3-di-t-butylthiophene was prepared by the action of sulphur dichloride on 2,3-di-t-butylbuta-1,3-diene. It was found that the reaction was most efficient when slow addition of the sulphur dichloride was made to a solution of the 2,3-dimethylbutadiene in dichloromethane with 10% triethylamine to scavenge the HCl produced. After filtering, the product was distilled off as a colourless liquid (scheme 34).

3-Diazopentane-2,4-dione was stirred in the 3,4-dimethylthiophene at room temperature using rhodium acetate as catalyst, furnishing the 2-thienyl adduct (52) in 6% yield with no other observed product (scheme 34).



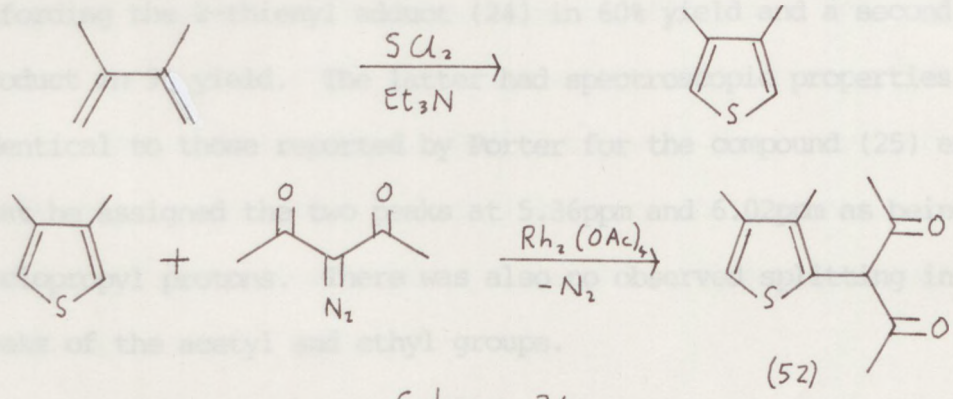
(49) (50)

Scheme 32.



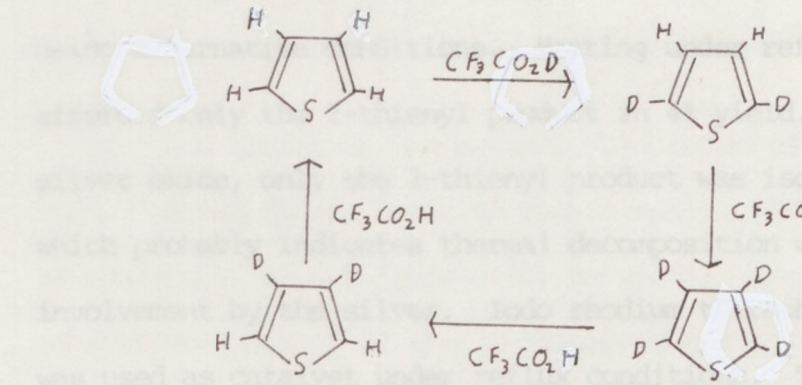
(51)

Scheme 33.

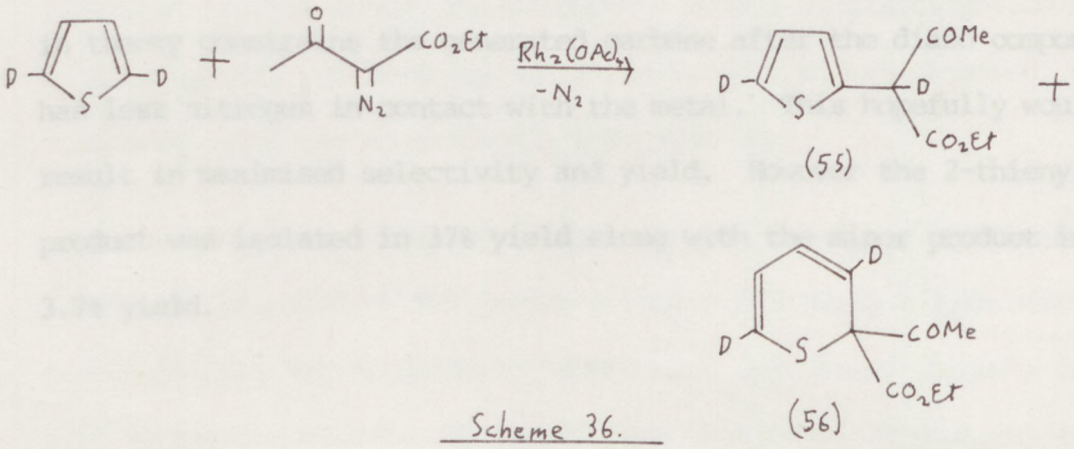


(52)

Scheme 34



Scheme 35.

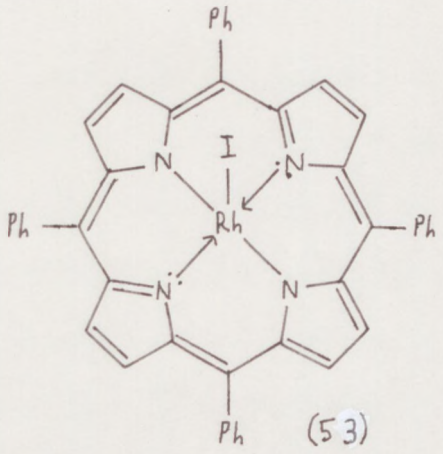


(55) (56)

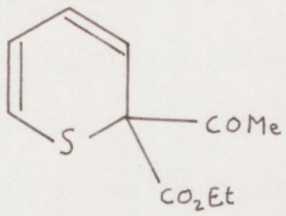
Scheme 36.

The reaction of ethyl diazoacetoacetate with thiophene was reinvestigated. A.E.A. Porter et al. [9] have reported that this reaction gave the 2-thienyl product (24) and the cyclopropanated thiophene (25) (scheme 20). However, anomalous assignments of the cyclopropyl protons, reported by Porter, suggested that they were in fact vinyl protons (5.36 (1H, d, J=9Hz), 5.67 (1H, dd, J=7, and 3Hz), 6.02 (1H, dd, J=9, and 3Hz), 6.64d (1H, d, J=7Hz). Repeating the reaction as described in the literature, the diazo compound and thiophene were heated under reflux conditions with rhodium acetate affording the 2-thienyl adduct (24) in 60% yield and a second product in 9% yield. The latter had spectroscopic properties identical to those reported by Porter for the compound (25) except that he assigned the two peaks at 5.36ppm and 6.02ppm as being for cyclopropyl protons. There was also no observed splitting in the peaks of the acetyl and ethyl groups.

An attempt was made to optimise the yield of the minor product by using alternative conditions. Heating under reflux with no catalyst afforded only the 2-thienyl product in 4% yield. In the presence of silver oxide, only the 2-thienyl product was isolated in 5% yield, which probably indicates thermal decomposition with little or no involvement by the silver. Iodo rhodium tetraphenyl porphyrin (53) was used as catalyst under reflux conditions. This compound has been proposed [28] as a catalyst for diazo compound decomposition. The steric constraint of the bulky functionality around the rhodium, in theory constrains the generated carbene after the diazo compound has lost nitrogen in contact with the metal. This hopefully would result in maximised selectivity and yield. However the 2-thienyl product was isolated in 37% yield along with the minor product in 3.7% yield.



(53)



(54)

The minor product was submitted to extensive examination to determine its structure. All of the data is consistent with a 2H-thiopyran structure (54). Decoupling experiments on the vinyl protons established their positions on the ring assuming that H-4 has the lowest field signal. Porter reported that there were fine splittings in the methyl and ethyl peaks of the proton n.m.r. due to exo and endo isomerism of the cyclopropane. This was not observed in our spectrum.

The C^{13} n.m.r. provided four peaks with a multiplicity of two (c.f. vinyl carbons) at 126.4, 126.7, 127.1 and 128.9ppm.

Standard titration was performed to establish the number of carbon carbon double bonds in the molecule. A known quantity of standardised Wij's solution (ICl in glacial acetic acid) was added to a known quantity of the 2H-thiopyran and left to stand in the dark for half an hour. The residual ICl, (which had not added to the double bonds), were determined by adding KI and titrating the liberated I_2 with sodium thiosulphate. From a single titration with a small quantity of 2H-thiopyran a result of 1.88 was obtained, more consistent with two double bonds than with one.

The reaction was repeated using thiophene 2,5-d_2. The thiophene 2,5-d_2 was prepared to 90% isotopic purity following a literature procedure [29] by refluxing thiophene with successive aliquots of trifluoroacetic acid-d. It was claimed that complete deuteration

and then back protonation could be performed as illustrated in scheme 35. An attempt was made to prepare thiophene-3,4-d_2 following scheme 35 but it was found that, after prolonged reflux, the thiophene became very impure and loss through evaporation was too excessive. As reported in the literature [29], it was found that sulphuric acid-d_2 would not exchange deuterium with thiophene.

The reaction of ethyl diazoacetoacetate with thiophene-2,5-d_2 (scheme 36) afforded the 2-thienyl adduct (55) in 60% yield and the 2H-thiopyran (56) in 11% yield. The 2-thienyl compound had an interesting proton n.m.r. in showing a methine group singlet at 5.05ppm (approximately 0.2H) and an enol singlet at 13.47ppm (approximately 0.8H). The methyl of the acetyl also showed singlets at 1.96ppm (1.50H) and 2.24ppm (0.50H) respectively of the acetyl in the enol and non-enol tautomers. However the fact that proton resonance could be seen on all positions (with a total integral of 3) indicated that the deuteron is labile and has exchanged for a proton which tautomerises between the acetyl protons and the methine next to the acetyl. In addition, fine splittings were seen at the base of the acetyl peak indicative of the CH_2D pentet. The pattern of protons on the thiophene ring was reduced to two doublets (J=4Hz, 6.85 and 7.05ppm) as expected.

The proton n.m.r. of the deuterated 2H-thiopyran (56) was similar to that of the fully protonated product except that the vinyl peaks were simplified to two doublets (J=3Hz). The peaks at 5.36 and 6.64ppm disappeared consistent with their assignment in the protonated product.

The C^{13} n.m.r. of the 2H-thiopyran product (56) is of interest in that due to the considerably slower relaxation of C^{13}-D over C^{13}-H, at normal pulse intervals the C^{13}-D peaks tend to disappear [30]. In

this case the peaks at 126.4 and 126.7ppm disappeared.

The only previous example of a 2H-thiopyran obtained from a net "ring" expansion product with thiophene is that between a 6-diazopenicillanate ester and thiophene as reported in the literature review [21]. The vinyl signals came in multiplets between 5.76 and 6.36ppm which is a similar chemical shift range to this new example.

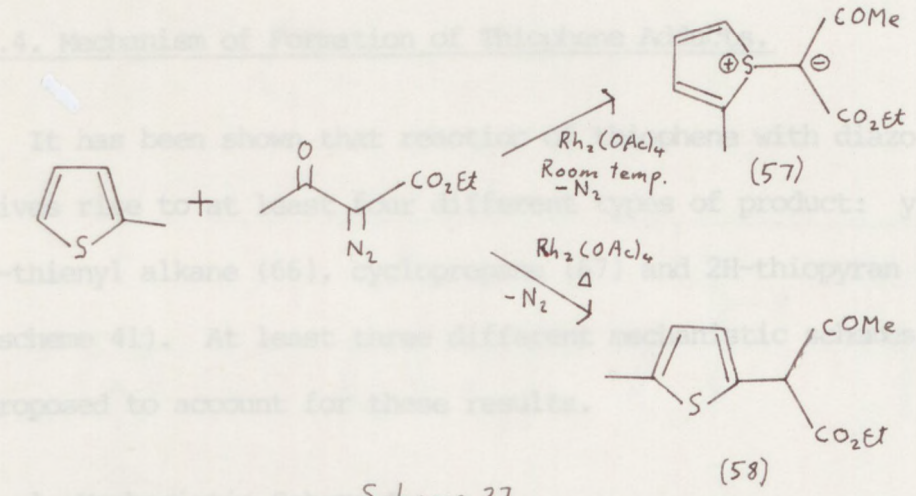
Attempts were made to prepare the 2H-thiopyran with a substituted thiophene. Ethyl diazoacetoacetate and 2-methylthiophene were stirred overnight at room temperature with rhodium acetate furnishing the crude ylid, 2-methylthiophenium carboethoxyacetylmethylide (57), quantitatively, which when purified on prep. t.l.c. yielded the 2-thienyl adduct (58) in 3% yield, along with purified ylid (57) (scheme 37). However repeating the reaction under reflux conditions furnished the 2-thienyl adduct (58) in 97% yield. In both cases there was no evidence of a 2H-thiopyran product.

Ethyl diazoacetoacetate was then reacted with 3,4-dimethylthiophene. After stirring at room temperature with rhodium acetate the ylid 3,4-dimethylthiophenium carboethoxy-acetylmethylide (59) was obtained quantitatively (scheme 38). As with the methylthiophenium ylid, submitting a sample to prep. t.l.c. afforded the 2-thienyl adduct (60) in 3% along with purified ylid (59) in 90% yield. A sample of the ylid when refluxed in benzene until no trace of the ylid remained afforded the 2-thienyl adduct (60) in 60% yield. When a catalytic quantity of rhodium acetate was added to the benzene the conversion to the rearranged product (60) became almost quantitative. In all cases no trace of the 2H-thiopyran was observed.

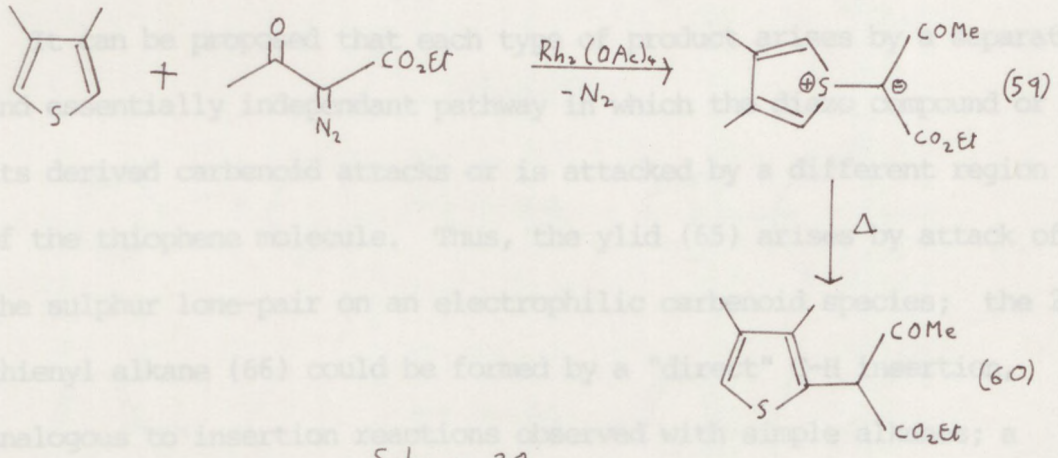
A reaction between another 2-diazo-3-ketoester and thiophene was

attempted. Ethyl diazobenzoylacetate (61) was prepared by treatment of ethyl benzoylacetate with carboxybenzene-4-sulphonyl azide as with previous examples. It was then refluxed in thiophene in the presence of rhodium acetate (scheme 39). The diazo compound proved to be remarkably stable requiring eight hours reflux before the diazo absorption band ($2140cm^{-1}$) disappeared in the infra red, as opposed to the reaction being complete well within half an hour for ethyl diazoacetoacetate. The 2-thienyl adduct (62) was isolated in 88% yield with no evidence of a 2H-thiopyran derivative.

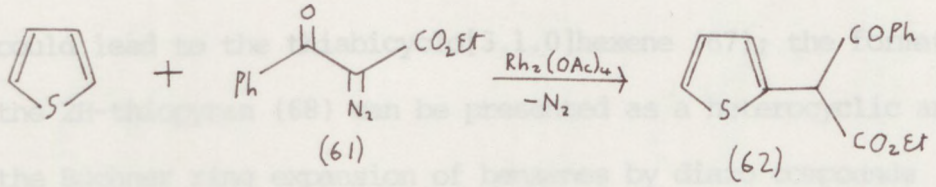
Departing from diazocarbonyl compounds thiophene was then reacted with diphenyl diazomethane (63) which was prepared by the action of mercuric oxide on benzophenone hydrazone. Adding the diazo compound slowly to a refluxing solution of thiophene containing a catalytic quantity of rhodium acetate afforded only the azine (64) with no observed adduct of thiophene (scheme 40).



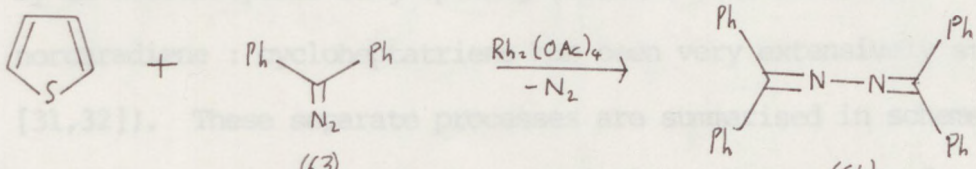
Scheme 37.



Scheme 38.



Scheme 39



Scheme 40.

2.4. Mechanism of Formation of Thiophene Adducts.

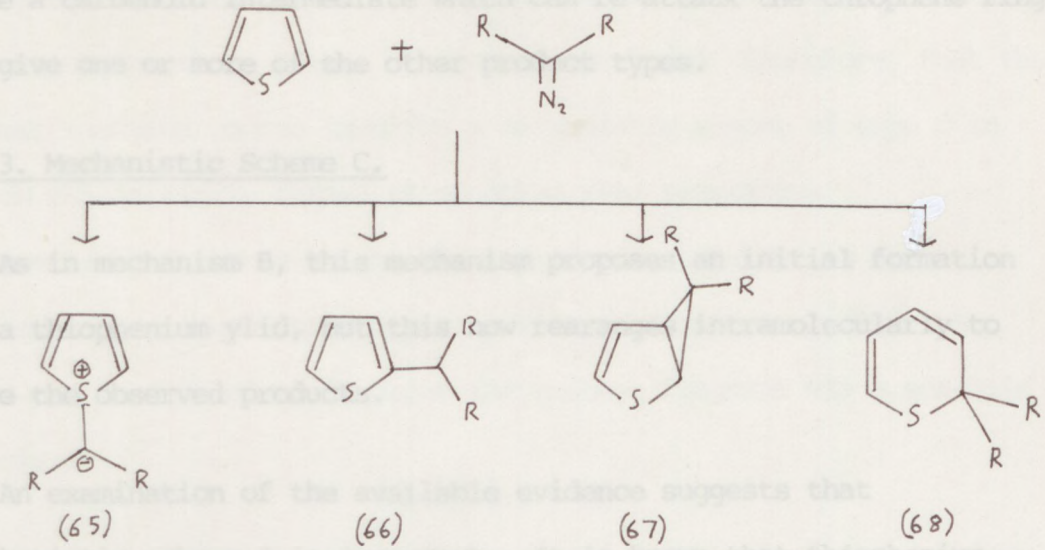
It has been shown that reaction of thiophene with diazo compounds gives rise to at least four different types of product: ylid (65), 2-thienyl alkane (66), cyclopropane (67) and 2H-thiopyran (68) (scheme 41). At least three different mechanistic schemes can be proposed to account for these results.

1. Mechanistic Scheme A.

It can be proposed that each type of product arises by a separate and essentially independant pathway in which the diazo compound or its derived carbenoid attacks or is attacked by a different region of the thiophene molecule. Thus, the ylid (65) arises by attack of the sulphur lone-pair on an electrophilic carbenoid species; the 2-thienyl alkane (66) could be formed by a "direct" C-H insertion, analogous to insertion reactions observed with simple alkanes; a "concerted cyclopropanation" of the 2,3 double bond of the thiophene could lead to the thiabicyclo[3.1.0]hexene (67); the formation of the 2H-thiopyran (68) can be presented as a heterocyclic analogue of the Buchner ring expansion of benzenes by diazo compounds - ascribable to a "cyclopropanation" of the aromatic ring followed by an electrocyclic ring opening (valence tautomerism of norcaradiene : cycloheptatriene has been very extensively studied [31,32]). These separate processes are summarised in scheme 42, the reactive species being shown as a simple carbene purely for convenience.

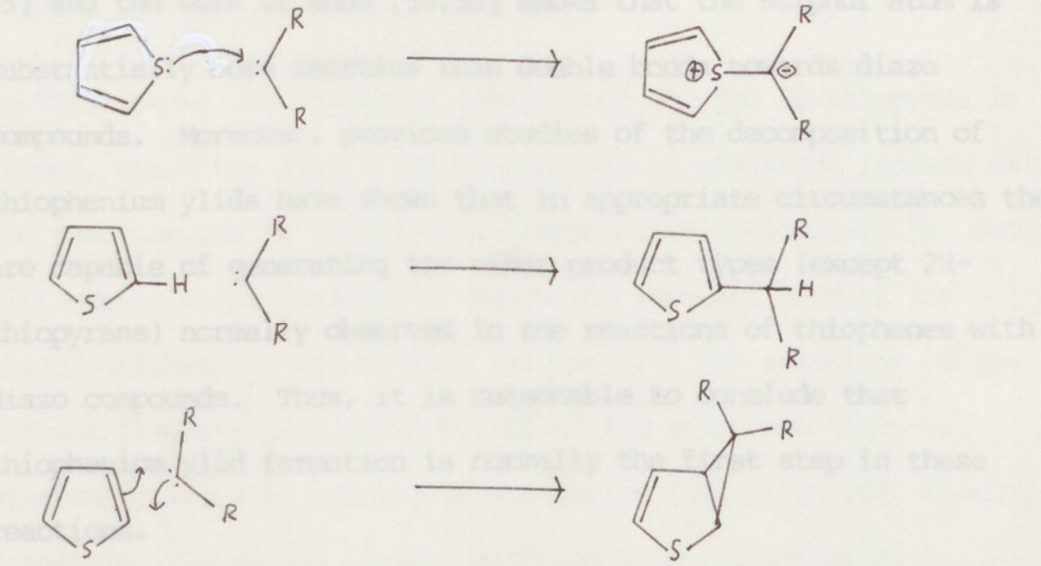
2. Mechanistic Scheme B.

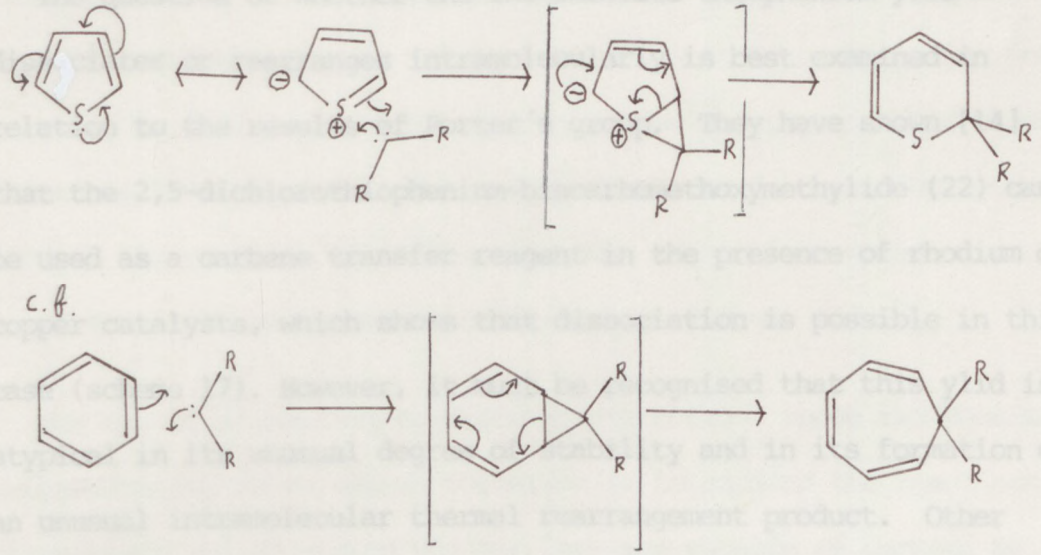
This takes the view that a thiophenium ylid is always the initial product of reaction of a diazo compound with a thiophene derivative. After its initial formation, the thiophenium ylid dissociates to



(65) (66) (67) (68)

Scheme 41.





c.f.

Scheme 42.

give a carbenoid intermediate which can re-attack the thiophene ring to give one or more of the other product types.

3. Mechanistic Scheme C.

As in mechanism B, this mechanism proposes an initial formation of a thiophenium ylid, but this now rearanges intramolecularly to give the observed products.

An examination of the available evidence suggests that mechanistic scheme A is incorrect. It is known that thiophenium ylids form readily under a wide variety of conditions [9,13,19,33-35] and the work of Ando [34,35] shows that the sulphur atom is substantially more reactive than double bonds towards diazo compounds. Moreover, previous studies of the decomposition of thiophenium ylids have shown that in appropriate circumstances they are capable of generating the other product types (except 2H-thiopyrans) normally observed in the reactions of thiophenes with diazo compounds. Thus, it is reasonable to conclude that thiophenium ylid formation is normally the first step in these reactions.

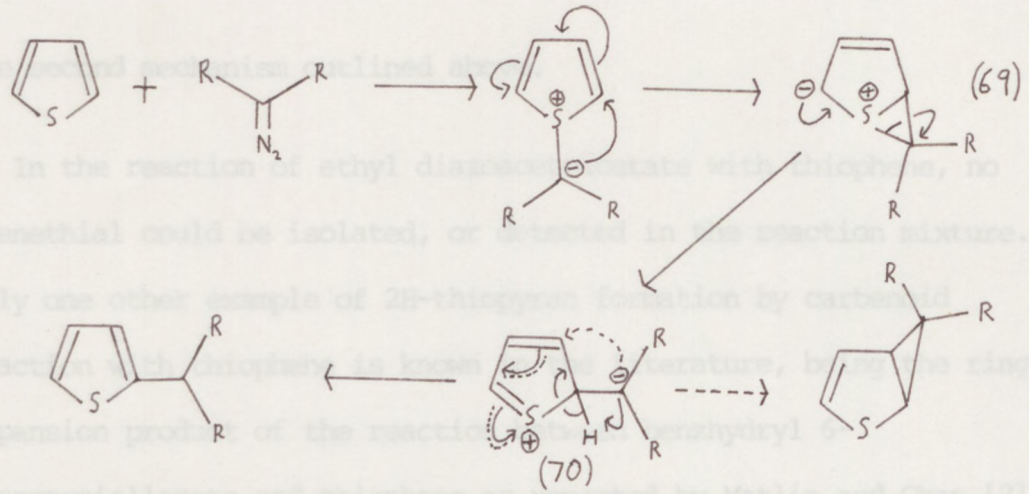
The question of whether the intermediate thiophenium ylid dissociates or rearranges intramolecularly is best examined in relation to the results of Porter´s group. They have shown [14] that the 2,5-dichlorothiophenium-biscarbomethoxymethylide (22) can be used as a carbene transfer reagent in the presence of rhodium or copper catalysts, which shows that dissociation is possible in this case (scheme 17). However, it must be recognised that this ylid is atypical in its unusual degree of stability and in its formation of an unusual intramolecular thermal rearrangement product. Other ylids examined gave "normal" rearrangement and failed to show any crossover [12] when reacted in the presence of other thiophenes, nor

was there any transfer of carbene to alkenes nor any carbene dimer formation for these ylids. It can be concluded, therefore, that the normal reaction course involves a mechanistic scheme of type C in which the initially formed thiophenium ylid rearranges intramolecularly to give the final products. However in special circumstances where intramolecular rearrangement is blocked, the ylid can be induced to transfer the carbene fragment via a metallic carrier.

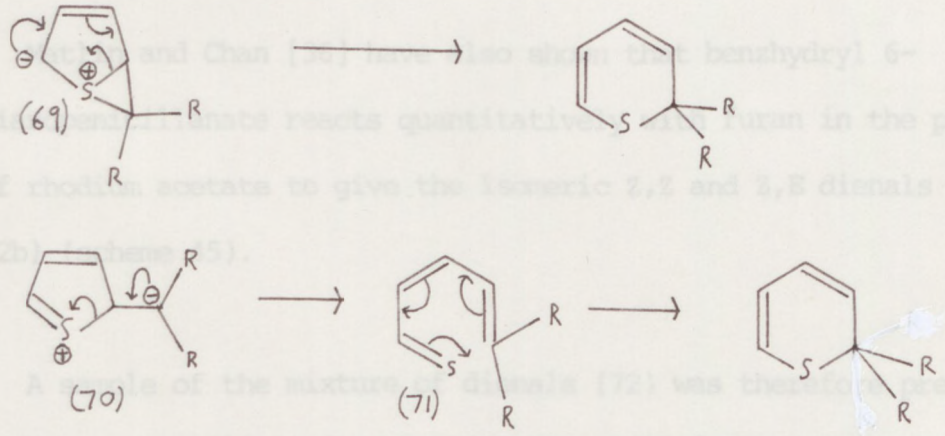
Based on this mechanistic picture, the formation of the 2-thienyl alkane and cyclopropane type products can be accounted for by the general pathways shown in scheme 43.

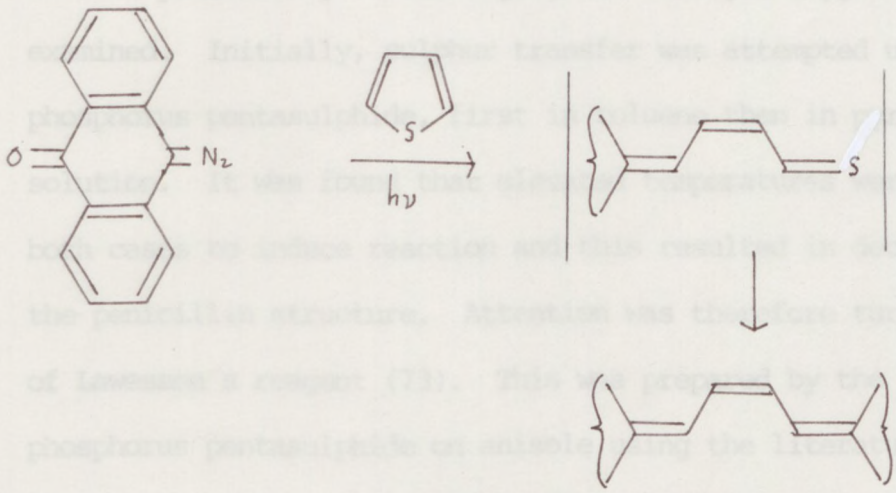
This leaves the remaining question of how the 2H-thiopyran is formed, since two distinct processes can be envisaged (scheme 44). The reaction can be viewed as a heterocyclic analogue of the Buchner ring expansion of benzene, in which the internal bond of the thiabicyclohexene (69) breaks, leading to a net insertion of the carbene fragment into the C-S bond of the thiophene ring. Alternatively, ring opening of zwitterion (70) would give rise to a dienethial, in direct analogy with the known ring-opening condensation of diazo compounds with furans which gives isolable dienals. The dienethials (71) are expected to be unstable and not normally isolable, but might undergo a 6π-electrocyclic ring closure affording 2H-thiopyrans. The polyene products described by Reverdy [20] in the reaction of 10-diazoanthrone with thiophene are also consistent with an intermediate dienethial (scheme 44).

One way of attempting to discriminate between these two possible mechanisms for 2H-thiopyran formation is to examine the reactions of dienethials and determine whether they are capable of serving as intermediates. Thus, if a dienethial could be shown to undergo cyclisation to a 2H-thiopyran, this would show the feasibility of

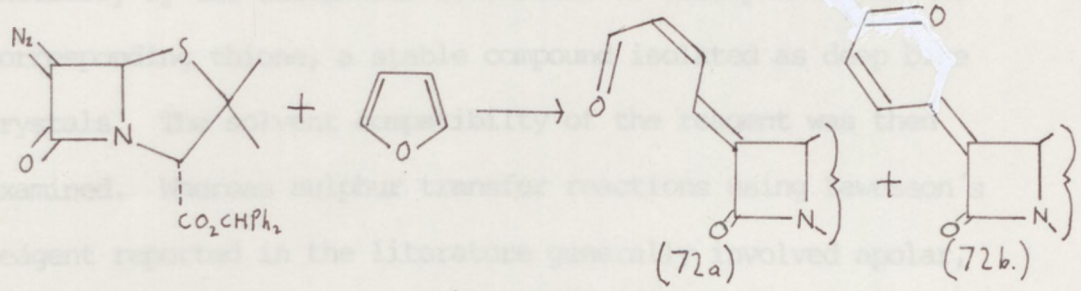


Scheme 43.





Scheme 44.



Scheme 45.

the second mechanism outlined above.

In the reaction of ethyl diazoacetoacetate with thiophene, no dienethial could be isolated, or detected in the reaction mixture. Only one other example of 2H-thiopyran formation by carbenoid reaction with thiophene is known in the literature, being the ring expansion product of the reaction between benzhydryl 6-diazopenicllanate and thiophene as reported by Matlin and Chan [21] (scheme 26).

Matlin and Chan [36] have also shown that benzhydryl 6-diazopenicillanate reacts quantitatively with furan in the presence of rhodium acetate to give the isomeric Z,Z and Z,E dienals (72a and 72b) (scheme 45).

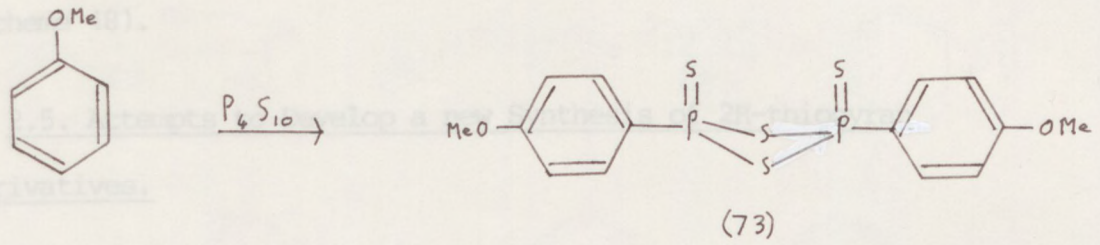
A sample of the mixture of dienals (72) was therefore prepared and the possibility of exchanging the aldehyde oxygen for sulphur examined. Initially, sulphur transfer was attempted using phosphorus pentasulphide, first in toluene then in pyridine solution. It was found that elevated temperatures were needed in both cases to induce reaction and this resulted in decomposition of the penicillin structure. Attention was therefore turned to the use of Lawesson´s reagent (73). This was prepared by the action of phosphorus pentasulphide on anisole using the literature procedure [37] (scheme 46). The activity of the reagent was demonstrated initially by the successful conversion of benzophenone to the corresponding thione, a stable compound isolated as deep blue crystals. The solvent compatibilty of the reagent was then examined. Whereas sulphur transfer reactions using Lawesson´s reagent reported in the literature generally involved apolar, hydrocarbon solvents at elevated temperatures, it was found that reactions with benzophenone could also be effected very smoothly in

pyridine solution at room temperature offering better prospects for the survival of the β-lactam in the present case.

When benzhydryl 6-diazopenicillanate was reacted with furan to generate the dienals (72) and the product was treated with Lawesson´s reagent (73) in pyridine solution at room temperature (or, in fact, in toluene suspension at reflux), the 2H-thiopyran (39) was isolated in about 15% yield (scheme 47). The product showed identical spectra to those of a sample prepared by the direct condensation of benzhydryl 6-diazopenicillanate with thiophene. Again, only one isomer was observed and its stereochemistry was confirmed by the observation of n.O.e.´s between the protons on the 8-methyl and 21-H on the 2H-thiopyran ring using n.O.e. difference spectroscopy.

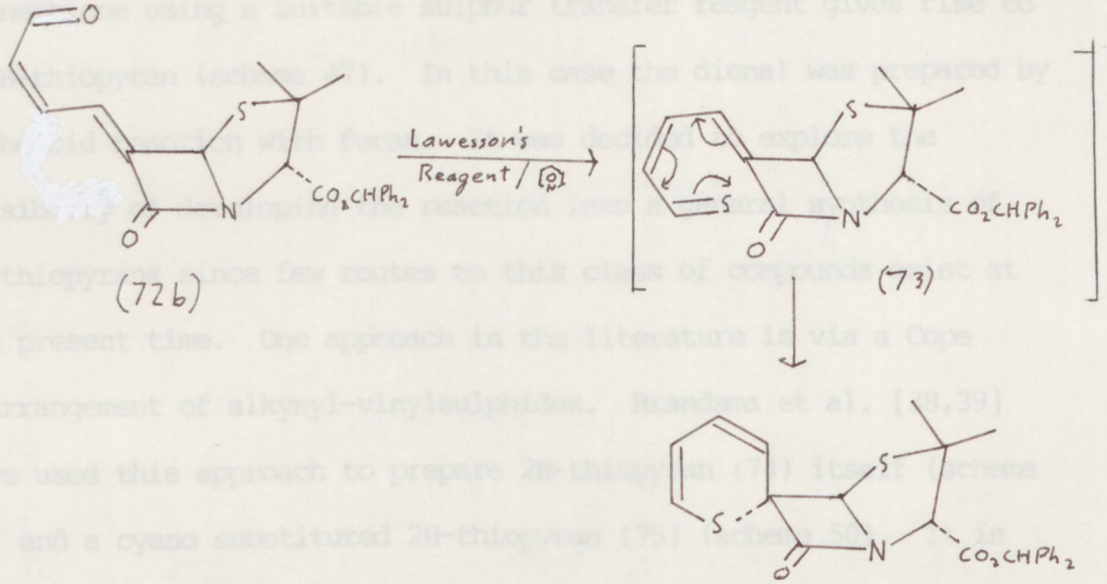
The result indicates that that the origin of the stereochemistry in the formation of only one of the two possible isomeric compounds in these reactions must depend upon a preferred conformation of the dienethial. The steric effect of the folded penicillin nucleus and the 8-methyl should discourage attack of sulphur on the top face of the β-lactam ring. The predicted favouring of cyclisation by attack on the bottom face (73) is in agreement with the experimental observations (scheme 47).

It has thus been demonstrated that a dienethial could be an intermediate in the carbenoid ring expansion of thiophene to a 2H-thiopyran. Although the feasibilty of this pathway has been established the results do not, of course, rule out the possibility of the alternative Büchner type ring expansion reaction actually occurring. Nevertheless, it is now attractive to consider a unified reaction scheme in which the zwitterion (70) is a common intermediate which gives rise to all of the known product types



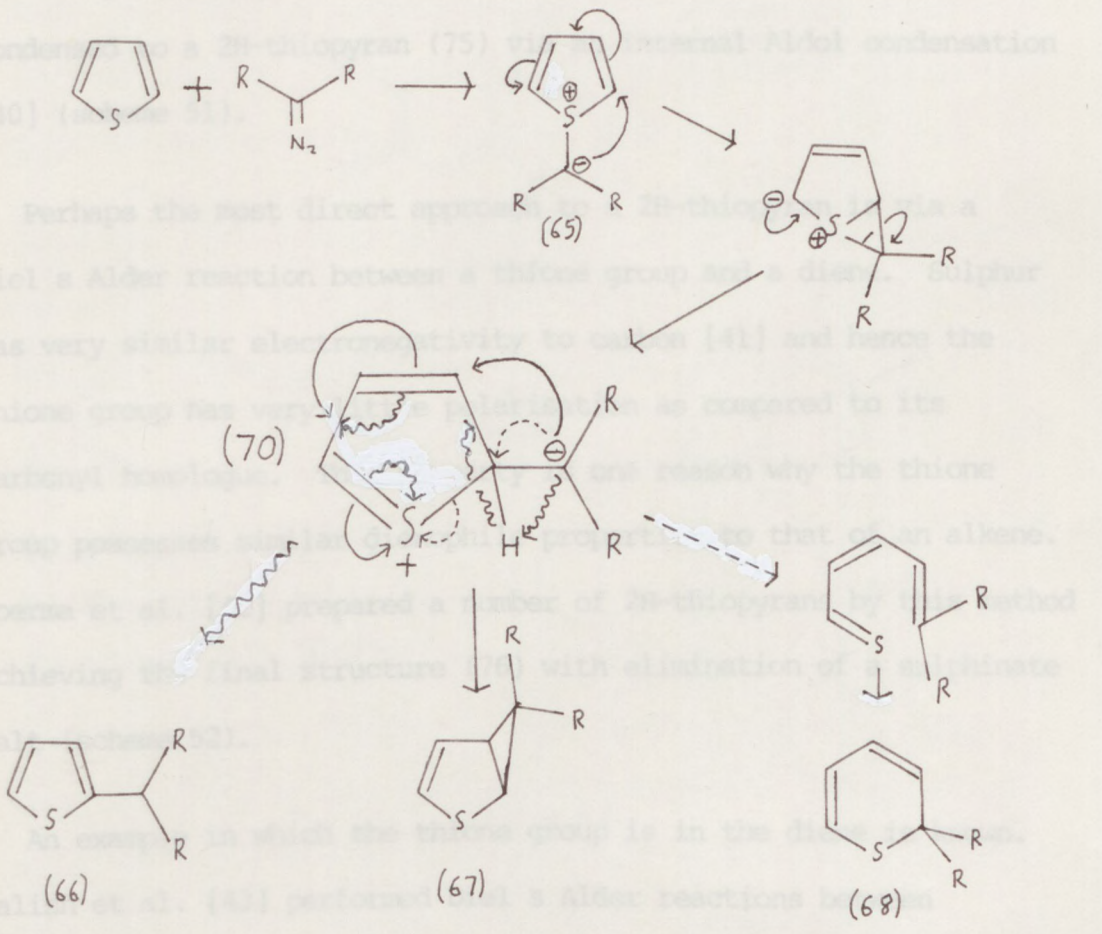
(73)

Scheme 46



(72b) (73) (39)

Scheme 47



Scheme 48

(scheme 48).

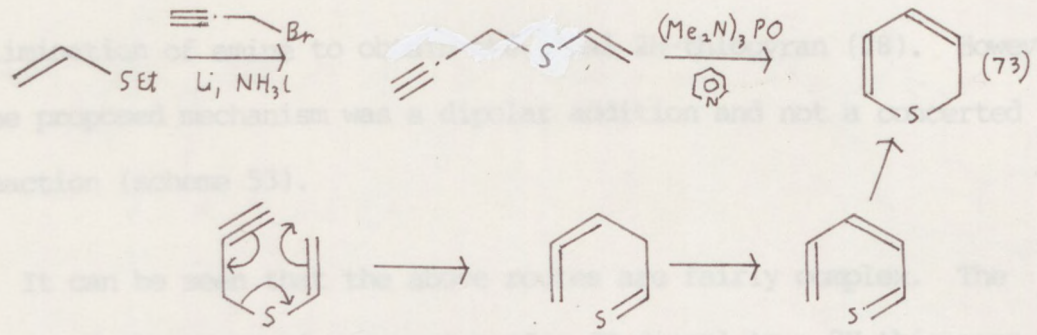
2.5. Attempts to Develop a new Synthesis of 2H-thiopyran Derivatives.

It has been established above that conversion of a 2Z-dienal to a dienethione using a suitable sulphur transfer reagent gives rise to a 2H-thiopyran (scheme 47). In this case the dienal was prepared by carbenoid reaction with furan. It was decided to explore the possibilty of developing the reaction into a general synthesis of 2H-thiopyrans since few routes to this class of compounds exist at the present time. One approach in the literature is via a Cope rearrangement of alkynyl-vinylsulphides. Brandsma et al. [38,39] have used this approach to prepare 2H-thiopyran (74) itself (scheme 49) and a cyano substituted 2H-thiopyran (75) (scheme 50). It is interesting that the proposed intermediate is a cis-dienethial.

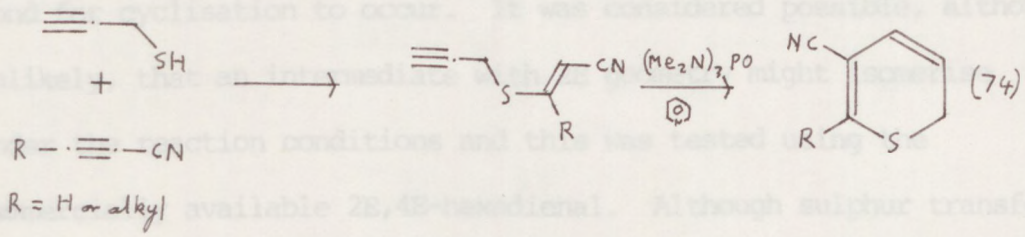
Divinylsulphides with a terminal aldehyde group have been condensed to a 2H-thiopyran (75) via an internal Aldol condensation [40] (scheme 51).

Perhaps the most direct approach to a 2H-thiopyran is via a Diel s Alder reaction between a thione group and a diene. Sulphur has very similar electronegativity to carbon [41] and hence the thione group has very little polarisation as compared to its carbonyl homologue. This property is one reason why the thione group possesses similar dienophile properties to that of an alkene. Boerma et al. [42] prepared a number of 2H-thiopyrans by this method achieving the final structure (76) with elimination of a sulphinate salt (scheme 52).

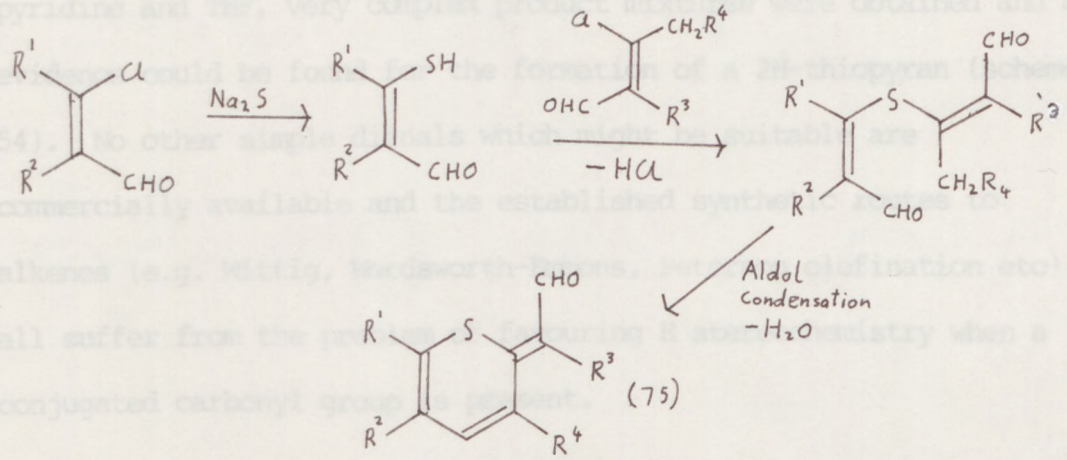
An example in which the thione group is in the diene is known. Kalish et al. [43] performed Diel s Alder reactions between vinylthiones (77) and maleic anhydride, this time relying on the



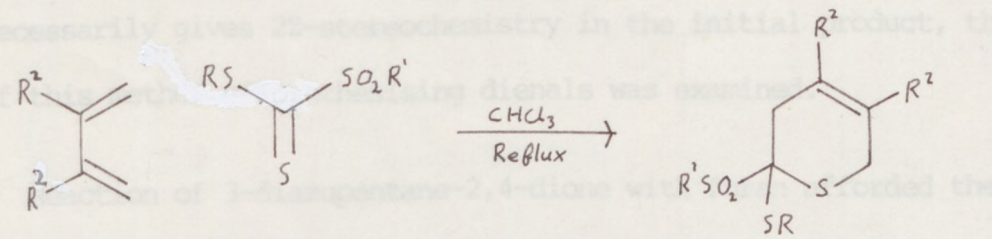
Scheme 49.



Scheme 50.



Scheme 51.



R = p-tolyl, R' = Ph, R² = H.

R = R' = p-Cl-C6H4-, R² = H.

R = p-tolyl, R' = Ph, R² = Me

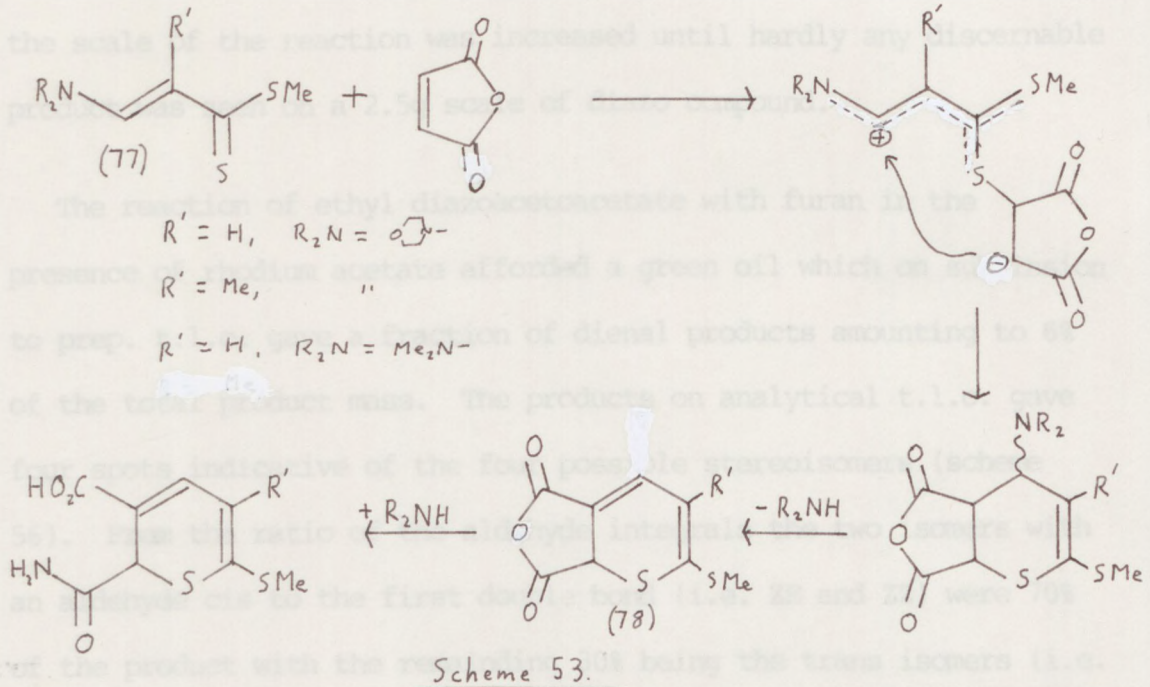
Scheme 52.

elimination of amine to obtain the final 2H-thiopyran (78). However the proposed mechanism was a dipolar addition and not a concerted reaction (scheme 53).

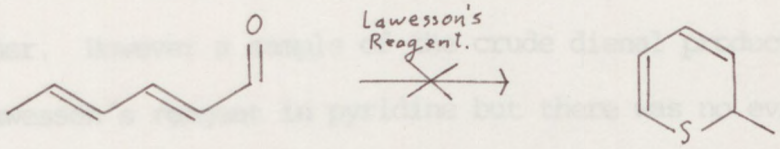
It can be seen that the above routes are fairly complex. The proposed new route of conversion of a 2Z-dienal to a 2H-thiopyran is unfortunately constrained by the obvious requirement for a 2Z double bond for cyclisation to occur. It was considered possible, although unlikely, that an intermediate with 2E geometry might isomerise under the reaction conditions and this was tested using the commercially available 2E,4E-hexadienal. Although sulphur transfer appeared to be taking place on reaction with Lawesson´s reagent in pyridine and THF, very complex product mixtures were obtained and no evidence could be found for the formation of a 2H-thiopyran (scheme 54). No other simple dienals which might be suitable are commercially available and the established synthetic routes to alkenes (e.g. Wittig, Wadsworth-Emmons, Peterson olefination etc) all suffer from the problem of favouring E stereochemistry when a conjugated carbonyl group is present.

Since the ring opening reaction of furan with diazo compounds necessarily gives 2Z-stereochemistry in the initial product, the use of this method of synthesising dienals was examined.

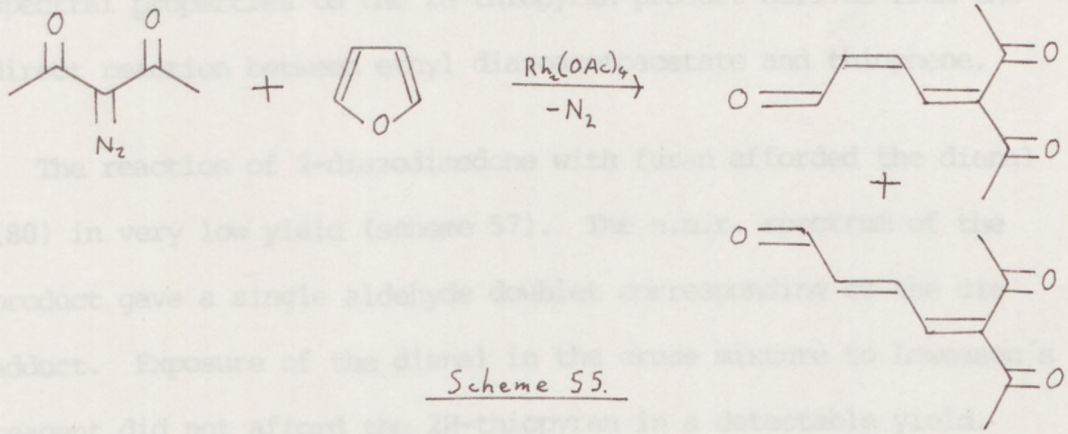
Reaction of 3-diazopentane-2,4-dione with furan afforded the dienal in poor yield (scheme 55). 500mg of diazo compound gave the dienal product in 16% yield, the n.m.r. of which demonstrated that there was a 7:3 ratio of cis (79a) and trans isomers (79b). An aldehyde doublet at 10.36ppm is taken as being due to the cis isomer, downfield of the trans aldehyde doublet at 9.76ppm owing to the anisotropic effect of the first double bond which is not present in the trans isomer (both J=7Hz). The yield curiously decreased as



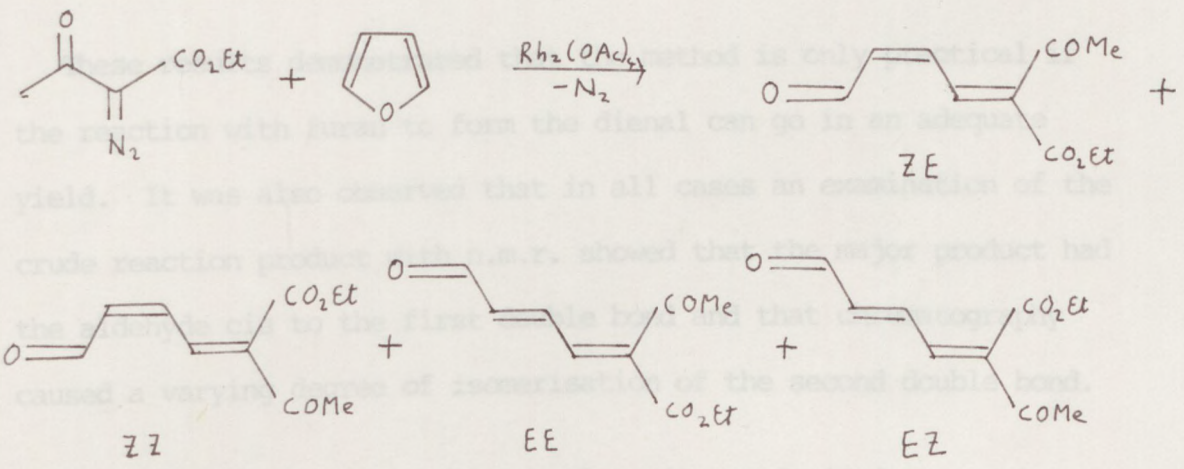
Scheme 53.



Scheme 54.



Scheme 55.



Scheme 56.

the scale of the reaction was increased until hardly any discernable product was seen on a 2.5g scale of diazo compound.

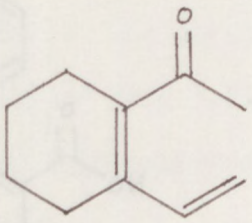
The reaction of ethyl diazoacetoacetate with furan in the presence of rhodium acetate afforded a green oil which on submission to prep. t.l.c. gave a fraction of dienal products amounting to 6% of the total product mass. The products on analytical t.l.c. gave four spots indicative of the four possible stereoisomers (scheme 56). From the ratio of the aldehyde integrals the two isomers with an aldehyde cis to the first double bond (i.e. ZE and ZZ) were 70% of the product with the remainding 30% being the trans isomers (i.e. EE and EZ). The yield was considered too low to pursue the reaction further. However a sample of the crude dienal product was submitted to Lawesson´s reagent in pyridine but there was no evidence of a 2H-thiopyran being formed; a result if obtained should give identical spectral properties to the 2H-thiopyran product derived from the direct reaction between ethyl diazoacetoacetate and thiophene.

The reaction of 2-diazodimedone with furan afforded the dienal (80) in very low yield (scheme 57). The n.m.r. spectrum of the product gave a single aldehyde doublet corresponding to the cis adduct. Exposure of the dienal in the crude mixture to Lawesson´s reagent did not afford the 2H-thiopyran in a detectable yield.

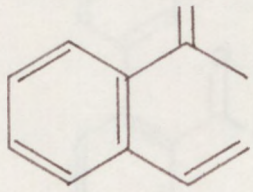
These results demonstrated that the method is only practical if the reaction with furan to form the dienal can go in an adequate yield. It was also observed that in all cases an examination of the crude reaction product with n.m.r. showed that the major product had the aldehyde cis to the first double bond and that chromatography caused a varying degree of isomerisation of the second double bond.

As a final approach to this problem, it was decided to examine the reaction of dienecarbonyl compounds in which the 2,3

unsaturation would be present in a ring, thus forcing Z stereochemistry on the system. Molecules of types (81) and (82) were convenient suitable targets. Prelimary work with aromatic analoques was therefore carried out in the hope of obtaining some encouraging results.



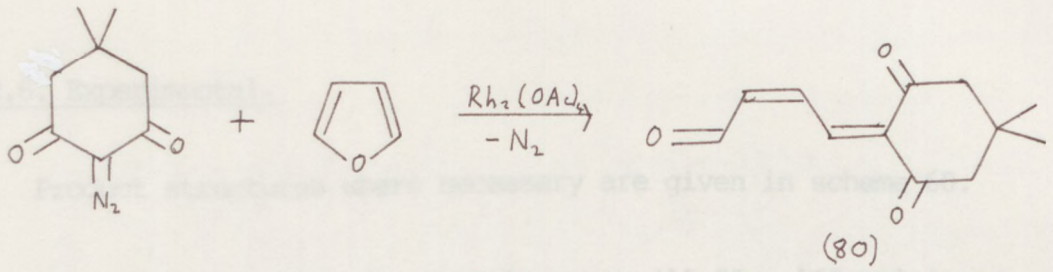
(81)



(82)

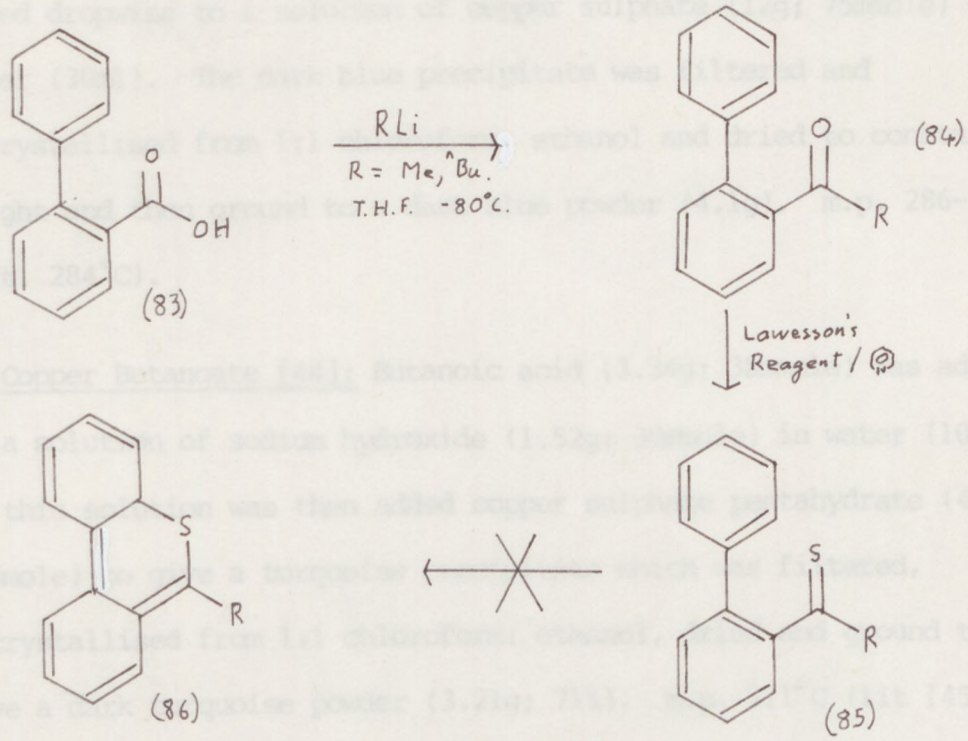
Addition of methyl or butyl lithium to phenylbenzoic acid (83) afforded the required biphenyl ketones (84) (scheme 58). Sulphur transfer reactions were successfully achieved with Lawesson´s reagent in pyridine. However, there was no evidence for cyclisation of the thiones (85) to 2H-thiopyrans (86).

This failure to cyclise is obviously due, at least in part, to the disruption of aromaticity of the two benzene rings which would be required in forming the products (86). An attempt was to prepare a simple vinyl analogue by lithiation of 2-chlorostyrene (87) followed by in situ condensation with acetyl chloride (scheme 59). However, only polystyrene was detected following workup and further efforts to develop this synthetic approach to 2H-thiopyrans were abandoned.



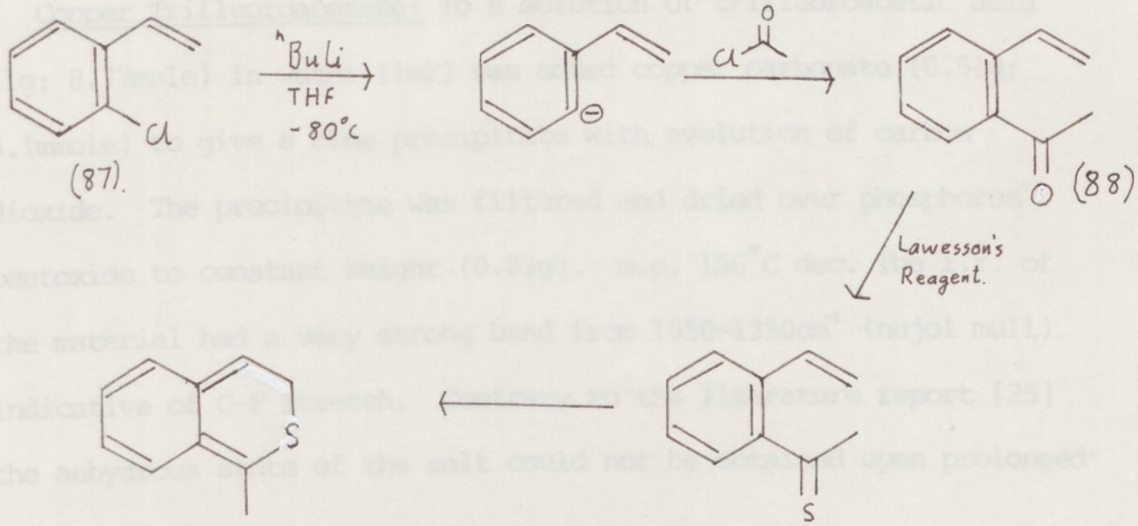
(80)

Scheme 57.



(83) (84) (85) (86)

Scheme 58.



(87) (88)

Scheme 59.

2.6. Experimental.

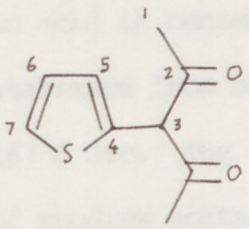
Product structures where necessary are given in scheme 60.

Copper Acetylacetonate: Acetylacetone (15.05g; 160mmole) was added dropwise to a solution of copper sulphate (12g; 75mmole) in water (30ml). The dark blue precipitate was filtered and recrystallised from 1:1 chloroform: ethanol and dried to constant weight and then ground to a dark blue powder (4.1g). m.p. 286-288°C (lit. 284°C).

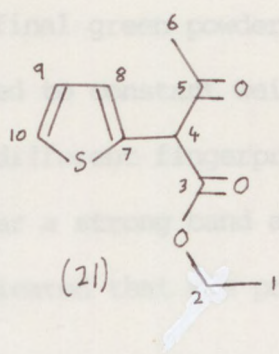
Copper Butanoate [44]: Butanoic acid (3.34g; 38mmole) was added to a solution of sodium hydroxide (1.52g; 38mmole) in water (10ml). To this solution was then added copper sulphate pentahydrate (4.74g; 19mmole) to give a turquoise precipitate which was filtered, recrystallised from 1:1 chloroform: ethanol, dried and ground to give a dark turquoise powder (3.21g; 71%). m.p. 211°C (lit [45], 225°C dec.).

Copper Trifluoroacetate: To a solution of trifluoroacetic acid (1g; 8.77mole) in water (1ml) was added copper carbonate (0.51g; 4.1mmole) to give a blue precipitate with evolution of carbon dioxide. The precipitate was filtered and dried over phosphorus pentoxide to constant weight (0.89g). m.p. 156°C dec. The i.r. of the material had a very strong band from 1050-1350cm^{-1} (nujol mull) indicative of C-F stretch. Contrary to the literature report [25] the anhydrous state of the salt could not be obtained upon prolonged drying under vacuum.

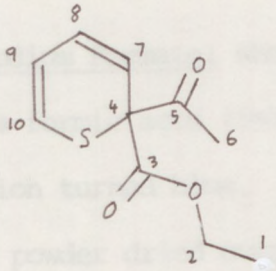
Rhodium Pivalate: A solution of rhodium acetate hydrate (172mg; 0.36mmole) and pivalic acid (3g; 29.4mmole) in benzene (15ml) was stirred under reflux for four hours. The benzene and excess pivalic acid was evaporated off under vacuum at 95°C. The green crystalline



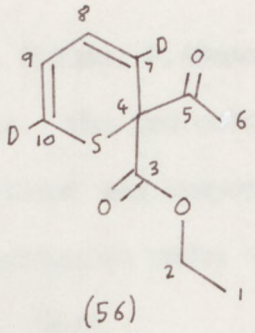
(42)



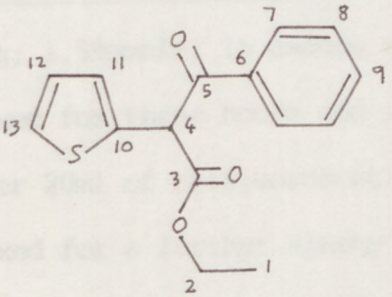
(21)



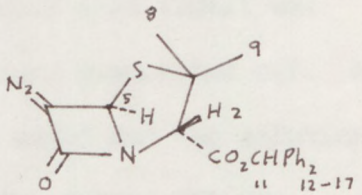
(54)



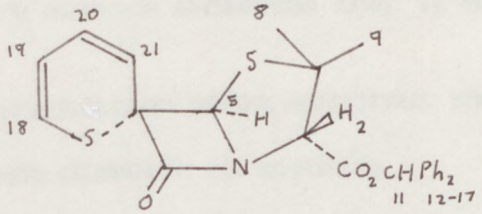
(56)



(62)



(37)



(39)

Scheme 60.

residue was given a repeated treatment with another aliquot of pivalic acid in benzene to leave a final green powder which was recrystallised from benzene and dried to constant weight (200mg). m.p. 187°C dec. The i.r. showed a different fingerprint region to that of rhodium acetate in particular a strong band at 1220cm^{-1} (nujol mull). The lack of O-H stretch indicated that the product was anhydrous.

Rhodium Formate: Rhodium Chloride (100mg; 0.48mmole) was refluxed in 50% formic acid (5ml) for one hour. The red colour of the solution turned blue. The excess solvent was evaporated off and the green powder dried over phosphorus pentoxide under vacuum to leave a green powder (92mg; 98%). m.p. 120°C (dec).

Rhodium Trifluoroacetate: A solution of rhodium acetate hydrate (604mg; 1.59mmole) in excess trifluoroacetic acid (20ml) was refluxed for three hours and the excess acid evaporated off. A further 20ml of trifluoroacetic acid was added and the solution refluxed for a further ninety minutes. The excess TFA was evaporated off and the residue recrystallised from benzene and dried to constant weight (932mg, 58%). The infra red was saturated in the region of C-F stretching modes (1150-1250cm^{-1}, nujol mull) and the presence of an O-H stretch indicated that it was hydrated.

An attempted preparation using anhydrous rhodium oxide failed as the oxide would not dissolve in anything.

Ethyl Diazoacetate [46]: To a stirred solution of glycine ethyl ester hydrochloride (13.02g; 93mmole) and sodium acetate (65mg) in water (15ml) kept at 18-20°C. was added an ice cold solution of sodium nitrite (9.77g; 142mmole) in water (15ml). The solution immediately changed to a yellow colour. Ethanol free ether (10ml; kept over calcium chloride to remove the ethanol) was then added

followed by dropwise addition of 10% sulphuric acid (1.55ml). The reaction was stirred for a further fifteen minutes keeping the temperature at 18-20°C. The mixture was then poured into a separating funnel and the aqueous layer returned to the reaction flask. The ether layer was immediately poured into excess 10% sodium carbonate solution, washed with water and tested for neutrality with litmus and finally stored in an ice bath. The procedure was repeated twice with fresh ether on the original aqueous layer of sodium nitrite. The treated ether layers were combined, dried over anhydrous sodium sulphate and evaporated to dryness to give a yellow liquid (7.99g; 70%). $\delta(CDCl_3)$: 1.33 (3H,t), 4.31 (2H,q), 4.87 (1H,s). νmax ($CHCl_3$): 3110w, 2980w, 2120vs, 1690vs, 1400m, 1380s, 1350s, 1340m, 1250m, 1190m.

1-Carboethoxycycloheptatriene (43) [23]: Ethyl diazoacetate (1g; 8.77mmole) in benzene (5ml) was added dropwise over an hour to a stirred solution of rhodium trifluoroacetate (25mg) in benzene (10ml). After a further half hour of stirring the diazo absorption band (2120cm^{-1}) had disappeared in the i.r. The excess benzene was evaporated off to leave a brown liquid 1-carboethoxycycloheptatriene (1.202g; 100%). $\delta(CDCl_3)$: 1.35 (3H,t), 2.60 (1H,t), 4.37 (2H,q), 5.56 (2H,m), 6.38 (2Hm), 6.76 (2H,m). ν max ($CHCl_3$): 3030w, 2980w, 1725vs, 1370m, 1300m, 1270m, 1030, 690.

3-Diazopentane-2,4-dione with Thiophene: 3-Diazopentane-2,4-dione (300mg; 2.5mmole) was added dropwise to a stirred mixture of catalyst (5mg; see discussion) in thiophene (5ml). The mixture was stirred at room temperature then if necessary refluxed until the diazo absorption band (2120cm^{-1}) had disappeared in the i.r. The thiophene was evaporated off and the residue submitted to prep. t.l.c. eluting with dichloromethane. In all cases the first band eluted was 3-(2´-thienyl)-pentane-2,4-dione (42) as a white

crystalline solid (42) (yields given in discussion). m.p. 55-56°C. δ ($CDCl_3$): 2.04 (6H,s), 7.00 (1H,d,J=3Hz), 7.16 (1H,dd,J=3, 5Hz), 7.56 (1H,d,J=5Hz), 17.2 (1H,s) 100% enolised methine. ν max ($CHCl_3$): 3040w, 2980w, 1590s, 1350m, 1400m, 1260vs, 1205, 910w, 895w, 700vs. C^{13} δ ($CDCl_3$): 24.1q (C1), 107.1s (C3), 127.3d 127.7d 129.4d (C5,6,7), 138.0s (C4), 192.0s (C2). m/e: 182 (M+, 100%), 168 (1.2%), 140 (14.8%), 139 (55.21%), 83 (2.3%). λ max (MeOH): 260nm (log ε 4.26), 315nm (log ε 4.26). Found: C, 59.45; H, 9.26%; $C_9H_{10}O_2S$ requires C, 59.34; H, 9.25.

2,5-Dimethylthiophene [26]: Hexane-2,5-dione (100g; 0.88mole) was added dropwise to phosphorus pentasulphide (78g; 0.351mole) in a flask fitted with an efficient reflux condenser. After the initial reaction had subsided the mixture was refluxed for 45 minutes with rapid stirring. The product was distilled collecting the fraction 134-136°C which was collected as a colourless liquid stored over molecular sieve (63g; 64%). δ ($CDCl_3$): 2.42 (6H,s), 6.55 (2H,s).

3-Diazopentane-2,4-dione with 2,5-Dimethylthiophene: 3-Diazopentane-2,4-dione (4g; 31.8mmole) was added dropwise to a stirred solution of rhodium acetate hydrate (25mg) in 2,5-dimethylthiophene (15ml). The solution was stirred overnight upon which the diazo absorption band (2120cm^{-1}) had disappeared in the i.r. Evaporation of solvent left a red crystalline mass of crude ylid, 2,5-dimethylthiophenium-bisacetylmethylide (51) (4.79g; 100%). m.p. 45°C, but did not solidify on cooling. δ ($CDCl_3$): 2.22 (6H,s), 2.45 (6H,s), 6.80 (2H,s). ν max ($CHCl_3$): 3550w, 3020w, 300w, 1725m, 1590vs, 1370vs, 1330vs, 1240m, 1020w, 910m, 820m. m/e: 210 (M+, 17.0%), 167 (79.0%), 125 (100%), 112 (93.7%). λ max (MeOH): 245nm (log ε 4.28), 270nm (log ε 4.10). Attempts to obtain a sample with correct microanalytical data failed. A sample was purified by column chromatography eluting with dichloromethane giving a

red:brown solid which could not be induced to crystallise using a variety of solvents (pet. ether, acetonitrile, dichloromethane and methanol).

3,4-Dimethylthiophene: Sulphur Dichloride (50g; 0.485mole) was added to a solution of 2,3-dimethylbuta-1,3-diene (25g; 0.305mole) in dichloromethane with 10% triethylamine (100ml). The solution was stirred for one hour. The mixture was filtered and washed with water (50ml) and the filtrate dried over anhydrous sodium sulphate. The excess solvent was evaporated off and the product distilled as a colourless liquid collecting the fraction 137-139°C (12.5g; 37%). δ ($CDCl_3$): 2.19 (6H,s), 6.94 (2H,s).

3-Diazopentane-2,4-dione with 3,4-Dimethylthiophene: 3-Diazopentane-2,4-dione (0.5g; 3.97mmole) was added to a solution of rhodium acetate hydrate (5mg) in 3,4-dimethylthiophene (4ml). The solution was stirred at room temperature for fourty eight hours before the diazo absorption band (2120cm^{-1}) had disappeared in the i.r. The thiophene was evaporated off to leave a brown oil which was submitted to prep. t.l.c. eluting with dichloromethane. Five bands were eluted the second one being the only one identified as the 2-thienyl adduct (52) obtained as a pale oil (51mg; 6%). δ ($CDCl_3$): 1.97s and 1.99s (9H), 2.22(3H,s), 6.99 (1H,s), 16.93 (1H,s) enolised methine; the molecule is 100% enolised. νmax ($CHCl_3$): 3550w, 3040m, 2980m, 1620vs, 1360m, 1260s, 940w, 905w, 710w. m/e: 210 (M+, 47.6%), 167 (92.5%), 111 (24%). λmax (MeOH): 250nm (log ε 4.05), 265nm (log ε 3.99). Found: C, 62.59; H, 6.60%; $C_{11}H_{14}O_2S$ requires C, 62.86; H, 6.67%.

Ethyl Diazoacetoacetate with Thiophene: Ethyl diazoacetoacetate (2g; 12.8mmole) was added slowly over an hour to a stirred refluxing solution of rhodium acetate hydrate (10mg) in thiophene (10ml). A sample analysed by i.r. showed that the diazo absorption band had

disappeared (2140cm^{-1}). The excess thiophene was evaporated off to leave a red oil (2.57g) which was submitted to column chromatography eluting with dichloromethane then dichloromethane with increasing amounts of ethyl acetate. Following an initial impurity band (26.3mg). The second band eluted was the 2-thienyl adduct, ethyl-3-oxo-2-(2´-thienyl)-butanoate (24), obtained as a yellow oil (1.62g; 60%). δ ($CDCl_3$): 1.30 (3H,t), 2.01 (2.25H,s) and 2.3 (0.75H,s) acetyl of enol and non-enol tautomers respectively , 4.26 (2H,q), 6.98 (1H,d,J=4Hz), 7.20 (1H,dd,J=4, 5Hz), 7.49 (1H,d,J=5Hz), 5.10 (0.25H,s) and 13.61 (0.75H,s) non-enol and enolised methine; the molecule is about 75% enolised. ν max ($CHCl_3$): 3550w, 3030m, 2980s, 2930m, 1720vs, 1640s, 1360m, 1400s, 1335vs, 1255vs, 1060vs, 920m, 850s, 695s. C^{13} δ ($CDCl_3$): 14.3q (C1), 20.2q (C6), 55.0d (C4), 60.0t (C2), 105.5s (C7), 93.3d 118.6d 134.9d (C8-10), 169.6s (C3), 204.3s (C5).

The third band eluted was the 2H-thiopyran, 2-ethoxycarbonyl-2-acetylthiacyclohexa-3,5-diene (54) a colourless oil (247mg; 9%). δ ($CDCl_3$): 1.32 (3H,t), 2.26 (3H,s), 4.23 (2H,q), 5.36 (1H,d,J=9Hz, C7-H), 5.67 (1H,dd,J=7, 3Hz, C9-H), 6.02 (1H,dd,J=9, 3Hz, C8-H), 6.64 (1H,d,J=7Hz, C10-H). Decoupling experiments: Irradiate 5.36 then 6.02 dd → d; Irradiate 5.67 then 6.02 dd → d and 6.64 d → s; Irradiate 6.02 then 5.36 d → s and 5.67 dd → d; Irradiate 6.64 then 5.67 dd → d. ν max ($CHCl_3$): 3030w, 2980m, 2930w, 1690s, 1640s, 1405m, 1380m, 1350m, 1080vs, 970m. C^{13} δ ($CDCl_3$): 14.1q (C1), 20.1q (C6), 60.9t (C2), 96.9s (C4), 126.4d 126.7d 127.1d 128.9d (C7-10), 176.9s (C3), 200.0s (C5). m/e: 212 (M+, 18.7%), 170 (58.4%), 167 (5.23%), 139 (11.6%), 97 (58.4%), 96 (39.2%). λ max (MeOH): 265nm (log ε 4.28).

The number of double bonds was determined by titration. The 2H-thiopyran (200mg; 0.943mmole) in dichloromethane (10ml) was added to

previously standardised Wij's solution (30ml, 0.188M, ICl in glacial acetic acid, standardised by thiosulphate titration). After being left to stand in the dark for thirty minutes 15% aqueous KI (10ml) was then added followed by water (50ml). The solution was titrated against (0.1M) sodium thiosulphate solution (previously standardised with potassium dichromate) using starch indicator with a permanent clear colour taken as the end point.

The ICl adds to the double bond hence 1mole 2H-thiopyran is equivalent to 2mole ICl. Therefore 200mg 0.943mmole 2H-thiopyran will require 1.886mmole ICl. Taking $ICl + KI \rightarrow KCl + I_2$, and $I_2 + Na_2S_2O_3 \rightarrow Na_2S_4O_6 + 2NaI$ it was found that the final solution required 77.3ml of 0.1M thiosulphate at the end point.

77.3ml 0.1M $Na_2S_2O_3$ = 1.221g = 7.728mmole = 3.864mmole I_2 = 3.864mmole ICl.

30ml of 0.188M ICl solution added contains 0.9165g or 5.64mmole ICl.

Therefore the 2H-thiopyran absorbed 5.64 - 3.864 = 1.776mmole ICl. 200mg of 2H-thiopyran required 1.886mmole ICl for two double bonds therefore the number of double bonds in the molecule is (1.776/1.886) x 2 = 1.88 double bonds (i.e. to be inferred as two double bonds).

Thiophene-2,5-d_2 [29]: Deuterium oxide (7.5ml) was slowly added to trifluoroacetic anhydride (15ml) to give a 20% solution of TFA-d. Thiophene (10ml) was stirred vigorously with half of the TFA-d under reflux overnight to give 75% deuteration at the 2,5 positions. Repeating the procedure with the remainder of the TFA-d gave 90% deuteration as determined by the ratio of the characteristic thiophene twin doublets centred at 7.14ppm, as opposed to the

singlet of the thiophene-d_2 at 7.17ppm. The final product was washed with water, dried over anhydrous sodium sulphate and distilled (84-85°C) to give a colourless liquid (5.2ml).

Ethyl Diazoacetoacetate with Thiophene-2,5-d : Ethyl diazoacetoacetate (1g; 6.4mmole) was added dropwise over half an hour to a stirred refluxing solution of rhodium acetate hydrate (10mg) in thiophene d_2 (5ml) after which the diazo absorption band (2140cm^{-1}) had disappeared in the i.r. The excess thiophene was evaporated off and retrieved to leave a red brown oil which was submitted to prep. t.l.c. eluting with 10% ethyl acetate in dichloromethane. The first band eluted was the 2-thienyl adduct, ethyl-2-(2´-thienyl)-3-oxo-butanoate -2,5´-d (55), obtained as a yellow oil (827mg; 60%). $\delta(CDCl_3)$: 1.24 (3H,t), 1.96 (1.50H,s) and 2.24 (0.50H,s) acetyl of enol and non-enol tautomers respectively, 2.23 (2H,q), 5.05 (0.20H,s), 6.85 (1H,d,J=3Hz), 7.05 (1H,d,J=3Hz), 13.47 (0.80H,s).

The second band eluted was the 2H-thiopyran, 2-carboethoxy-2-acetylthiacyclohexa-3,5-diene-3,6-d_2 (56), obtained as a red oil (147mg; 11%). $\delta(CDCl_3)$: Virtually identical to the spectrum of the protonated adduct except that only two vinyl signals were present 5.69 (1H,d,J=3Hz, C9-H), 6.04 (1H,d,J=3Hz, C8-H). $C^{13}\delta(CDCl_3)$: 14.2q (C1), 20.1q (C6), 59.9t (C2), 93.2s (C4), 127.4d 129.0d (C8,9), 176.4s (C3), 200.0s (C5).

Ethyl Diazoacetoacetate with 2-Methylthiophene: Ethyl diazoacetoacetate (1.1g; 7.05mmole) was added to a solution of rhodium acetate hydrate (10mg) in 2-methylthiophene (15ml). After stirring at room temperature for fourteen hours the diazo absorption band (2140cm^{-1}) had disappeared in the i.r. The excess thiophene was evaporated off to leave a grey solid which was the thiophenium ylid, 2-methylthiophenium-carboethoxy-acetylmethylide (57) (1.60g; 100%)

which when recrystallised from dichloromethane gave a white solid. m.p. 102°C (dec). $\delta(CDCl_3)$: 1.25 (3H,t), 2.27 (3H,s), 2.52 (3H,s, c.f. 2.60 in 2-methylthiophene), 4.17 (2H,q), 6.75 (1H,d,J=5Hz), 6.85 (1H,d,J=4Hz), 7.10 (1H,dd,J=5, 4Hz). m/e: 212 (M+, 24.3%), 169 (20.6%), 84 (33.1%). λ max (MeOH): 245nm (log ε 4.15), 270 (log ε 3.95).

A sample (1g) when submitted to prep. t.l.c. eluting with dichloromethane gave the purified ylid (735mg) plus 19.9mg (3%) of the 2-thienyl adduct (58) which was a pale oil. $\delta(CDCl_3)$: 1.29 (3H,t), 2.05 (1.5H,s) and 2.34 (1.5H,s) acetyl of enol and non-enol tautomers respectively, 2.59 (3H,s), 4.38 (2H,q), 5.05 (0.5H,s, methine), 6.85 (1H,d), 7.12 (1H,d), 13.7 (0.5H,s enol); the molecule is about 50% enolised. νmax ($CHCl_3$): 3030w, 2990w, 1725vs, 1660s, 1590s, 1390s, 1335s, 1250s, 1060vs, 920m, 850s, 695s. m/e: 226 (M+, 5.8%), 197 (2.6%), 183 (23.8%), 181 (8.1%), 97 (52.2%). ν max (MeOH): 245nm (log ε 4.29). Found: C, 58.62; H, 6.21%; $C_{11}H_{14}O_2S$ requires C, 58.41; H, 6.19%.

The reaction was repeated by adding the diazo compound dropwise to a refluxing solution of rhodium acetate in thiophene. A work-up on prep. t.l.c., after the diazo absorption band had disappeared, gave the 2-thienyl adduct in 96% yield.

Ethyl diazoacetoacetate with 3,4-Dimethylthiophene: Ethyl diazoacetoacetate (1g; 6.41mmole) was added to a solution of rhodium acetate hydrate (10mg) in 3,4-dimethylthiophene (10ml). After stirring at room temperature for seventeen hours the diazo absorption band (2140cm^{-1}) had disappeared in the i.r. The excess thiophene was evaporated off to leave a purple solid which was the crude ylid, 3,4-dimethylthiophenium- ethoxycarbonyl-acetylmethylide (59), (1.54g, 100%). 500mg of this material was submitted to prep.

t.l.c. eluting with dichloromethane. Six bands were eluted four of which were of low weight and gave complex spectra. The sixth band was purified ylid (59) (448.4mg; 90%). m.p. 75-77°C. $\delta(CDCl_3)$: 1.20 (3H,t), 2.13 (6H,s), 2.41 (3H,s), 4.06 (2H,q), 6.57 (2H,s). ν max ($CHCl_3$): 3030m, 2985s, 1720vs, 1640s, 1360m, 1410s, 1345m, 1250s, 1055s, 915m. m/e: 240 (M+, 22.7%), 197 (3.3%), 195 (7.7%), 194 (56.3%), 167 (8.9%), 129 (30.0%), 113 (20.2%), 112 (5.3%), 111 (24.0%). λmax (MeOH): 270nm (log ϵ 4.20).

The first band was the 2-thienyl adduct (60) obtained as a colourless oil (21.3mg; 2.8%). $\delta(CDCl$): 1.22 (3H,t), 1.89 (3H,s), 1.93 (3H,s), 2.17 (3H,s), 4.21 (2H,q), 6.86 (1H,s), 13.28 (1H,s). ν max ($CHCl_3$): 3020w, 2980m, 1720s, 1640s, 1360m, 1410m, 1340m, 1245vs, 1055s, 910m, 845m. m/e: 240 (M+, 39.5%), 198 (25.9%), 194 (100%), 157 (80.7%), 152 (75.6%), 139 (56.8%), 129 (57.2%), 124 (55.6%). max (MeOH): 250nm (log ϵ 4.15).

Thermal Rearrangement of 3,4-Dimethylthiophenium-carboethoxy-acetylmethylide: Two reactions were performed. i). The ylid (100mg; 0.417mmole) in benzene (5ml) was refluxed until no further change was observed with analytical t.l.c. Submission of the crude product to t.l.c. eluting with dichloromethane afforded the 2-thienyl adduct in 60% yield (60.1mg). ii). The reaction was repeated in the presence of rhodium acetate hydrate (5mg); the 2-thienyl adduct was furnished quantitatively (100mg).

2-Diazodimedone (49) with Thiophene: 2-Diazodimedone (5g; 30.1mmole) was added to a solution of rhodium acetate hydrate (50mg) in thiophene (60ml). The solution was stirred at room temperature overnight upon which the diazo absorption band had disappeared in the i.r. (2140cm^{-1}). The excess thiophene was evaporated off to leave a crude white solid which was the 2-thienyl adduct (50) (672mg; 100%) which was recrystallised from 1:1 chloroform :

methanol. m.p. 68-69°C. δ(DMSO-d_6): 1.07 (6H,s), 2.47 (4H,s), 4.50 (1H,s), 7.00 (1H,dd,J=4, 6Hz), 7.30 (1H,d,J=6Hz), 7.68 (1H,d,J=4Hz). The molecule appears to be 100% non-enolised. νmax (nujol mull): 1725s, 1570w, 1305m, 1155m, 1030m. m/e: 222 (M+, 15.8%), 192 (1.8%), 139 (17.8%). λmax (MeOH): 270nm (log ϵ 3.79), 300 (log ϵ 3.85). Found: C, 64.99; H, 6.50%; $C_{12}H_{13}O_2S$ requires C, 64.86; H, 6.31%.

Ethyl Diazobenzoylacetate (61): Ethyl benzoylacetate (3g; 15.6mmole) was added to a stirred suspension of carboxybenzene-4-sulphonyl azide (4.25g; 18.73mmole) in methanol (50ml). This was followed by dropwise addition of triethylamine (3.78g; 37.5mmole) upon which the azide went into solution. The solution was stirred overnight at room temperature protected from light. The methanol was evaporated off to leave a slurry of white crystals which were taken up in dichloromethane (300ml) and filtered. The filtrate was washed with 0.5M NaOH and then with water. The aqueous washings were then further extracted with dichloromethane. The filtrate and dichloromethane extracts were combined, dried over anhydrous sodium sulphate and evaporated to dryness to leave a green liquid (3.22g; 95%). δ($CDCl_3$): 1.25 (3H,t), 4.27 (2H,q), 7.3-7.8 (5H,m). νmax ($CHCl_3$): 3040w, 2980w, 2140vs, 1620s, 1720vs, 1445w, 1370s, 1270s, 1170m, 1115s, 940 and 920m.

Ethyl Diazobenzoylacetate with Thiophene: Ethyl diazobenzoylacetate (2.9g; 13.3mmole) was added dropwise over half an hour to a refluxing solution of rhodium acetate hydrate (10mg) in thiophene (15ml). After seven hours the diazo absorption band (2140cm^{-1}) had disappeared in the i.r. The excess thiophene was evaporated off to leave a red oil (3.69g) which was submitted to column chromatography eluting with dichloromethane. Following an initial small impurity band the second band eluted was the 2-thienyl

adduct, ethyl-3-oxo-3-phenyl-2(2´-thienyl)propanoate (62), which was an oil (3.20g; 88%). The oil was distilled at 220°C (2mm Hg) which crystallised on standing. m.p. 88-89°C. $\delta(CDCl_3)$: 1.22 (3H,t), 4.28 (2H,q), 5.96 (0.95H,s), 6.98-7.20 and 7.2-7.6 (8H,m), 13.84 (0.05H,s) the molecule is about 5% enolised). νmax ($CHCl_3$): 3080w, 3030w, 2980m, 1740vs, 1690vs, 1600s, 1450m, 1370m, 1265vs, 1090m, 1020m, 910m, 835m. C^{13} $\delta(CDCl_3)$: 14.0q (Cl), 55.5d (C4), 62.23t (C2), 126.9d 127.5d 128.0d 129.1d 129.8d 134.0d (C7-9, 11-13), 131.0s 134.0s (C6,10), 168.3s (C3), 192.4s (C5). m/e: 274 (M+, 7.5%), 229 (1.6%), 228 (8.4%), 201 (1.4%), 105 (100%). λmax (MeOH): 210nm (log ε 4.43), 245nm (log ε 4.54). Found: C, 65.72; H, 5.12%; $C_{15}H_{14}SO_3$ requires C, 65.69; H, 5.11%.

Diphenyl Diazomethane (63) [47]: I). Hydrazine hydrate (2.34g; 46.8mmole) was added to benzophenone (5g; 27.5mmole) in absolute ethanol (30ml). The mixture was refluxed overnight. The bulk was reduced to 10ml upon which white crystals of benzophenone hydrazone appeared. The solution was cooled in an ice bath, filtered and the white crystals dried under vacuum (2.33g; 92%). $\delta(CDCl_3)$: 5.49 (2H,s, exchanged with D_2O), 7.36 7.52 (10H,m). ν max ($CHCl_3$): 3410m, 3060m, 2995s, 1660m, 1610m, 1590s, 1495s, 1440s, 695vs, 650vs.

II). Anhydrous sodium sulphate (2.31g) and absolute ethanol saturated with KOH (0.8ml) was added to benzophenone hydrazone (2.00g; 10.2mmole) in dry ether (31ml). The solution was stirred vigorously and mercuric oxide (5.39g; 24.8mmole, Hopkin and William´s) was then added. The solution was stirred rapidly for eighty minutes maintaining the oxide suspension. The solution was then filtered and the ether evaporated off. The residue was taken up in 40-50 pet. ether, refiltered and evaporated to dryness to leave red crystals (1.96g; 99%). m.p. 29-30°C (lit. 29-32). $\delta(CDCl_3$): 7.17 m. ν max: 3050w, 2140vs, 1590w, 1490m, 1265vs, 1210vs, 800-

700s.

Diphenyl Diazomethane with Thiophene: Diphenyl diazomethane (500mg; 2.58mmole) was added dropwise to a stirred refluxing solution of rhodium acetate hydrate (5mg) in thiophene (5ml). After one hour the diazo absorption band had disappeared in the i.r. The solution was evaporated to dryness to leave a brown oil (592mg) which was submitted to prep. t.l.c. eluting with dichloromethane. Many bands were eluted, but the only one which was identified was the azine of the diazo compound (64) (412mg). Found: C, 86.97; H, 5.62; N, 8.05%; $C_{26}H_{20}N_2$ requires C, 86.67; H, 5.56; N, 7.78%.

2,4-Bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide (Lawesson's Reagent) (73) [35]: A solution of phosphorus pentasulphide (20g; 42mmole) in anisole (200ml) was refluxed overnight. With cooling pale yellow crystals of the product appeared which were recrystallised from toluene (25.3g; 75%). m.p. 228-230°C, (lit. 227). δ(Pyridine-d_5): 3.69 (6H,s), 6.73-7.10 (4H,m), 8.40-8.85 (4H,m). νmax (nujol mull): 1985m, 1580m, 1560m, 1290m, 1260m, 1170m, 1080m, 830w, 790w.

Diphenylthione: Lawesson's reagent (540mg; 1.34mmole) was added to a solution of benzophenone (200mg; 1.10mmole) in sodium dry toluene (40ml). After stirring as a suspension at room temperature overnight, there was no noticeable change in the carbonyl stretch in the i.r. The mixture was then stirred at 80 C for thirty minutes following the reaction on analytical t.l.c. Evaporation of the toluene gave deep blue crystals (214mg; 98%). m.p. 53-54°C (lit [48], 53-54°C). νmax ($CHCl_3$): 3040w, 2970w, 2970w, 1595s, 1500m, 1460m, 1300s, 1260s, 1180m, 1120vs (missing in i.r. of benzophenone), 1020m, 930vs, 690s, 720s.

3-Diazopentane-2,4-dione with Furan: 3-Diazopentane-2,4-dione (500mg; 0.24mmole) was added dropwise with stirring to a solution of rhodium acetate hydrate (5mg) in furan (10ml). After stirring at room temperature for twelve hours the diazo absorption band (2120cm^{-1}) had disappeared in the i.r. The excess furan was evaporated off to leave a brown oil (558mg) which was submitted to prep. t.l.c. eluting with dichloromethane. Seven bands were obtained which all gave complex spectra with the exception of the fifth one which was the dienal, 5-acetyl-6-oxo-hepta-2,4-dienal, obtained as a colourless oil (105.4mg; 16%) which was a mixture of cis and trans isomers (79a, 79b) (70% cis, 30% trans). $\delta(CDCl_3)$: 2.46 (6H,s), 6.1-6.6 (2H,m), 7.0-7.4 (1H,m), 7.9-8.1 (1H,m), 9.78 (0.3H,d,J=7Hz), 10.39 (0.7H,d,J=7Hz). νmax: 3030m, 3010m, 2920w, 1680vs, 1670vs, 1620m, 1580m, 1420w, 1360m, 1255m, 1105m, 1010m, 960m. λmax (MeOH): 265nm (log ε 4.25). Both isomers had very similar rf values. Attempts to separate them by prep. t.l.c. did not succeed.

The reaction was repeated on a 100mg scale. Using benzaldehyde (98mg) (aldehyde-H = 10.00ppm) as an internal standard the proton n.m.r. of the crude reaction material showed that the dienal was produced in about 15% yield and was entirely the cis isomer. The reaction was repeated on a 1g scale with an estimated yield of about 8%. On a 2.5g and 3g scale very little (<2%) of dienal was observed (in all cases purely the cis isomer).

Ethyl Diazoacetoacetate with Furan: Ethyl diazoacetoacetate (253mg; 1.62mmole) was added to a stirred solution of rhodium acetate hydrate (5mg) in furan (5ml). The diazo absorption band (2140cm^{-1}) had disappeared in the i.r. after stirring at room temperature for twenty hours. The excess furan was evaporated off to leave a green oil (312mg) which was submitted to prep. t.l.c. eluting with a 10% solution of ethyl acetate in dichloromethane.

The third band eluted was the dienal product (18.6mg; 6%) obtained as a colourless oil. $\delta(CDCl_3)$: 1.42 (3H,t), 2.44 (3H,s), 4.40 (2H,q), 6.3-6.6 (2H,m), 7.2-7.6 (2H,m) 9.7 (0.3H,d,J=8Hz), 9.74 (0.7H,d,J=8Hz). νmax ($CHCl_3$): 3060m, 3020s, 2980m, 1720s, 1690s, 1520s, 1420s, 1210vs, 1045s, 920m. λmax (MeOH): 270nm (log ε 4.30). Analytical t.l.c. gave four spots close together indicative of the ZZ, ZE, EZ and EE isomers.

The sample was stirred with a slight excess of Lawesson's reagent (50mg) in pyridine (5ml) at reflux for thirty minutes. Evaporation of solvent and submission to prep. t.l.c. eluting with dichloromethane afforded no product relating to 2-acetyl-2-carboethoxy-thiacyclohexa-2,4-diene (54).

2-Diazodimedone with Furan: 2-Diazodimedone (500mg; 3.01mmole) was added to a solution of rhodium acetate hydrate (10mg) in furan (10ml). After stirring at room temperature for seventeen hours the diazo absorption band (2140cm^{-1}) had disappeared in the i.r. The excess thiophene was evaporated off to leave a brown oil. The crude n.m.r. was complex with only a small doublet (10.02ppm) corresponding to the dienal (80) the integral for which indicated that the required product was in very low yield. 50mg of Lawesson's reagent in pyridine (10ml) was added and after thirty minutes reflux no product corresponding to a 2H-thiopyran derivative was observed.

Benzhydryl-6-diazopenicillanate (37) [21]: 1M Perchloric acid (12ml) was added to an ice cold two-phase system of benzhydryl-6-aminopenicillanate (2.18g; 5.6mmole) in dichloromethane (400ml) and sodium nitrite (0.93g; 13mmole) in water (400ml). The bulk was shaken vigorously for five minutes after which the bright yellow dichloromethane layer was separated, washed with dilute sodium bicarbonate solution, dried over anhydrous sodium sulphate and

evaporated to dryness to leave a bright yellow foam (2.15g; 96%). m.p. 86-87°C; (lit, 85-87°C). $\delta(CDCl_3)$: 1.24 (3H,s, C9-H), 1.63 (3H,s, C8-H), 4.80 (1H,s, C2-H), 6.17 (1H,s, C5-H), 6.91 (1H,s, C11-H), 7.35 (10H,m, aromatic H). ν max ($CHCl_3$): 3020m, 2090vs, 1755s. λ max (MeOH): 514nm (log ε 5.14), 218nm (log ε 5.08).

Benzhydryl-6-diazopenicillanate with Furan [21]: Benzhydryl-6-diazopenicllanate (2g; 5.09mmole) was added to a solution of rhodium acetate hydrate (15mg) in furan (25ml). The diazo absorption band (2090cm^{-1}) disappeared in the i.r. after stirring at room temperature for two hours. The excess furan was evaporated off to leave a yellow solid (100%), m.p. 54-59°C, which was a 2:1 mixture of ZE and ZZ isomers of the 6-dienal penicillanate (72a, 72b). $\delta(CDCl_3)$: The penicillin peaks had virtually the same chemical shift as above. Additional multiplets were at 6.14 (1H,dd,J=12 and 5Hz), 7.24 (obscured by aromatic multiplet), 7.66 (1H,d,J=10Hz), 10.12 and 10.16 (total 1H, each d, J=8Hz). ν max ($CHCl_3$): 3090w, 3030w, 1765s, 1740vs, 1675s.

Benzhydryl-6-dienalpenicllanate with Lawesson's reagent: Lawesson's reagent (11.4g; 3.46mmole) was added to a solution of benzhydryl-6-dienalpenicillanate (1g; 2.31mmole, mixture of isomers from previous experimental) in dry toluene (25ml). The solution was refluxed for one hour and then the excess toluene evaporated off to leave a brown oil (1.12g) which was submitted to prep. t.l.c. eluting with dichloromethane. The first band was the impure 2H-thiopyran (39) obtained as an oil (161mg; 14%) which was repurified on prep. t.l.c. (obtained 132mg of pure product). $\delta(CDCl_3)$ (250MHz): 1.28 (3H,s, C9-H), 1.62 (3H,s, C8-H), 4.54 (1H,s, C2-H), 5.34 (1H,s C5-H), 5.76 (1H,d,J=10Hz, C21-H), 6.25 (2H,m, C19,20-H), 6.37 (1H,d,J=9Hz, C18-H), 7.34 (10H,m, C12-H). Nuclear Overhauser differences were observed between C21-H and C8-H on irradiation of

C8-H. νmax ($CHCl_3$): 1775s, 1740s. λ max (MeOH): 215nm (log ϵ 4.15).

EE-hexa-2,4-dienal with Lawesson's Reagent: To a solution of hexadienal in dry T.H.F. (150ml) was added Lawesson's reagent (6.3g; 15.6mmole) which went into solution on reflux. The reaction was followed by analytical t.l.c. and after one hour the starting material spot had disappeared (rf 0.75 in dichloromethane). The product mixture was distilled. The temperature was increased and after collecting the THF (67°C) the residual black tar was heated to 180°C but no product was collected. An n.m.r. of the THF fraction did not show any presence of 2H-thiopyran.

Standardisation of Alkyl Lithiums: To a solution of diphenylacetic acid (0.5g; 2.358mmole), in dry THF (10ml), stirred under nitrogen, was added dropwise from a syringe the alkyl lithium (methyl or n-butyl). The solution first went cloudy due to the precipitation of lithium diphenylacetate. Addition was continued dropwise until a permanent yellow occured in the solution indicative of the anion of the diphenylacetate. The volume of alkyl lithium added was noted and hence the molarity of the solution could be determined (i.e. 2.358mmole of alkyl lithium had been added to completely generate the diphenylacetate).

2-Phenylbenzoic acid with i). Alkyllithium and ii). Lawesson's Reagent: To a solution of 2-phenylbenzoic acid (1g; 5.03mmole) in dry THF at -90°C under dry nitrogen was added dropwise over five minutes 1.00M n-butyllithium in hexane (5.03ml, 322mg, 5.03mmole). The solution was stirred and allowed to warm to room temperature. The excess solvent was evaporated off to leave a colourless oil, 1'-oxopentyl-2-phenylbenzene (84), (1.20g; 100%). δ($CDCl_3$): 0.70 (3H,t), 1.00 (2H,s), 1.32 (2H,p), 2.21 (2H,t), 7.29 (9H,m). ν max ($CHCl_3$): 3020w, 2980m, 2930w, 1690vs, 1600s, 1345m, 1210m, 760m, 705w. m/e: 238 (M+, 4.7%), 181 (100%), 179 (3.9%), 152 (29.3%), 151

(7.0%), 76 (3.3%).

1g (4.20mmole) of the product was then added to a solution of Lawesson's reagent (2.55g; 6.3mmole) in pyridine. After stirring at room temperature for eighteen hours no further change was observed on analytical t.l.c. (dichloromethane). The excess pyridine was evaporated off and the brown product extracted with dichloromethane. The resulting brown solution was evaporated to dryness to leave a brown solid which was submitted to prep. t.l.c. eluting with a 10% solution of ethyl acetate in dichloromethane. The first band eluted was the thione (85) (672mg; 63%) obtained as a yellow solid. m.p. 57-59.5°C. $\delta(CDCl_3)$: 0.80 (3H,t), 1.20-1.55 (6H,m), 7.72 (9H,m). ν max ($CHCl_3$): 3030w, 2980m, 2930w, 1455m, 1380m, 1210m, 1110s, 760m, 705w. m/e: 254 (M+, 8.2%), 197 (5.8%), 177 (2.5%). Found: C, 80.09; H, 7.09%; $C_{17}H_{18}S$ requires C, 80.31; H, 7.09%. There was no evidence of a cyclisation product.

The reaction was repeated using methyllithium in ether. The procedure was identical with the final thioacetyl product being separated in 52% yield. m.p. 53-55°C. $\delta(CDCl_3)$: 1.05 (3H,s), 7.75 (9H,m). νmax ($CHCl_3$): 3030w, 2980m, 2930w, 1455m, 1380m, 1360s, 1210m, 1115s, 760m. m/e: 212 (M+, 15.1%), 197 (1.1%), 153 (16.0%).

2-Chlorostyrene with i). Methyllithium, ii). Acetyl Chloride:

1.00M n-Butyllithium in hexane (21.7ml, 21.7mmole) was added to a solution of 2-chlorostyrene (3g; 21.7mmole) in dry THF at -80°C. The solution was stirred for half an hour after which acetyl chloride (1.70g; 21.7mmole) was added. The solution was allowed to warm to room temperature and left for an hour. The excess THF was evaporated off to leave a gum with the characteristic smell of polystyrene. An n.m.r. of the crude product was complex with little evidence for the desired product, 2-acetylstyrene (88).

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CHAPTER THREE.

Studies with Chiral Catalysts for Asymmetric Cyclopropanation.

"Therefore do not throw away your confidence, which has a great reward." (Hebrews 10.35).

3.1. Literature Review on Asymmetric Induction Organic Reactions.

3.1.1. Introduction.

Many forms of isomerism exist but the one that has caused the greatest interest is that of optical isomerism. Any asymmetric carbon atom, i.e. one which is attached to four different groups, displays optical isomerism as seen by the structures of lactic acid (1) and (2) (scheme 1). They are mirror images which cannot be superimposed upon each other, i.e. they are enantiomers. Unlike other forms of isomerism, normally the only way the two structures physically differ is in the way that they affect the plane of polarised light which is passed through the compound. One turns the plane clockwise (i.e. dextrorotary or d) and the other anticlockwise (i.e. laevorotatory or l), although this simple property cannot be directly corollated with one specific absolute configuration. Enantiomers are identical in all other physical properties and in their chemical behaviour. Hence enantiomers are often difficult to separate from a racemic mixture and the synthesis of a specific enantiomer often relies on an optically pure starting material or some alternative novel approach. Often in a synthesis of an enantiomeric product the step which transfers the chirality to the molecule is the most critical.

Interest in optical isomerism is more than academic curiosity since in many cases optically pure products are required. Many enzymes in nature work upon and produce one specific enantiomer. Thus many chemicals related to biochemistry are required as a specific enantiomer. In many areas the need for optical purity is important, alkaloids (3) (scheme 2) such as morphine, codeine and heroin being examples. R-Anordrin (4) [1] is a very active female oral contraceptive, whereas the S-enantiomer is inactive, hence for

the drug to be most effective the absolute stereochemistry must be provided for in a synthesis. These are a few examples of an enormous area with many implications and hence many chemists have studied methods of obtaining and synthesising optically pure products, some of whose efforts have been looked at in reviews [2-4].

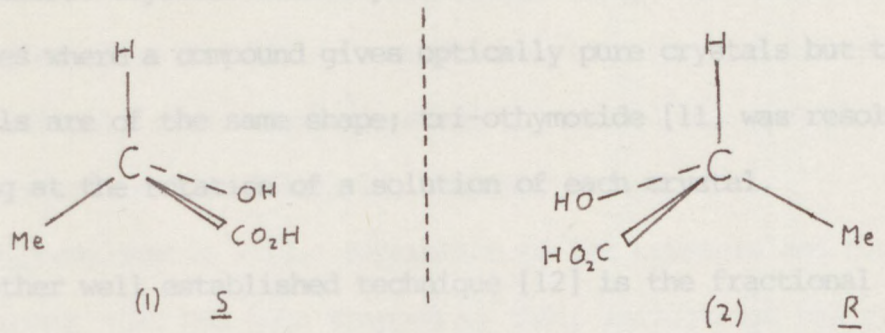
A usual approach is to use optically active synthons in producing a molecule and thus avoiding the need to create new chiral centres in the molecule. An alternative is to use asymmetric synthesis whereby an enantiomer is produced in excess starting with optically inactive starting materials. Asymmetric syntheses have been defined [5] as "Those reactions which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical processes". The definition recognises that in an asymmetric synthesis, where an optically active product is made from optically inactive starting materials, an optically active intermediate is needed, be it another part of the molecule, an optically active solvent, reagent or catalyst. Attempts [6] have been made at "absolute asymmetric synthesis" where there is no chiral intermediacy but repeated failure has supported the generally accepted view that such a reaction is impossible. Indeed it has been stated [7] that, "No optically active material can be created if all starting materials and conditions are optically inactive." It is now accepted that for asymmetric synthesis to occur there must be some involvement by some optically active intermediate. However an alternatively accepted view is that absolute asymmetric synthesis can occur if there is an external "chiral force" on the reaction, but there must be no chiral chemical intermediate. Plane polarised light [8] has been used for this purpose, but only slight rotations (less than 1°) have been observed.

In considering asymmetric synthesis there are many additional examples of steric control. For example [9], the 19-methyl in the steroid, 3-oxo-cholestane (5) is in an S-configuration with the methyl above the β-face of the A-ring. Reduction of the carbonyl in the 3-position with sodium borohydride gives 3-hydroxy-cholestane. The 3-position is now a new asymmetric carbon with a 74% excess of the R-configuration. This is due to the steric constraint of the 19-methyl over the β-face hindering approach of the borohydride from this direction (scheme 3). However, although there is a diastereomeric excess in this reaction, the resulting product is not a mixture of enantiomers but of diastereomers. Hence asymmetric synthesis by this approach needs the destruction of an asymmetric centre in a synthesised diastereomer or otherwise it is a special case of steric control.

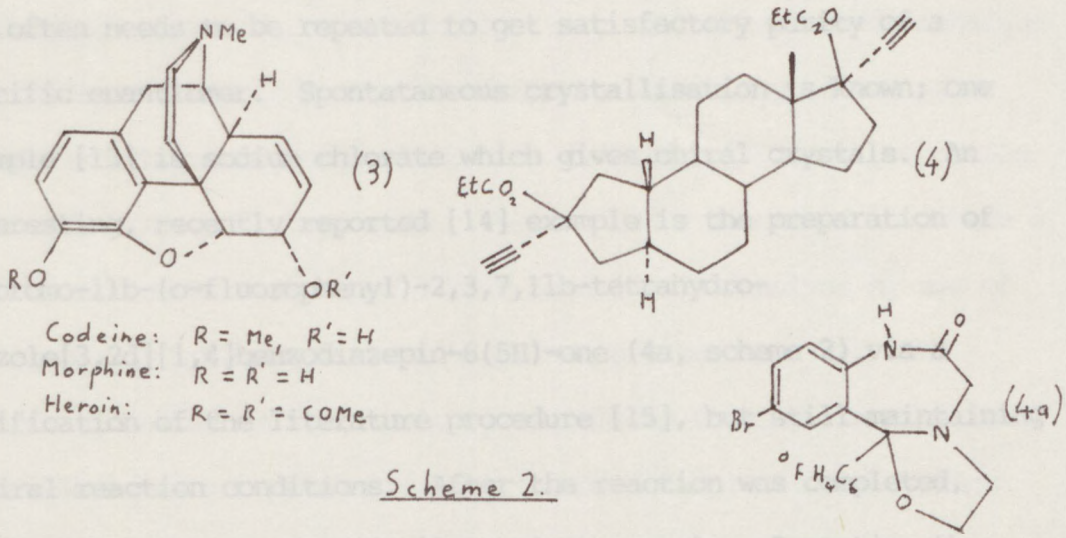
Several methods of asymmetric synthesis have been established.

3.1.2. Physical Methods of Obtaining Enantiomers.

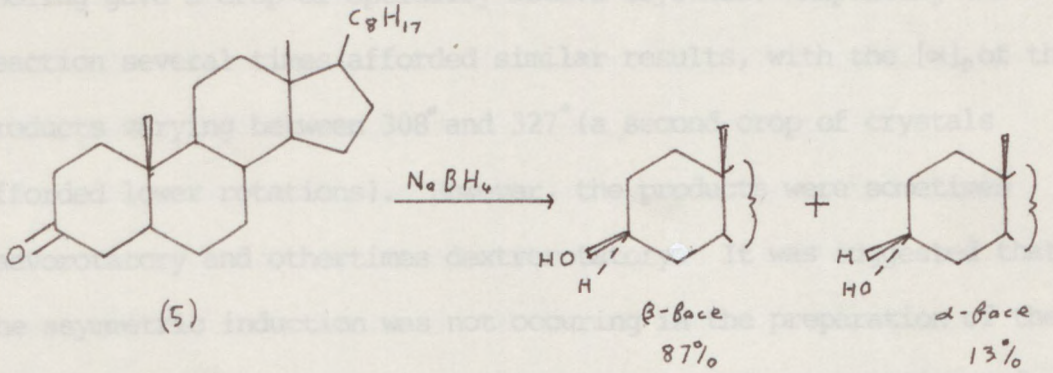
To physically separate enantiomeric crystals from each other is the oldest method for obtaining an optically active compound. Sometimes a racemic product will crystallise to produce crystals of one specific enantiomer. However such examples are rare. Heptahelicenes [10] can be separated by this method into the enantiomeric M and P isomers (6a,6b) (scheme 4). The crystal of the P-enantiomer has a shape which is a mirror image of the M-enantiomer and can be separated manually by looking at each crystal. However the technique is laborious often needing a microscope to see the crystal structure and their manual separation requires care of judgment and well grown crystals. Often in such cases the crystals will only crystallise into enantiomeric crystals under special conditions. For example, sodium ammonium tartrate will only give



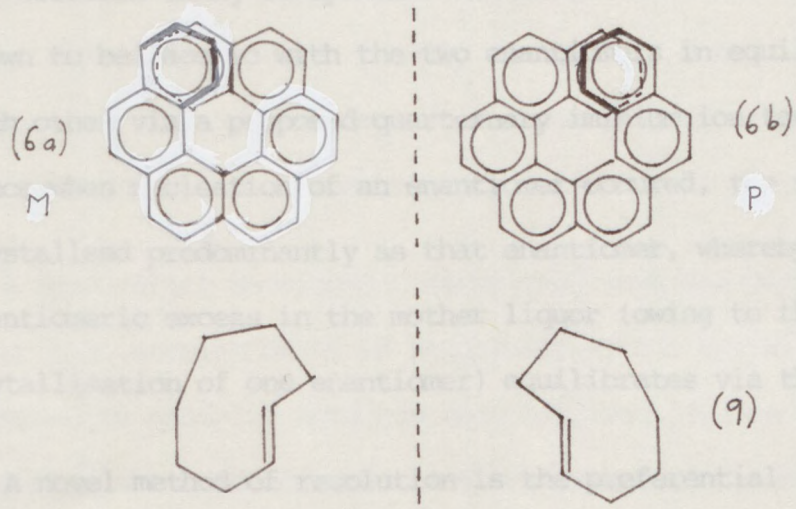
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

enantiomeric crystals when crystallised below 27°C. There are examples where a compound gives optically pure crystals but the crystals are of the same shape; tri-othymotide [11] was resolved by looking at the rotation of a solution of each crystal.

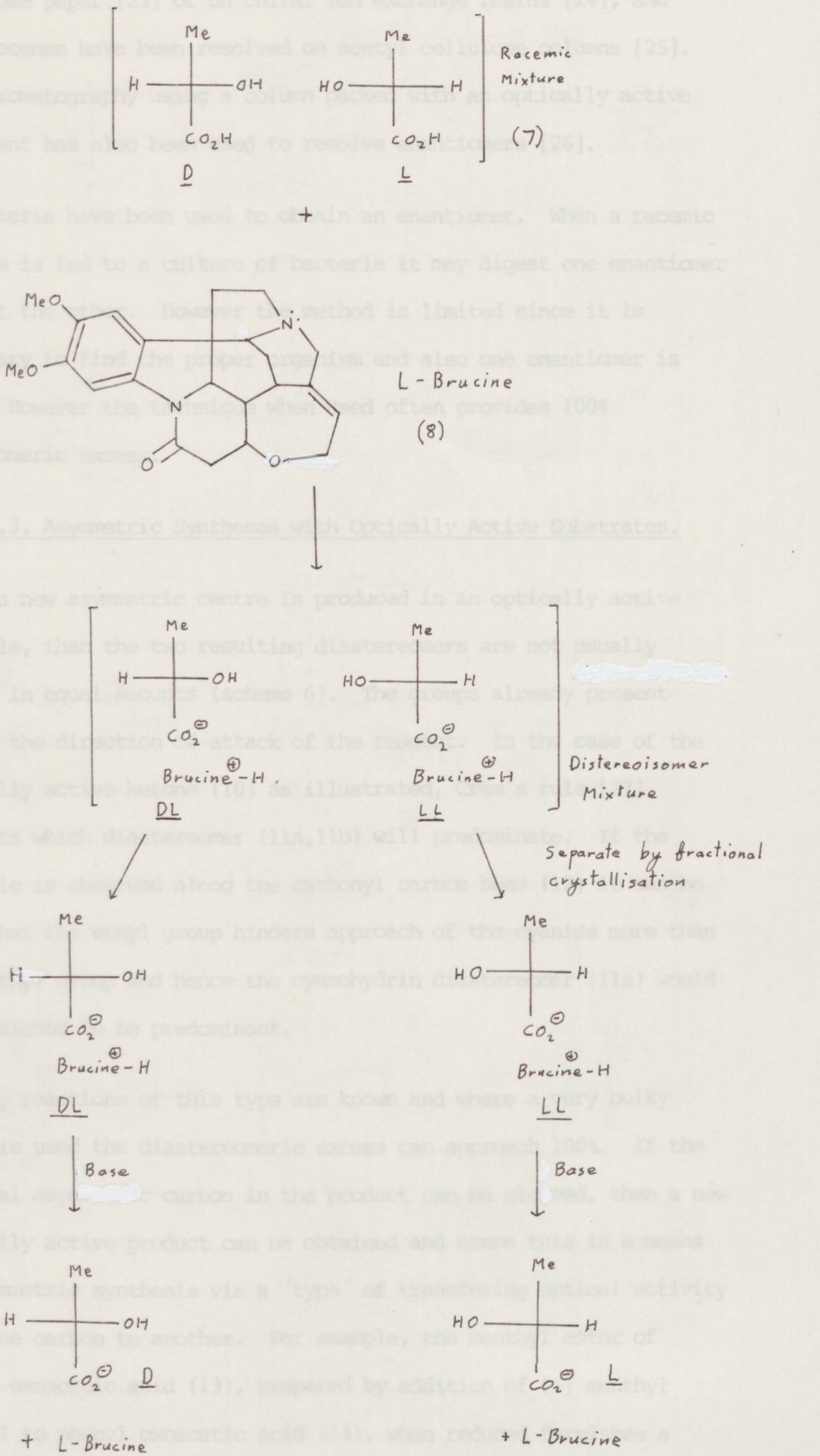
Another well established technique [12] is the fractional recrystallisation of an enantiomer from a solution of the racemate by seeding with a specific enantiomer. Such a process requires care and often needs to be repeated to get satisfactory purity of a specific enantiomer. Spontataneous crystallisation is known; one example [13] is sodium chlorate which gives chiral crystals. An interesting, recently reported [14] example is the preparation of 10-bromo-11b-(o-fluorophenyl)-2,3,7,11b-tetrahydro-oxazole[3,2d][1,4]benzodiazepin-6(5H)-one (4a, scheme 2) via a modification of the literature procedure [15], but still maintaining achiral reaction conditions. After the reaction was completed, cooling gave a crop of optically active crystals. Repeating the reaction several times afforded similar results, with the $[\alpha]_D$ of the products varying between 308° and 327° (a second crop of crystals afforded lower rotations). However, the products were sometimes laevorotatory and othertimes dextrorotatory. It was suggested that the asymmetric induction was not occuring in the preparation of the product, but was occuring via crystallisation of one enantiomer from the solution owing to spontaneous nucleation. The mother liquor was shown to be racemic with the two enantiomers in equilibrium with each other via a proposed quarternary iminium ion tautomerism. Hence when nucleation of an enantiomer occured, the racemic mixture crystallsed predominantly as that enantiomer, whereby the growing enantiomeric excess in the mother liquor (owing to the crytallisation of one enantiomer) equilibrates via this tautomerism.

A novel method of resolution is the preferential incorporation of

one enantiomer in an inclusion compound. Many crystals have chiral type interstices in which one enantiomer of a racemic solvent preferentially fits. For example [16], the polymer cyclodextrin has been crystallised in 2-methyl-, chloro-, bromo- or hydroxyphenylacetic acid. Separation of the crystals and recovering the solvent that has been trapped in their interstices has given the R-enantiomer in a 3-12% enantiomeric excess.

Chemical means of resolution is a very well established technique whereby a racemate is converted to diastereomers (by adding an optically active compound) which have different physical properties and hence are easily separated. The method is described in scheme 5 whereby a racemic mixture of lactic acid (7) is resolved by use of the naturally occuring optically active base brucine (8). The method is limited in that the compound chosen to give the mixture of diastereomers must add exclusively to the molecule in the correct position and must be able to be removed to regenerate the enantiomer. Also the mixture of diastereomers often needs to be fractionally crystallised several times for good separation. However many important resolutions have been achieved using the technique which has been thoroughly discussed [12,17-19]. For example, trans cyclooctene (9) (scheme 4) was resolved [20] by conversion to a platinum complex containing an optically active amine. Fortunately many optically active bases occur naturally (e.g. alkaloids) and are readily available. Other methods for separation of diastereoisomers have been studied; an example is the use of vapour phase chromatography [21].

A more recent development where much work has been done is to use selective association of an enantiomer with a chiral adsorbant. For example, DL mandelic acid has been resolved [22] on amylose and starch columns, amino acids have been resolved by chromatography on


Me
H
OH
CO2H
D
Me
HO
H
CO2H
L
Racemic Mixture
(7)
+
MeO
MeO
N
O
O
L-Brucine
(8)
Me
H
OH
CO2⊖
Brucine⊕-H
DL
Me
HO
H
CO2⊖
Brucine⊕-H
LL
Distereoisomer Mixture
Separate by fractional crystallisation
Me
H
OH
CO2⊖
Brucine⊕-H
DL
Me
HO
H
CO2⊖
Brucine⊕-H
LL
Base
Base
Me
H
OH
CO2⊖
D
Me
HO
H
CO2⊖
L
+ L-Brucine
+ L-Brucine

Scheme 5.

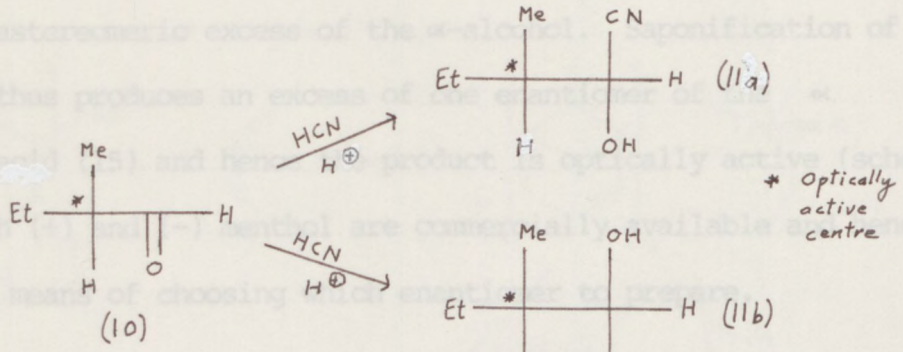
cellulose paper [23] or on chiral ion exchange resins [24], and metallocenes have been resolved on acetyl cellulose columns [25]. Gas chromatography using a column packed with an optically active absorbent has also been used to resolve enantiomers [26].

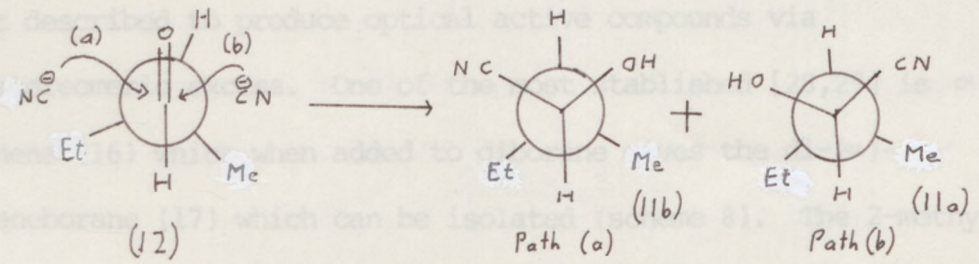
Bacteria have been used to obtain an enantiomer. When a racemic mixture is fed to a culture of bacteria it may digest one enantiomer and not the other. However the method is limited since it is necessary to find the proper organism and also one enantiomer is lost. However the technique when used often provides 100% enantiomeric excess.

3.1.3. Asymmetric Syntheses with Optically Active Substrates.

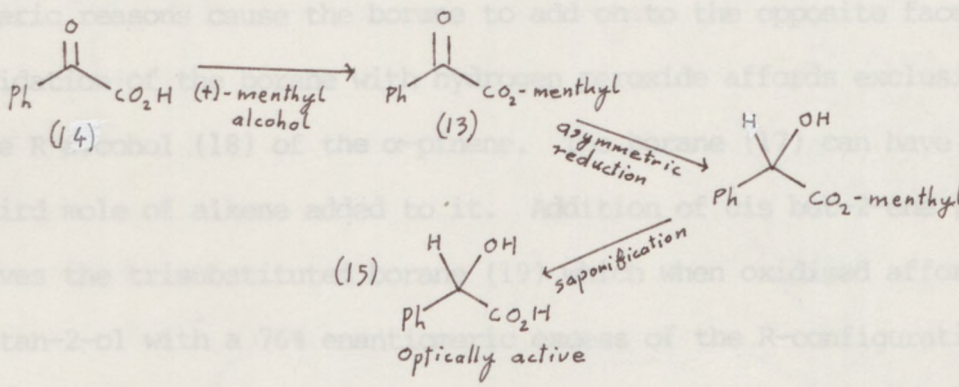
If a new asymmetric centre is produced in an optically active molecule, then the two resulting diastereomers are not usually formed in equal amounts (scheme 6). The groups already present direct the direction of attack of the reagent. In the case of the optically active ketone (10) as illustrated, Cram´s rule [27] predicts which diastereomer (11a,11b) will predominate. If the molecule is observed along the carbonyl carbon bond (12) it can be seen that the ethyl group hinders approach of the cyanide more than the methyl group and hence the cyanohydrin diastereomer (11a) would be predicted to be predominant.

Many reactions of this type are known and where a very bulky group is used the diastereomeric excess can approach 100%. If the original asymmetric carbon in the product can be cleaved, then a new optically active product can be obtained and hence this is a means of asymmetric synthesis via a ´type´ of transfering optical activity from one carbon to another. For example, the menthyl ester of phenyl oxoacetic acid (13), prepared by addition of (+) menthyl alcohol to phenyl oxoacetic acid (14), when reduced furnishes a

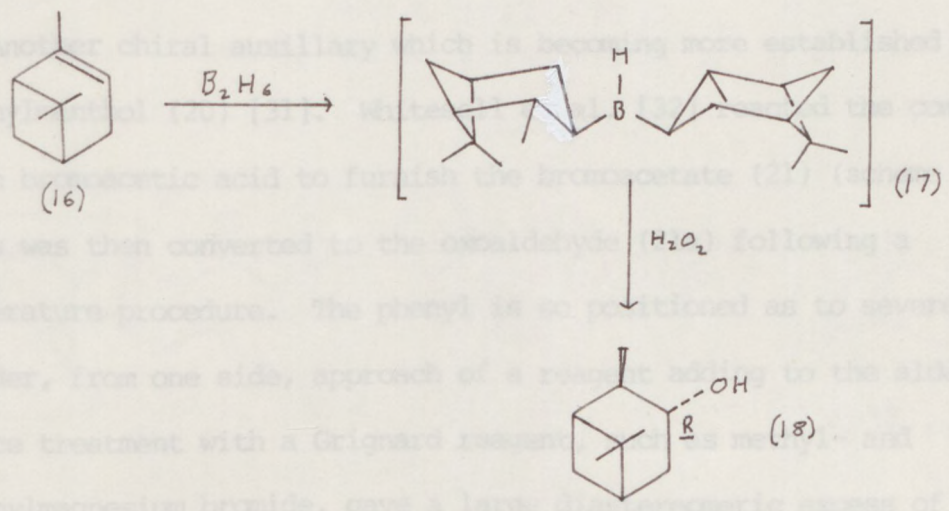




Scheme 6.



Scheme 7.

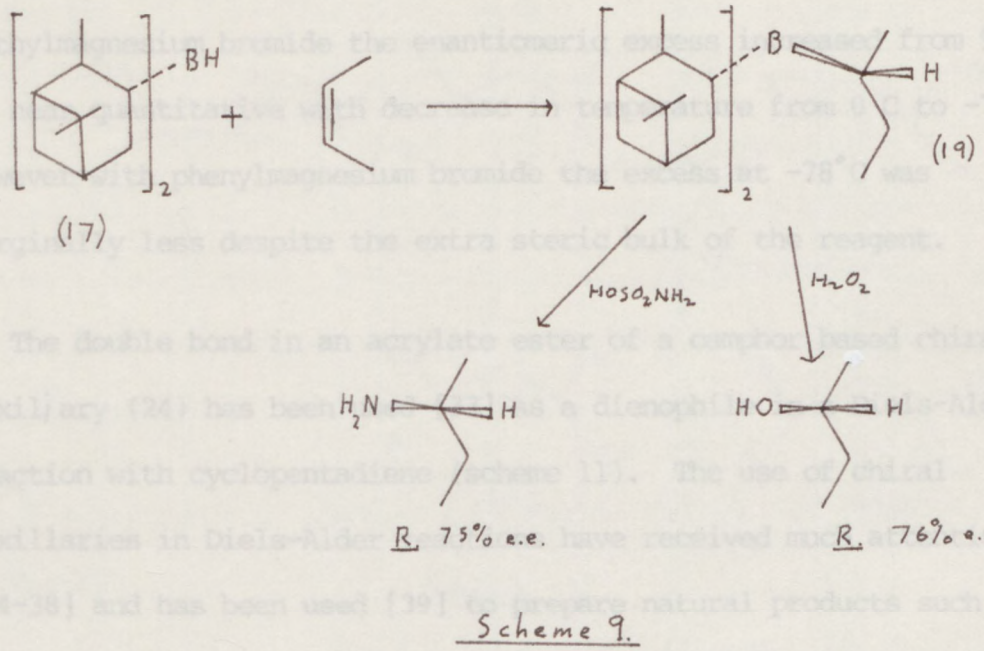


Scheme 8.

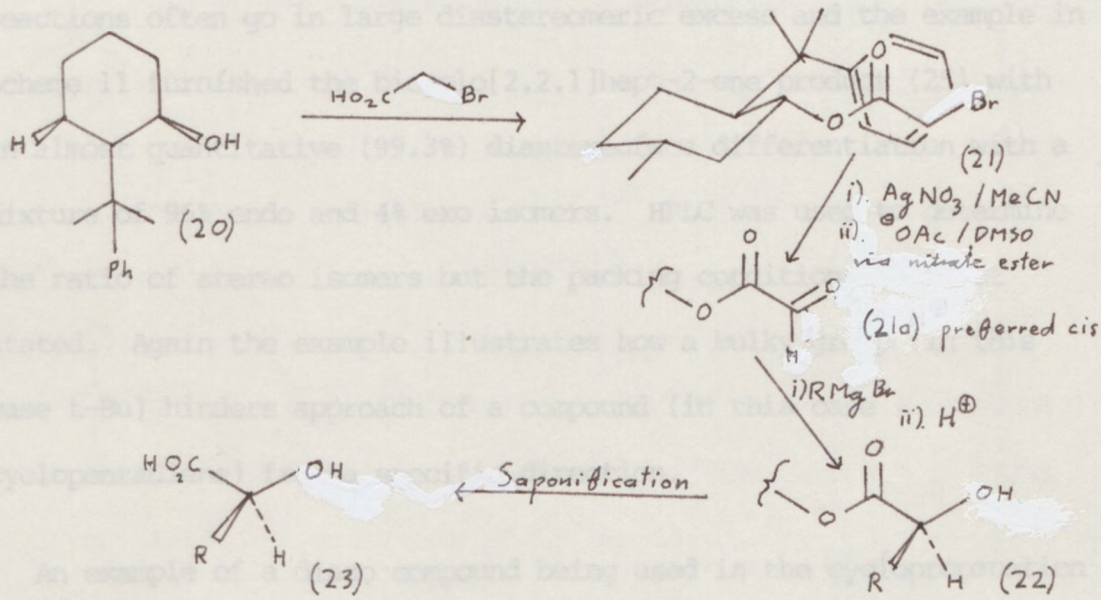
large diastereomeric excess of the α-alcohol. Saponification of the alcohol thus produces an excess of one enantiomer of the α -hydroxyacid (15) and hence the product is optically active (scheme 7). Both (+) and (-) menthol are commercially available and hence offers a means of choosing which enantiomer to prepare.

There are several other examples of bulky optically active molecules, or chiral auxiliaries, which can be used in the manner just described to produce optical active compounds via diastereomeric excess. One of the most stablished [28,29] is α -pinene (16) which when added to diborane gives the di-(α)-pineneborane (17) which can be isolated (scheme 8). The 2-methyl group in the compound is fixed in an S configuration owing to the cis addition of the B-H bond, whilst the bridging methyl groups for steric reasons cause the borane to add on to the opposite face. Oxidation of the borane with hydrogen peroxide affords exclusively the R alcohol (18) of the α-pinene. The borane (17) can have a third mole of alkene added to it. Addition of cis but-2-ene [30] gives the trisubstituted borane (19) which when oxidised affords butan-2-ol with a 76% enantiomeric excess of the R-configuration (scheme 9). Treatment with sulphamic acid affords isobutylamine with a 75% enantiomeric excess of the R-configuration.

Another chiral auxillary which is becoming more established is 8-phenylmenthol (20) [31]. Whitesell et al. [32] reacted the compound with bromoacetic acid to furnish the bromoacetate (21) (scheme 10). This was then converted to the oxoaldehyde (21a) following a literature procedure. The phenyl is so positioned as to severely hinder, from one side, approach of a reagent adding to the aldehyde. Hence treatment with a Grignard reagent, such as methyl- and phenylmagnesium bromide, gave a large diastereomeric excess of the alcohol product (22) which in turn gave a large enantiomeric excess



Scheme 9.

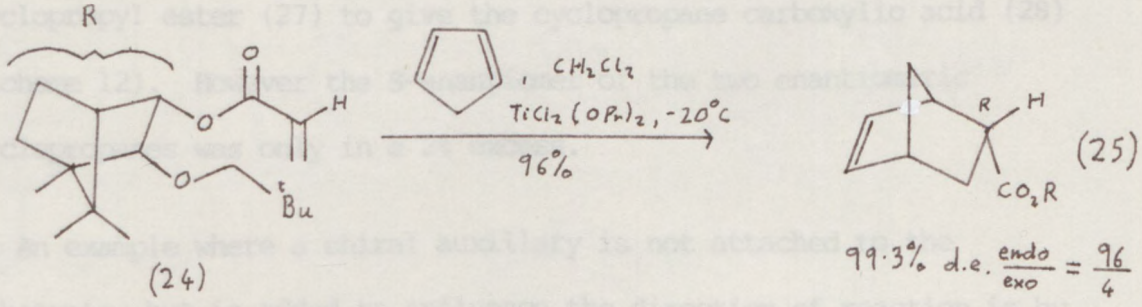


R = Me, e.e. = 90% 0°C

e.e. = 99.4% -78°C

R = Ph, e.e. = 99.1% -78°C

Scheme 10.



99.3% d.e. $\frac{endo}{exo} = \frac{96}{4}$

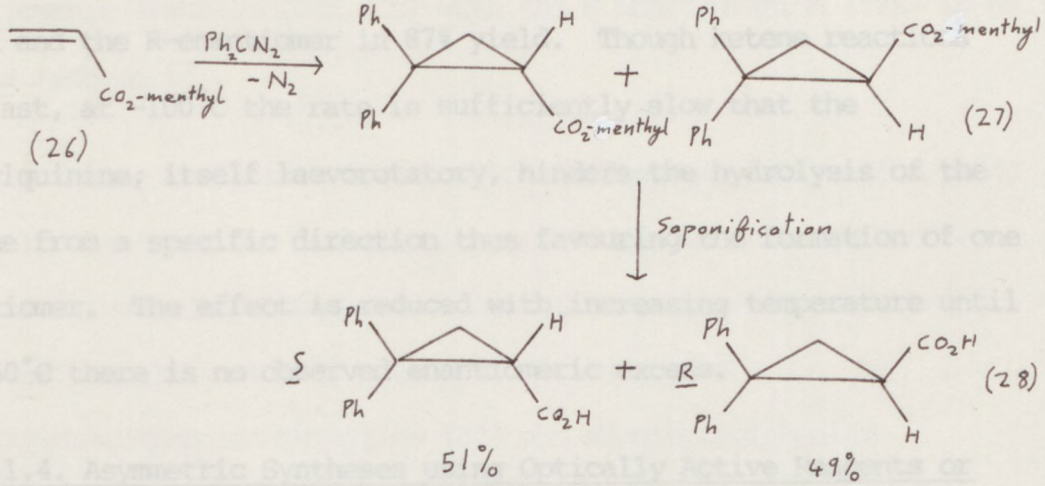
Scheme 11.

of the β-hydroxy acid (23) upon saponification. With methylmagnesium bromide the enantiomeric excess increased from 90% to near quantitative with decrease in temperature from 0 C to -78°C. However with phenylmagnesium bromide the excess at -78°C was marginally less despite the extra steric bulk of the reagent.

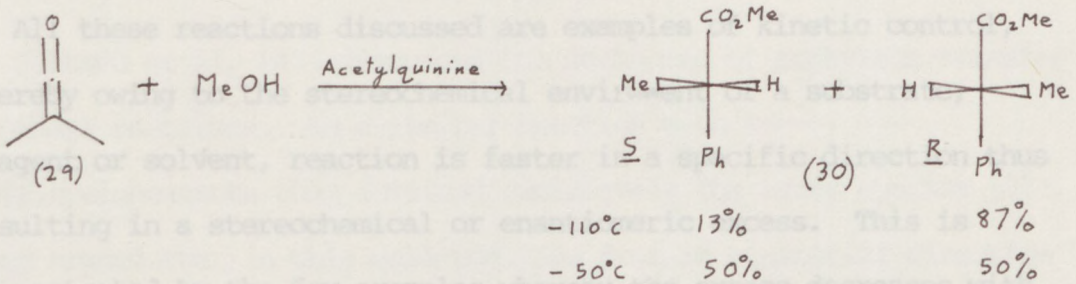
The double bond in an acrylate ester of a camphor based chiral auxiliary (24) has been used [33] as a dienophile in a Diels-Alder reaction with cyclopentadiene (scheme 11). The use of chiral auxillaries in Diels-Alder reactions have received much attention [34-38] and has been used [39] to prepare natural products such as (-)-β-santalene, a constituent of santalwood. Such Diels-Alder reactions often go in large diastereomeric excess and the example in scheme 11 furnished the bicyclo[2.2.1]hept-2-ene product (25) with an almost quantitative (99.3%) diastereoface differentiation with a mixture of 96% endo and 4% exo isomers. HPLC was used to determine the ratio of stereo isomers but the packing conditions were not stated. Again the example illustrates how a bulky group (in this case t-Bu) hinders approach of a compound (in this case cyclopentadiene) from a specific direction.

An example of a diazo compound being used in the cyclopropanation of a double bond attached to a chiral auxillary is by Walborsky and Pitt [40] who reacted (+)menthyl ester of propenoic acid (26) with diphenyl diazomethane, followed by saponification of the resulting cyclopropyl ester (27) to give the cyclopropane carboxylic acid (28) (scheme 12). However the S-enantiomer of the two enantiomeric cyclopropanes was only in a 2% excess.

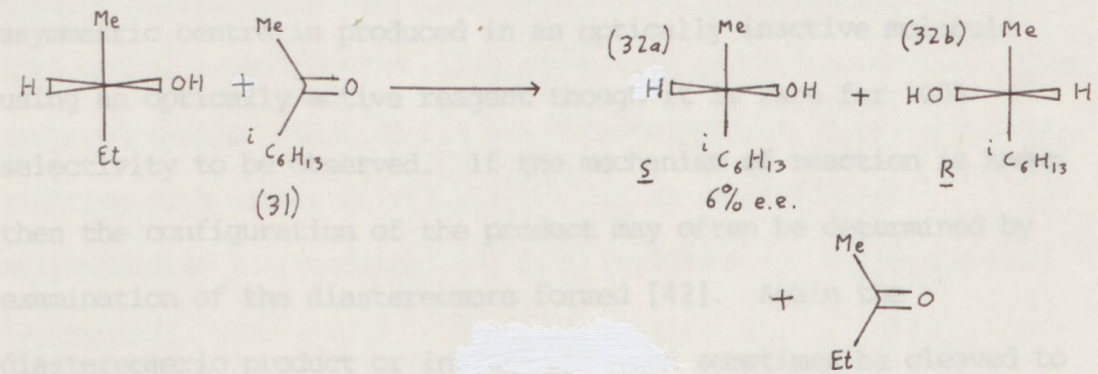
An example where a chiral auxillary is not attached to the substrate, but is added to influence the direction of reaction is by Pracejus [41] who reacted methyl phenylketene (29) with methanol in the presence of acetylquinine (scheme 13). At -100°C the S-



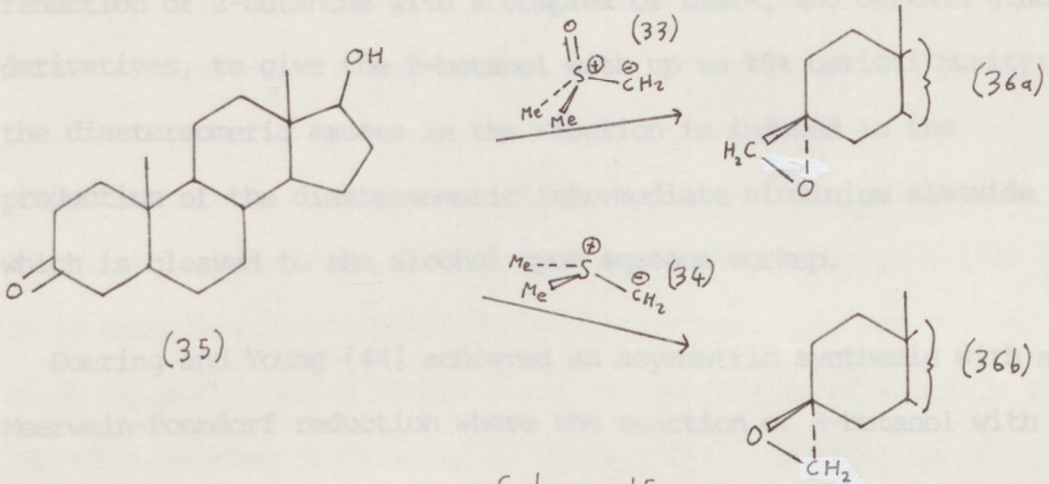
Scheme 12.



Scheme 13.



Scheme 14.



Scheme 15.

enantiomer of the methyl ester product (30) was obtained in 13% yield and the R-enantiomer in 87% yield. Though ketene reactions are fast, at -100°C the rate is sufficiently slow that the acetylquinine, itself laevorotatory, hinders the hydrolysis of the ketene from a specific direction thus favouring the formation of one enantiomer. The effect is reduced with increasing temperature until at -50°C there is no observed enantiomeric excess.

3.1.4. Asymmetric Syntheses using Optically Active Reagents or Solvents.

All these reactions discussed are examples of kinetic control, whereby owing to the stereochemical environment of a substrate, reagent or solvent, reaction is faster in a specific direction thus resulting in a stereochemical or enantiomeric excess. This is demonstrated by the few examples whereby the excess decreases with increase in temperature. There are many examples where a new asymmetric centre is produced in an optically inactive molecule using an optically active reagent though it is rare for 100% selectivity to be observed. If the mechanism of reaction is known then the configuration of the product may often be determined by examination of the diastereomers formed [42]. Again the diastereomeric product or intermediate can sometimes be cleaved to produce an optically active product. An example [43] is the reduction of 2-butanone with a complex of $LiAlH_4$ and certain glucose derivatives, to give the 2-butanol with up to 15% optical purity; the diastereomeric excess in the reaction is induced in the production of the diastereomeric intermediate aluminium alkoxide which is cleaved to the alcohol upon aqueous workup.

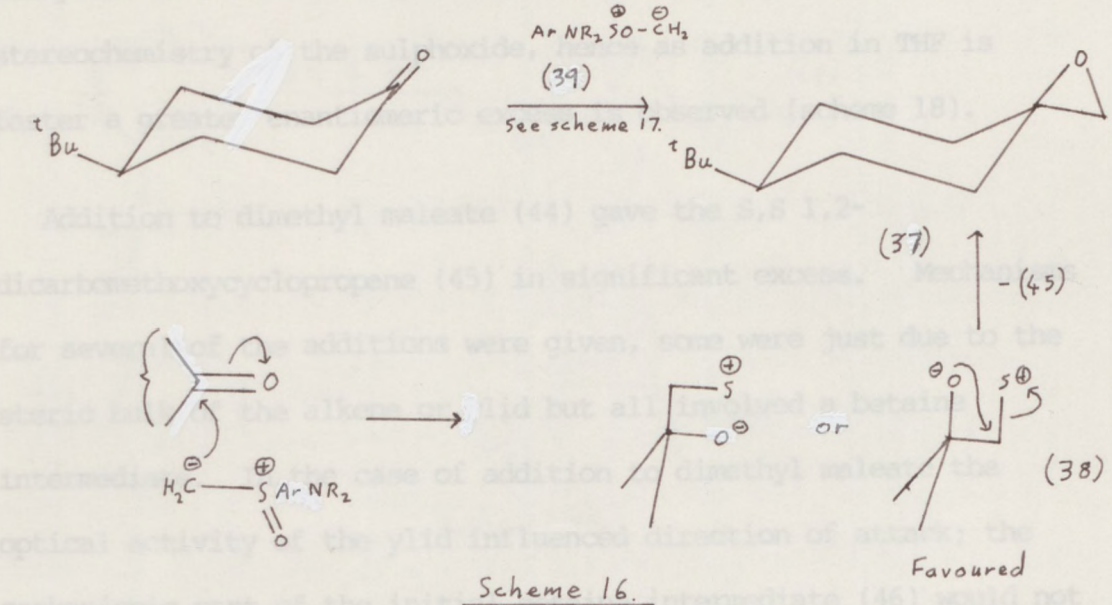
Doering and Young [44] achieved an asymmetric synthesis with a Meerwein-Ponndorf reduction where the reaction of R-butanol with

isohexyl methylketone (31) afforded a mixture of the two enantiomeric alcohols (32a,32b) with the S configuration (32a) in 6% excess (scheme 14).

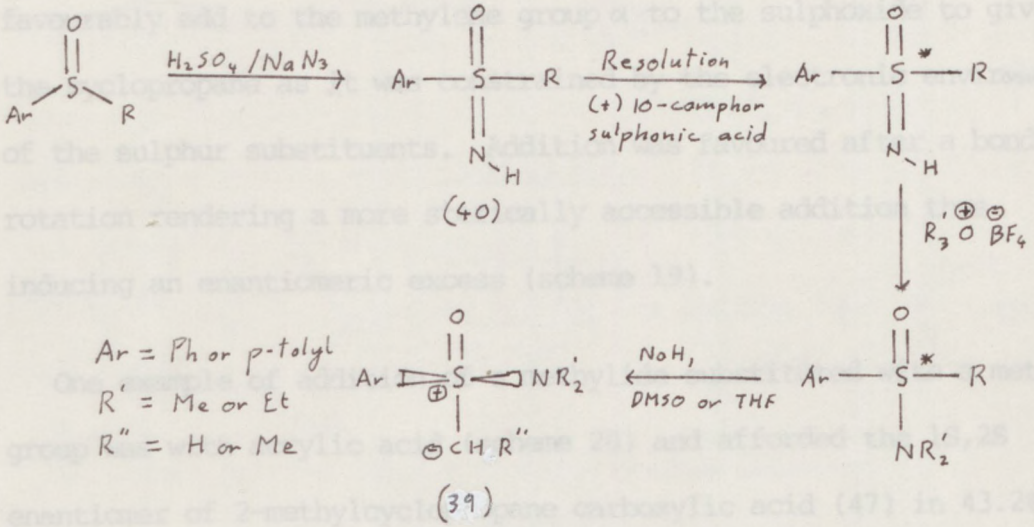
It is known that dialkylsulphonium and dialkyloxosulphonium ylids not only transfers the carbanionic part of the molecule to double bonds to give cyclopropanes but also are very specific for forming epoxides with ketones [45]. Cook et al. [46] added dimethyloxosulphonium methylide (33) and dimethylsulphonium methylide (34) to dihydrotestosterone (35) and obtained epoxides of opposite stereochemistry (36a,36b) (scheme 15).

Johnson et al. [47] discussed the mechanism of methylide transfer in these reactions. In a similar reaction with 4-t-butylcyclohexanone they obtained exclusively the trans epoxide (37). They argued that in this case addition from an equitorial direction was sterically favoured. The intermediate in the reaction is a betaine intermediate (38) (scheme 16). They demonstrated [47] that with chiral oxosulphonium ylids asymmetric induction occured. They prepared several enantiomeric amino oxosulphonium methylides (39) starting with either chiral sulphoxides or resolving the sulphoxoimine intermediate (40) with (+)10-camphor sulphonic acid (scheme 17).

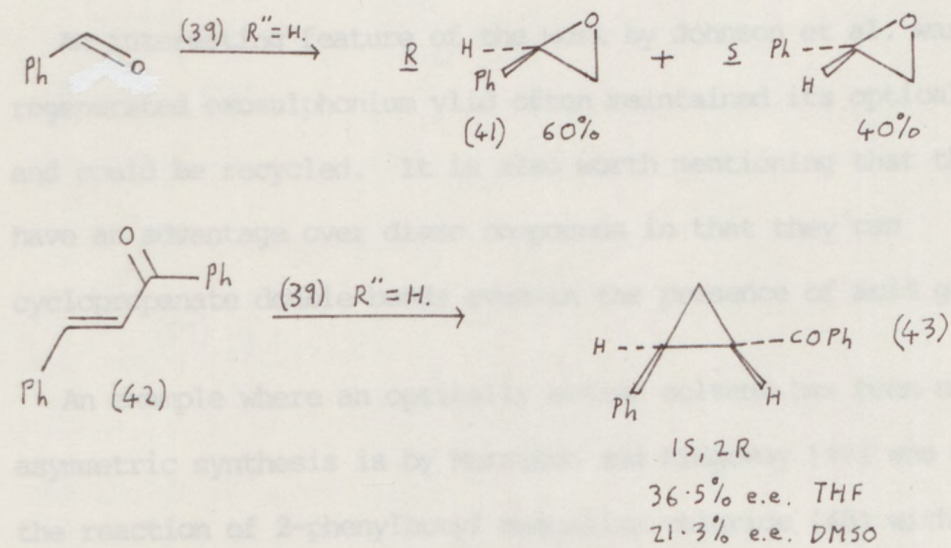
Johnson et al. [46] performed a large number of methylide transfers with the enantiomeric oxosulphonium methylide (39) with ketones and alkenes. Large enantiomeric excesses were not observed but were typically between 20 and 40%. Benzaldehyde gave R 2-phenyloxi rane (41) in 20% enantiomeric excess (scheme 18). Trans phenethenyl phenyl ketone (42) gave the 1S,2R cyclopropane (43) in 36.5% enantiomeric excess in THF which interestingly was reduced to 21.3% in DMSO. DMSO solvates polar compounds more effectively than THF thus reducing their speed of reactivity. The addition of



Scheme 16.



Scheme 17.



Scheme 18.

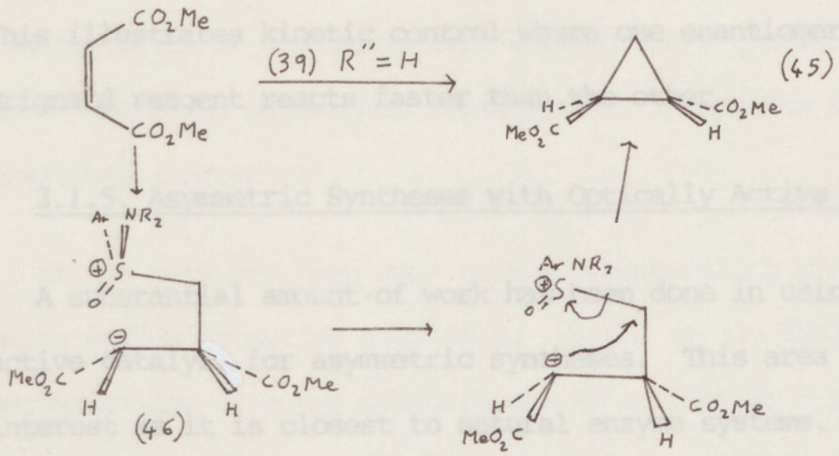
methylide is a kinetically controlled process, influenced by the stereochemistry of the sulphoxide, hence as addition in THF is faster a greater enantiomeric excess is observed (scheme 18).

Addition to dimethyl maleate (44) gave the S,S 1,2-dicarbomethoxycyclopropane (45) in significant excess. Mechanisms for several of the additions were given, some were just due to the steric bulk of the alkene or ylid but all involved a betaine intermediate. In the case of addition to dimethyl maleate the optical activity of the ylid influenced direction of attack; the carbanionic part of the initial betaine intermediate (46) would not favourably add to the methylene group α to the sulphoxide to give the cyclopropane as it was constrained by the electronic environment of the sulphur substituents. Addition was favoured after a bond rotation rendering a more sterically accessible addition thus inducing an enantiomeric excess (scheme 19).

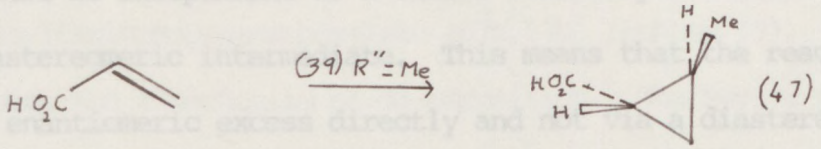
One example of addition of a methylide substituted with a methyl group was with acrylic acid (scheme 20) and afforded the 1S,2S enantiomer of 2-methylcyclopropane carboxylic acid (47) in 43.2% enantiomeric excess.

An interesting feature of the work by Johnson et al. was that the regenerated oxosulphonium ylid often maintained its optical activity and could be recycled. It is also worth mentioning that these ylids have an advantage over diazo compounds in that they can cyclopropanate double bonds even in the presence of acid groups.

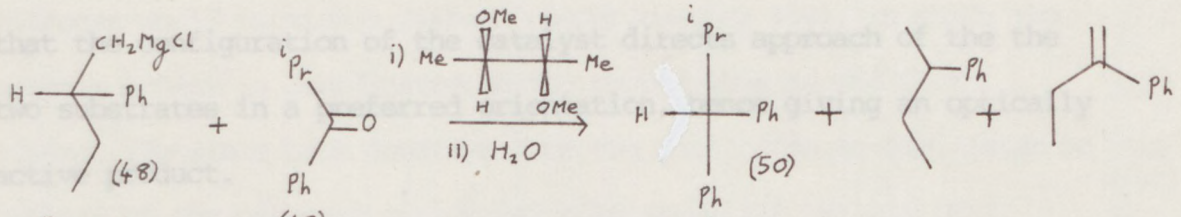
An example where an optically active solvent has been used in asymmetric synthesis is by Morrison and Ridgeway [49] who considered the reaction of 2-phenylbutyl magnesium chloride (48) with isopropyl-phenylketone in the presence of an optically active ether (scheme 21). The main addition product (50) was obtained with an



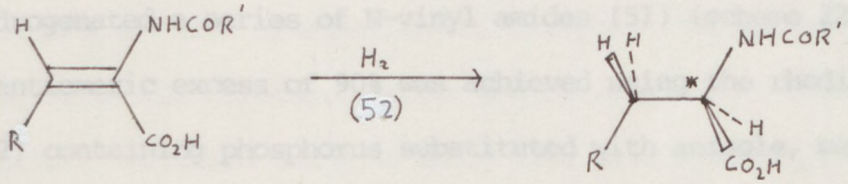
Scheme 19.

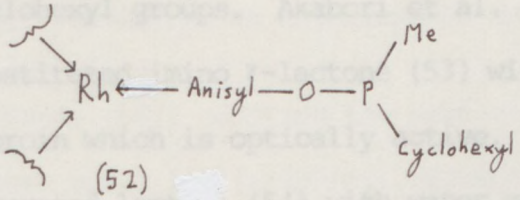


Scheme 20.



Scheme 21.





Scheme 22.

excess 8.4% of one enantiomer although which one was not stated. This illustrates kinetic control where one enantiomeric form of the Grignard reagent reacts faster than the other.

3.1.5. Asymmetric Syntheses with Optically Active Catalysts.

A substantial amount of work has been done in using an optically active catalyst for asymmetric syntheses. This area is of most interest as it is closest to natural enzyme systems. Also, unlike many of the previous examples, the production of a new asymmetric centre is independant of a chiral auxillary and hence there is no diastereomeric intermediate. This means that the reaction induces an enantiomeric excess directly and not via a diastereomeric excess. Hence such reactions could be considered as 'purer' examples of asymmetric synthesis. The general theory behind such catalysis is that the configuration of the catalyst directs approach of the the two substrates in a preferred orientation, hence giving an optically active product.

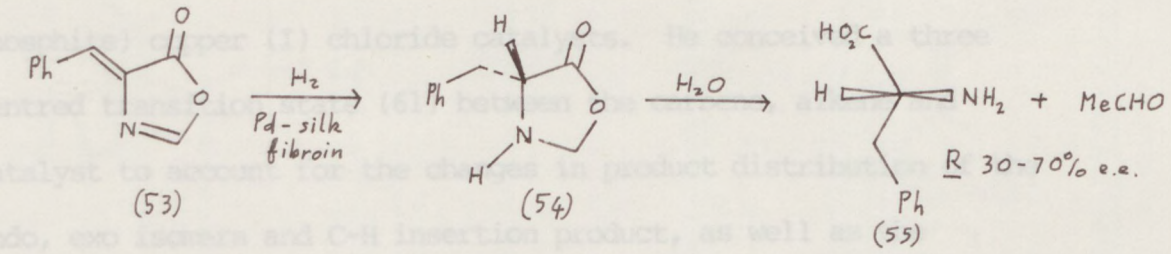
Much work has been done on asymmetric hydrogenation [50,51]. One of the most effective examples is by Knowles et al. [52] who hydrogenated a series of N-vinyl amides (51) (scheme 22). An enantiomeric excess of 90% was achieved using the rhodium complex (52) containing phosphorus substituted with anisole, methyl and cyclohexyl groups. Akabori et al. [53] hydrogenated a vinyl substituted imino γ-lactone (53) with palladium bonded on to silk fibroin which is optically active. Workup of the resulting saturated lactone (54) with water gave the amino acid (55), β-phenyl alanine, with an enantiomeric excess of between 30-70% of the R-configuration (scheme 23).

Natural enzymes can be used for asymmetric synthesis. Chibata [54] developed a method for preparing pure L-amino acids from the

racemic amides using amino acyclase. The enzyme gave only the L-configuration of the amino acid leaving the D-configuration of the amide which was separated, racemised and then given a repeat treatment (scheme 24).

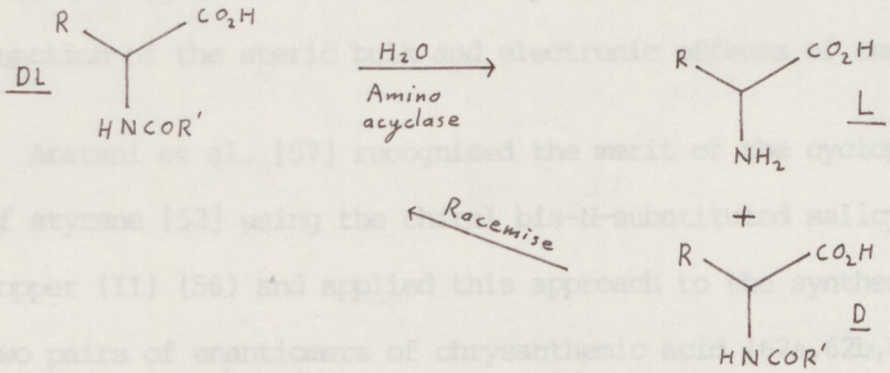
Little work has been done on the decomposition of diazo compounds using optically active catalysts. Nozaki et al. [55] studied the decomposition of ethyl diazoacetate in styrene in the presence of the chiral complex bis [N-(R)-α-phenethylsalicylaldiminato]-copper (II) (56) and obtained a mixture of the optically active ethyl 2-phenylcyclopropanacarboxylate (57a,57b) (scheme 25). They postulated a mechanism of decomposition. The square planar chelate would undergo electrophilic attack on the carbon atom of the diazo compound to give a complex (58) (scheme 26). Elimination of nitrogen would furnish a carbene copper complex (59), in which the carbene moiety is coordinated to the copper atom as the fifth ligand. Possible back donation from the metal atom to the vacant Pz orbital of the carbenic carbon may help stabilise the complex. Nozaki et al. [53] pointed out that the reacting carbenoid species may either be (58) or (59) which reacts with the styrene to give the cyclopropane with elimination of nitrogen. The approach of the styrene to the carbenoid carbon centre would be encouraged from a specific direction owing to the chiral enviroment of the ligand hence furnishing an enantiomeric excess.

Moser [56], adopting the same reaction, achieved an enantiomeric excess using [(-)[tribornyl phosphite] copper (I) chloride (60) (scheme 27). He analysed the enantiomeric mixture of cis and trans isomers (57a,57b) by g.l.c, which indicated a 3.2% and 2.6% enantiomeric excess of one enantiomer in the optically active cis and trans geometrical forms. The work was part of a more general study, examining the change in product distribution of the reaction

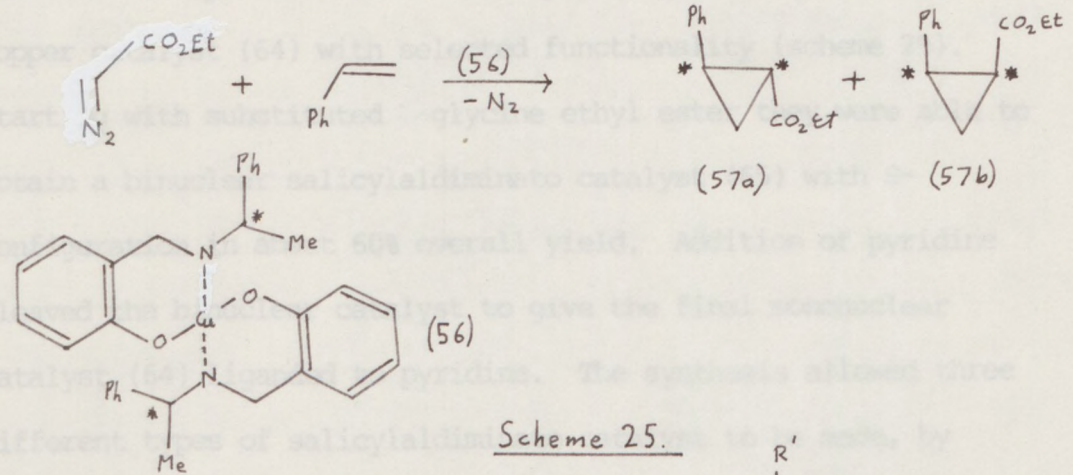


(53) (54) (55)

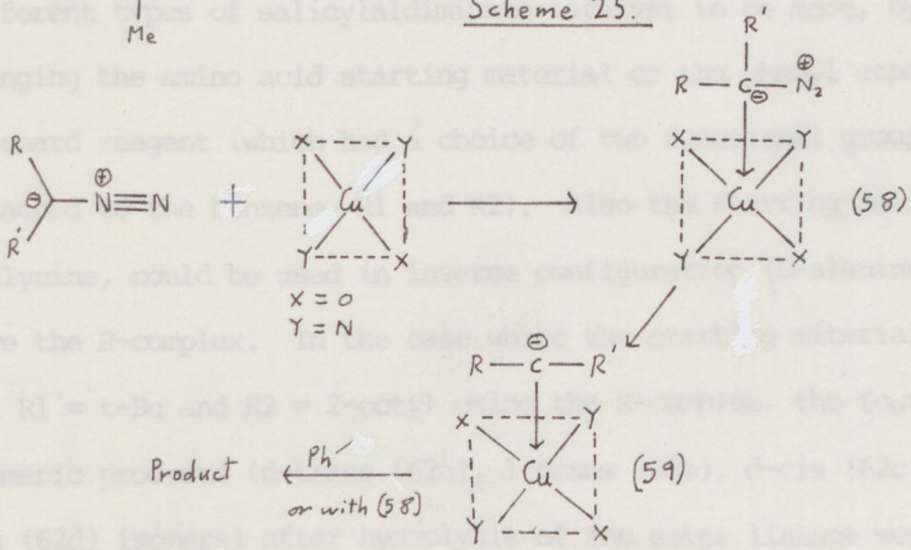
Scheme 23.



Scheme 24.



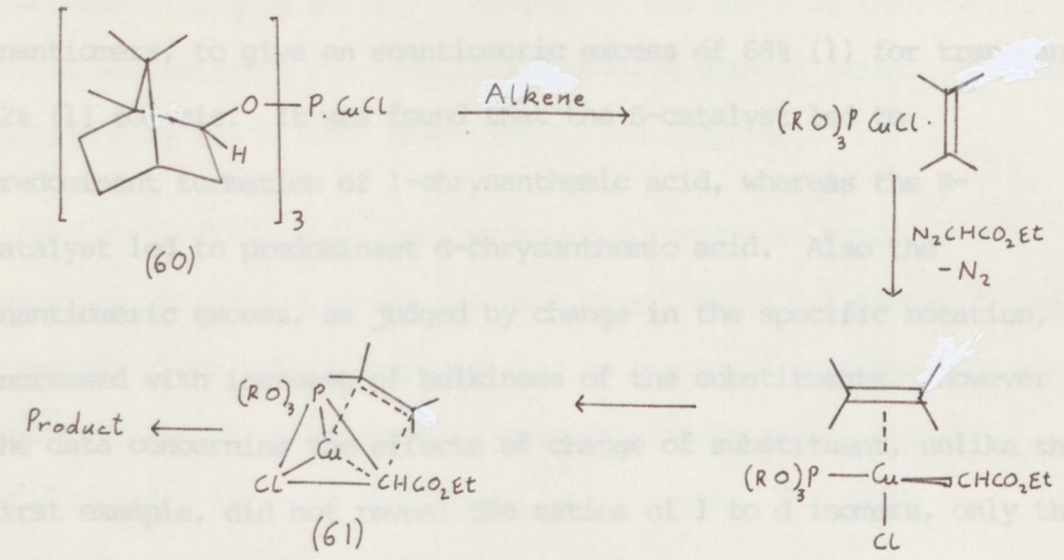
Scheme 25.



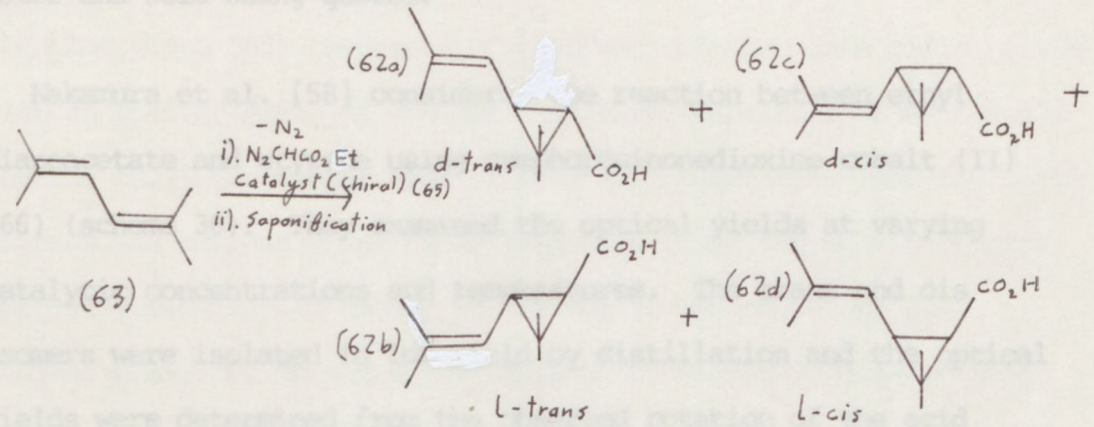
Scheme 26.

between alkenes and ethyl diazoacetate using different (trialkyl phosphite) copper (I) chloride catalysts. He conceived a three centred transition state (61) between the carbene, alkene and catalyst to account for the changes in product distribution of the endo, exo isomers and C-H insertion product, as well as the enantiomeric excess observed with cyclopropanes from styrene (scheme 27). He argued that the isomeric product distribution occured as a function of the steric bulk and electronic effects of the ligand.

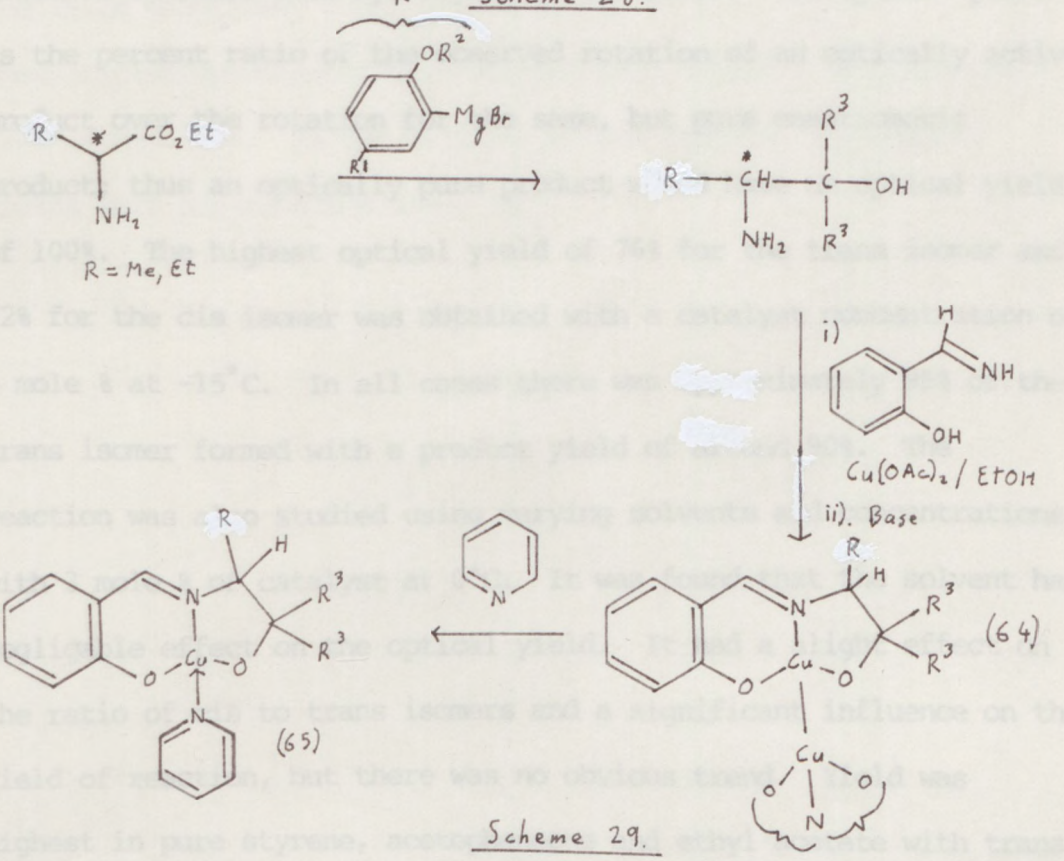
Aratani et al. [57] recognised the merit of the cyclopropanation of styrene [52] using the chiral bis-N-substituted salicylaldiminato copper (II) (56) and applied this approach to the synthesis of the two pairs of enantiomers of chrysanthemic acid (62a,62b,62c and 62d) starting with 2,5-dimethylhexa-2,4-diene 63 (scheme 28). They modified the synthesis of the catalyst to produce a mononuclear copper catalyst (64) with selected functionality (scheme 29). Starting with substituted D-glycine ethyl ester they were able to obtain a binuclear salicylaldiminato catalyst (65) with S-configuration in about 60% overall yield. Addition of pyridine cleaved the binuclear catalyst to give the final mononuclear catalyst (64) liganded to pyridine. The synthesis allowed three different types of salicylaldiminato catalyst to be made, by changing the amino acid starting material or the phenyl ether Grignard reagent (which had a choice of two functional groups attached to the benzene, R1 and R2). Also the starting amino acid, D-glycine, could be used in inverse configuration (D-alanine) to give the R-complex. In the case where the starting material was R = Et, R1 = t-Bu and R2 = 2-octyl using the S-complex, the four isomeric products (d-trans (62a), l-trans (62b), d-cis (62c) and l-cis (62d) isomers) after hydrolysis of the ester linkage were analysed by g.l.c., and an enantiomeric excess for each of the trans



Scheme 27.



Scheme 28.



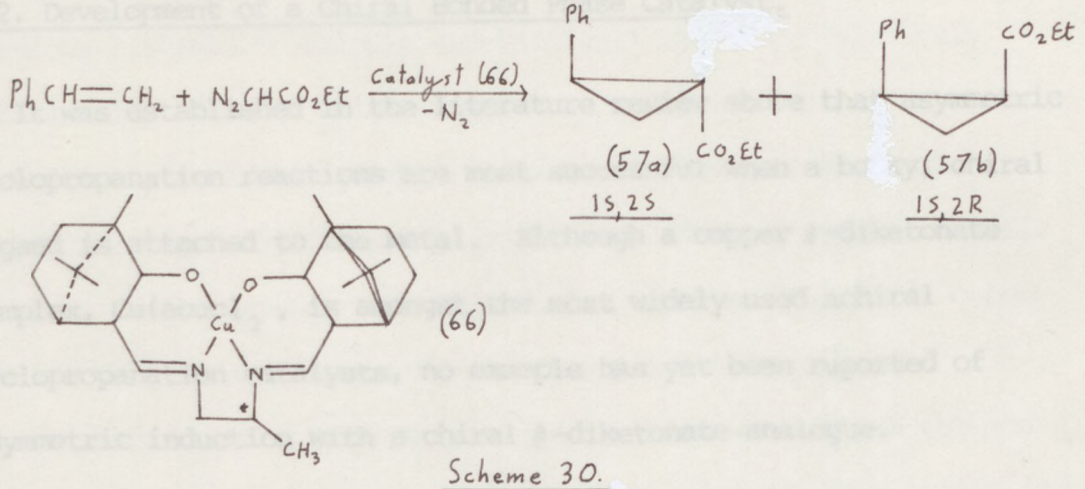
Scheme 29.

and cis isomers was determined from the ratio of l over d enantiomers, to give an enantiomeric excess of 68% (l) for trans and 62% (l) for cis. It was found that the S-catalyst led to predominant formation of l-chrysanthemic acid, whereas the R-catalyst led to predominant d-chrysanthemic acid. Also the enantiomeric excess, as judged by change in the specific rotation, increased with increase of bulkiness of the substituents. However the data concerning the effects of change of substituent, unlike the first example, did not reveal the ratios of l to d isomers, only the specific rotations of the mixture of cis and trans isomers for the ester and acid being quoted.

Nakamura et al. [58] considered the reaction between ethyl diazoacetate and styrene using camphorquinonedioxime cobalt (II) (66) (scheme 30). They examined the optical yields at varying catalytic concentrations and temperatures. The trans and cis isomers were isolated in low yield by distillation and the optical yields were determined from the observed rotation of the acid products obtained from hydrolysis of the ester. The optical yield is the percent ratio of the observed rotation of an optically active product over the rotation for the same, but pure enantiomeric product; thus an optically pure product would have an optical yield of 100%. The highest optical yield of 76% for the trans isomer and 72% for the cis isomer was obtained with a catalyst concentration of 3 mole % at -15°C. In all cases there was approximately 95% of the trans isomer formed with a product yield of around 90%. The reaction was also studied using varying solvents and concentrations with 3 mole % of catalyst at 0°C. It was found that the solvent had negligable effect on the optical yield. It had a slight effect on the ratio of cis to trans isomers and a significant influence on the yield of reaction, but there was no obvious trend. Yield was highest in pure styrene, acetopheneone and ethyl acetate with trans

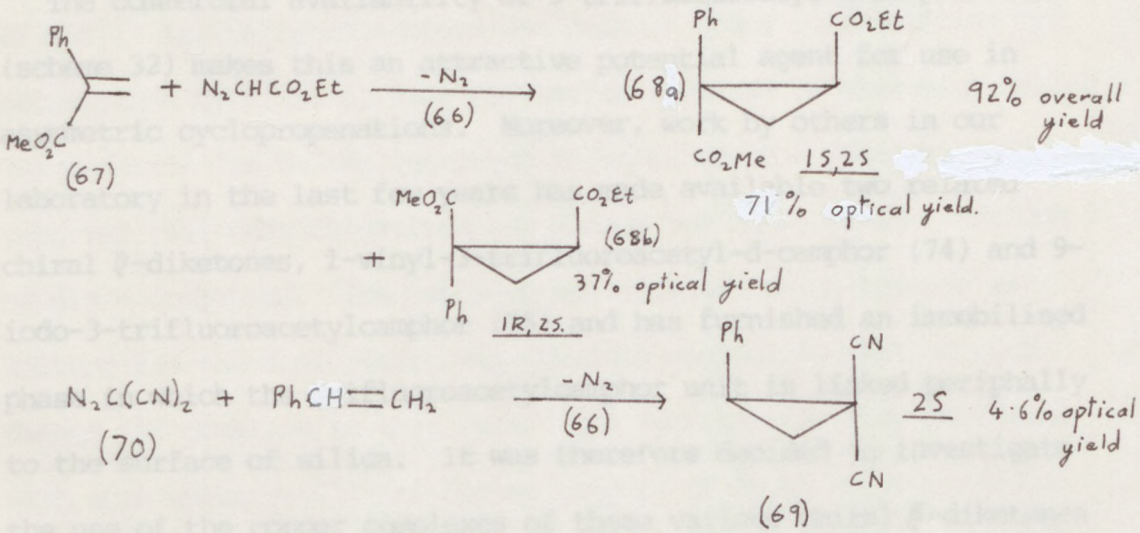
predominant with no solvent. However it was observed that optical purity and observed reaction rate decreased with dilution. This was explained by the solvent deactivating the catalyst.

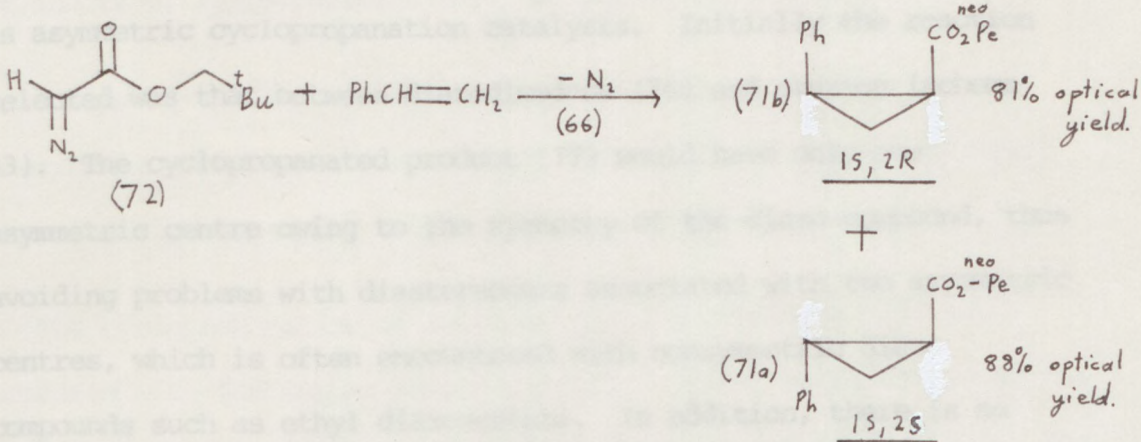
Nakamura et al. [56] then performed an extensive study of reactions of ethyl diazoacetate with other alkene substrates in the presence of the cobalt catalyst (66) to give cyclopropanes. In many cases the optical yield could not be determined as the specific rotation for, the pure enantiomer, was unknown. The range of examples include ethyl-2-phenyl-2-carbomethoxycyclopropanecarboxylate (68) derived from methyl 2-phenylacrylate (67) (scheme 31) which was obtained in a yield of 92% with an optical yield of 71% for the 1S,2S enantiomer (68a) and 37% for the 1R,2S enantiomer (68b). They also considered reactions with styrene and various other diazo compounds using the cobalt complex. Optical yields varied from 4.6% for the 2S enantiomer of 2,2-dicyano-phenylcyclopropane (69) derived from dicyano diazomethane (70) (scheme 31) to 88% for the 1S,2S enantiomer (71a) and 81% for the 1S,2R enantiomer (71b) of neo-pentyl 2-phenylcyclopropanecarboxylate derived from n-pentyl diazoacetate (72) (scheme 31). In the majority of the examples the optical yields were large, often above 70%.



(66)

Scheme 30.





Scheme 31.

3.2. Development of a Chiral Bonded Phase Catalyst.

It was established in the literature review above that asymmetric cyclopropanation reactions are most successful when a bulky, chiral ligand is attached to the metal. Although a copper β-diketonate complex, $Cu(acac)_2$, is amongst the most widely used achiral cyclopropanation catalysts, no example has yet been reported of asymmetric induction with a chiral β-diketonate analogue.

The commercial availability of 3-trifluoroacetyl-d-camphor (73) (scheme 32) makes this an attractive potential agent for use in asymmetric cyclopropanations. Moreover, work by others in our laboratory in the last few years has made available two related chiral β-diketones, 1-vinyl-3-trifluoroacetyl-d-camphor (74) and 9-iodo-3-trifluoroacetylcamphor (75) and has furnished an immobilised phase in which the trifluoroacetylcamphor unit is linked periphally to the surface of silica. It was therefore decided to investigate the use of the copper complexes of these various chiral β-diketones as asymmetric cyclopropanation catalysts. Initially the reaction selected was that between diazodimedone (76) and styrene (scheme 33). The cyclopropanated product (77) would have only one asymmetric centre owing to the symmetry of the diazo compound, thus avoiding problems with diastereomers associated with two asymmetric centres, which is often encountered with nonsymmetric diazo compounds such as ethyl diazoacetate. In addition, there is no problem with the separation of exo and endo isomers owing to the acyclic nature of the styrene double bond. Also the phenyl group will provide a good chromophore for uv detection by TLC and HPLC. The cyclopropane product's simple structure should be easy to recognise by spectroscopy, especially n.m.r.

The reaction was catalysed with the copper salt of commercially

available 3-(trifluoroacetyl)-d-camphor (73) (facam). Most of the previous literature examples use catalysts which are relatively inaccessible. Thus to obtain asymmetric induction with a commercially available product would be of great benefit. The copper salt was satisfactorily prepared by addition of a methanolic solution of the camphor derivative to an aqueous solution of copper acetate to give a green precipitate which was filtered and recrystallised. The cyclopropanation reaction was carried out and the cyclopropane (77) was furnished in 36% yield and gave a mean $[\alpha]_D$ of -55°. Initially chloroform was used in order to solubilise the polystyrene by-product, thus preventing increase in viscosity during the reaction due to the formation of polystyrene. However it was reported [59] that chloroform can damage the catalyst in reactions of diazo compounds. The reaction was repeated using benzene as solvent and the same result was obtained suggesting that no such damage was occuring in this case. The reaction was also performed with some unrecrystallised copper complex of facam which proved to be inactive, illustrating a need for purity of the catalyst.

1-Vinyl-3-trifluoroacetyl camphor (vinylfacam) (74) has previously been prepared by another worker [60] in this laboratory, starting with d-camphor sulphonyl chloride (78) (scheme 34).

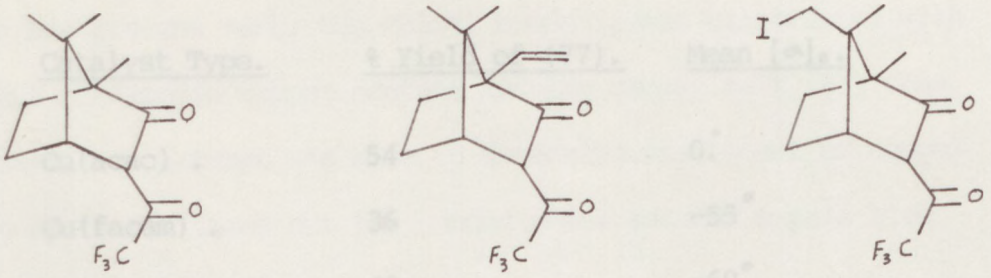
The cyclopropanation of styrene with diazodimedone (76) was repeated with the copper complex of vinyl facam, which furnished the cyclopropane (77) in 48% yield with a mean $[\alpha]$ of -60° ($\pm 10^\circ$). The error limits on the rotation are quite large owing to the low concentration of the solution. Concentrations varied from 40 to 100mg in 10ml of dichloromethane which in a 2dm long tube gave rotations in the order of -0.5 to $-1.8 \pm 0.1^\circ$ (reading error in polarimeter). However, the values of $[\alpha]_D$ for each of the readings did not differ by more than 10° from the mean $[\alpha]_D$. $[\alpha]_D$ values

were taken from the equation:- $[\alpha]_D$ = observed rotation / (Tube length (dm) x Conc. g per ml). A problem encountered in the reaction was that the catalyst (with a strong green colour) had an rf slightly less than the product and the product had to be repurified two or three times to be colourless. It was observed that the rotation was less with contaminated samples. As the catalyst has a + rotation then the observed - rotation is obviously due to the product. However the extensive purification required resulted in significant mechanical losses. Another problem was polystyrene by-product which was removed by evaporating down the crude reaction product, taking it up in chloroform and then pouring it into excess methanol precipitating the polystyrene. However, residues remained in the supernatant and persisted throughout the subsequent work-up procedures, being seen as small impurity peaks in the aliphatic and aromatic regions of the proton n.m.r.

9-Iodo-3-trifluoroacetylcamphor (9-iodofacam) (75) has also been prepared by another worker [61] in this laboratory, using the method shown (scheme 35).

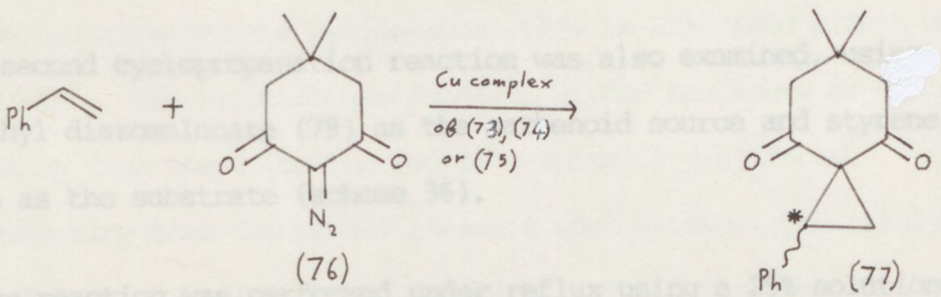
The cyclopropanation reaction was repeated with copper bis-(9-iodo-3-trifluoroacetyl-d-camphorate), to see whether the steric bulk of the iodine would influence the optical activity of the product. The catalyst had to be recrystallised before it was active but repeating the reaction in benzene furnished the cyclopropane (77) in 21% yield with a mean $[\alpha]$ of -44° which is significantly lower compared to the previous reactions.

As a control reaction, the same cyclopropanation was also effected using copper acetylacetonate as catalyst. The cyclopropane product (77) was obtained in 54% yield with a mean rotation of zero. Thus the best result in this asymmetric cyclopropanation reaction in terms of both chemical and optical yield was obtained with the



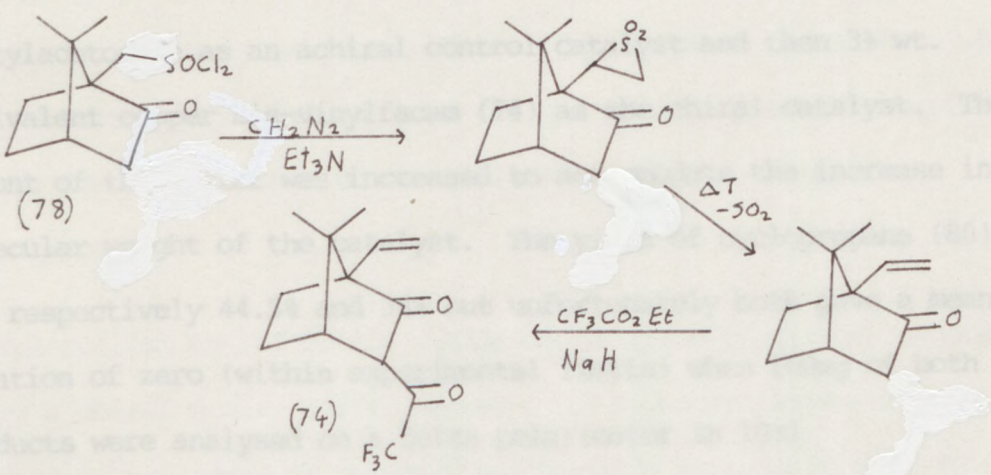
(73) (74) (75)

Scheme 32.



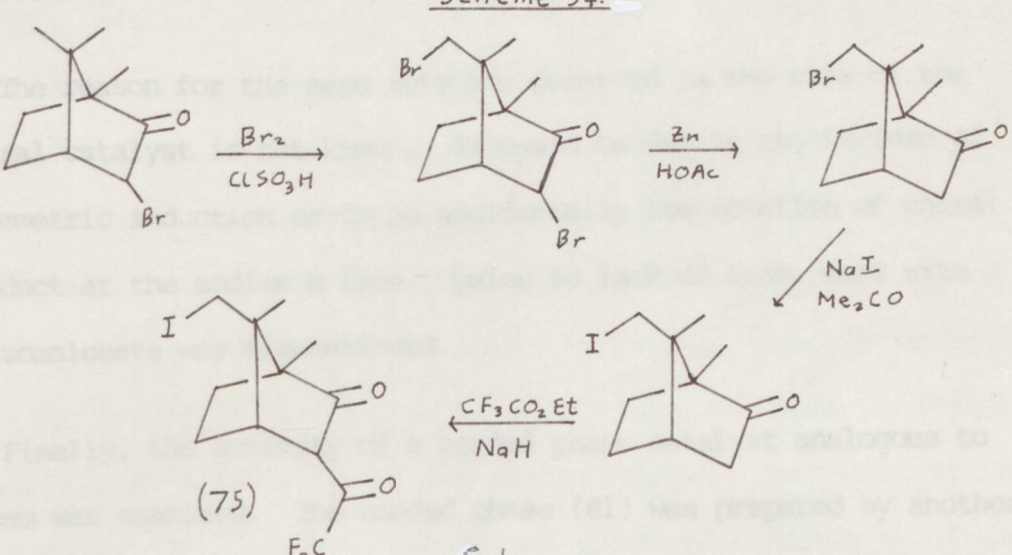
(76) (77)

Scheme 33.



(78) (74)

Scheme 34.



(75)

Scheme 35.

vinylfacam (Table 1).

Catalyst Type.	% Yield of (77).	Mean $[\alpha]_D$.
Cu(acac) .	54	0°
Cu(facam) .	36	-55°
Cu(vinylfacam) .	48	-60°
Cu(9-iodofacam).	21	-44°

Table 1.

A second cyclopropanation reaction was also examined, using dimethyl diazomalonate (79) as the carbenoid source and styrene again as the substrate (scheme 36).

The reaction was performed under reflux using a 25% solution of styrene in benzene with a 1.5% wt. equivalent of copper acetylacetonate as an achiral control catalyst and then 3% wt. equivalent copper bis-vinylfacam (74) as the chiral catalyst. The amount of the latter was increased to accommodate the increase in molecular weight of the catalyst. The yield of cyclopropane (80) was respectively 44.5% and 34% but unfortunately both gave a mean rotation of zero (within experimental limits) when 100mg of both products were analysed on a Zeiss polarimeter in 10ml dichloromethane solution using 589nm sodium light.

The reason for the zero rotation observed in the case of the chiral catalyst is not known. It could be due to the failure of asymmetric induction or to an accidentally low rotation of chiral product at the sodium D line. Owing to lack of time, work with diazomalonate was discontinued.

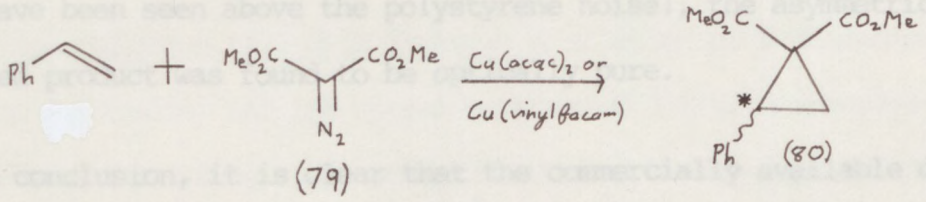
Finally, the activity of a bonded phase catalyst analogous to facam was examined. The bonded phase (81) was prepared by another

worker [57] starting with vinylfacam as shown in scheme 37.

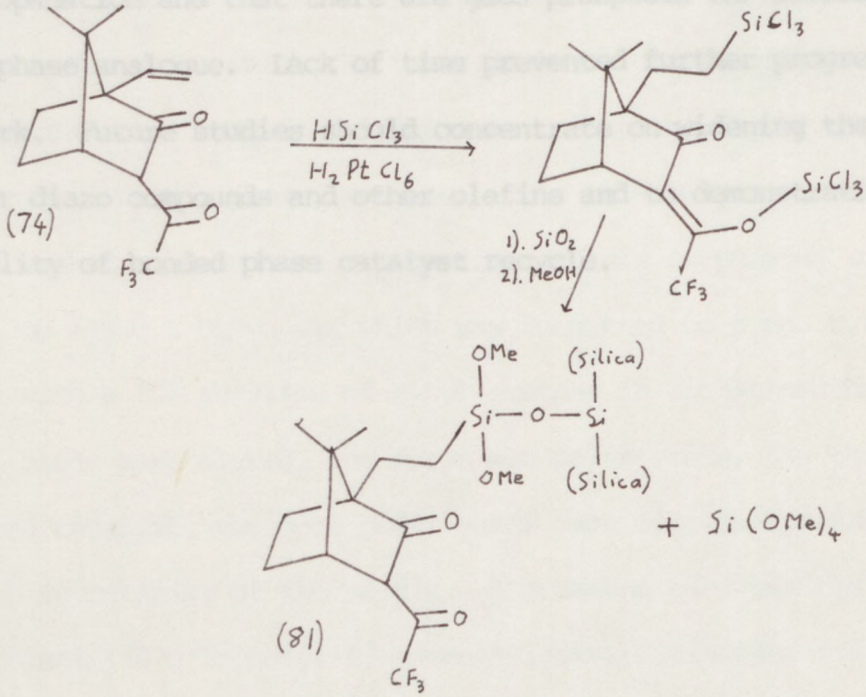
In the present work, the chiral bonded phase was treated with aqueous methanolic copper acetate and the copper salt (82) thus obtained. No attempt was made to determine the amount of copper taken up by the facam but the bonded phase assumed a pale blue colouration.

Repeating the reaction between diazodimedone and styrene stirring the bonded phase copper facam as a suspension in styrene and chloroform afforded the cyclopropane (77) in 43% yield with a mean $[\alpha]_D$ of -59°. The reaction was complete within ten hours as opposed to twenty four hours for the copper complex of vinylfacam, demonstrating that the bonded phase is more active. The catalyst after filtering had assumed a greenish tint and was contaminated with polystyrene. The catalyst was washed in ethyl acetate but did not resume the original blue colour. It proved to be inactive when the reaction was repeated, which was disappointing but was probably due in the present case to contamination with a coating of polystyrene.

The optical purity of the cyclopropanation product was assessed using a chiral n.m.r. shift reagent. In a control experiment, $Eu(facam)_3$ was added in measured portions up to a total of 1 Eq. to a $CDCl_3$ solution of racemic cyclopropane (77) produced by $Cu(acac)_2$ catalysis. One of the cyclopropane protons (2.33m) moved gradually upfield and also split into two separate signals (for 1Eq of $Eu(facam)_3$ the signals appeared at 2.33ppm (broad d) and 2.00ppm (broad d), the integral was complicated by the presence of a weak polystyrene background). When this n.m.r. experiment was repeated with the optically active product from the bonded phase catalysed reaction, the same cyclopropyl-H signal shifted , but appeared only as a single signal. Thus, within the limits of sensitivity of this



Scheme 36.



Scheme 37.

n.m.r. experiment (±10% max; any signal remaining at 2.33ppm could not have been seen above the polystyrene noise), the asymmetrically induced product was found to be optically pure.

In conclusion, it is clear that the commercially available d-facam has potential for use in asymmetric induction catalysts for cyclopropanation and that there are good prospects for developing a bonded phase analogue. Lack of time prevented further progress with this work. Future studies should concentrate on widening the scope to other diazo compounds and other olefins and to demonstrating the possibility of bonded phase catalyst recycle.

3.3. Experimental.

2-Diazodimedone (77) with Styrene: A solution of 2-diazodimedone (500mg; 3.0lmmole) and the copper complex of 3-trifluoroacetyl-d-camphorate (73) (20mg) in styrene (15ml) and benzene was refluxed for twenty four hours after which the diazo absorption band (2140cm^{-1}) had disappeared in the i.r. The excess solvent was evaporated off to leave a brown gum which was taken up in chloroform (20ml) and slowly poured into methanol (200ml) precipitating polystyrene as a plastic solid with a fine suspension. The bulk was filtered and the residue washed with methanol. The filtrate was evaporated to dryness to leave a brown wax which was submitted to prep. t.l.c. eluting with a 10% solution of ethyl acetate in dichloromethane. Several bands were eluted, the first was polystyrene, the third was recovered catalyst, two more polar bands gave complex spectra in addition to material at the origin. The second band was the cyclopropane (77), 1-phenyl-6,6-dimethylspiro[2,5]octane-4,8-dione obtained as a pale green oil (262mg; 36%). A proton n.m.r. of the material showed polystyrene peaks whilst analytical t.l.c. showed contamination with catalyst. The rotation of several samples (48mg-88mg) were measured in dichloromethane (10ml) using a Zeiss polarimeter. The value of $[\alpha]_D$ was calculated for each reading of a total of ten readings and averaged to give a mean $[\alpha]_D$ of -24°. The product was resubmitted to prep. t.l.c. to give a colourless oil (116mg). δ($CDCl_3$): 1.07 (6H,s), 1.58 (2H,m), 2.33 (s, overlapping with small multiplet (5H), 6.99 (5H,m). The spectrum has small peaks around the methyl singlet (0.6-1.4ppm) and the phenyl multiplet (6.7-7.0) which are attributed to polystyrene. νmax ($CHCl_3$): 3060w, 3010m, 2920s, 1705vs, 1620s, 1490m, 1450m, 1360m, 1210m, 1090m, 900s. m/e: 242 (82.3%, M+), 241 (10.3%), 227 (3.1%), 185 (42.5%), 171 (31.1%), 165 (8.3%), 158 (9.2%), 144 (27.5%), 139

(60.7%), 115 (36.3%), 105 (100%). λ max (MeOH): 215nm (log ϵ 4.01). Found C, 79.58; H, 7.69%; $C_{16}H_{18}O_2$ requires C, 79.34; H, 7.44%. Several attempts were made to obtain analytically pure material; the error is attributed to polystyrene. The mean $[\alpha]_D$ of the sample was -55° ($\pm 10^\circ$).

The reaction was repeated under identical conditions using the copper complex of 1-vinyl--3-trifluoroacetyl-d-camphorate (74) (15mg). The diazo absorption band in the i.r. had disappeared after twenty fours under reflux. The cyclopropane (77) was initially separated as a pale green oil (350mg; 48%). Repurification furnished a colourless oil (182mg) which gave a mean $[\alpha]_D$ of -60° ($\pm 10^\circ$). The oil on prolonged standing gave pale yellow crystals m.p. 65-67°C.

The reaction was repeated with the copper complex of 9-iodo-3-trifluoroacetyl-d-camphorate (75). The reaction needed 32 hours reflux for the diazo absorption band to disappear in the i.r. The cyclopropane (77) was obtained as a green oil (153mg; 21%). Resubmission to chromatography separated most of the catalyst impurity (1.7mg) but the product (110mg) maintained a pale green colour and gave a mean $[\alpha]_D$ of -44° ($\pm 15^\circ$, owing to the smaller quantities of sample used in the measurements).

The reaction was repeated with copper acetyl acetonate requiring sixteen hours reflux for the diazo absorption band to disappear in the i.r. The cyclopropane (77) was furnished as a colourless oil (394mg; 54%) which gave a mean $[\alpha]_D$ of 0° ($\pm 10^\circ$).

The reaction was repeated using the copper complex of the chiral bonded phase (82) (60mg), which was stirred as a suspension. The diazo absorption band disappeared after ten hours reflux. The cyclopropane (77) was obtained as a colourless oil (313mg; 43%) and

gave a mean $[\alpha]_D$ of -59°. During the work-up the bonded phase catalyst was separated by filtering the chloroform solution before it was poured into the methanol. The catalyst had changed from a pale blue to a dark yellow catalyst. It was washed in ethyl acetate, upon which it became a powder as before, but was a pale yellow colour. It proved inactive upon repeating the reaction with the diazo absorption band still present after reflux for two days.

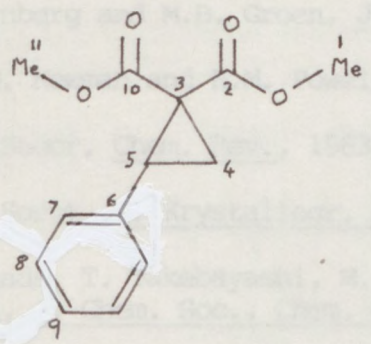
Dimethyl Diazomalonate (79) with Styrene: A solution of dimethyl diazomalonate (79) (500mg; 3.16mmole) and copper acetylacetonate (10mg) in styrene (15ml) and benzene (40ml) was refluxed for eighteen hours after which the diazo absorption band (2120cm^{-1}) had disappeared in the i.r. The work-up procedure was identical to above and the cyclopropane (80), 1,1-dicarbomethoxy-2-phenylcyclopropane, was furnished as a colourless oil (165mg; 45%). δ ($CDCl_3$): 1.68 (2H,m), 2.10 (1H,dd,J=9 and 8Hz), 3.21 (3H,s), 3.63 (3H,s), 6.89 (5H,m). ν max ($CHCl_3$): 3040m, 3005m, 2960m, 1725vs, 1605w, 1495w, 1440s, 1375m, 1335s, 1280vs, 1195m, 1180m, 1135s, 1100m, 970m, 910vs, 700m. $C^{13}\delta$ ($CDCl_3$): 19.14t C4, 32.62d C5, 37.37s C3, 52.28q and 52.86q C1 and C11, 127.67d 128.45d 128.71d C7-9, 134.90s C6, 167.38s and 170.64s C2 and C10. m/e: 234 (5.4%, M+), 202 (15.7%), 174 (3.6%), 171 (15.9%), 170 (45.6%), 143 (5.6%), 129 (5.6%), 121 (72.2%), 115 (100%), 105 (14.9%), 91 (17.9%). λ max (MeOH): 215nm (log ε 4.05). Found C, 66.85; H, 6.19%; $C_{13}H_{14}O_4$ requires C, 66.67; H, 5.98%. The mean $[\alpha]_D$ was 0° (±5°).

The reaction was repeated using the copper complex of 1-vinyl-3-trifluoroacetyl-d-camphorate (20mg). The diazo absorption band had disappeared after twenty four hours reflux. The cyclopropane (80) was furnished as a colourless oil (240mg; 34%) with a mean $[\alpha]_D$ of 0° (±5°).

Copper Complexes of (73), (74) and bonded phase (81): The camphor (73), (74) (500mg) in methanol (1ml) was added to a solution of copper acetate (500mg) in water (10ml) to give a dark green precipitate, which was filtered and recrystallised from 50% aqueous methanol.

The silica bonded phase camphorate (81) (100mg) was stirred as a suspension overnight in a solution of copper acetate (500mg) in 50% aqueous methanol. The bonded phase was filtered and washed with water, then methanol and dried under vacuum to leave a pale blue powder of the copper complex (82) (104mg).

The copper complex of 9-iodofacam had been prepared by another worker [59] but needed to be crystallised from 50% aqueous methanol before it was active.



3.4. References.

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CHAPTER FOUR.

Some Miscellaneous Studies in Diazo Chemistry.

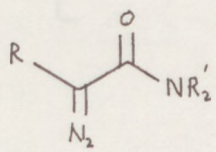
(1) (2)

"But my righteous one shall live by faith, and if he shrinks back my soul has no pleasure in him." (Hebrews 10.38).

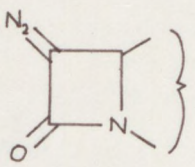
4.1. Synthesis of 2-Diazo-3-phenylpropanoic acid N,N-dimethylamide.

4.1.1. Introduction.

2-Diazo-amide compounds (1) (with the exception of the α-diazo-β-lactam antibiotics (2)) are a very little studied class of compounds.



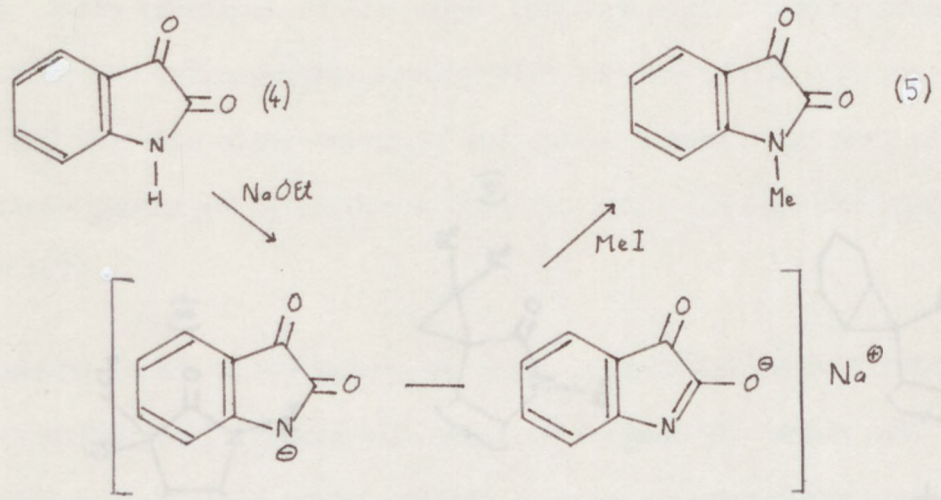
(1)



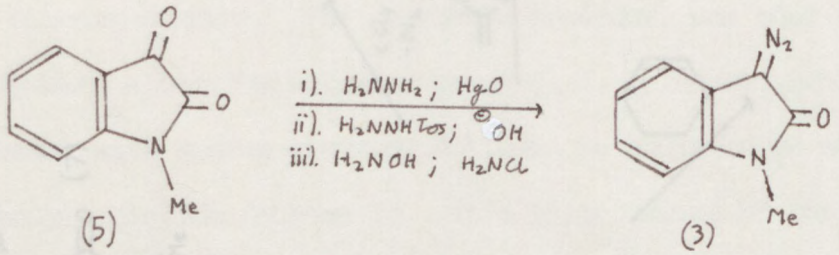
(2)

One of the most extensive studies was by Mariconi and Murray [1] with N-methyl-3-diazooxindole (3). Using isatin (4) as the starting material, they prepared the N-methyl derivative (5) in two steps by treatment with base to give the sodium salt followed by methyl iodide to give N-methylisatin (5) (scheme 1). They used three different routes to obtain the required diazo compound using i). Hydrazine to prepare the 3-hydrazone followed by oxidation to the diazo compound with mercuric oxide (yield 62%), ii). A Bamford Stevens reaction where the tosyl hydrazone was cleaved with base (yield 84%) and iii). A Forster reaction where the oxime was cleaved by alkaline chloramine oxidation (yield 58%) (scheme 2).

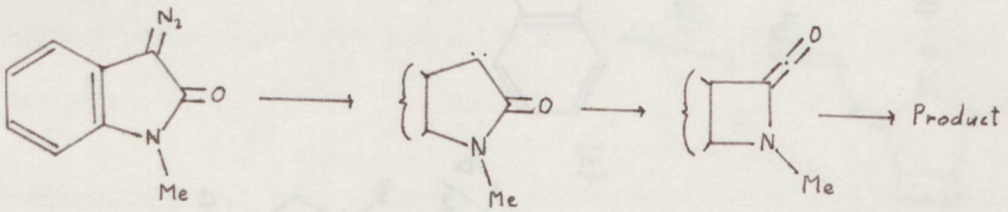
Quite extensive studies were performed with the compound (scheme 3). Pyrolysis in ethanol afforded the azine (6) (1.7%) and the ethyl ether (24%). Treatment with bromine in carbon tetrachloride gave the 3,3-dibromo derivative (7) (89%), whereas interestingly with carbon tetrachloride alone a trichloromethyl-chloro adduct (8) was isolated. A cyclopropanation with 1,1-diphenylethene was achieved in high yield (9), whereas with cyclohexene an unseparated mixture of endo and exo isomers (10a,10b) were obtained in 27%



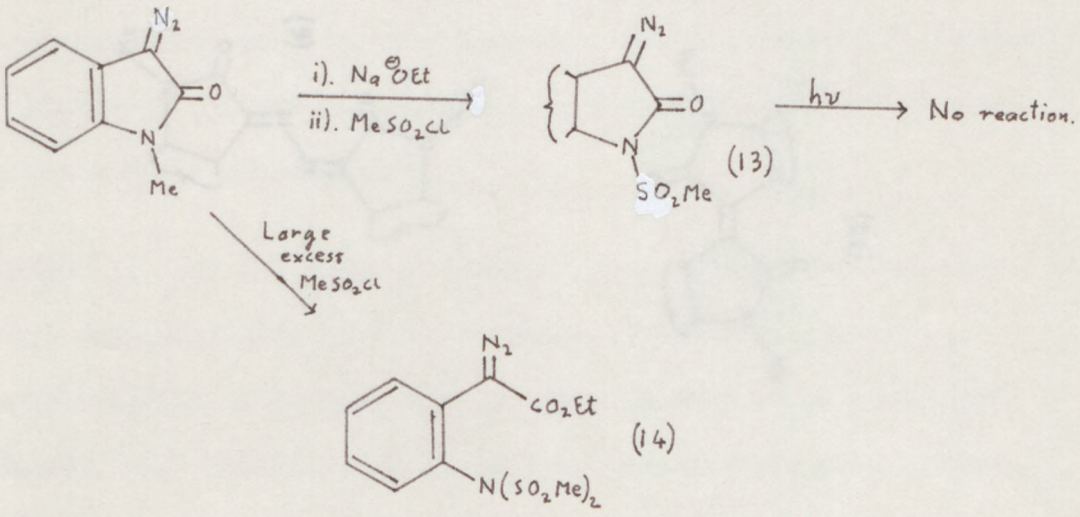
Scheme 1.



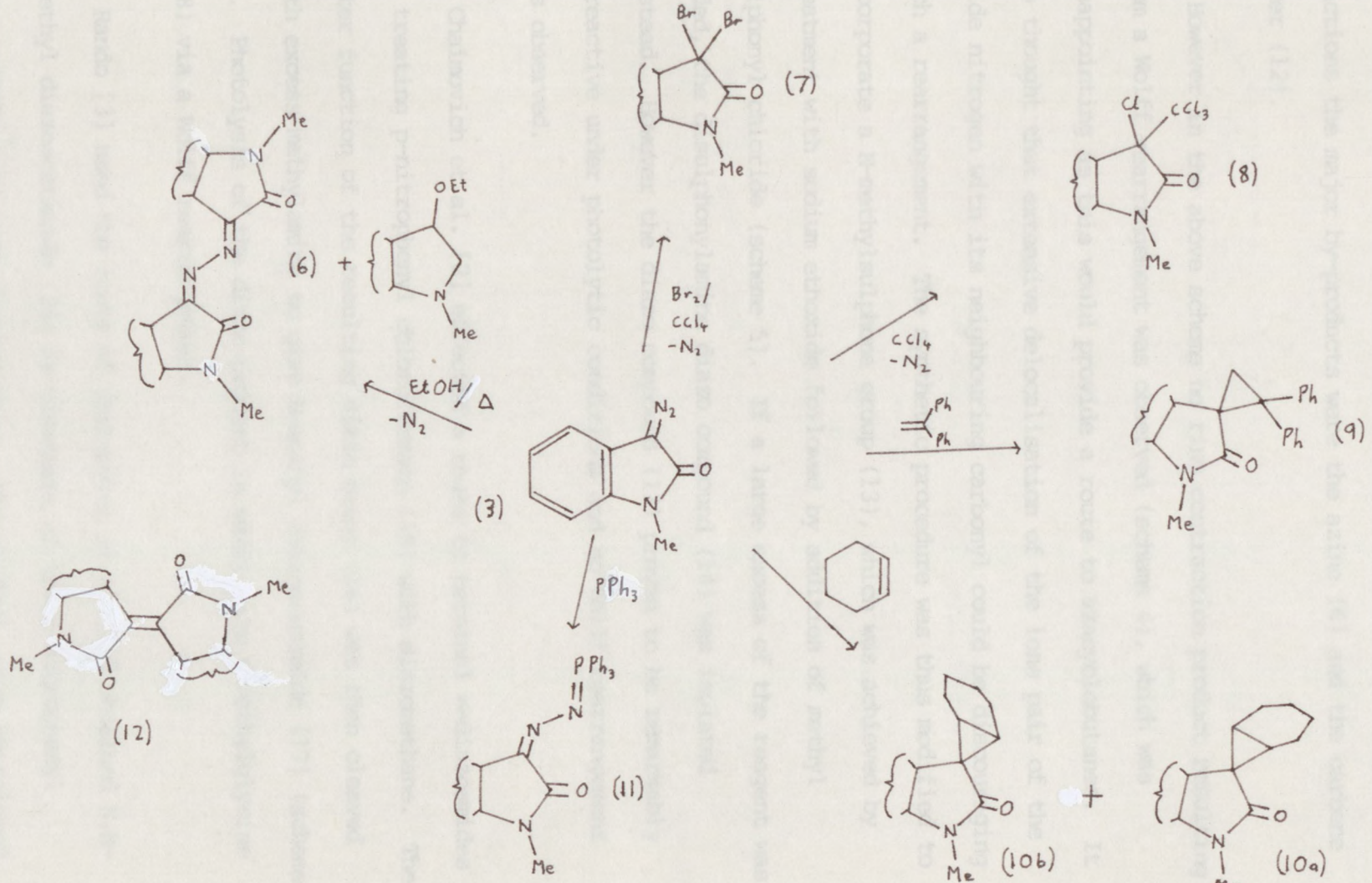
Scheme 2.



Scheme 4.



Scheme 5.


Me
N
O
N
N
Me
(6)
+
OEt
N
Me
EtOH / Δ
-N2
Br2 / CCl4 -N2
Br
Br
O
N
Me
(7)
Cl
CCl3
O
N
Me
(8)
CCl4 -N2
Ph
Ph
Ph
Ph
O
N
Me
(9)
N2
O
N
Me
(3)
PPh3
PPh3
N
N
O
N
Me
(11)
O
N
Me
O
Me
N
O
(12)
O
N
Me
(10b)
+
O
N
Me
(10a)

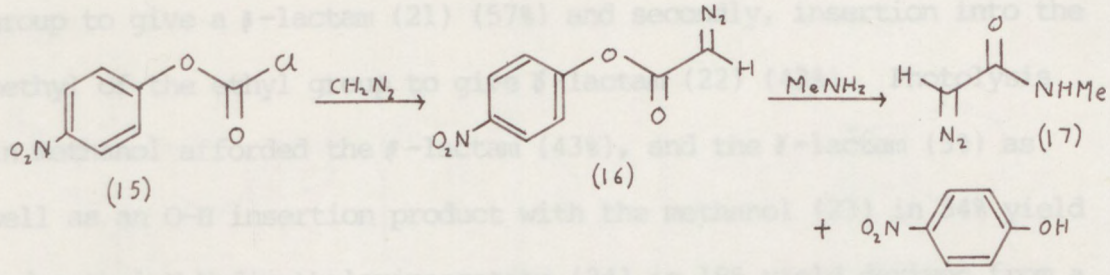
Scheme 3.

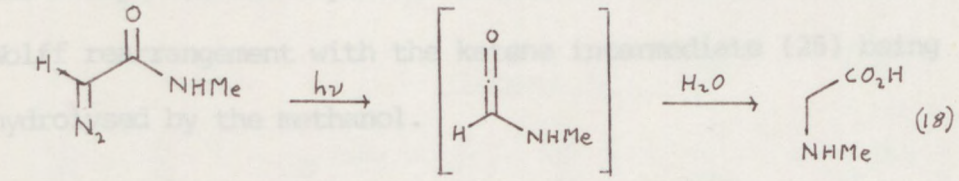
yield. Also treatment of the diazo compound with triphenylphosphine furnished the triphenylphosphazine (11) in good yield. It was observed that the diazo compound decomposed slowly. In many of the reactions the major by-products were the azine (6) and the carbene dimer (12).

However in the above scheme no ring contraction product resulting from a Wolff rearrangement was observed (scheme 4), which was disappointing as this would provide a route to azacyclobutanes. It was thought that extensive delocalisation of the lone pair of the amide nitrogen with its neighbouring carbonyl could be discouraging such a rearrangement. The synthetic procedure was thus modified to incorporate a N-methylsulphone group (13), which was achieved by treatment with sodium ethoxide followed by addition of methyl sulphonyl chloride (scheme 5). If a large excess of the reagent was added, the disulphonylamine diazo compound (14) was isolated instead. However the diazo compound (13) proved to be remarkably unreactive under photolytic conditions and no Wollf rearrangement was observed.

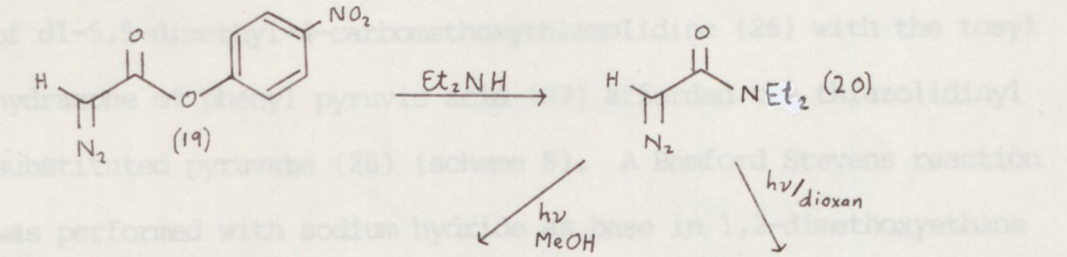
Chaimovich et al. [2] effected a route to terminal α-diazoamides by treating p-nitrophenyl chloroformate (15) with diazomethane. The ester function of the resulting diazo ester (16) was then cleaved with excess methylamine to give N-methyl diazoacetamide (17) (scheme 6). Photolysis of the diazo product in water gave N-methylglycine (18) via a Wolff rearrangement.

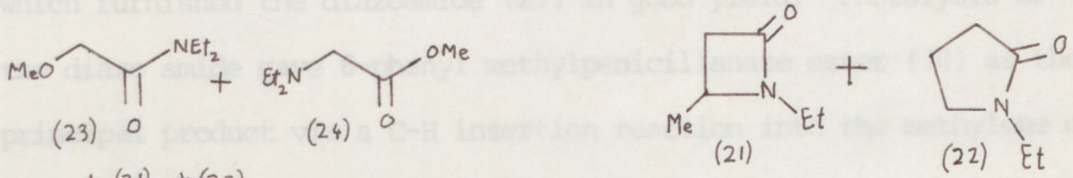
Rando [3] used the route of Chaimovich et al. and obtained N,N-diethyl diazoacetamide (20) by treatment of the p-nitrophenyl diazoacetate (19) with diethylamine. The product, when photolysed in dioxan, was observed to give two C-H insertion products (scheme 7). Firstly, insertion into the C-H of methylene of the N-ethyl

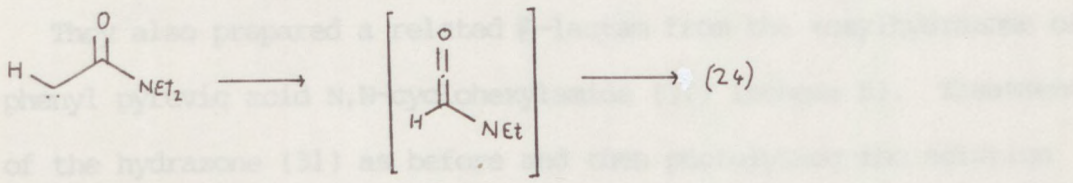




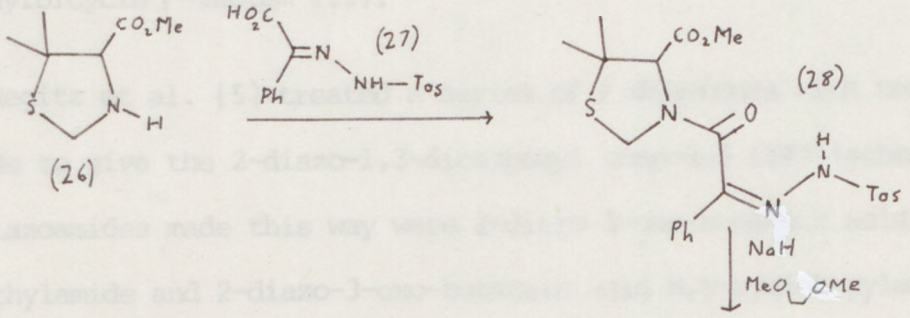
Scheme 6.







Scheme 7.



Scheme 8.

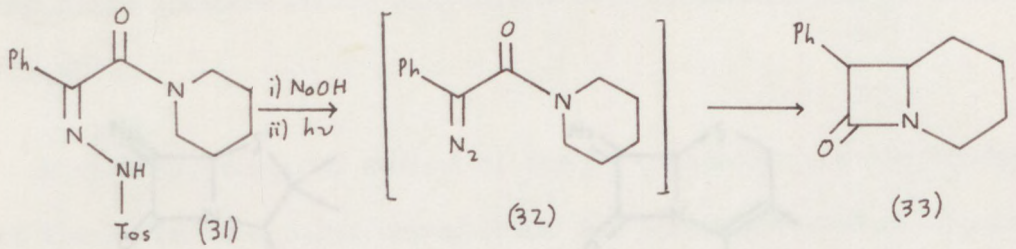
group to give a β-lactam (21) (57%) and secondly, insertion into the methyl of the ethyl group to give γ-lactam (22) (43%). Photolysis in methanol afforded the β-lactam (43%), and the γ-lactam (5%) as well as an O-H insertion product with the methanol (23) in 34% yield and methyl N,N-dimethylaminoacetate (24) in 18% yield derived from a Wolff rearrangement with the ketene intermediate (25) being hydrolysed by the methanol.

Corey and Felix [4] recognised the potential of the above reaction as an alternative route to β-lactam antibiotics. Treatment of dl-5,5-dimethyl-4-carbomethoxythiazolidine (26) with the tosyl hydrazone of phenyl pyruvic acid (27) afforded the thiazolidinyl substituted pyruvate (28) (scheme 8). A Bamford Stevens reaction was performed with sodium hydride as base in 1,2-dimethoxyethane which furnished the diazoamide (29) in good yield. Photolysis of the diazo amide gave 6-phenyl methylpenicillanate ester (30) as the principal product via a C-H insertion reaction into the methylene of the thiazolidine.

They also prepared a related β-lactam from the tosylhydrazone of phenyl pyruvic acid N,N-cyclohexylamide (31) (scheme 9). Treatment of the hydrazone (31) as before and then photolysing the solution without isolating the intermediate diazo compound (32) gave the 7-phenylbicyclo β-lactam (33).

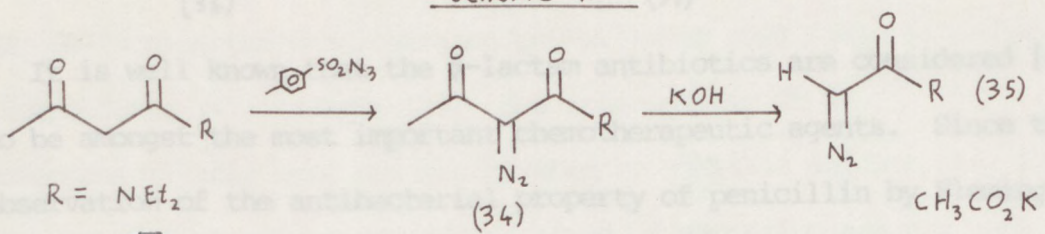
Regitz et al. [5] treated a series of β-diketones with tosyl azide to give the 2-diazo-1,3-dicarbonyl compound (34) (scheme 10). 2-Diazoamides made this way were 2-diazo-3-oxo-butanoic acid N,N-diethylamide and 2-diazo-3-oxo-butanoic acid N,N-cyclohexylamide. These could be then cleaved to the terminal diazoamide (35) with methanolic potassium hydroxide solution.

By far the most studied class of 2-diazoamides are the 6-



(31) (32) (33)

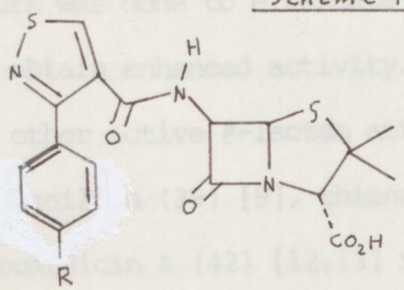
Scheme 9.



R = NEt_2 (34) (35)

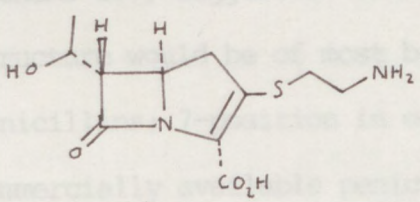


Scheme 10.

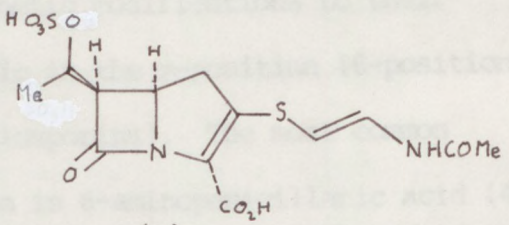


(38) R = H

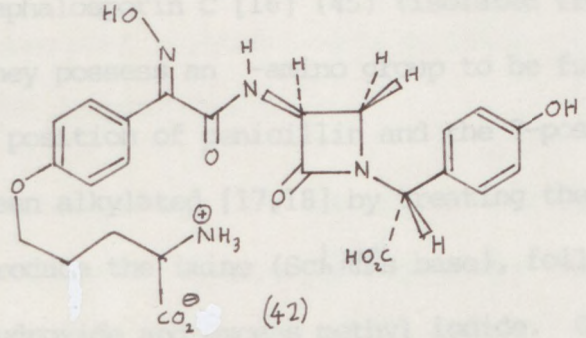
(39) R = Cl



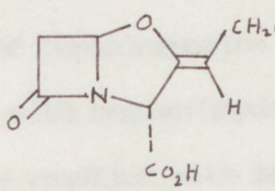
(40)



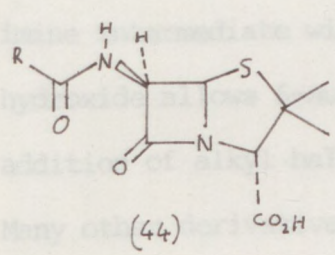
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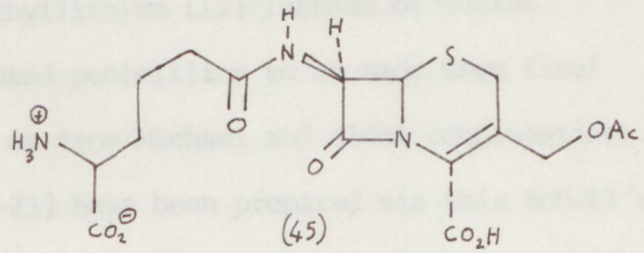
(42)



(43)



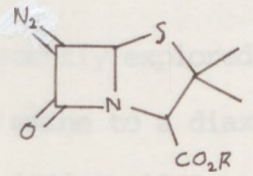
(44)



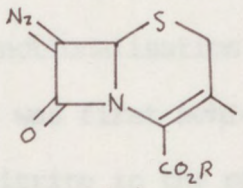
(45)

Scheme 11.

diazopenicillanates (36) and 7-diazocephalosporanates (37).



(36)



(37)

It is well known that the β-lactam antibiotics are considered [6] to be amongst the most important chemotherapeutic agents. Since the observation of the antibacterial property of penicillin by Fleming some fifty years ago and Cephalosporium acremonium by Brotzu [7] in 1945, much work was done to elucidate their structure and then modify it to obtain enhanced activity. This, coupled with the discovery of other active β-lactam antibiotics, such as oxacillin (38) [8], cloxacillin (39) [9], thienamycin (40) [10], olivanic acid (41) [11], nocardicin A (42) [12,13] and clavulanic acid (43) [14] (scheme 11), suggested that synthetic modifications to their structure would be of most benefit in the α-position (6-position in penicillins; 7-position in cephalosporins). The most common commercially available penicillin is 6-aminopenicillanic acid (44) (6-APA) obtained from penicillin fermentations [15] and along with cephalosporin C [16] (45) (isolated from cephalosporium acremonium), they possess an -amino group to be functionalised. For example the 6 position of penicillin and the 7-position of cephalosporins have been alkylated [17,18] by treating the amine with benzaldehyde to produce the imine (Schiff's base), followed by reaction with sodium hydroxide and excess methyl iodide. Generating the carbanion of the imine intermediate with methyllithium [19] instead of sodium hydroxide allows 6-substituted penicillins to be made from final addition of alkyl halides, or from Michael and aldol condensations. Many other derivatives [20-23] have been prepared via this Schiff's base method just described. Other methods of functionalisation from

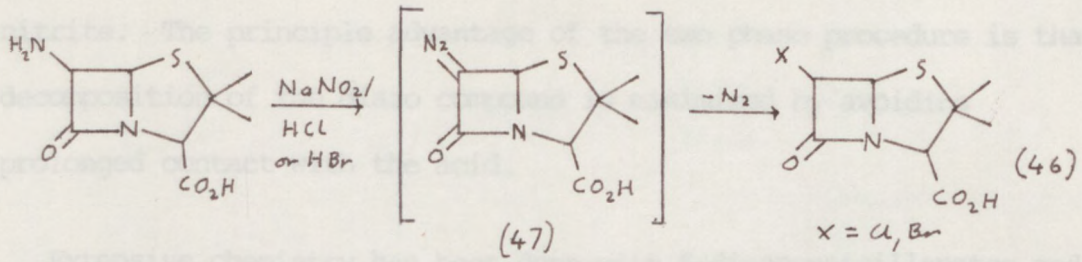
the amine include direct alkylation with methanesulphenyl chloride (CH_3SCl).

A recently explored method of functionalisation is via conversion of the amine to a diazo group which was first achieved by Cignarella et al. [24] in 1962, using sodium nitrite in the presence of HCl or HBr to furnish the 6-halogenated penicillanic acid (46) via a diazo intermediate (47) (scheme 12). The intermediacy of 6-diazopenicillanic acid was established by McMillan and Stoodley [25] who showed that extensive incorporation of deuterium occured when the deamination was carried out in DCl solution.

By esterifying the carboxylic acid on the 2-position the diazo compound can be isolated under the aforementioned reaction conditions. Preferred esters are those which can be readily cleaved after reaction to regenerate the final penicillanic acid product, either chemically (e.g. p-nitrobenzyl [26] and benzhydryl groups [27]) or biologically (e.g. pivaloyloxymethyl groups [28]).

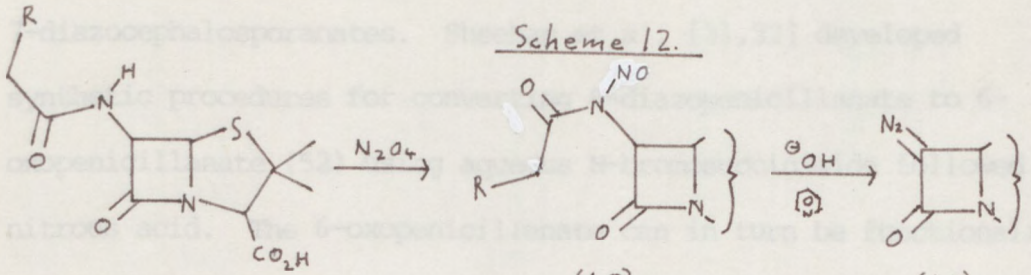
Other methods of diazotisation of penicillanic esters include a method by Hauser and Sigg [29] who prepared the 6-N-nitrosoamide (48) by treatment of 6-aminopenicillanates with N_2O_4 (scheme 13). Subsequent treatment with pyridine afforded the 6-diazopenicillanate (49) in poor yield.

Cama et al. [30] developed a two phase procedure whereby benzhydryl 7-diazocephalosporanate (50) was prepared, in which the p-toluene sulphonate of benzhydryl 7-aminocephalosporanate in dichloromethane was treated with an aqueous nitrous acid solution. In 1978, Sheehan applied Cama´s two phase procedure to the conversion of benzhydryl 6-aminopenicillanate (51) to its diazo derivative in good yield (scheme 14). Nitrous acid was generated in the aqueous phase by the action of perchloric acid on sodium



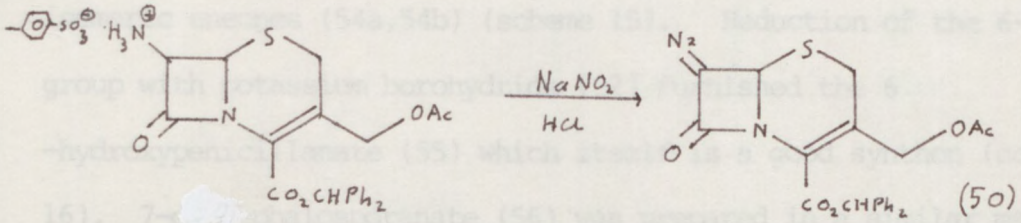
(47) (46)

Scheme 12.

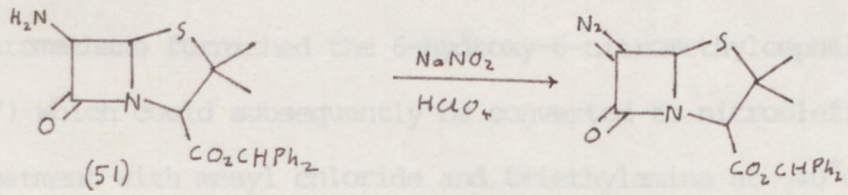


(48) (49)

Scheme 13.

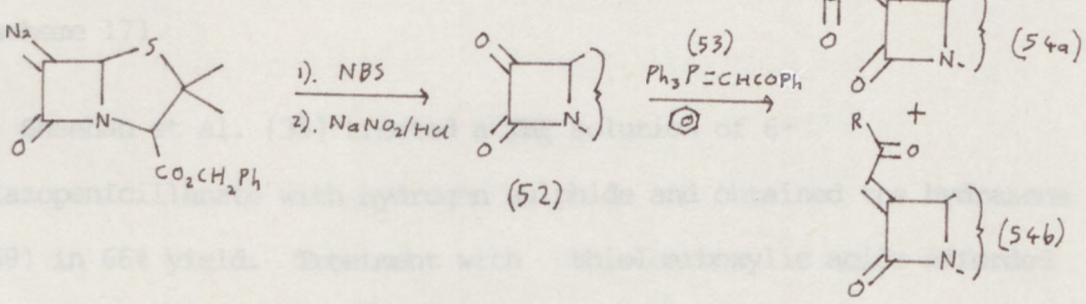


(50)



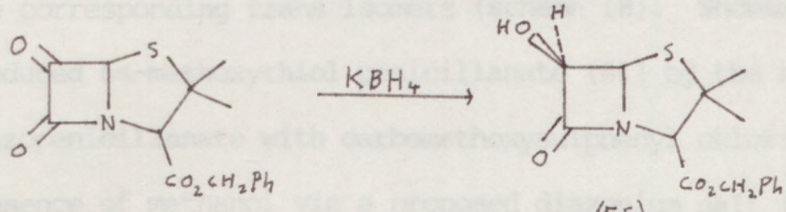
(51)

Scheme 14.



(52) (54a) (54b)

Scheme 15.



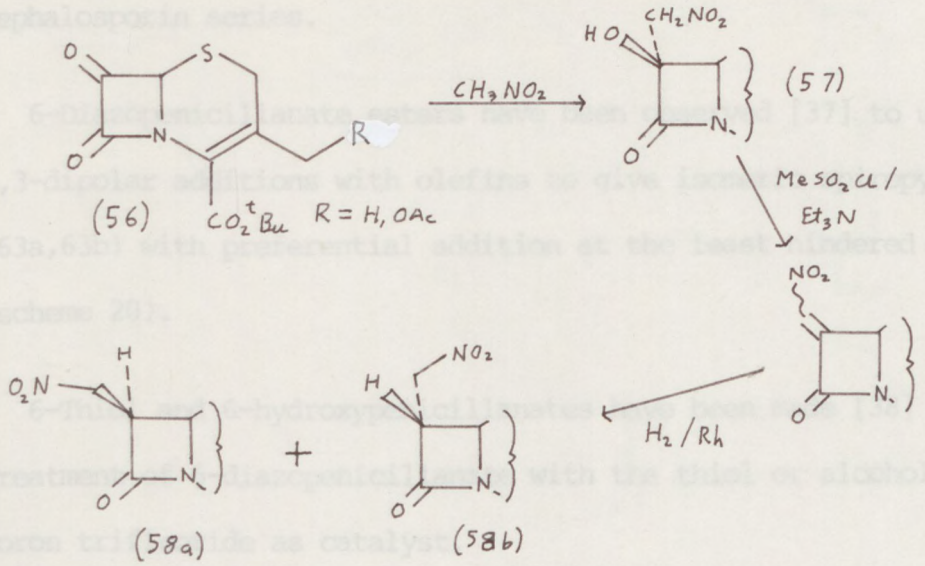
(55)

Scheme 16.

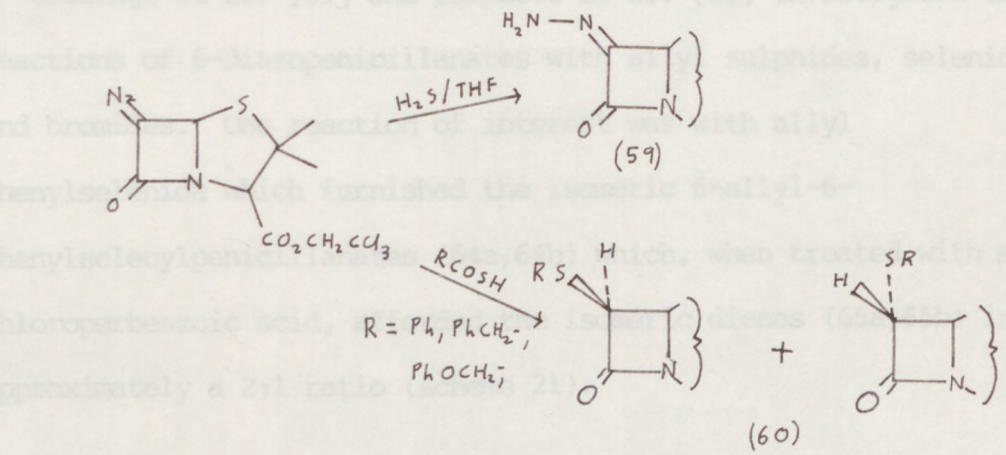
nitrite. The principle advantage of the two phase procedure is that decomposition of the diazo compound is minimized by avoiding prolonged contact with the acid.

Extensive chemistry has been done with 6-diazopenicillanates and 7-diazocephalosporanates. Sheehan et al. [31,32] developed synthetic procedures for converting 6-diazopenicillanate to 6-oxopenicillanate (52) using aqueous N-bromosuccinimide followed by nitrous acid. The 6-oxopenicillanate can in turn be functionalised especially by using Wittig reagents such as the readily available benzoylmethylene-triphenylphosphorane (53) which furnished [33] the isomeric eneones (54a,54b) (scheme 15). Reduction of the 6-oxo group with potassium borohydride [32] furnished the 6 -hydroxypenicillanate (55) which itself is a good synthon (scheme 16). 7-oxocephalosporanate (56) was prepared in a similar manner again producing a useful synthon. For example [34] addition of nitromethane furnished the 6-hydroxy-6-nitromethylcephalosporanate (57) which could subsequently be converted to nitroolefins by treatment with mesyl chloride and triethylamine at -40°C. The nitrooelfin was then catalytically reduced to the isomeric nitro products (58a,58b) using tris (triphenylphosphine) rhodium chloride (scheme 17).

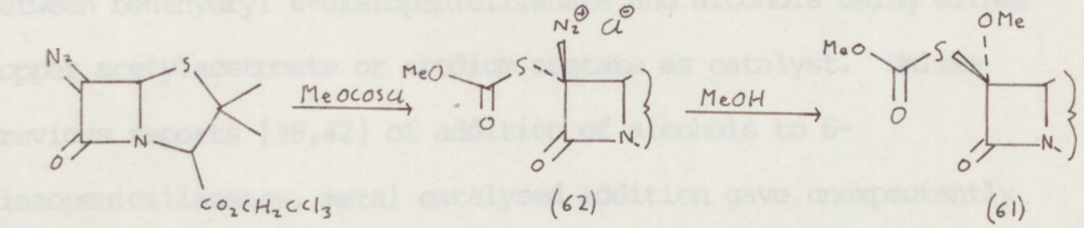
Sheehan et al. [35] treated a THF solution of 6-diazopenicillanate with hydrogen sulphide and obtained the hydrazone (59) in 66% yield. Treatment with thiolcarboxylic acids afforded predominantly the cis 6-thiol esters (60) with small quantities of the corresponding trans isomers (scheme 18). Sheehan et al. [36] produced 6α-methoxythiol penicillanate (61) by the reaction of 6-diazopenicillanate with carbomethoxysulphenyl chloride in the presence of methanol via a proposed diazonium salt intermediate (62) (scheme 19). Similar results were reported for the corresponding



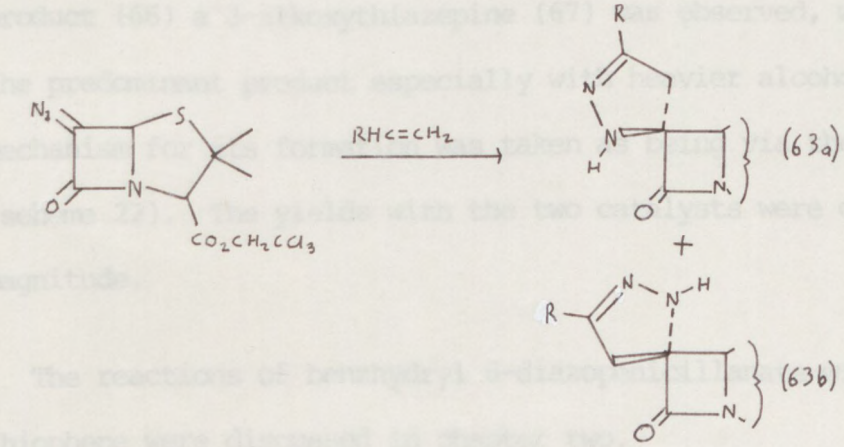
Scheme 17.



Scheme 18.



Scheme 19.



Scheme 20.

cephalosporin series.

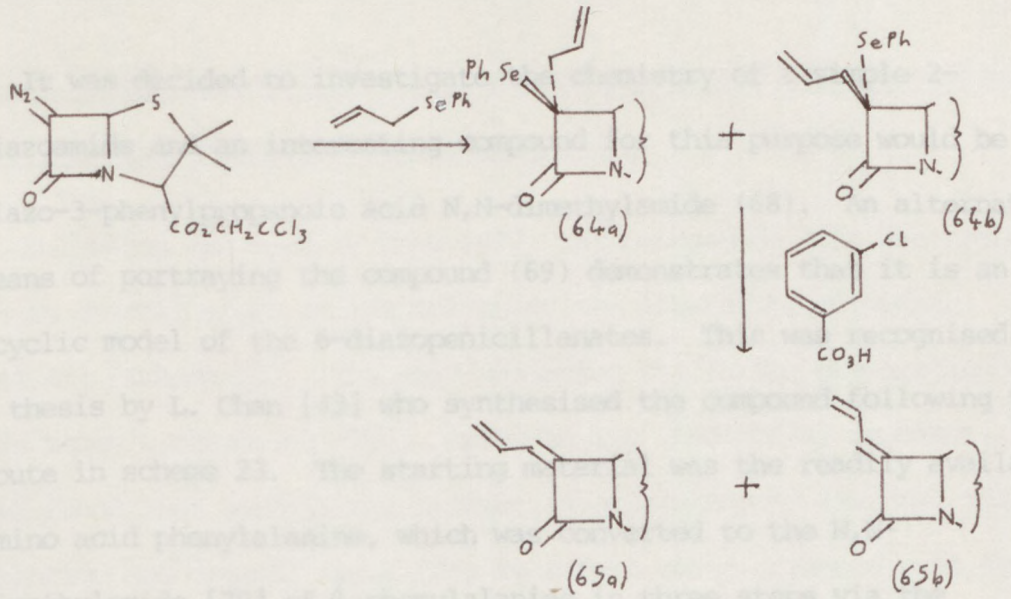
6-Diazopenicillanate esters have been observed [37] to undergo 1,3-dipolar additions with olefins to give isomeric spiropyrazolines (63a,63b) with preferential addition at the least hindered α-side (scheme 20).

6-Thiol and 6-hydroxypenicillanates have been made [38] by treatment of 6-diazopenicillanate with the thiol or alcohol using boron trifluoride as catalyst.

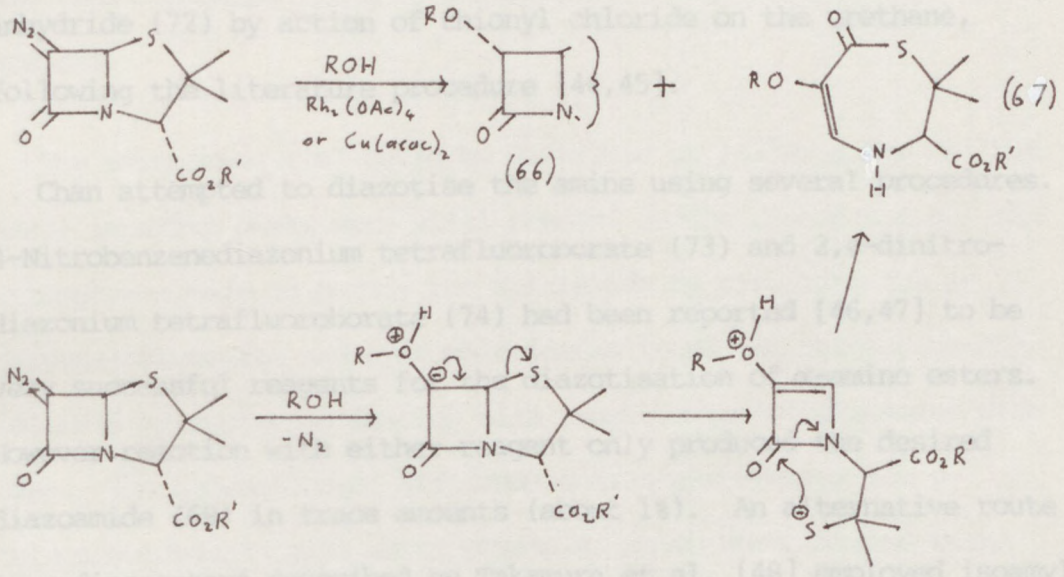
Giddings et al. [39] and Campbell et al. [40] investigated the reactions of 6-diazopenicillanates with allyl sulphides, selenides and bromides. One reaction of interest was with allyl phenylselenide which furnished the isomeric 6-allyl-6-phenylselenylpenicillanates (64a,64b) which, when treated with m-chloroperbenzoic acid, afforded the isomeric dienes (65a,65b) in approximately a 2:1 ratio (scheme 21).

Matlin and Chan [41] considered the metal catalysed reaction between benzhydryl 6-diazopenicillanate and alcohols using either copper acetylacetonate or rhodium acetate as catalyst. Unlike previous reports [38,42] of addition of alcohols to 6-diazopenicillanates, metal catalysed addition gave unexpectantly different behaviour. In addition to the 6-alkoxypenicillanate product (66) a 3-alkoxythiazepine (67) was observed, which was often the predominant product especially with heavier alcohols; the mechanism for its formation was taken as being via the oxonium ylid (scheme 22). The yields with the two catalysts were of similar magnitude.

The reactions of benzhydryl 6-diazopenicillanate with furan and thiophene were discussed in chapter two.



Scheme 21.



Scheme 22

It was decided to investigate the chemistry of a simple 2-diazoamide and an interesting compound for this purpose would be 2-diazo-3-phenylpropanoic acid N,N-dimethylamide (68). An alternative means of portraying the compound (69) demonstrates that it is an acyclic model of the 6-diazopenicillanates. This was recognised in a thesis by L. Chan [43] who synthesised the compound following the route in scheme 23. The starting material was the readily available amino acid phenylalanine, which was converted to the N,N-dimethylamide [70] of β-phenylalanine in three steps via the urethane (71) using benzyl chloroformate and via the Leuch's anhydride (72) by action of thionyl chloride on the urethane, following the literature procedure [44,45].

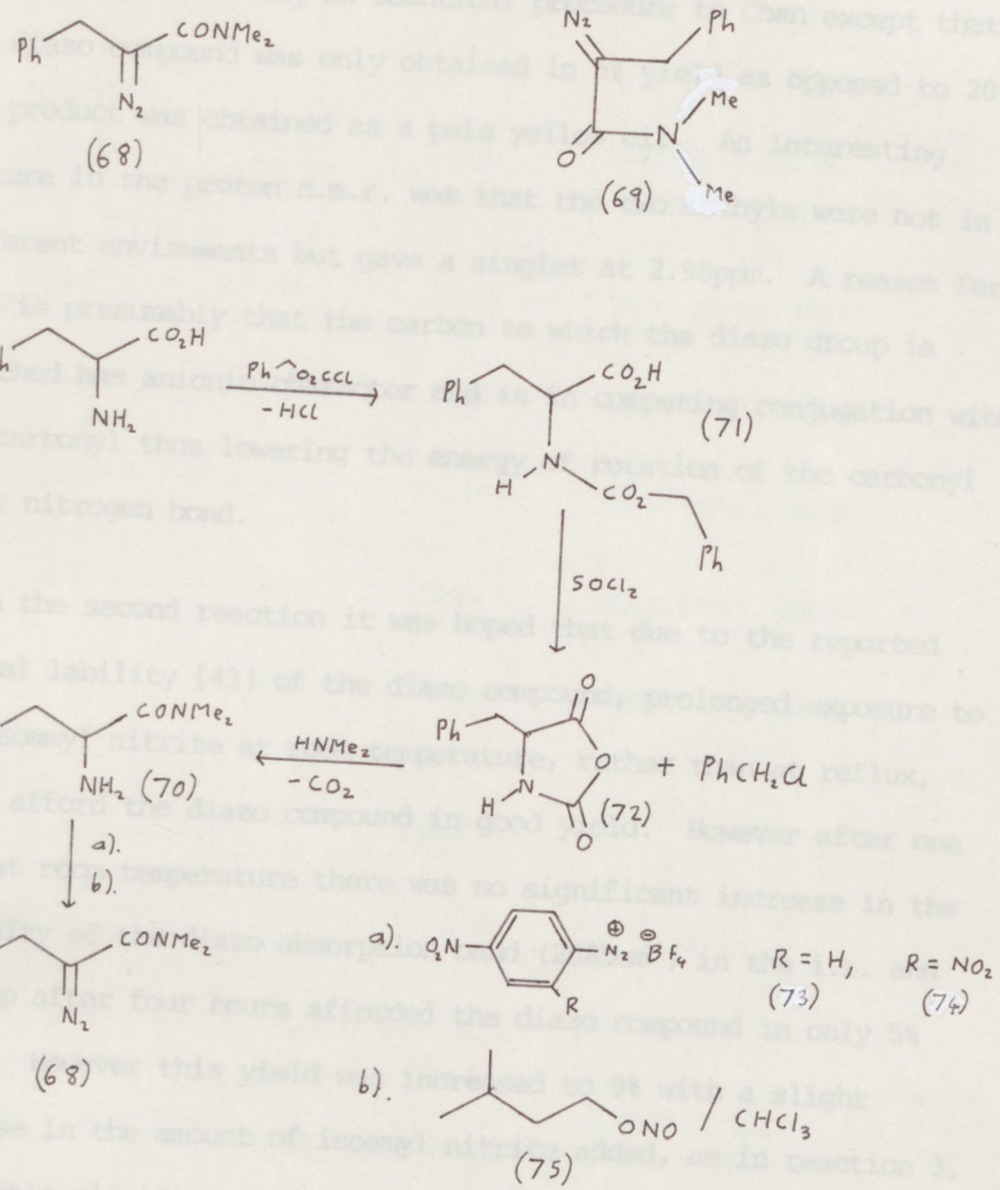
Chan attempted to diazotise the amine using several procedures. 4-Nitrobenzenediazonium tetrafluoroborate (73) and 2,4-dinitrodiazonium tetrafluoroborate (74) had been reported [46,47] to be very successful reagents for the diazotisation of α-amino esters. However reaction with either reagent only produced the desired diazoamide (68) in trace amounts (about 1%). An alternative route to α-diazoesters described by Takamura et al. [48] employed isoamyl nitrite (75) as the nitrosating agent. Applying the method, refluxing the α-aminoamide (70) with 1.2 Eq. of isoamyl nitrite in chloroform containing 0.3 Eq. of acetic acid for fifteen minutes, afforded the diazoamide (68) in 20% yield, after workup on column chromatography using neutral alumina. No further effort was made to improve the yield but the compound (68) was reported to be labile, acid sensitive, decomposing even on silica gel chromatography.

4.1.2. Synthesis of 2-Diazo-3-phenylpropanoic acid N,N-dimethylamide (68) from the Aminoamide Derivative (70).

Following the work by Chan [43], the aminoamide (70) was prepared in an overall yield of 19% following the literature procedure [44,45] (scheme 23). The only variation was in the preparation of the Leuch's anhydride (72). Owing to its insolubilty in ether, it was found that washing the product in ether removed residual thionyl chloride and organic impurities to afford white crystals with the correct melting point. Thus a recrystallisation from benzene, which was time consuming owing to the anhydride's poor solubilty, was avoided.

The aminoamide (70) could be distilled at 145°C (0.5mm Hg) but small impurity peaks were still present in the proton n.m.r. An attempt was made to purify the aminoamide by preparing the p-toluene-sulphonate and hydrochloride salts of the crude product followed by recrystallisation with regeneration of the amine with base. The hydrochloride afforded no crystals whereas the p-toluenesulphonate gave white crystals, which when treated with aqueous KOH afforded pure aminoamide. Column chromatography also provided pure aminoamide. The two methyl groups of the amide nitrogen gave singlets at 2.75 and 2.91ppm due to the hindered rotation of the carbonyl amide nitrogen bond (because of conjugation of the nitrogen lone pair with the carbonyl), thus placing the methyl groups in different magnetic enviroments in relation to the anisotropic effect of the carbonyl. The proton n.m.r. was taken at 50°C in $CDCl_3$ and 120°C in chlorobenzene. The two singlets were observed to move together almost coalescing at 120°C.

The diazotisation of the aminoamide (70) with isoamyl nitrite (75) using an analogous procedure to Chan [43] was studied, varying


Ph
CONMe2
N2
(68)
N2
Ph
Me
N
O
Me
(69)
Ph
CO2H
NH2
Ph CO2CCl
- HCl
Ph
CO2H
N
H
CO2
Ph
(71)
SOCl2
Ph
CONMe2
NH2 (70)
HNMe2
- CO2
Ph
O
O
N
H
O
(72)
+ PhCH2Cl
a).
b).
Ph
CONMe2
N2
(68)
a).
O2N
N2 BF4
R
R = H, (73)
R = NO2 (74)
b).
ONO
/ CHCl3
(75)

Scheme 23.

the reaction conditions as demonstrated in Table 1. The first reaction was following an identical procedure to Chan except that the diazo compound was only obtained in 5% yield as opposed to 20%. The product was obtained as a pale yellow oil. An interesting feature in the proton n.m.r. was that the two methyls were not in different environments but gave a singlet at 2.98ppm. A reason for this is presumably that the carbon to which the diazo group is attached has anionic character and is in competing conjugation with the carbonyl thus lowering the energy of rotation of the carbonyl amide nitrogen bond.

In the second reaction it was hoped that due to the reported thermal lability [43] of the diazo compound, prolonged exposure to the isoamyl nitrite at room temperature, rather than at reflux, would afford the diazo compound in good yield. However after one hour at room temperature there was no significant increase in the intensity of the diazo absorption band ($2085cm^{-1}$) in the i.r. and work-up after four hours afforded the diazo compound in only 5% yield. However this yield was increased to 9% with a slight decrease in the amount of isoamyl nitrite added, as in reaction 3, but little significance is attached to this result. However the yield increased to 12% when a catalytic amount of acetic acid was added as in reaction 4 whilst the yield of 0%, when no acetic acid was added as in reaction 5, demonstrated the necessity of acid catalysis in this reaction. Repeating reaction 4 with only a slight increase in reaction time had little significant change in the yield (reaction 6).

An attempt was made to improve the yield by using a two phase procedure whereby the amide (70) was in the organic phase and catalyst in an aqueous phase. Table 2 gives the conditions used. Both procedures, whereby the nitrosating reagent was sodium nitrite

	Ph(NH$_2$)CONMe$_2$ mmole	^{i}AmONO mmole	AcOH mmole	Reaction Conditions	% yield Ph(N$_2$)CONMe$_2$
1.	2.79	3.34	0.84	Reflux 15min.	5
2.	2.79	3.34	0.84	Room temp. 4hrs.	5
3.	2.60	3.43	0.84	Room temp. 4hrs.	9
4.	2.60	3.43	0.083	Room temp. 40min.	12.
5.	2.60	3.43	None	Room temp. 40min.	0
6.	2.60	3.43	Drop	Room temp. 1hr.	10

Table 1

	← Organic layer →		← Aqueous layer →		
	Ph(NH$_2$)CONMe$_2$ mmole	^{i}AmONO mmole		Reaction conditions	Yield % Ph(N$_2$)CONMe$_2$
1.	2.60	3.43	H_2SO_4 0.5M 20ml.	Room temp. 15mins.	0
2.	2.60	—	$NaNO_3$ 3.9mmole. H_2SO_4 1% 15ml.	0°C 15min.	0
3.	2.60	—	$NaNO_3$ 3-9mmole. H_2SO_4 1% 15ml.	0°C 1hr. Room temp. 4hrs.	0
4.	2.60	—	$NaNO_3$ 23.4mmole. H_2SO_4 5% 15ml.	0°C 1hr. Room temp. 4hrs.	0

Table 2.

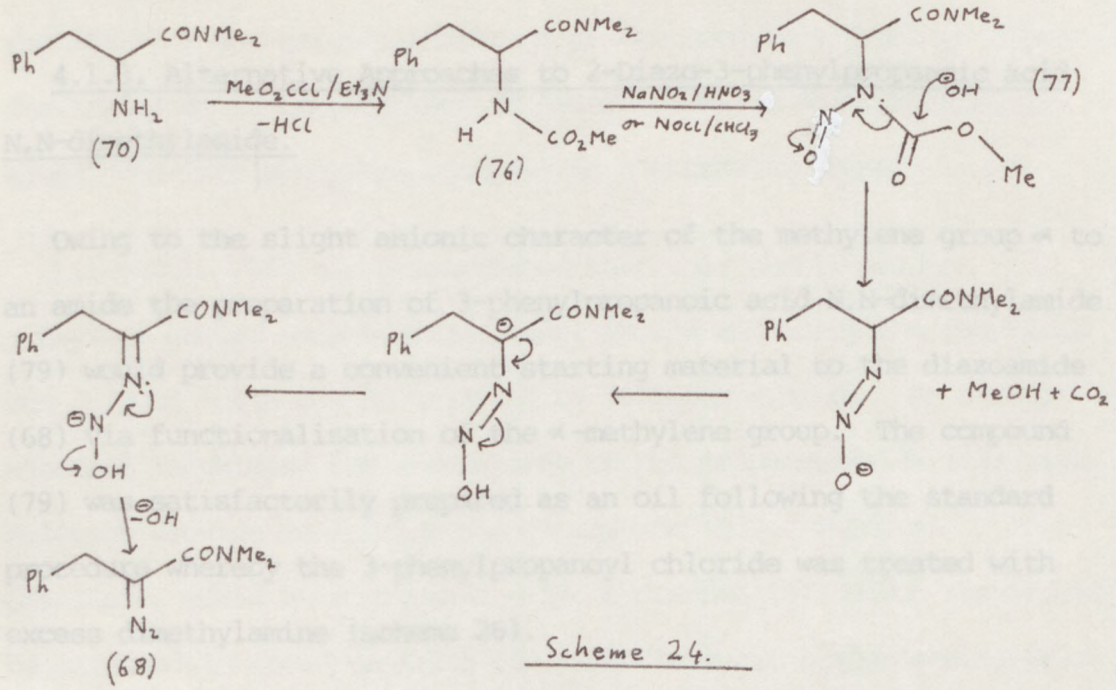
and sulphuric acid in the aqueous phase or sulphuric acid in the aqueous phase with isoamyl nitrite in the organic phase, gave no yield of the diazoamide. Even perchloric acid in place of sulphuric acid in analogy to the preparation of 6-diazopenicillanate ester gave no observed yield of diazoamide. It was decided to abandon further work on the direct diazotisation of the aminoamide and to explore different approaches to improve the yield in the hope of developing a convenient route to α-diazoamides.

Using the aminoamide (70) as the starting material, an alternative approach would be to convert it to a urethane (76) with methyl chloroformate. This, in turn, could in principle, be nitrosated and the resulting N-nitrosourethane (77) could then be converted to the diazoamide (68) with base (scheme 24). The preparation of the urethane proceeded in high yield with methyl chloroformate using triethylamine as an acid scavenger. This was found to be better than pyridine, which gave impure product. However the nitrosation of the urethane could not be effected cleanly. Several procedures were attempted using a two phase procedure with the urethane in dichloromethane and sodium nitrite and nitric acid in the aqueous phase. One prolonged reaction gave a product with a new stretching frequency at 1440cm^{-1} in the i.r. indicative of the N-NO stretch. However, analytical t.l.c. and the presence of an N-H stretch in the i.r. demonstrated that the product was still largely contaminated with starting material.

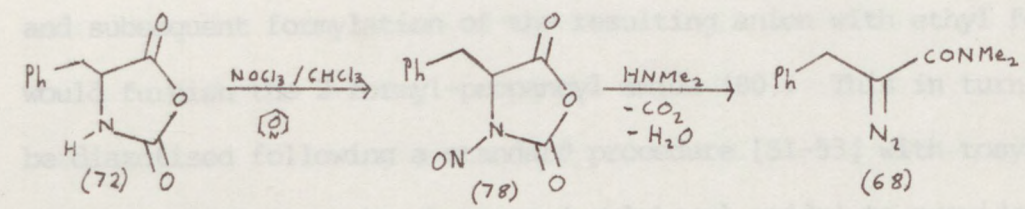
An alternative approach to nitrosation is to use nitrosyl chloride as proposed by Llewellyn and William's [49] who used solutions of nitrosyl chloride in chloroform to nitrosate the N-H groups in uridine structures. Owing to the price of commercial gaseous nitrosyl chloride it was decided to prepare the gas following the method of Konvisor et al. [50] who used the action of

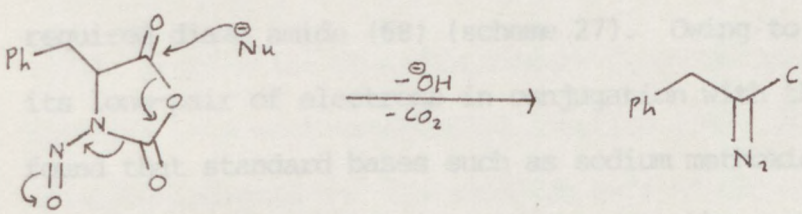
conc. nitric acid on potassium chloride, the approximate equation for which is $3KCl + 4HNO_3 \rightarrow 3KNO_3 + Cl_2 + NOCl + 2H_2O$ (at 60°C). They reported that the reaction favoured the production of nitrosyl chloride at lower temperatures whereas at higher temperatures chlorine tended to predominate although the reaction proceeded at a considerably increased rate. A cleaner method was the action of nitrogen dioxide on potassium chloride but this was avoided owing to the difficulties in preparing clean nitrogen dioxide, however the presence of chlorine from the nitric acid method should not be a significant problem. The reaction was carried out at 0°C and the gas passed through purified dry chloroform. It was found that the chloroform gained 2.5g in weight after six and a half hours. An i.r. demonstrated a strong peak at 1830cm^{-1} indicative of the Cl-NO stretch with insignificant trace of Cl-Cl stretch (730-580cm^{-1}). However when the urethane (76) was stirred with the solution of nitrosyl chloride no nitrosation was observed with starting material only being recovered.

An interesting reaction was the attempted nitrosation of Leuch's anhydride (72). This of course would be impossible by standard procedures owing to the sensitivity of the anhydride to hydrolysis, however nitrosyl chloride would be a feasible alternative. The distinct advantage offered by N-nitroso Leuch's anhydride (78) would be that it could be converted to the diazoamide (68) by dimethylamine in one step with elimination of carbon dioxide and water. However any nucleophile in theory could be used allowing the N-nitroso Leuch's anhydride to be a convenient starting material to a host of α-diazoesters and amides (scheme 25). Unfortunately the Leuch's anhydride showed no nitrosation product upon prolonged exposure to nitrosyl chloride in chloroform. In the reaction pyridine was used as an acid scavanger; it was found that an equivalent amount had to be used and that an excess caused the

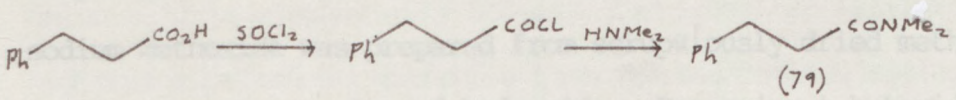


Scheme 24.

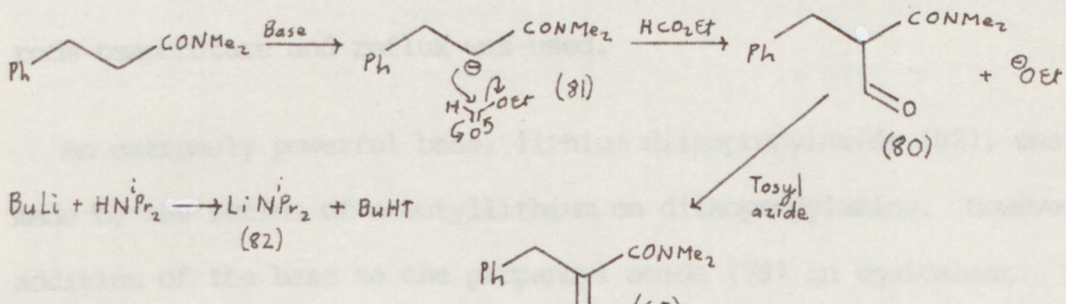




Scheme 25.



Scheme 26.



Scheme 27.

Leuch's anhydride to decompose.

4.1.3. Alternative Approaches to 2-Diazo-3-phenylpropanoic acid N,N-dimethylamide.

Owing to the slight anionic character of the methylene group α to an amide the preparation of 3-phenylpropanoic acid N,N-dimethylamide (79) would provide a convenient starting material to the diazoamide (68) via functionalisation of the α-methylene group. The compound (79) was satisfactorily prepared as an oil following the standard procedure whereby the 3-phenylpropanoyl chloride was treated with excess dimethylamine (scheme 26).

It was hoped that treatment of the propanoyl amide (79) with base and subsequent formylation of the resulting anion with ethyl formate would furnish the 2-formyl-propanoyl amide (80). This in turn could be diazotised following a standard procedure [51-53] with tosyl azide (or perhaps carboxybenzene-4-sulphonyl azide) to provide the required diazo amide (68) (scheme 27). Owing to the nitrogen having its lone-pair of electrons in conjugation with the carbonyl, it was found that standard bases such as sodium methoxide and potassium t-butoxide were not sufficient to generate the required anion (81), as demonstrated by the return of starting material in the presence of ethyl formate. Various reaction conditions were attempted. The sodium methoxide was prepared from scrupulously dried methanol to avoid any contamination of hydroxide. Potassium t-butoxide was added in dimethylsulphoxide. Prolonged exposure to the bases at room temperature and reflux was used.

An extremely powerful base, lithium diisopropylamide (82), was made by the action of n-butyllithium on diisopropylamine. However addition of the base to the propanoyl amide (79) in equivalent amount and four fold excess in the presence of ethyl formate only

returned starting material after workup. It is apparent from these results that the anionic character of the methylene group α to the dimethylamide is insufficient to enter the α-carbanionic chemistry associated with methylene groups α to a ketone or ester.

Literature [54] has demonstrated that some weakly acidic methylene groups neighbouring phenyl groups and acetylene functions can in some instances be oxidised by selenium dioxide. An attempt was made to oxidise the α-methylene of the propanoylamide (79) with selenium dioxide to furnish the α-oxoamide (83). This, in principle, could be converted to the hydrazone (84) which then could be oxidised to the diazoamide (68) with mercuric oxide (scheme 28). However, no reaction was observed when the propanoylamide was stirred with a suspension of selenium dioxide in acetic acid solution. It was decided to abandon trying to exploit any reactivity of the α-methylene group of the propanoyl amide and adopt alternative approaches.

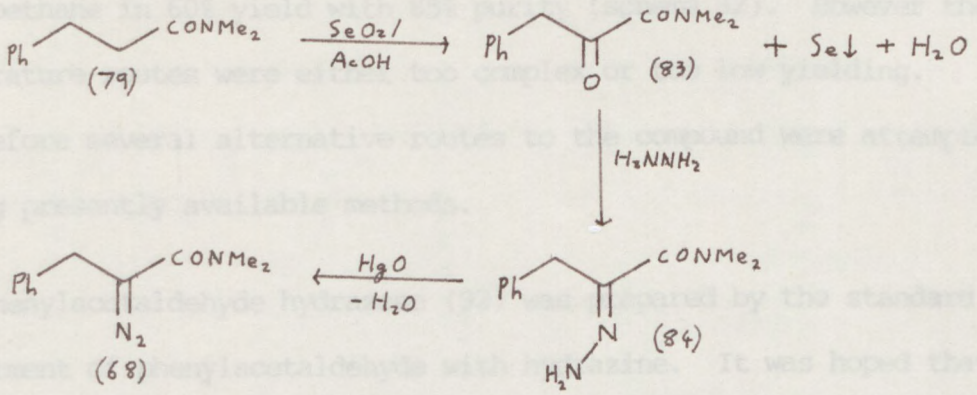
The preparation of α-diazoesters from the amino acid starting material is a well established reaction [55]. Two phase procedures are often adopted and the ammonium salt of the amine is often used to help prevent polymerisation of the free amino acid and encourage solubility for reaction in the organic phase. Thus, treatment of an amino acid in alcohol with HCl gas, furnishes the alkyl ester hydrochloride and is therefore a convenient method, employing readily available amino acids. Takamura et al. [48] also demonstrated that the free amine ester can be treated directly with isoamyl nitrite in the presence of acetic acid to provide the diazoester. It was found that treatment of α-phenylalanine with a 10% solution of sulphuric acid in ethanol, provided the hydrogen sulphate of the ethyl ester (85), which was readily converted to the free amine ethyl ester (86) with potassium carbonate solution

(scheme 29). Submitting this to isoamyl nitrite furnished the diazoethyl ester (87) quantitatively. A principle advantage of this route was that it avoided the use of HCl gas, which is both expensive and time consuming to use. In fact, for purposes of comparison, the hydrochloride was prepared and the corresponding diazo compound was isolated in low yield, using a two phase procedure.

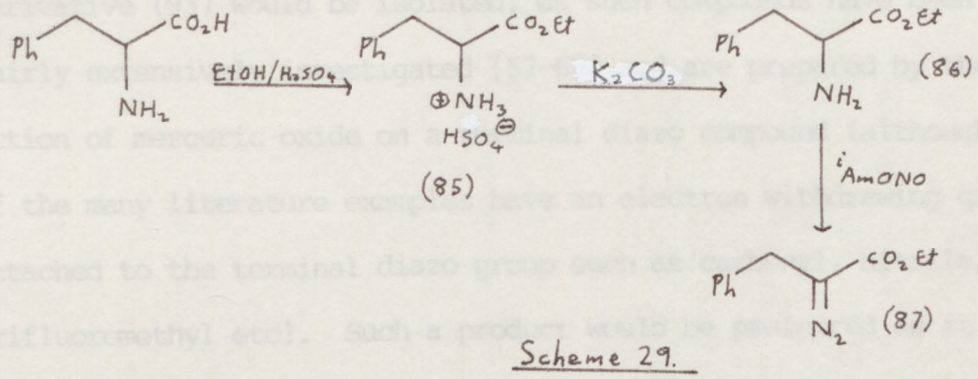
The ethyl diazoester product (87) was then treated with lithium dimethylamide, which was generated by the action of n-butyllithium on dimethylamine. It was hoped that an exchange reaction would occur with elimination of ethoxide, which is the weaker base (scheme 30). Though dimethylamide is a powerful base it is not sterically hindered like diisopropylamide and it was hoped that it would be sufficiently nucleophilic to add to the carbonyl of the ester. However no exchange was observed with recovery of starting material.

Experimenting with the 3-phenylpropanoyl chain was discontinued and it was decided to approach the molecule from a different direction. A suitable approach would be to couple 2-phenyl diazoethane (88) with dimethylcarbamyl chloride (89) in analogy to the standard procedure of preparing an α-diazoketone by treatment of an acid chloride with diazomethane (scheme 31). It was expected that the chloride of dimethylcarbamyl chloride was an effective enough leaving group to couple with the acidic proton of the terminal diazo group of 2-phenyl diazoethane.

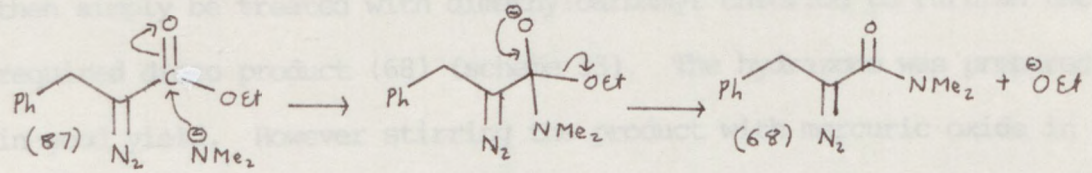
The principle problem was the preparation of 2-phenyl diazoethane. Very little was offered in the literature on the preparation of the compound. The highest yielding route was by Moritoni et al. [56] who prepared the tosylhydrazone of phenylacetaldehyde (90) which was then lithiated and the resulting



Scheme 28.

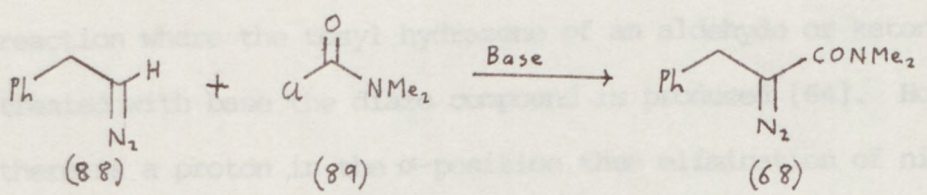


Scheme 29.

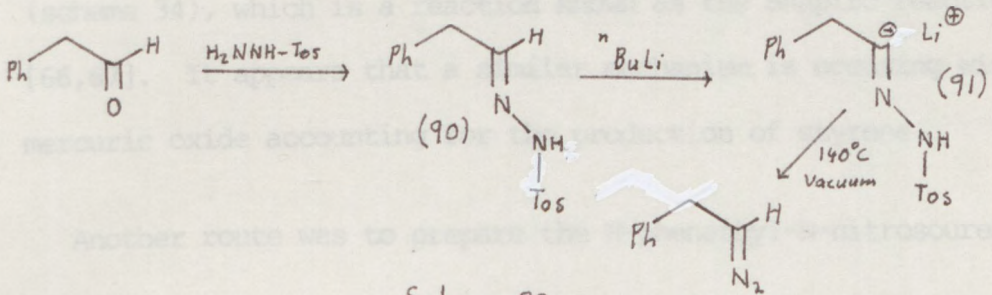


$BuLi + HNMe_2 \rightarrow LiNMe_2 + BuH$

Scheme 30.



Scheme 31.

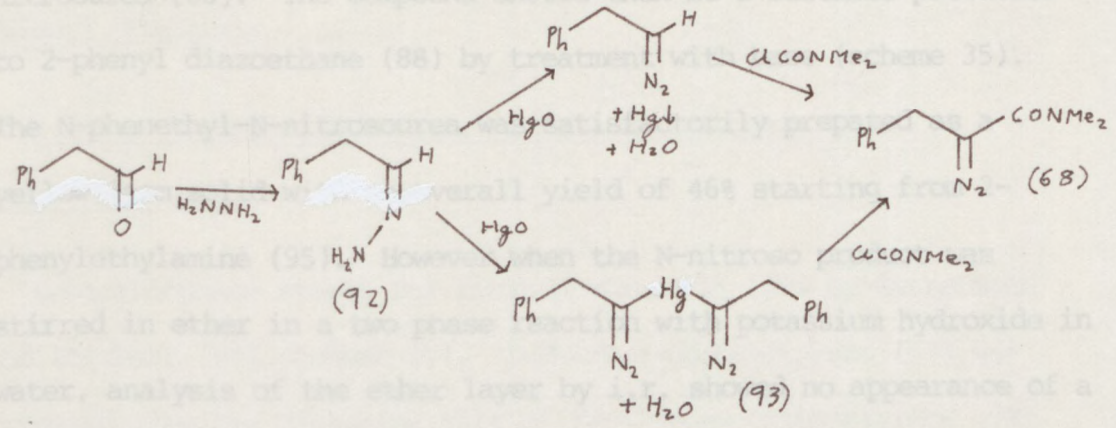


Scheme 32.

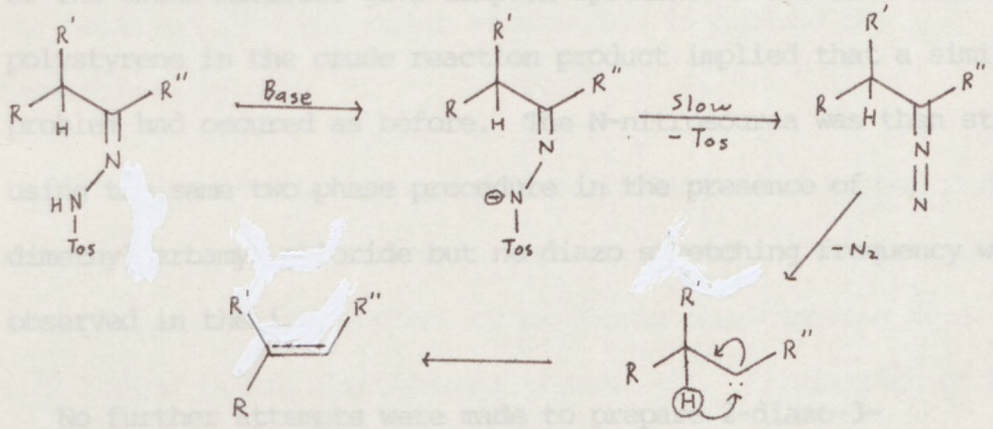
anion (91) pyrolysed under vacuum at 140°C to give 2-phenyl diazoethane in 60% yield with 85% purity (scheme 32). However the literature routes were either too complex or too low yielding. Therefore several alternative routes to the compound were attempted using presently available methods.

Phenylacetaldehyde hydrazone (92) was prepared by the standard treatment of phenylacetaldehyde with hydrazine. It was hoped that this could be oxidised to the required diazo compound with mercuric oxide. A plausible possibilty would be that the didiazo mercury derivative (93) would be isolated, as such compounds have been fairly extensively investigated [57-62] and are prepared by the action of mercuric oxide on a terminal diazo compound (although all of the many literature examples have an electron withdrawing group attached to the terminal diazo group such as carbonyl, nitrile, trifluoromethyl etc). Such a product would be preferred as it could then simply be treated with dimethylcarbamyl chloride to furnish the required diazo product (68) (scheme 33). The hydrazone was prepared in good yield. However stirring the product with mercuric oxide in absolute ethanol gave a dark grey solid and styrene (isolated as polystyrene). Analysis of the solid showed no diazo stretching frequency in the i.r. It is known [63] that in the Bamford Stevens reaction where the tosyl hydrazone of an aldehyde or ketone is treated with base the diazo compound is produced [64]. However if there is a proton in the α-position then elimination of nitrogen occurs via a proposed carbene intermediate [65] (though some evidence [63,64] suggests a concerted process) to give the olefin (scheme 34), which is a reaction known as the Shapiro reaction [66,67]. It appears that a similar mechanism is occurring with mercuric oxide accounting for the production of styrene.

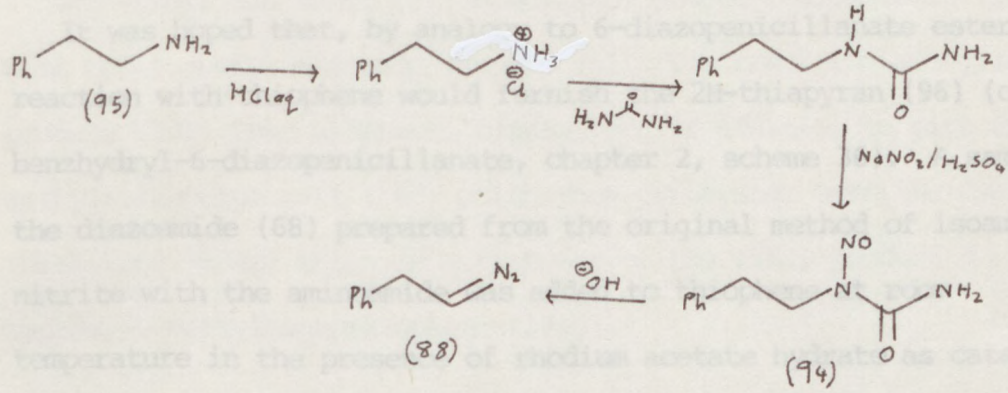
Another route was to prepare the N-phenethyl-N-nitrosourea (94)



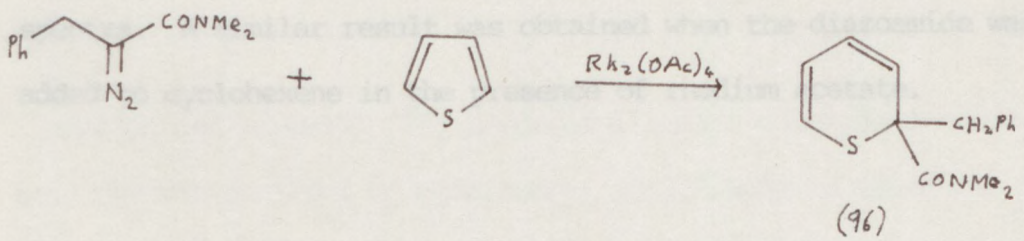
Scheme 33.



Scheme 34.



Scheme 35.



Scheme 36.

adapting the literature procedure for the preparation of N-methyl-N-nitrosurea [68]. The compound should then be a suitable precursor to 2-phenyl diazoethane (88) by treatment with base (scheme 35). The N-phenethyl-N-nitrosourea was satisfactorily prepared as a yellow foam solid with an overall yield of 46% starting from 2-phenylethylamine (95). However when the N-nitroso product was stirred in ether in a two phase reaction with potassium hydroxide in water, analysis of the ether layer by i.r. showed no appearance of a diazo stretching frequency. Evaporation of the ether and analysis of the crude material gave complex spectra. A distinct smell of polystyrene in the crude reaction product implied that a similar problem had occured as before. The N-nitrosourea was then stirred using the same two phase procedure in the presence of dimethylcarbamyl chloride but no diazo stretching frequency was observed in the i.r.

No further attempts were made to prepare 2-diazo-3-phenylpropanoic acid N,N-dimethylamide.

It was hoped that, by analogy to 6-diazopenicillanate esters, reaction with thiophene would furnish the 2H-thiapyran (96) (c.f. benzhydryl-6-diazopenicillanate, chapter 2, scheme 36). A sample of the diazoamide (68) prepared from the original method of isoamyl nitrite with the aminoamide was added to thiophene at room temperature in the presence of rhodium acetate hydrate as catalyst. Decomposition was swift and workup of the crude product by prep. t.l.c. afforded a complex mixture of products with no identifiable spectra. A similar result was obtained when the diazoamide was added to cyclohexene in the presence of rhodium acetate.

4.2. Attempt to Develop a New Synthesis of Benzothiophenes from 2-Thienyl Compounds.

4.2.1. Literature Review on Methods of Synthesis of Benzothiophenes.

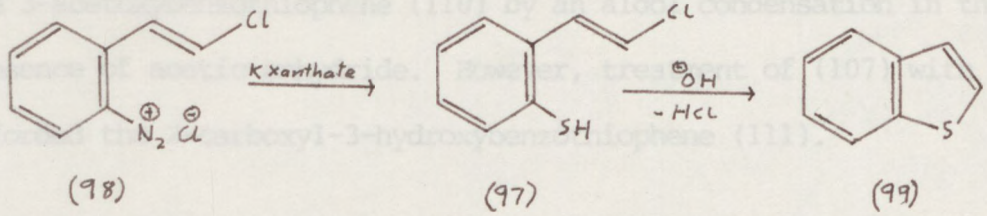
Benzothiophene itself was first prepared in 1893 by Gattermann and Lockhart [69] (scheme 37). 2-Thiol-ω-chlorostyrene (97) was prepared from the diazonium salt of 2-chloro-ω-chlorostyrene (98) using potassium xanthate. Treatment of the product with base gave the necessary intramolecular elimination to produce the benzothiophene (99).

This approach via intramolecular elimination of a substituted benzene is a major approach to benzothiophenes. Campaigne and Cline [70] produced benzothiophene by oxidising thiolcinnamic acid (100) with iodine in hot nitrobenzene (scheme 38). Elimination of HI and decarboxylation gave benzothiophene (99).

Von Auwers and Arndt [71] acetylated p-methylthioanisole (101) with chloroacetyl chloride (scheme 39). The resulting acetylated product (102) then underwent intramolecular addition to give the methylsulphonium salt (103) which when pyrolysed, gave the cyclic thiaketone (104a) which is a tautomer of the final product 3-hydroxy-5-methylbenzothiophene (104b).

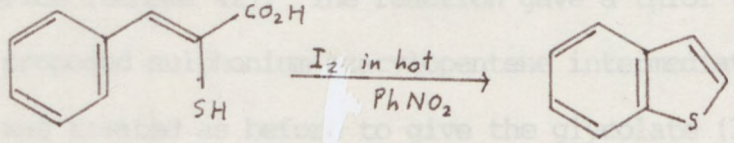
Mayer [72] prepared a series of 2-carbonylbenzothiophenes (105) by treatment of the sodium salt of 2-thiol-benzaldehyde (106) with chlorooxalylesters (scheme 40).

Hansch and Lindwall [73] prepared a phenyl sulphide dicarboxylic acid derivative (107) by addition of acetic acid to the thiol (108) which in turn had been made from the corresponding diazonium salt (109) (scheme 41). The dicarboxylic acid could then be converted to



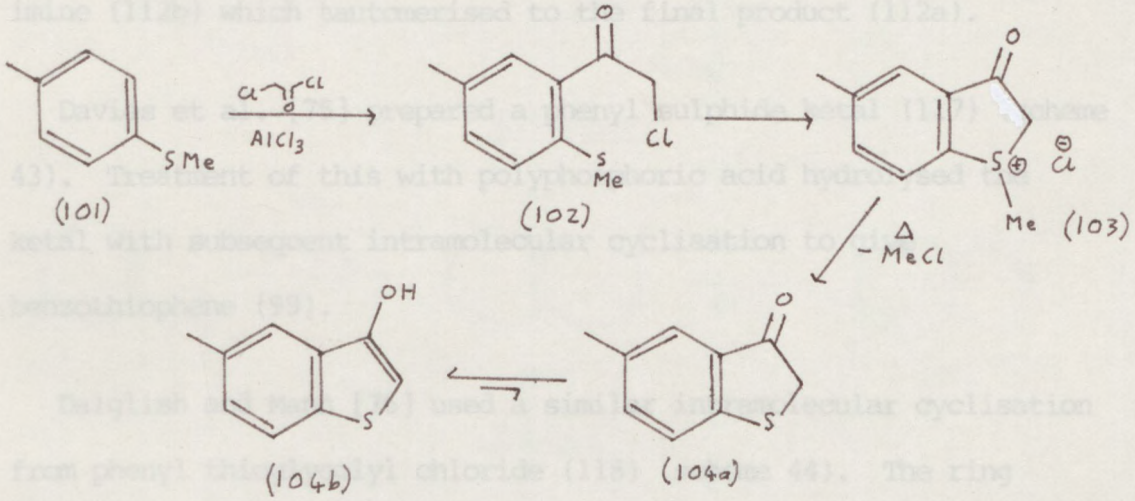
(98) (97) (99)

Scheme 37.



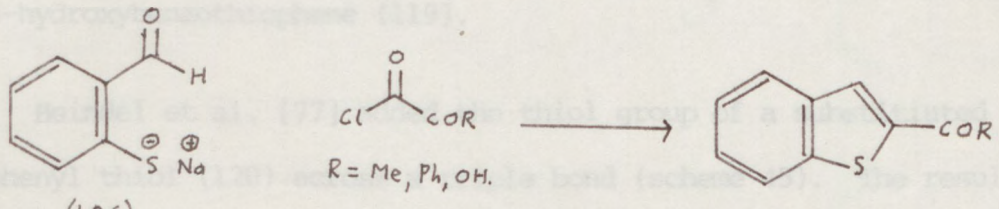
(100) (99)

Scheme 38.



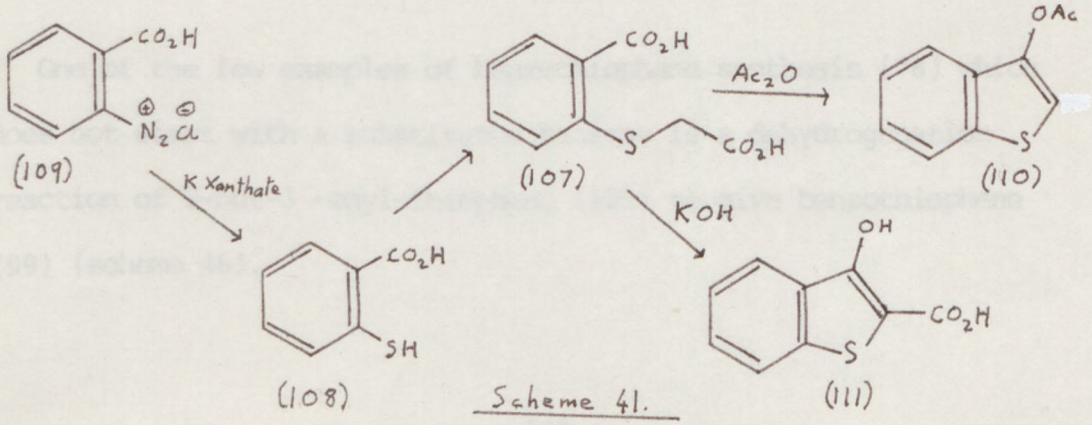
(101) (102) (103) (104b) (104a)

Scheme 39.



(106) (105)

Scheme 40.



(109) (108) (107) (110) (111)

Scheme 41.

the 3-acetoxybenzothiophene (110) by an aldol condensation in the presence of acetic anhydride. However, treatment of (107) with base afforded the 2-carboxyl-3-hydroxybenzothiophene (111).

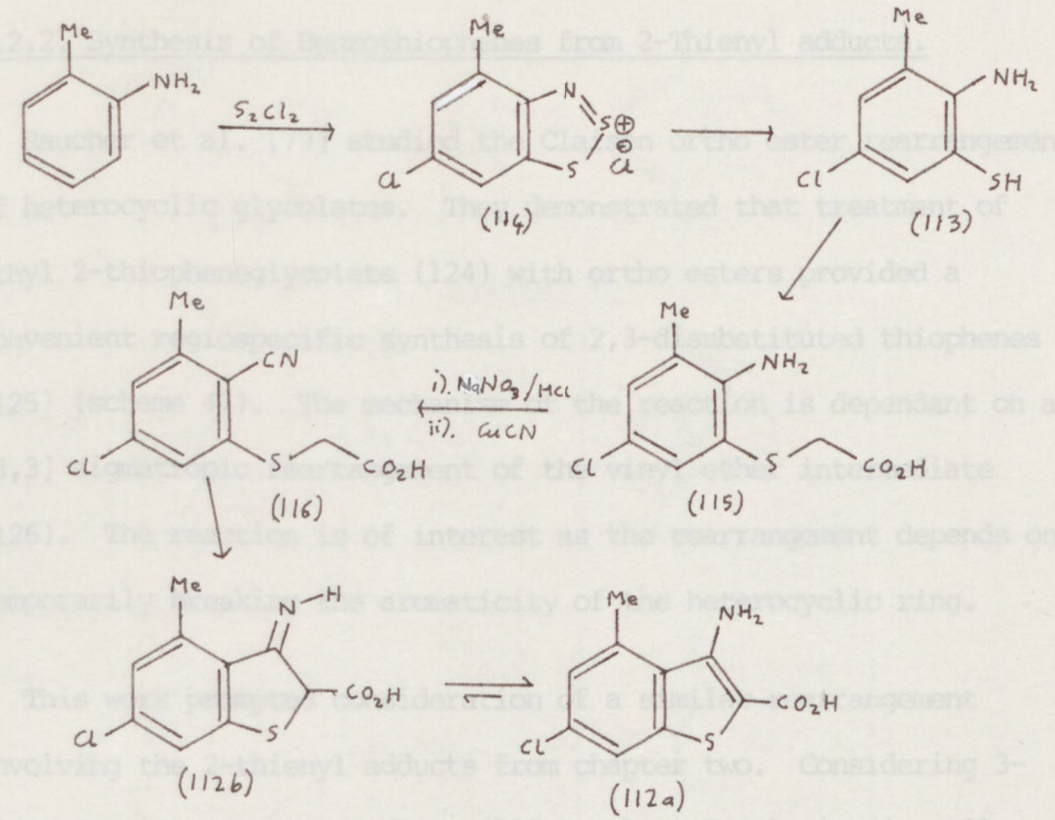
Casella [74] prepared a highly functionalised amino benzothiophene (112a) starting with o-toluidine and disulphur dichloride (scheme 42). The reaction gave a thiol toluidine (113) via a proposed sulphonium azacylopentene intermediate (114). The thiol was treated as before to give the glycolate (115), whilst the amine was diazotised and treated with cuprous chloride to give the nitrile (116). An intramolecular Thorpe type cyclisation gave the imine (112b) which tautomerised to the final product (112a).

Davies et al. [75] prepared a phenyl sulphide ketal (117) (scheme 43). Treatment of this with polyphosphoric acid hydrolysed the ketal with subsequent intramolecular cyclisation to give benzothiophene (99).

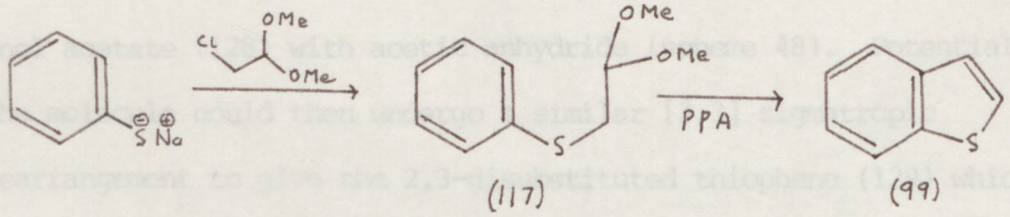
Dalglish and Mann [76] used a similar intramolecular cyclisation from phenyl thioglycolyl chloride (118) (scheme 44). The ring closure was achieved by a Friedal Craft´s acylation reaction to give 3-hydroxybenzothiophene (119).

Heindel et al. [77] added the thiol group of a substitiuted phenyl thiol (120) across a triple bond (scheme 45). The resulting trans dicarbomethooxyalkene (121) then underwent a Dieckmann cyclisation to give the substituted 3-hydroxybenzothiophene (122).

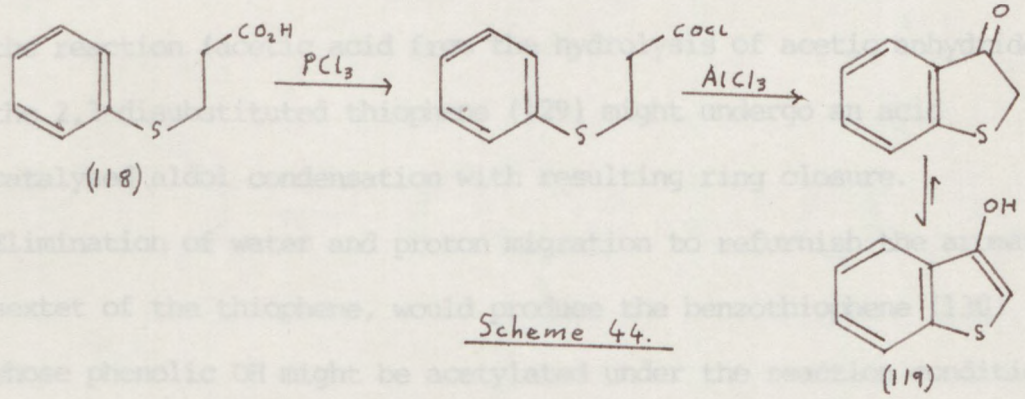
One of the few examples of benzothiophene synthesis [78] which does not start with a substituted benzene is a dehydrogenation reaction of 2-but-3´-enyl-thiophene (123) to give benzothiophene (99) (scheme 46).



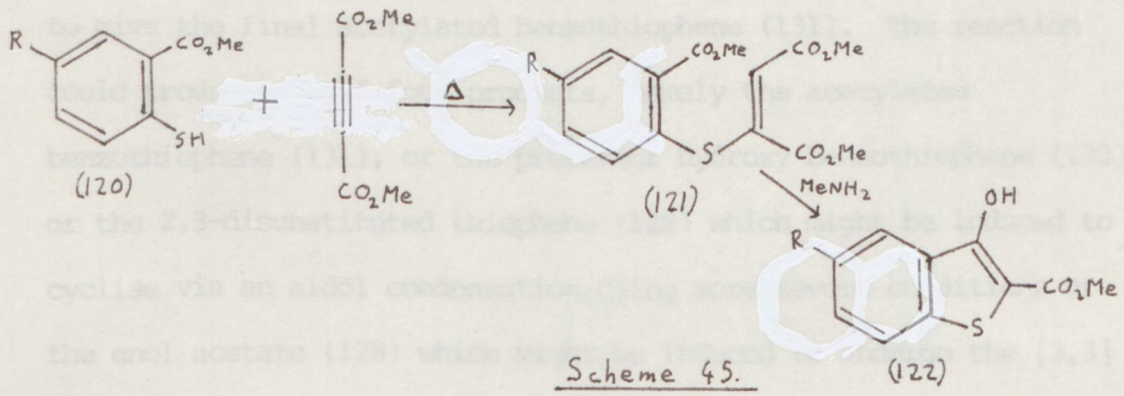
Scheme 42.



Scheme 43.



Scheme 44.

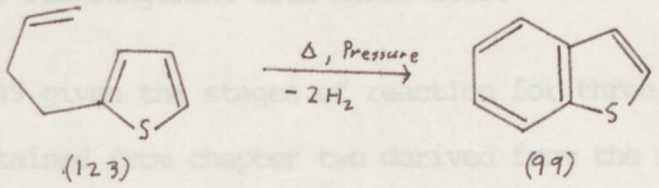


Scheme 45.

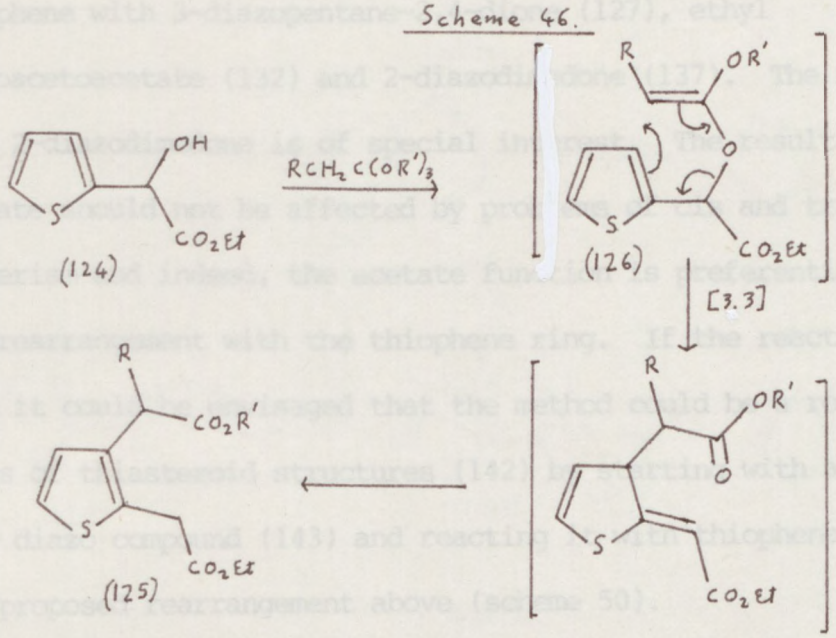
4.2.2. Synthesis of Benzothiophenes from 2-Thienyl adducts.

Raucher et al. [79] studied the Claisen ortho ester rearrangement of heterocyclic glycolates. They demonstrated that treatment of ethyl 2-thiopheneglycolate (124) with ortho esters provided a convenient regiospecific synthesis of 2,3-disubstituted thiophenes (125) (scheme 47). The mechanism of the reaction is dependent on a [3,3] sigmatropic rearrangement of the vinyl ether intermediate (126). The reaction is of interest as the rearrangement depends on temporarily breaking the aromaticity of the heterocyclic ring.

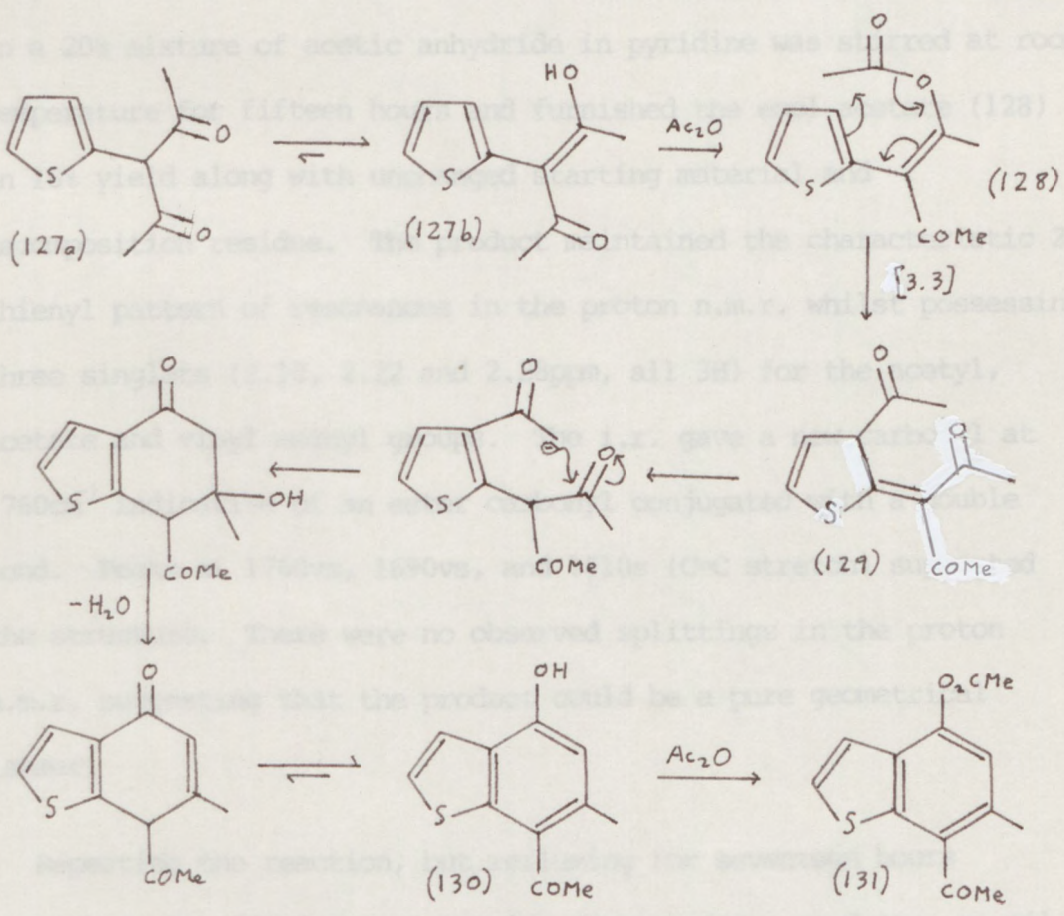
This work prompted consideration of a similar rearrangement involving the 2-thienyl adducts from chapter two. Considering 3-(2´-thienyl)-pentane-2,4-dione (127a), the molecule is virtually 100% enolised (127b) and the enol should readily be converted to the enol acetate (128) with acetic anhydride (scheme 48). Potentially, the molecule could then undergo a similar [3,3] sigmatropic rearrangement to give the 2,3-disubstituted thiophene (129) which is the 2-thienyl adduct with an additional acetyl group at the 3-position. It would be reasonable that, with the resulting acid in the reaction (acetic acid from the hydrolysis of acetic anhydride), the 2,3-disubstituted thiophene (129) might undergo an acid catalysed aldol condensation with resulting ring closure. Elimination of water and proton migration to refurnish the aromatic sextet of the thiophene, would produce the benzothiophene (130) whose phenolic OH might be acetylated under the reaction conditions to give the final acetylated benzothiophene (131). The reaction could produce one of four products, namely the acetylated benzothiophene (131), or the precursor hydroxy benzothiophene (130), or the 2,3-disubstituted thiophene (129) which might be induced to cyclise via an aldol condensation using more severe conditions or the enol acetate (128) which might be induced to undergo the [3,3]



Scheme 46.



Scheme 47.



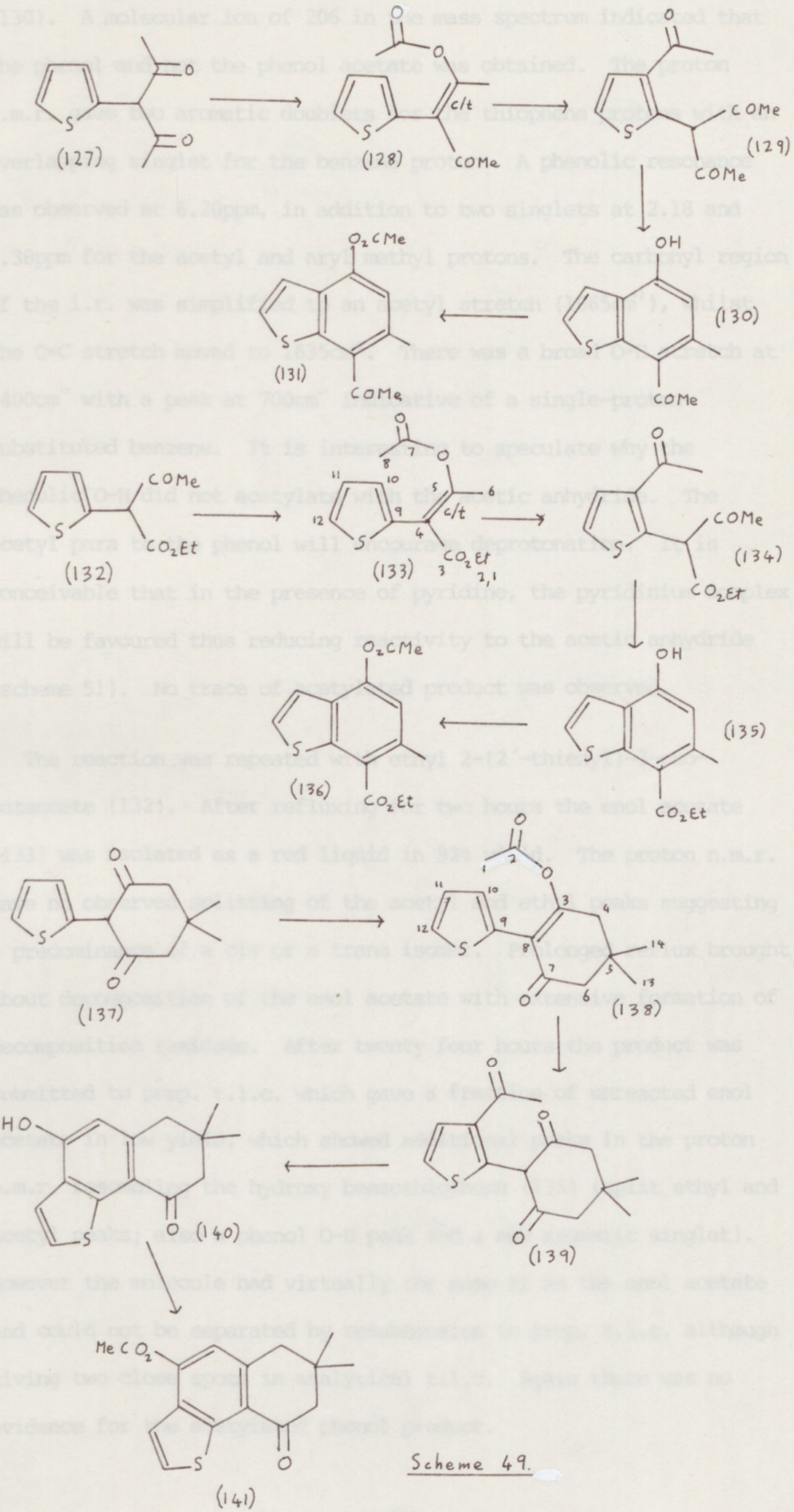
Scheme 48.

sigmatropic rearrangement with Lewis acid.

Scheme 49 gives the stages of reaction for three of the 2-thienyl adducts obtained from chapter two derived from the reaction of thiophene with 3-diazopentane-2,4-dione (127), ethyl diazoacetoacetate (132) and 2-diazodimedone (137). The reaction with 2-diazodimedone is of special interest. The resulting enol acetate should not be affected by problems of cis and trans isomerism and indeed, the acetate function is preferentially placed for rearrangement with the thiophene ring. If the reaction succeeds then it could be envisaged that the method could be a route to a new class of thiasteroid structures (142) by starting with a decalin type diazo compound (143) and reacting it with thiophene followed by the proposed rearrangement above (scheme 50).

A solution of 3-(2´-thienyl)pentane-2,4-dione (127) (scheme 49) in a 20% mixture of acetic anhydride in pyridine was stirred at room temperature for fifteen hours and furnished the enol acetate (128) in 16% yield along with unchanged starting material and decomposition residue. The product maintained the characteristic 2-thienyl pattern of resonances in the proton n.m.r. whilst possessing three singlets (2.10, 2.22 and 2.28ppm, all 3H) for the acetyl, acetate and vinyl methyl groups. The i.r. gave a new carbonyl at 1760cm^{-1} indicative of an ester carbonyl conjugated with a double bond. Peaks at 1760vs, 1690vs, and 1610s (C=C stretch) supported the structure. There were no observed splittings in the proton n.m.r. suggesting that the product could be a pure geometrical isomer.

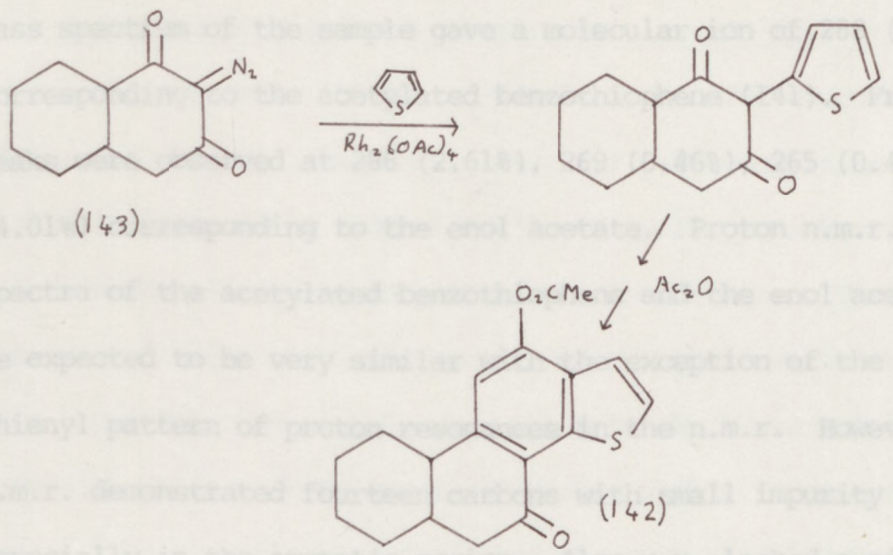
Repeating the reaction, but refluxing for seventeen hours furnished, in addition to extensive decomposition products, an oil in 2% yield whose spectra supported the phenolic benzothiophene


(127)
(128)
c/t
COMe
(129)
COMe
(130)
OH
O_2CMe
(131)
COMe
(132)
COMe
CO_2Et
(133)
c/t
CO_2Et
(134)
COMe
CO_2Et
(135)
OH
CO_2Et
(136)
O_2CMe
CO_2Et
(137)
(138)
(139)
HO
(140)
$MeCO_2$
(141)

Scheme 49.

(130). A molecular ion of 206 in the mass spectrum indicated that the phenol and not the phenol acetate was obtained. The proton n.m.r. gave two aromatic doublets for the thiophene protons with an overlapping singlet for the benzene proton. A phenolic resonance was observed at 6.20ppm, in addition to two singlets at 2.18 and 2.38ppm for the acetyl and aryl methyl protons. The carbonyl region of the i.r. was simplified to an acetyl stretch (1665cm^{-1}), whilst the C=C stretch moved to 1635cm^{-1}. There was a broad O-H stretch at 3400cm^{-1} with a peak at 700cm^{-1} indicative of a single-proton-substituted benzene. It is interesting to speculate why the phenolic O-H did not acetylate with the acetic anhydride. The acetyl para to the phenol will encourage deprotonation. It is conceivable that in the presence of pyridine, the pyridinium complex will be favoured thus reducing reactivity to the acetic anhydride (scheme 51). No trace of acetylated product was observed.

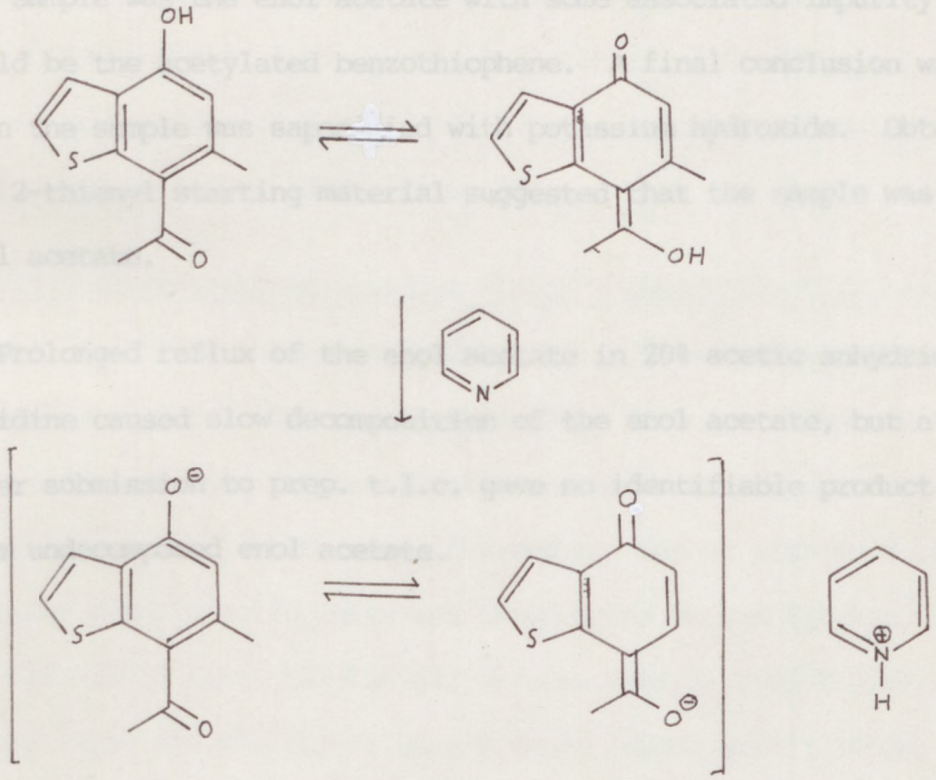
The reaction was repeated with ethyl 2-(2´-thienyl)-3-oxo-butanoate (132). After refluxing for two hours the enol acetate (133) was isolated as a red liquid in 92% yield. The proton n.m.r. gave no observed splitting of the acetyl and ethyl peaks suggesting a predominance of a cis or a trans isomer. Prolonged reflux brought about decomposition of the enol acetate with extensive formation of decomposition residues. After twenty four hours the product was submitted to prep. t.l.c. which gave a fraction of unreacted enol acetate in low yield, which showed additional peaks in the proton n.m.r. resembling the hydroxy benzothiophene (135) (split ethyl and acetyl peaks; also a phenol O-H peak and a new aromatic singlet). However the molecule had virtually the same rf as the enol acetate and could not be separated by resubmission to prep. t.l.c. although giving two close spots in analytical t.l.c. Again there was no evidence for the acetylated phenol product.



(143)

(142)

Scheme 50.



Scheme 51.

The reaction was repeated with 2-(2´-thienyl)dimedone which furnished the enol acetate (138) quantitatively as a red liquid. A mass spectrum of the sample gave a molecular ion of 288 (0.86%) corresponding to the acetylated benzothiophene (141). Fragment peaks were observed at 286 (2.61%), 269 (0.46%), 265 (0.43%) and 264 (4.01%) corresponding to the enol acetate. Proton n.m.r. and i.r. spectra of the acetylated benzothiophene and the enol acetate, would be expected to be very similar with the exception of the observed 2-thienyl pattern of proton resonances in the n.m.r. However, C^{13} n.m.r. demonstrated fourteen carbons with small impurity peaks, especially in the aromatic region. Also u.v. lacked a significant absorption around 220nm expected for a benzene. This suggested that the sample was the enol acetate with some associated impurity which could be the acetylated benzothiophene. A final conclusion was made when the sample was saponified with potassium hydroxide. Obtaining the 2-thienyl starting material suggested that the sample was the enol acetate.

Prolonged reflux of the enol acetate in 20% acetic anhydride in pyridine caused slow decomposition of the enol acetate, but a sample after submission to prep. t.l.c. gave no identifiable product apart from undecomposed enol acetate.

4.3. Experimental.

N-Carbobenzoxy-2-amino-3-phenylpropanoic acid (71) [44-45]:

Benzyl chloroformate (58.8g; 0.345mole) was added dropwise over fifteen minutes to a stirred solution of ℓ-DL-phenylalanine (50g; 0.305mole) and sodium hydroxide (32g; 0.8mole) in water (1l). The solution was stirred overnight at room temperature. The bulk was then washed twice with ether, and then HCl conc. was added dropwise with rapid stirring to ph3, upon which the bulk was a mass of white crystals, which were filtered and washed with a large excess of water. The crystals were dried under vacuum at 50°C overnight and then recrystallised from 50% ethyl acetate in 60-80 pet. ether to afford soft white crystals (59.6g; 65%). m.p. 100-101°C (lit: 102° C). δ(acetone-d_6): 2.08 (1H,m), 3.22 (2H,t), 4.64 (2H,m), 5.13 (1H,s, exchanged with D_2O), 7.42 (10H,m). νmax (nujol mull): 3320m, 1695s, 1540w, 1460s, 1380m, 755m, 700m.

2,5-Dioxo-4-benzyloxazolidine (Leuch's Anhydride) (72) [44,45]:

Freshly distilled thionyl chloride (70g; 0.518mole) was added to N-carbobenzoxy-3-phenylpropanoic acid (30g; 0.1mole). The solution was stirred at room temperature for one hour, during which orange crystals appeared, which were filtered and washed with cold ether, to leave a white solid which was dried under vacuum (10.1g; 53%). m.p. 127-128°C (lit: 127-128°C). δ(acetone-d_6): 2.07 (1H,m), 3.23 (2H,m), 4.90 (1H,t), 7.39 (10H,s). νmax (nujol mull): 3440w, 1850w, 1785s, 700w.

2-Amino-3-phenylpropanoic acid N,N-dimethylamide (70) [44,45]: A solution of 2,5-dioxo-4-benzyloxazolidine (30g; 0.157mole) in anhydrous dimethylamine (250ml) was stirred in an icebath overnight. The dimethylamine was evaporated off and collected in a liquid nitrogen trap to leave a pale green gum which from proton n.m.r. was

seen to be about 90% pure product, which was distilled (145°C, 0.5mmHg) to give a colourless oil (16.2g; 54%) which still showed small impurity peaks in the proton n.m.r. A sample of the crude product (from subsequent preparations) was submitted to column chromatography eluting with a 10% solution of ethyl acetate in dichloromethane. The product was an oil with a clean proton n.m.r. and attempts to produce crystals from chloroform, methanol and ether failed. δ ($CDCl_3$): 1.75 (2H,s, exchanges with D_2O), 2.75 (3H,s), 2.91 (5H,s, overlapping methyl and methylene group with slight splitting at base of peak), 3.92 (1H,t), 7.18 (5H,m). A sample was run at 50°C in $CDCl_3$ and at 120°C in chlorobenzene. The two methyl singlets (2.75 and 2.91) moved together and were almost a singlet at 120°C. ν max ($CHCl_3$): 3370m, 1640vs, 700m.

A sample of crude material (200mg) was purified by adding to it a solution of p-toluenesulphonic acid (250mg) in methanol (2ml). The mixture was evaporated to dryness to leave a crystalline foam of the p-toluene-sulphonate. This was recrystallised from an ethyl acetate ether mixture giving a crop of white crystals after standing overnight (122mg; 23%). m.p. 159-160°C. δ ($CDCl_3$): 2.21 (3H,s), 2.31 (4H,s, overlapping methyl and methine proton), 2.69 (3H,s), 7.14 (5H,m), 7.76 and 8.08 (5H,m). The amide was regenerated by washing a dichloromethane solution of the sulphonate with aqueous KOH, followed by water, drying over anhydrous sodium sulphate and evaporating to dryness. A colourless oil was obtained with identical spectra to the product obtained by column chromatography.

The hydrochloride was also prepared via the addition of HCl. dil. to a methanolic solution of the aminoamide but this failed to crystallise.

2-Diazo-3-phenylpropanoic acid N,N-dimethylamide (68): Two methods were used:- I). A one phase procedure and II). A two phase procedure. Section 4.1.2. discusses the reaction conditions and amounts of reagent used. The highest yielding methods are given here.

I). Isoamyl nitrite (400mg; 3.43mmole), followed by a drop of glacial acetic acid, was added to a solution of 2-amino-3-phenylpropanoic acid N,N-dimethylamide (500mg; 2.60mmole) in chloroform (6ml). The solution was stirred at room temperature for one hour and then washed with cold 0.5M H_2SO_4, water and dried over anhydrous sodium sulphate. Evaporation of the solvent yielded a green oil which was submitted to prep. t.l.c. using neutral alumina eluting with 4:6 acetone:pet. ether (40-50°C). The first band eluted was the pure diazoamide obtained as a yellow oil (62mg; 12%). δ ($CDCl_3$): 2.98 (6H,s), 3.70 (2H,s), 7.19 (5H,m). ν max ($CHCl_3$): 2085vs, 1620vs, 1495m, 1390m, 1095m.

II). 500mg of the aminoamide in chloroform (20ml) was stirred with sodium nitrite (269mg; 3.9mmole) in 1% sulphuric acid (15ml). The ether layer was analysed by i.r. for the presence of a diazo absorption band but no band appeared after one hour at 0°C and then four hours at room temperature.

N'-Carbomethoxy-2-amino-3-phenylpropanoic acid N,N-dimethylamide (76): Methyl chloroformate (2.22g; 23.5mmole) was added dropwise over fifteen minutes to a solution of 2-amino-3-phenylpropanoic acid N,N-dimethylamide (3g; 15.6mmole) in 7:3 triethylamine and dichloromethane stirred in an ice bath. The white precipitate of triethylammonium chloride was filtered and the filtrate washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to leave a pale green oil which was approximately 80%

product as seen by proton n.m.r. The oil was submitted to column chromatography eluting with 50% ethyl acetate in dichloromethane to give a colourless oil (2.17g; 59%). δ ($CDCl_3$): 1.98 (1H,s, exchanges with D_2O), 2.70 (3H,s), 2.92 (3H,s), 3.04 (2H,d), 3.71 (3H,s), 3.91 (1H,t), 7.35 (5H,m). ν max (CHCl): 3410w, 1720m, 1645s, 1500m, 1405w, 1140w, 700w. m/e: 250 (M+, 2.3%), 178 (66.7%), 176 (51%), 150 (17.3%), 146 (35%), 131 (24.6%), 126 (46.1%). Found: C, 62.30; H, 7.20; N, 11.04%; $C_{13}H_{18}N_3O_2$ requires C, 62.40; H, 7.20; N, 11.20%.

Nitrosyl Chloride [50]: Nitric acid concentrated (30ml; 0.676mole) was added slowly over an hour to potassium chloride (25g; 0.336mole) which had previously been dried at 200°C under vacuum. The reaction flask was kept in an ice bath. The whole apparatus was constantly swept by a slow stream of dry nitrogen, which carried the yellow evolving nitrosyl chloride gas, bubbling it through pure chloroform (free from ethanol and water) (200ml) kept at -45°C to minimise evaporation. The gas finally went to atmosphere through a bubbler. After six and a half hours the chloroform had increased in weight by 2.79g and had assumed a clear yellow colour; this meant that the molarity of nitrosyl chloride was 0.213M. The solution was stored in a freezer and used within two days. The i.r. showed little detail with a strong absorption at 1830cm^{-1} with no discernable Cl-Cl stretch in the region of 730-580cm^{-1}.

Attempted Nitrosation of N´-Carbomethoxy-2-amino-3-phenylpropanoic acid N,N-dimethylamide (76): A solution of sodium nitrite (2g; 23.5mmole) in water (5ml) was added to a solution of N´-carbomethoxy-2-amino-3-phenylpropanoic acid N,N-dimethylamide (500mg; 1.79mmole) in dichloromethane (5ml). The two phases were stirred rapidly and 70% nitric acid (10ml) was added dropwise. The reaction was followed by t.l.c. and after an initial rapid development of new spots, little change was observed after one hour.

The dichloromethane layer was separated, washed with sodium bicarbonate solution, dried over anhydrous sodium sulphate and evaporated to dryness to give a green oil which was submitted to prep t.l.c. using a 50% solution of ethyl acetate in dichloromethane. The first band eluted (22mg) was unidentified. The third band (318mg) was starting material, whereas the second band (72mg) was separated as a pale green crystalline solid. The spectra was similar to the starting material, except that no trace of N-H was observed in the proton n.m.r. The i.r. showed a reduced N-H stretch at 3410cm^{-1}, with a new medium peak at 1445cm^{-1}, indicative of N-NO, which was expected to be much stronger. A mass spectrum failed to give the required molecular ion. Two spots on analytical t.l.c. showed that the product was not pure and it was assumed that the required product had been made in a very impure state. The reaction was repeated for one hour at ice temperature and overnight at room temperature. However in both cases no desired product was identified.

The reaction was attempted by addition of 0.213M nitrosyl chloride in chloroform (47ml; 10mmole) to a solution of the urethane (500mg; 2mmole) in dry pyridine. After stirring at 0°C for two hours then at room temperature for two hours the excess solvent was evaporated off to leave a brown oil which, when submitted to prep. t.l.c. eluting with 50% ethyl acetate in dichloromethane, afforded starting material (164mg) as the fourth band with five other bands which gave complex spectra.

Attempted nitrosation of Leuch's anhydride (72) with Nitrosyl Chloride: Leuch's anhydride (1g; 5.24mmole) was added to a 0.213M solution of nitrosyl chloride in chloroform (35ml; 10.7mmole) and pyridine (0.414g; 5.24mmole) (an excess caused the anhydride to decompose during reaction). The solution was stirred at 0°C under

nitrogen for ninety minutes then at room temperature for three hours. The sample was split into two (i) and (ii). With (i) the excess solvent was evaporated off, but the major product after workup on prep. t.l.c. (1:1 ethyl acetate : dichloromethane) was starting material with other small yielding unidentifiable bands. With (ii) an excess of dimethylamine was added. However the isolation of the aminoamide (70) with no presence of a diazo absorption band in the i.r. demonstrated that the Leuch's anhydride had not been nitrosated.

3-Phenylpropanoic acid N,N-dimethylamide (79): A solution of 3-phenylpropanoic acid (30g; 0.2mole) in distilled thionyl chloride (30ml) was stirred at room temperature for two hours. The excess thinyl chloride was then evaporated off, followed by azeotroping any residual thionyl chloride with benzene, to leave a pale liquid with the characteristic acid chloride stretch in the i.r. (1805cm^{-1}). This was then dissolved in dichloromethane (50ml) and cooled in an ice bath. The solution was then added dropwise to excess dimethylamine (50ml). The excess solvent was evaporated off and the residue taken up in dichloromethane (200ml), filtered, washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to leave a brown liquid which was distilled (112°C; 2mm Hg) to give a colourless liquid (20.12g; 57%). δ ($CDCl_3$): 2.24 (2H,m, second order), 2.80 (2H,m, second order), 2.92 (3H,s), 2.95 (3H,s), 7.29 (5H,m). ν max ($CHCl_3$): 3000s, 2940m, 1635vs, 1490s, 1450m, 1400s, 1145m.

Sodium Methoxide: Sodium (10g) was slowly added to methanol (150ml). The methanol was distilled through a column protected from moisture. To 100ml of this was slowly added freshly cut sodium (20g). The mixture was left to stand, protected from moisture, for three hours, after which the sodium had disappeared. The excess

methanol was evaporated off and the prdouct dried under vacuum at 60 C overnight to leave a white powder (46.96g). m.p. >320°C. δ (MeOH-d_4): 3.38s.

Attempted Formylation of 3-Phenylpropanoic acid N,N-dimethylamide (79): Sodium methoxide (3.8g; 70.4mmole) was added to a solution of 3-phenylpropanoic acid N,N-dimethylamide (5g; 28.25mmole) and ethyl formate (4.18g; 56.5mmole) in sodium dry ether (125ml). The suspension was stirred but no change was observed on analytical t.l.c. (1:1 ethylacetate:dichloromethane) after twenty two hours. The reaction was repeated using potassium t-butoxide (1.5g; 13.3mmole) in dimethyl sulphoxide (100ml) with the amide (1g; 5.65mmole) and ethyl formate (0.84g; 11.3mmole). The solution was refluxed for fifteen hours but no change was observed on analytical t.l.c.

Attempted Formylation of 3-Phenylpropanoic acid N,N-dimethylamide (79) using LDA: 1.07M n-butyllithium in hexane (21.4ml; 10.7mmole) was added to a solution of diisopropylamine (1.41g; 13.96mmole) in dry THF (30ml) under nitrogen at -80°C. The solution was left to stand at around this temperature for half an hour, after which 3-phenylpropanoic-N,N-dimethylamide (2g; 11.3mmole) and ethyl formate (1.67g; 22.6mmole) in dry THF (10ml) was added dropwise with stirring. The solution was allowed to warm to room temperature under nitrogen and then left stirring overnight. It was then slowly poured into excess water (100ml) and extracted with dichloromethane which was dried over anhydrous sodium sulphate and evaporated to dryness to leave a brown oil. A sample was submitted to prep. t.l.c. eluting with 1:1 ethyl acetate and dichloromethane but the major product was the starting material followed by substantial impurities. The reaction was repeated with an estimated four-fold excess of lithium diisopropylamide, but a similar result was

obtained.

Attempted Oxidation of 3-Phenylpropanoic acid N,N-dimethylamide (79) with Selenium Dioxide: 3-Phenylpropanoic-N,N-dimethylamide (500mg; 2.83mmole) was added to a solution of selenium dioxide (345mg; 3.11mmole) in 95% acetic acid. The solution was refluxed and followed with analytical t.l.c., but no change was observed after twenty hours, despite a small precipiate of black metallic selenium.

Ethyl 2-amino-3-phenylpropanoate (80): L-β-phenylalanine (2g; 12.1mmole) was added to a 10% solution of sulphuric acid in absolute ethanol (50ml). The amino acid went into solution upon heating and was refluxed overnight. The excess ethanol was evaporated off and the remaining solution basified with 5% potassium carbonate (50ml) to liberate the free amine. The solution was extracted with ether, dried over anhydrous sodium sulphate and evaporated to dryness to give a colourless oily liquid (1.46g; 62%). δ ($CDCl_3$): 1.24 (3H,t), 1.77 (2H,s, exchanged with D_2O), 2.96 (2H,m), 3.70 (1H,t), 4.15 (2H,q), 7.19 (5H,m). ν max ($CHCl_3$): 3390m, 3040m, 2990m, 1735vs, 1605m, 1500m, 1460m, 1445m, 1380w, 1190s, 1115m, 1030s, 885m, 860m, 700m.

Ethyl 2-diazo-3-phenylpropanoate (87): Isoamyl nitrite (629mg; 5.38mmole) and acetic acid (54mg; 0.9mmole) was added to a solution of ethyl 2-amino-3-phenylpropanoate (870mg; 4.48mmole) in chloroform (50ml). The solution was refluxed for one hour, cooled, washed with cold 1M H_2SO_4 , cold water and finally cold water saturated with $NaHCO_3$. The solution was then dried over anhydrous sodium sulphate and evaporated to dryness, removing all solvent to leave a green liquid (925mg; 100%). δ ($CDCl_3$): 1.27 (3H,t), 3.62 (2H,s), 4.24 (2H,q), 7.21 (5H,m). ν max ($CHCl_3$): 3040w, 2970m, 2100vs, 1670vs, 1455w, 1375s, 1335m, 1275m, 1180s, 1115s, 700m.

Ethyl 2-diazo-3-phenylpropanoate (87) using a Two Phase Procedure: HCl gas was bubbled through a solution of L-ℓ-phenylalanine (2g; 12.1mmole) in absolute ethanol (30ml) under reflux. The solution became clear, after which addition of HCl was continued for thirty minutes. The solution was allowed to cool, upon which a precipitate of yellow crystals appeared, which were filtered and dried under vacuum (2.19g). δ(MeOH-d_4): 1.25 (1H,t), 3.36 (3H,m), 4.37 (2H,t), 4.91 (3H,bs, exchanged with D_2O), 7.47 (5H,m). The product gave a white ppt. when added to an aqueous solution of silver nitrate. A solution of the crude crystals of the hydrochloride (2g, 8.75mmole) from above in water (25ml) with sodium acetate (50mg) and sodium nitrite (0.755g; 10.95mmole) had added to it ether (25ml). At 20°C 10% H_2SO_4 (0.5ml) was added and the two phases were stirred vigorously. The ether layer was separated after ten minutes and washed with sodium bicarbonate solution. Two further aliquots of ether were added to the nitrite solution and treated in a likewise manner. The ether aliquots were combined, dried over anhydrous sodium sulphate and evaporated to dryness. The brown oil 0.72g was submitted to prep. t.l.c. eluting with dichloromethane comtaining 10% ethyl acetate. The diazo product was the first band (0.29g; 14%) with substantial material remaining at the origin of the plates.

Attempted Exchange Reaction between Ethyl 2-diazo-3-phenylpropanoate (87) and Lithium Dimethylamide: 1.00M n-butyllithium (4.90ml; 4.90mmole) was added to a solution of dimethylamine (500mg; 11.1mmole) in dry THF (30ml) stirred at -80°C under nitrogen. The solution was left to stand for thirty minutes, after which ethyl 2-diazo-3-phenylpropanoate (500mg; 4.90mmole) in dry THF (10ml) was added. The solution was left to warm to room temperature and stirred under nitrogen overnight. The bulk was

poured into water (100ml) and extracted with dichloromethane which was dried over anhydrous sodium sulphate and evaporated to dryness to give a green oil which from proton n.m.r. was seen to be starting material.

Phenylacetaldehyde Hydrazone (92): Hydrazine hydrate (1.68g; 33.4mmole) was added to a solution of phenylacetaldehyde (2g; 16.7mmole) in absolute ethanol (30ml). The solution was refluxed for three hours, after which it was evaporated to one sixth of its original volume. Cooling failed to produce any crystals, so the excess ethanol and hydrazine was evaporated off to leave a liquid (2.24g; 100%). δ ($CDCl_3$): 3.20 (2H,d), 4.32 (2H,bs, exchanged with D O), 6.18 (1H,t), 6.75 (5H,m). ν max ($CHCl_3$): 3680m and 3605m, 3040m, 3010vs, 2970m, 1520m, 1480m, 1420m, 1220vs, 1040s, 1030s, 880m, 790-720vs.

Attempted Oxidation of Phenylacetaldehyde Hydrazone (92): Anhydrous sodium sulphate (2.3g) and absolute ethanol saturated with KOH (1ml) was added to a solution of phenylacetaldehyde hydrazone (2g; 14.9mmole) in dry ether (50ml). The solution was stirred vigorously and mercuric oxide (Hopkin's and Williams) 7.87g; 36.2mmole) was added. The bulk was stirred vigorously for ninety minutes thus maintaining the oxide suspension. The solution was then filtered. Analysis of the grey residue with i.r. (nujol mull) showed no presence of diazo stretch. The filtrate was evaporated to dryness, to leave a gum which smelt of styrene and from the proton n.m.r. gave peaks indicative of polystyrene (complex multiplets in the aryl and aliphatic region). An i.r. gave no trace of diazo stretch.

Phenethyl Ammonium Chloride: Conc. HCl (3.56ml; 41.5mmole) was added dropwise to a stirred solution of 2-phenylethylamine (95) (5g; 41.3mmole) in 50% aqueous methanol (100ml). The solution was stirred for thirty minutes and evaporated to dryness to leave white crystals (6.51g; 100%). m.p. 216-217°C, (lit [80], 217°C). Gave white ppt. when added to aqueous silver nitrate.

N-Phenethyl-N-nitrosourea (94): Urea (6.96g; 116mmole) was added to a solution of phenethyl ammonium chloride (5.5g; 34.9mmole) in water (60ml). The solution was refluxed for three hours, cooled and then sodium nitrite (2.76g; 40mmole) was added. The solution was further cooled to 0°C, upon which some crystals of N-phenethylurea appeared some of which were separated, dried and analysed, δ (acetone-d_6): 2.85 (2H,t), 3.43 (2H,t), 5.59 (2H,bs, exchanged with D_2O), 6.14 (1H,bs, exchanged with D_2O), 7.49 (5H,m). ν max ($CHCl_3$): 3520m, 3400m, 3040s, 2980m, 1670s, 1570s, 1490s, 1400s, 1255vs, 1080m, 955m, 890s, 860m, 760w, 690w. Ice cold water (200ml) was then added to dissolve the ppt. and the solution was then poured into ice (20ml), to which was added conc. H_2SO_4 (5ml), upon which yellow crystals were precipitated, which were filtered, washed with water and dried under vacuum to give soft yellow crystals (3.11g; 46%). ν max ($CHCl_3$): 3500m, 3400m, 3040m, 2980m, 1670s, 1560s, 1440m, 1400m, 1260s, 1080m, 860w, 700w. m e: 193 (M+, 14.6%), 192 (9.1%), 191 (5.5%), 185 (5%), 177 (18.1%), 163 (17.3%), 149 (100%), 119 (24.4%), 105 (36.2%). λ max (MeOH): 210nm (log ε 4.13). Found C, 56.02; H, 5.89; N, 21.85%; $C_9H_{11}N_3O_2$ requires C, 55.96; H, 5.70; N, 21.76%.

Reaction of N-Phenethyl-N-nitrosourea (94) with Base: N-Phenethyl-N-nitrosourea (500mg; 2.59mmole) was slowly added to a stirred, ice cold, double layer of ether (10ml) and potassium hydroxide (300mg; 5.36mmole) in water (5ml). The ether layer was

analysed by i.r. for the appearance of a diazo absorption band; however none was observed, and after stirring for one hour, the ether was evaporated down to leave a gum. There was a smell of polystyrene and proton n.m.r. gave a complex spectra. The reaction was repeated with dimethylcarbamyl chloride (278mg; 2.59mmole) in the ether. After an hour there was no evidence of diazo stretch and a proton n.m.r. of the crude reaction product after evaporation of the ether showed the presence of unreacted dimethylcarbamyl chloride with many impurities.

2-Diazo-3-phenylpropanoic acid N,N-dimethylamide (68) with Thiophene and Cyclohexene: 2-Diazo-3-phenylpropanoic-N,N-dimethylamide (250mg; 1.23mmole) was added to a stirred solution of rhodium acetate hydrate (5mg) in thiophene (5ml). The diazo absorption band (2085cm^{-1}) had disappeared in the i.r after stirring for thirty minutes at room temperature. The excess thiophene was evaporated off to leave a brown oil, which was submitted to prep. t.l.c. eluting with 10% ethyl acetate in dichloromethane. Five bands were obtained, all of which gave complex spectra.

The reaction was repeated using cyclohexene instead of thiophene, following an identical procedure. The final product gave seven bands on prep. t.l.c., all of which gave complex spectra.

Enol acetate (128) of 3-(2´-thienyl)-pentane-2,4-dione (127): 3-(2´-thienyl)-pentane-2,4-dione (3g; 16.5mmole) was stirred in a solution of acetic anhydride (2.6g; 27mmole) in dry pyridine (10ml) until there was no further change on analytical t.l.c. The solution was then poured into water (50ml) and then in dil. HCl. (150ml) and then extracted with dichloromethane which was dried over anhydrous sodium sulphate and evaporated to dryness to give a red liquid, which was submitted to prep. t.l.c. eluting with

dichloromethane. The first band eluted was unreacted 2-thienyl compound (80mg). The second was the enol acetate, 1-methyl-3-(2´-thienyl)-4-oxo-but-2-enyl acetate, separated as a red liquid (99.9mg; 16%). δ ($CDCl_3$): 2.10 (3H,s), 2.22 (3H,s), 2.28 (3H,s), 6.79 (1H,d,J=3Hz), 6.97 (1H,dd,J=5 and 3Hz), 7.32d (1H,J=5Hz). νmax ($CHCl_3$): 3030w, 3000w, 1760vs, 1690vs, 1610s, 1430m, 1370s, 1360s, 1290m, 1270m, 1180vs, 1160vs, 1015s, 915m, 8850m, 830m. Found C, 58.98; H, 5.39%; $C_{11}H_{12}O_3S$ requires C, 58.93; H, 5.36%.

The reaction was repeated, refluxing the solution for seventeen hours, starting with 3g of 2-thienyl compound in 20ml acetic anhydride and 80ml pyridine. The dark red product was submitted to column chromatography eluting with dichloromethane. No compound was eluted with a similar rf to the enol acetate starting material, except for a red band which was repurified on prep. t.l.c. to give a red oil, 4-hydroxy-6-methyl-7-acetylbenzothiophene (130), (69.1mg; 2%). δ ($CDCl_3$): 2.28 (3H,s), 2.38 (3H,s), 6.20 (1H,s), 7.04s overlapping with 7.06d, J=4Hz (both together 2H), 7.42 (1H,d,J=4Hz). ν max ($CHCl_3$): 3400w, 3010m, 2970w, 1665vs, 1640s, 1520w, 1440m, 1405s, 1355m, 1220m, 905w, 860w, 700w. m/e: 206 (M+, 90.6%), 205 (12.5%), 124 (10.5%), 122 (100%), 96 (13.1%), 85 (58.6%).

Enol Acetate (133) of Ethyl 2-(2´-thienyl)-3-oxo-butanoate (132):

A solution of ethyl 2-(2´-thienyl)-3-oxo-butanoate (500mg; 2.359mmole) and acetic anhydride (2.5g; 24.5mmole) in dry pyridine (10ml) was refluxed for two hours. The excess pyridine and acetic anhydride were evaporated off to leave a red oil, which was submitted to prep. t.l.c. eluting with dichloromethane. Three bands were eluted, the last two were impurities (38.6 and 35.4mg), whilst the first was the enol acetate, 1-methyl-2-(2´-thienyl)-2-carboethoxy-propenyl acetate (553mg; 92%) separated as a red liquid. δ ($CDCl_3$): 1.34 (3H,t), 2.19 (3H,s), 2.30 (3H,s), 4.37 (2H,q), 7.05

(2H, overlapping doublets, J=5 and 3Hz), 7.36 (1H,dd, J=5 and 3Hz). ν max ($CHCl_3$): 3030w, 3000w, 2980w, 2930w, 1760vs, 1715vs, 1640w, 1425w, 1365s, 1300s, 1190s, 1160vs, 1060s, 1015s, 905s, 850w. $C^{13}\delta$ ($CDCl_3$) (scheme 49): 14.13q C1, 19.21q C6 and C8, 61.65t C2 , 119.14s C5, 125.52s C9, 126.43d 126.56d 127.47d C10-12, 134.44s C4, 167.12s 168.29s C3 and 7. m/e: 254 (M+, 0.7%), 212 (38.5%), 180.1 (2.4%), 167 (21.4%), 166 (100%), 149 (4.2%), 130 (6.5%), 124 (81.3%). λ max (MeOH): 280nm (log ε 4.28). Found C, 56.49; H, 5.49%; $C_{12}H_{14}O_4S$ requires C, 56.69; H, 5.51%. The enol acetate was treated under the same conditions, with prolonged reflux, and gradually decomposed with no observed benzothiophene. A sample was then submitted to prep. t.l.c.

Enol Acetate (138) of 2-(2´-thienyl)dimedone (137): A solution of 2-(2´-thienyl)dimedone (5g; 22.5mmole) and acetic anhydride (25ml) was refluxed for two hours in dry pyridine (100ml). The excess pyridine and acetic anhydride were evaporated off to leave the enol acetate, 2-(2´-thienyl)-3-oxo-5,5-dimethylcyclohex-1-enyl acetate, obtained as a red liquid (5.96g; 100%). δ(CDCl): 2.12 (3H,s), 2.17 (3H,s), 2.45 (2H,s), 2.61 (2H,s), 7.03 (1H,dd, j=5 and 4Hz), 7.39 (2H, overlapping doublets, J=5 and 4Hz). ν max ($CHCl_3$): 3000w, 2960m, 2930w, 1670vs, 1630m, 1465m, 1420m, 1370s, 1150m, 1105m, 1190vs, 1145vs, 1020s, 895w, 845m. $C^{13}\delta$(CDCl) (scheme 49): 21.29q C1, 28.12q C13 and 14, 32.29s C5, 43.45t C4, 51.82t C6, 122.27s C3, 126.62d 127.86d 128.97d C10-12, 131.05s C8, 162.76s C2, 197.06s C7. m/e: 288 (0.9%), 286 (2.6%), 269 (0.5%), 265 (0.4%), 264 (M+, 4.0%), 246 (1.3%), 224 (4.6%), 223 (13.9%), 222 (100%), 207 (5.1%), 192, (1.9%), 165 (38.0%). λ max (MeOH): 280nm (log ε 4.33). Found C, 61.92; H, 5.97%; $C_{14}H_{16}O_3S$ requires C, 63.64; H, 6.06%. A sample of the enol acetate was refluxed in the same solution for twenty fours hours. No benzothiophene was observed amongst the decomposition products on submission to prep. t.l.c.

Saponification of the Enol Acetate of 2-(2´-thienyl)dimedone (138): A solution of the enol acetate (137) (200mg) and potassium hydroxide (500mg) in 5% aqueous ethanol (20ml) was refluxed for one hour. It was then cooled, acidified with dil. HCl. (pH 5) and evaporated to dryness to leave white crystals which, by n.m.r., were seen to be 2-(2´-thienyl)dimedone.

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Appendix I.

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The Reactions of Diazo Compounds with Thiophenes.

Diazo compounds are known to react with thiophenes to give thiophenium ylids, which can rearrange to 2-substituted thiophenes or 2-thiabicyclo[3.1.0]hexanes. The factors which affect the stability of the thiophenium ylids and their subsequent partitioning to the observed products will be reviewed and particular emphasis placed on the reaction pathways followed by 2-diazo-1,3-dicarbonyl compounds.

A new reaction pathway has been discovered in our laboratory in which thiophene reacts with a diazo compound to furnish a 2H-thiopyran, which is the product of a net ring expansion. Studies of the mechanism of this reaction and attempts to develop it into a general synthesis of 2H-thiopyrans will be reported.

Appendix II.

General Experimental Details.

H^1 n.m.r. spectra were recorded on a Jeol 100MHz continuous wave instrument as 10% solutions with TMS as internal standard.

C^{13} n.m.r. were recorded on a Jeol FX 60 instrument as dilute solution with TMS as internal standard and D_2O external lock.

Infrared spectra were recorded on a Perkin-Elmer 157G, 457 and 599 instrument.

Ultraviolet spectra were recorded on a Perkin-Elmer 402 instrument.

Mass spectra were recorded on a Kratos MS30 mass spectrometer.

Melting points were recorded on a Koffler hot-stage apparatus and are uncorrected.

Most solvents were distilled before use. Dichloromethane and ethyl acetate were pre-dried over phosphorus pentoxide. THF was distilled off $LiAlH_4$ and collected at 63-65°C.

Unless otherwise stated prep. t.l.c. used silica gel GF254 (Merck). A slurry of 130g silica in 240ml distilled water was spread on five 20 x 20cm plates to give a film of about 1mm thickness. The plates were left to stand at room temperature for one hour, then heated at 120°C overnight and stored in a dry atmosphere. Column chromatography used silica gel H type 60 (Merck) which required a pressure of approx. 500mm Hg. (which was obtained from a nitrogen cylinder) to obtain a normal flow rate. Analytical t.l.c. was performed on commercially available plastic backed silica sheets.

Optical rotations were measured on a Zeiss polarimeter using a 2dm polarimeter tube with a capacity of 10ml.