THE SYNTHESIS OF THE METHYL AND BENZYL ENOL-ETHERS OF 2,2-DIMETHYL-3-PHENYLCYCLOPROPANONE

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L.J. HOLDING, B.Sc. (Hons.)

Department of Organic Chemistry

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SUMMARY

1-Methoxy and 1-benzyloxy-3,3-dimethyl-2-phenylcyclopropene, the methyl and benzyl enol-ethers of 2,2-dimethyl-3-phenylcyclopropanone respectively, have been synthesised. The synthesis required a key intermediate, 4-methoxy-3,3-dimethyl-5-phenyl-3H-pyrazole in the case of the methyl enol-ether and 4-benzyloxy-3,3-dimethyl-5-phenyl-3H-pyrazole for the benzyl analogue. These compounds were synthesised by elimination of p-toluenesulphinic acid from 4-methoxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline and 4-benzyloxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline respectively. These compounds were produced by alkylation of 4-hydroxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline which was synthesised by a novel reaction involving the treatment of β,β-dimethylacrylophenone oxide with p-toluenesulphonylhydrazine under acidic conditions.

Elimination of p-toluenesulphinic acid from 4-methoxy-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline gave 4-methoxy-5,5-dimethyl-3-methylene-1-pyrazoline. A molecular rearrangement has been found to occur on elimination of p-toluenesulphinic acid from 4-alkoxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazolines. The products obtained from this rearrangement were 1-alkyl-3,5-diphenylpyrazoles.

All attempts to synthesise 4-hydroxy-5-methyl-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline proved unsuccessful.

Two other approaches towards the synthesis of 4-alkoxy-3H-pyrazoles are reported. The first approach involved 4-alkoxy-2-pyrazolines as intermediates but the attempted synthesis of these compounds was unsuccessful. The second pathway incorporating a 1,3-dipolar cycloaddition reaction between an alkynyl ether and a di-substituted diazocompound also proved unsuccessful.

STATEMENT

The work described in this thesis incorporates no material previously submitted for a degree in any University, except where due reference has been made in the text.

(L.J. Holding)

* * *

ACKNOWLEDGEMENTS

I wish to thank Dr. D.P.G. Hamon for his excellent guidance and enthusiasm during his supervision of this work.

This research was carried out during the tenure of a Commonwealth Postgraduate Award, which I gratefully acknowledge.

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PUBLICATIONS

Some of the work described in this thesis has been accepted for publication in the following papers:

"The synthesis of 4-hydroxy-5,5-dimethyl-1-p-toluenesulphonyl-2-pyrazolines", D.P.G. Hamon and L.J. Holding, Chem.Comm., 1970.

"The enol-ether of a cyclopropanone", D.P.G. Hamon and L.J. Holding, Chem.Comm., 1970.

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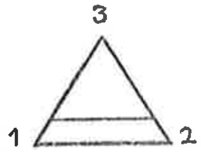
INTRODUCTION

Although cyclopropene (1) was first isolated in 1922,[1] it was not until recently that it and related substances received the attention they deserved.



(1)

As the cyclopropene skeleton incorporates a high degree of "Baeyer Strain", it makes the cyclopropene system a suitable subject for theoretical treatments of bonding in organic compounds.

Studies of the electron diffraction[2] and microwave[3] spectral properties of cyclopropene have enabled the structural parameters of the compound to be determined. The values obtained for the more accurate microwave spectral studies are outlined in Table 1.

Of special note are the bond lengths of the carbon-carbon double bond and the vinyl carbon-hydrogen bond. The decrease in the carbon-carbon double bond length relative to ethylene (1.314Å) indicates an increase in the S character of the σ-component of the double bond. This short bond length in cyclopropene should allow good π-overlap which should manifest itself in cyclopropene having a relatively strong double bond.

The short vinyl carbon-hydrogen single bond also indicates an

Table 1. Structural Parameters of Cyclopropene

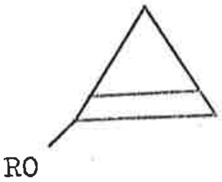
Parameter	Value
d (C=C)	1.300Å
d (C-C)	1.515Å
d $(C-H)_{vinyl}$	1.070Å
d $(C-H)_{methylene}$	1.087 ± .004Å
∅ (C-C-C)	50° 48'
∅ (C=C-H)	149° 55'
∅ (H-C-H)	114° 42' ± 10'

increase in the S contribution in the bonding orbitals of the carbon atom. From this short vinyl carbon-hydrogen bond length one would predict that cyclopropenes would possess properties intermediate between unstrained olefins and acetylenes.

In cyclopropene the angle between the carbon orbitals at the methylene position which are used in bonding to the ring is 105° 35'. As the carbon-carbon internuclear angle is 50° 48' these orbital formed bonds lie 27° 24' outside the direct internuclear line and are therefore termed "bent bonds". The "bent bond" distance has been calculated at 1.574Å along a 27° 24' arc.[3] The orbital deviation of 27° 24' from the internuclear line in cyclopropene constitutes a larger degree of "bond bending" than in cyclopropane where the corresponding value is about 22°.*

The unusual hybridization and bond "bending" in cyclopropene manifests itself in a high degree of ring strain. The heat of combustion of cyclopropene has been determined by the use of a flame calorimeter to be 485 ± 0.6 kcal/mole.[4] This corresponds to a heat of formation of 66.6 ± 0.6 kcal/mole. From these figures the extra strain energy in cyclopropene, above that in cyclopropane is close to 27 kcal/mole while the total strain in cyclopropene has been calculated to be 56 kcal/mole.[5]

Although many cyclopropenes have been synthesised and their chemical reactions studied[5] no reports of the synthesis of either cyclopropenyl ethers (2) or esters (3) have appeared. The synthesis and chemistry of these two systems was considered to be of great



(2) R = Alkyl or aryl

(3) R = R'CO[R' = Alkyl or aryl]

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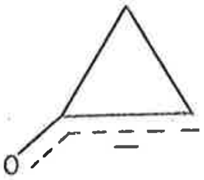
* The geometrical parameters of cyclopropane have not been determined with the same degree of accuracy as in the case of cyclopropene.

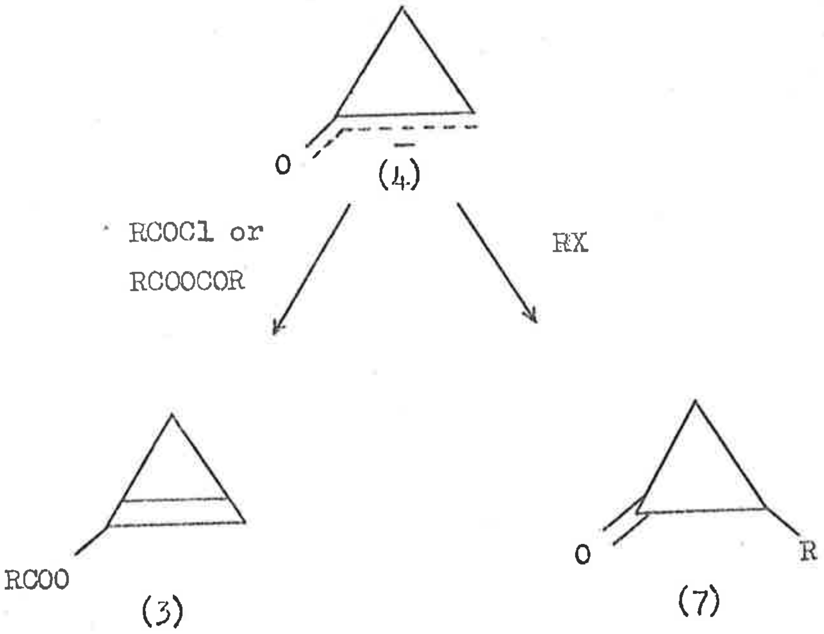
interest. Of particular interest was the generation of the cyclopropenol anion 4 which has two contributing forms, 5 and 6. Alkylation and acylation studies were planned on the above system.



(4)

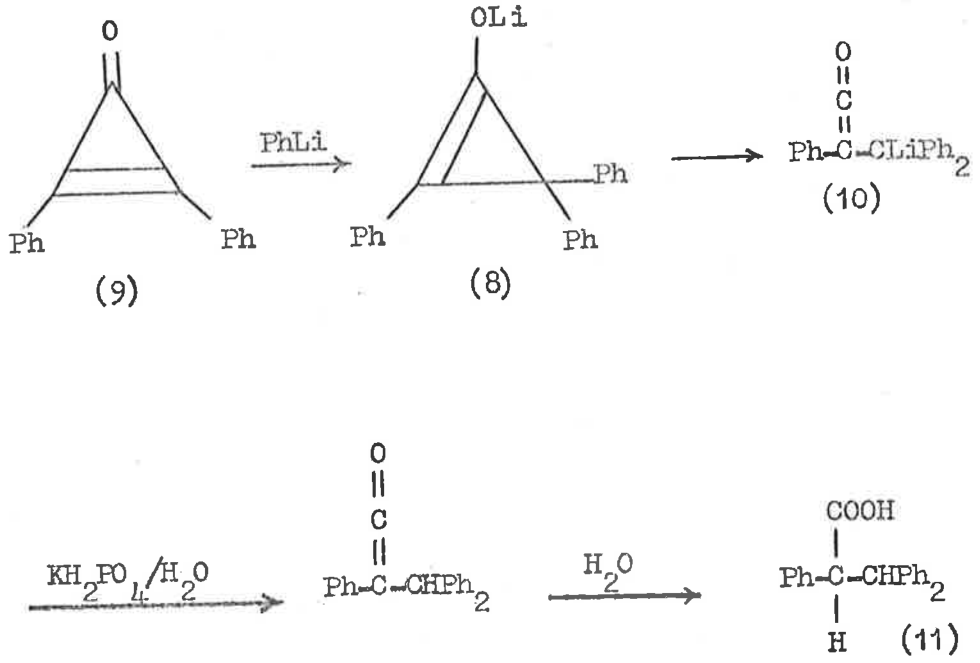
(5) (6)

Normally alkylation of enolate anions with alkyl halides favours carbon alkylation[6] although a few examples of oxygen alkylation are known.[7] It was therefore anticipated that alkylation of the anion 4 would lead to cyclopropanones (7). Acylation, however, favours the formation of O-acyl derivatives rather than C-alkylated products.[8] Reaction of the anion 4 with anhydrides or acid chlorides was therefore expected to give cyclopropenyl esters (3).

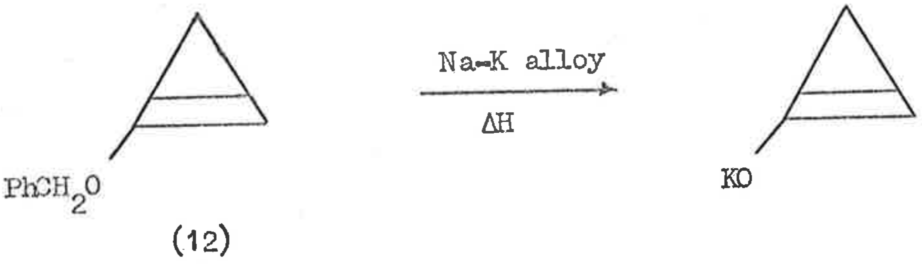


Recently,[9] the cyclopropenolate anion 8 has been postulated as an intermediate on the addition of phenyl lithium to diphenylcyclopropenone (9). The enolate anion rearranges to the ketenyl anion 10. The workers, however, have not determined whether the enolate anion 8 and the ketenyl anion exist in equilibrium. Addition of a saturated aqueous solution of potassium dihydrogen phosphate to a solution of the ketenyl anion in tetrahydrofuran gave α,β,β-triphenyl propionic acid (11). No alkylation or acylation studies have yet been reported for the anion 8.

Two separate routes to the cyclopropenolate anion were envisaged. It has been shown[10] that sodium-potassium alloy in ligroin under reflux cleaves benzyl ethers to the potassium salts of the corresponding alcohol and toluene, the salts being precipitated during

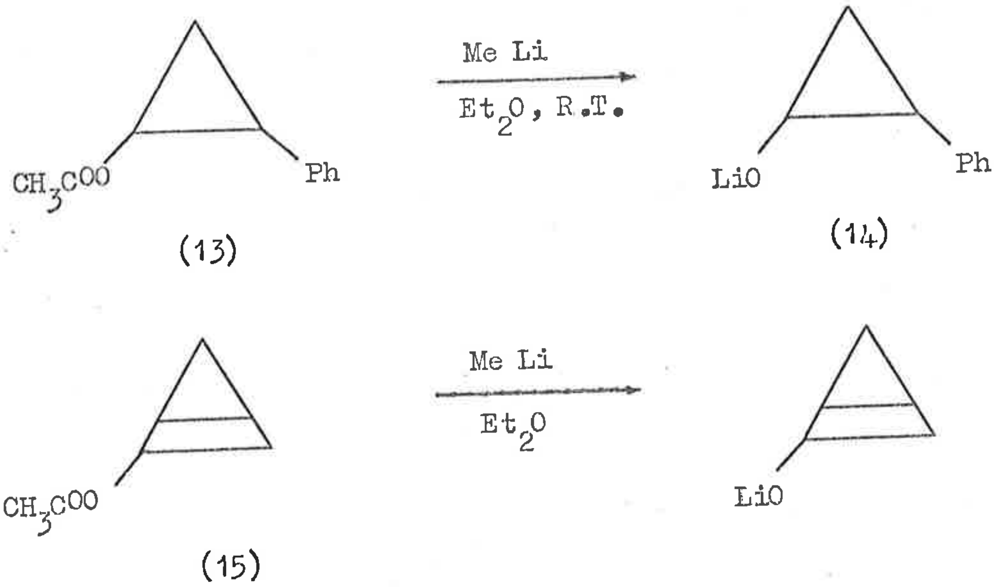


the reaction. If a benzyl cyclopropenyl ether (12) could be synthesised, it was anticipated that subsequent treatment with sodium-potassium alloy in ligroin under reflux could lead to the required anion. Since the reaction requires temperatures in the vicinity of



100°C, the thermal stability of the benzyl cyclopropenyl ether would be critical. Cyclopropene is smoothly isomerised to methyl acetylene at 425°C.[11] In the condensed phase it can only be kept for prolonged periods at liquid nitrogen temperatures.[1,11] Alkyl substitution, especially at the 3-position, enhances the stability of the system. The most stable cyclopropenes are those in which the hydrogens at C-3 have been replaced by alkyl groups. Neat 3,3-dimethylcyclopropene can be heated in a sealed tube at 100°C for many days without noticeable decomposition.[12] Substitution at the vinyl carbon also has a stabilizing effect on cyclopropene.[13] This stabilizing effect is not as pronounced as is the case with the methylene carbon. As the thermal stability of the benzyl cyclopropenyl ether is of extreme importance it was decided to attempt the synthesis of a fully substituted analogue.

A second possible route to the cyclopropenolate anion was based on work by De Puy et al.[14] He found that treatment of trans-2-phenylcyclopropyl acetate (13) with methyl lithium in ether at room temperature resulted in cleavage of the acetate group to give the lithium salt of trans-2-phenylcyclopropanol (14). Subsequent treatment of compound 14 with boric acid gave trans-2-phenylcyclopropanol. If a cyclopropenyl acetate (15) could be synthesised then subsequent treatment of compound 15 with methyl lithium could lead to the cyclopropenolate anion. Nucleophilic addition of the methyl lithium to the highly strained



double bond of the cyclopropenyl acetate could be a competing reaction. It has, however, been shown that electron withdrawing groups are necessary for such addition.[5] Simple alkylcyclopropenes are usually resistant to nucleophilic attack by alkoxide ion.[15] Steric effects also appear to be important in nucleophilic addition to cyclopropenes since Breslow and Dowd[16] have shown that 1,2,3-triphenyl-3-methylcyclopropene is recovered unchanged after prolonged treatment with potassium amide. Therefore, as in the case with the benzyl cyclopropenyl ether, the synthesis of a fully substituted analogue was planned.

The question of the synthesis of the benzyl cyclopropenyl ethers and cyclopropenyl acetates now arises. It was decided to determine a route to the benzyl ether of a trisubstituted cyclopropenol and later modify the route to give the corresponding cyclopropenyl acetate. Cyclopropenyl ethers, other than benzyl, would be of great use for reference compounds in the proposed alkylation studies. Therefore the synthesis of the other simple ethers was planned.

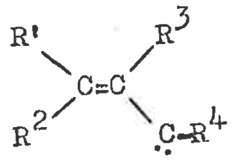
As cyclopropenyl ethers incorporate the cyclopropene skeleton the methods available for the synthesis of the unsaturated 3-membered ring were examined.

Closs[5] in an excellent review of the synthesis and the chemical and physical properties of cyclopropenes divides the routes to cyclopropenes into three classes, namely, β-elimination of cyclopropanes, addition of carbenes to acetylenes, and ring closure of acyclic precursors.

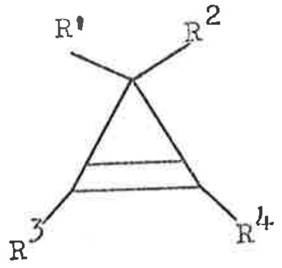
The thermally induced β-elimination of neutral molecules from suitably substituted cyclopropanes was avoided. The high temperatures (300-500°) necessary for the elimination may have had a deleterious effect on the end product, the stability of which was unknown. The base induced β-elimination of nitrite ion from nitro-substituted cyclopropanes[17] appears to be limited to aryl-substituted cyclopropanes where the aryl groups provide the necessary activation to facilitate the elimination.

The second route to cyclopropenes, that of addition of carbenes to acetylenes, suffers from a severe setback. Carbenes undergo extremely rapid intramolecular rearrangements and as the addition of carbenes to acetylenes constitutes only a minor reaction path the yields are consequently poor. As alkyl carbenes rearrange rapidly to olefins and cyclopropanes this method fails in the preparation of cyclopropenes alkylated at the 3-position. As we desired a cyclopropene disubstituted at the 3-position this method of synthesis was unsuitable.

The third general method of synthesis of cyclopropenes, that of ring closure of acyclic precursors, is thought to proceed through an alkenyl carbene (16).*



(16)



The hypothetical alkenyl carbene 17 can be generated by several methods. 1,3,3-Trimethylcyclopropene (21) results on addition of methylene chloride to 1,2-dimethylpropenyllithium[18] (18). The same compound is produced by α-dehydrochlorination of 1-chloro-2,3-dimethyl-2-butene[19] (19) and α-debromination of 1,1-dibromo-2,3-dimethyl-2-butene[19] (20).

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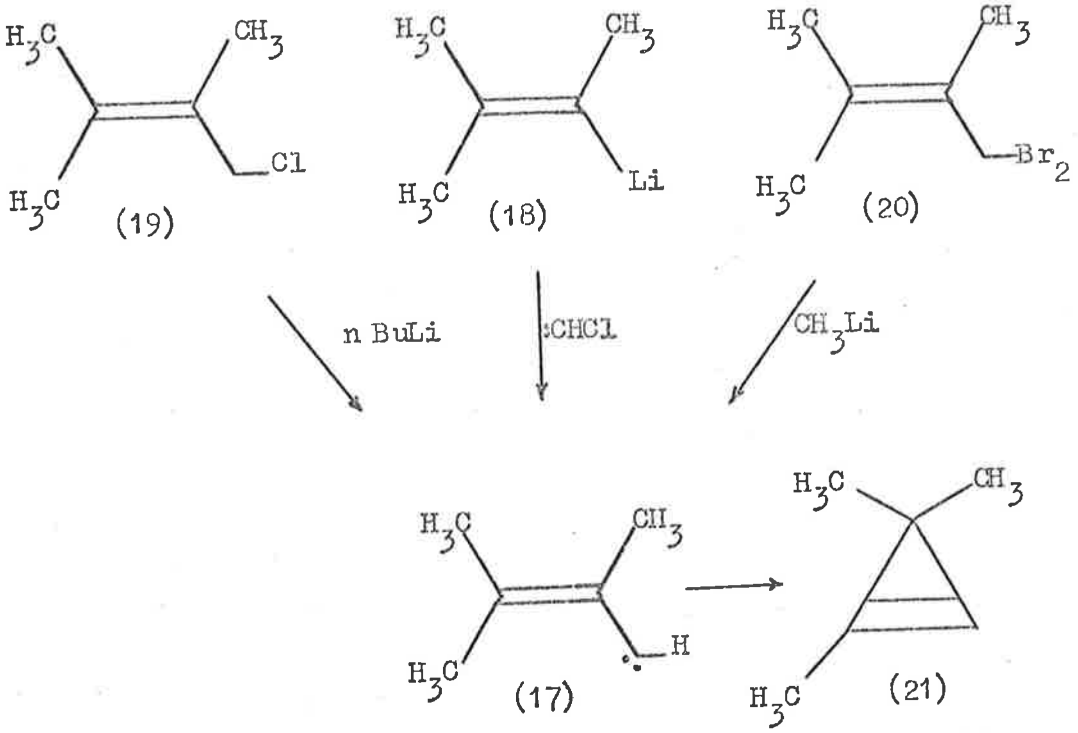
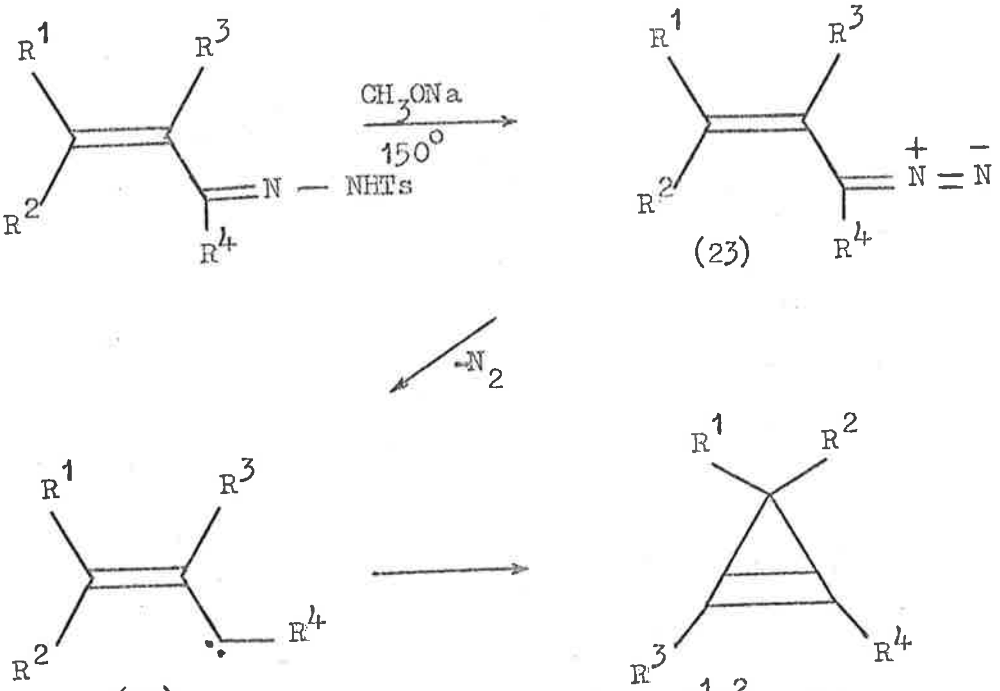
* It has not been established whether the carbon species is truly divalent.



Closs[12,19] has developed a convenient route to alkyl substituted cyclopropenes by the base-induced pyrolysis of p-toluenesulphonylhydrazones of α,β-unsaturated aldehydes and ketones. The reaction is thought to proceed by way of the alkenyl carbene 22, presumably generated from the diazoalkene 23. One important limitation of this route to cyclopropenes is that the α,β-unsaturated aldehyde or ketone must be di-alkylated in the β-position, otherwise pyrazole formation becomes the major reaction path.

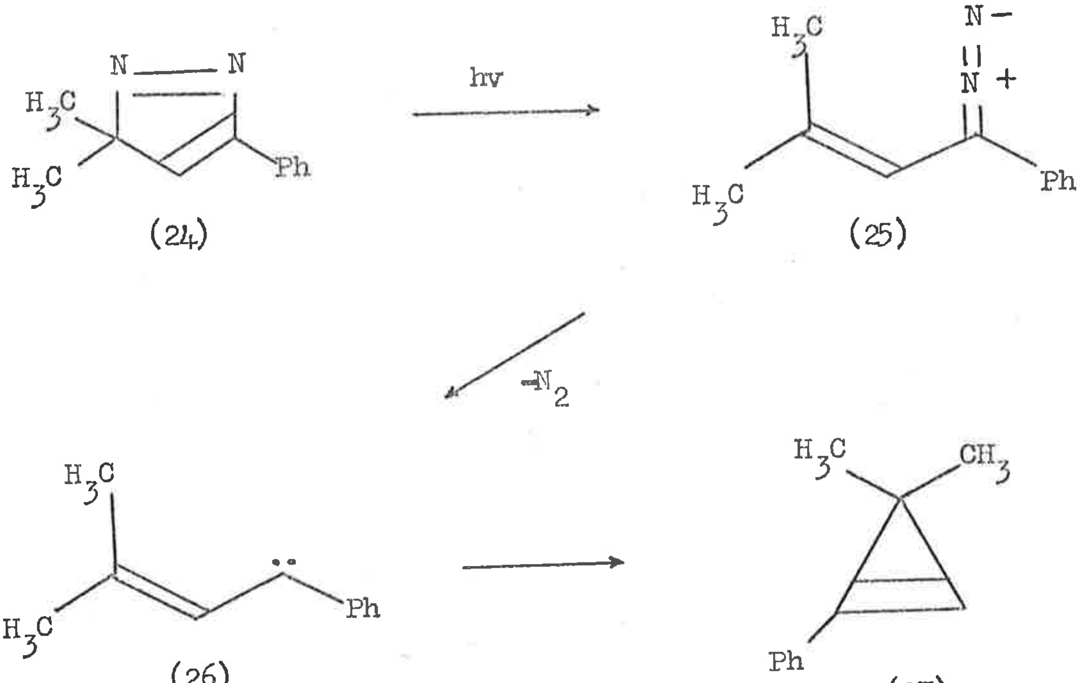
Recently[20,21,22] it has been found that irradiation of 3H-pyrazoles leads to cyclopropene formation, often in good yields. A study of the mechanism indicates that two distinct steps are involved.[20] 3,3-Dimethyl-5-phenyl-3H-pyrazole (24) initially undergoes ring opening



R^1R^2 = Alkyl.
R^3R^4 = Alkyl or H.

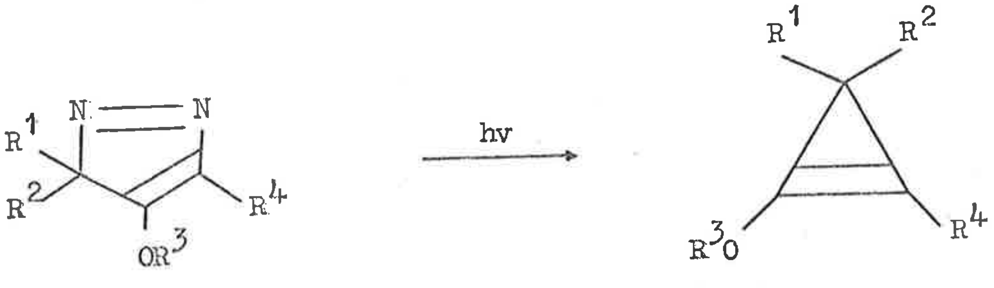
to the diazoalkene 25. Nitrogen is then eliminated from the diazoalkene, resulting in the formation of the alkenyl carbene 26, which then cyclises to the cyclopropene 27.

As irradiation can be carried out at very low temperatures this method of synthesis is particularly suited to the preparation of thermally unstable cyclopropenes. The photolysis of compounds of the general formula 28 was selected as the most promising route to cyclopropenyl ethers as the irradiation could be carried out at low temperatures if necessary. This method may also be applicable to the synthesis of trisubstituted cyclopropenyl acetates.



(24) (25) (26) (27)

Since 4-alkoxy-3H-pyrazoles (28) have not been reported, the various methods of synthesis of 3H-pyrazoles were examined with the intention of modifying the route to afford 4-alkoxy-3H-pyrazoles. Three possible routes are outlined below.



(28)

$R^1R^2R^4$ = Alkyl or aryl

R^3 = Alkyl

The first method involves the base-catalysed elimination of p-toluenesulphinic acid from 1-p-toluenesulphonyl-2-pyrazolines, disubstituted at the 5-position. Using this method p-toluenesulphinic acid has been eliminated from 5,5-dimethyl-3-phenyl-1-p-toluene-sulphonyl-2-pyrazoline (29) to give 3,3-dimethyl-5-phenyl-3H-pyrazole (30).[23]

(29) $R^1R^2 = CH_3$, $R^3 = H$, R^4 = Phenyl

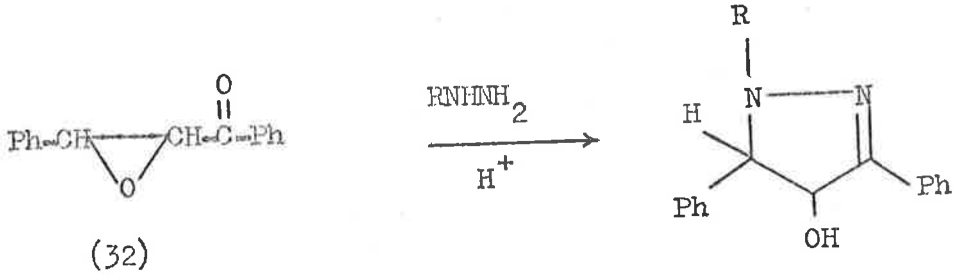
(31) $R^1R^2R^4$ = Alkyl or aryl, R^3 = OR[R = alkyl]

(30) $R^1R^2 = CH_3$, $R^3 = H$, R^4 = Phenyl.

If compounds of the general formula 31 could be synthesised it was anticipated that elimination of p-toluenesulphinic acid could lead to the required 4-alkoxy-3H-pyrazoles.

While α-keto epoxides usually react with hydrazine to yield allylic alcohols,[24] it has been known for some time[25] that aromatic α-keto epoxides, such as benzalacetophenone oxide (32), give 4-hydroxy-2-pyrazolines (33) when treated with hydrazine. Padwa[26] has extended this to the preparation of 4-hydroxy-3,5-diphenyl-1-p-toluenesulphonyl-

2-pyrazoline (34) by treatment of benzalacetophenone oxide with p-toluenesulphonylhydrazine under acidic conditions.



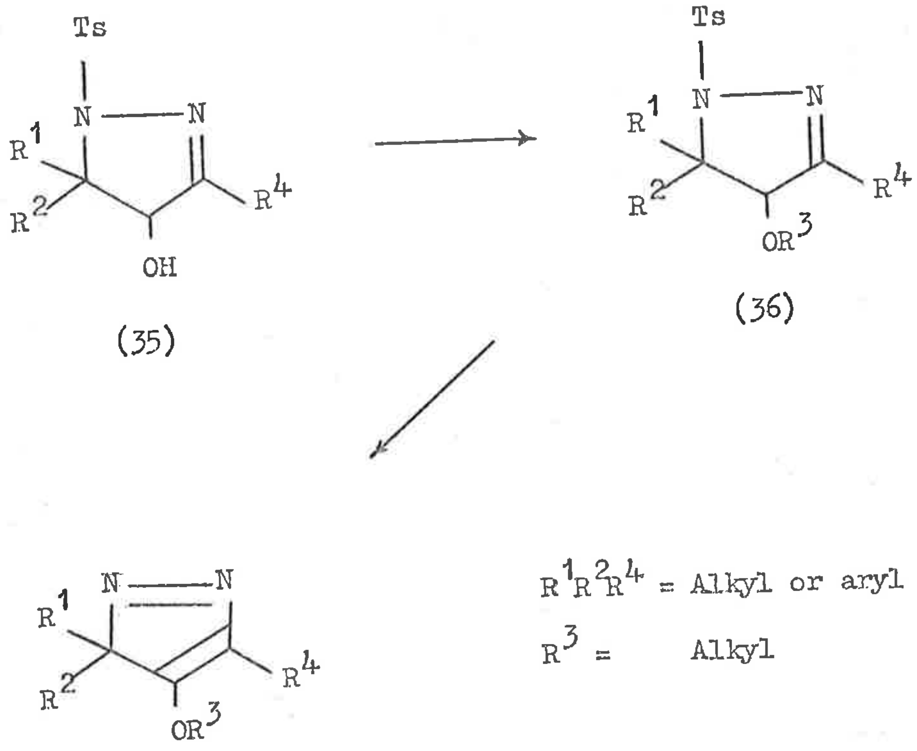
(32)

(33) R = H

(34) R = Tosyl

It was thought these pyrazolines were probably formed because the stability of a benzylic carbonium ion outweighed the stabilization resulting from a lone pair on nitrogen and this caused the benzylic carbon-oxygen bond of the epoxide to cleave in the intermediate hydrazone. Other groups capable of stabilizing a carbonium ion, particularly epoxides disubstituted at this position, should also yield similar pyrazolines. Such a reaction would make available compounds of the type 35. Transformation of compounds of general type 35 to the corresponding ether 36 followed by elimination of p-toluenesulphinic acid should give 4-alkoxy-3H-pyrazoles.

A second possible route to 4-alkoxy-3H-pyrazoles involved bromination followed by dehydrobromination of suitably substituted 2-pyrazolines. Closs[23] has shown that treatment of 5,5-dimethyl-3-phenyl-2-pyrazoline (37) with bromine gave 5-bromo-3,3-dimethyl-5-



(35)

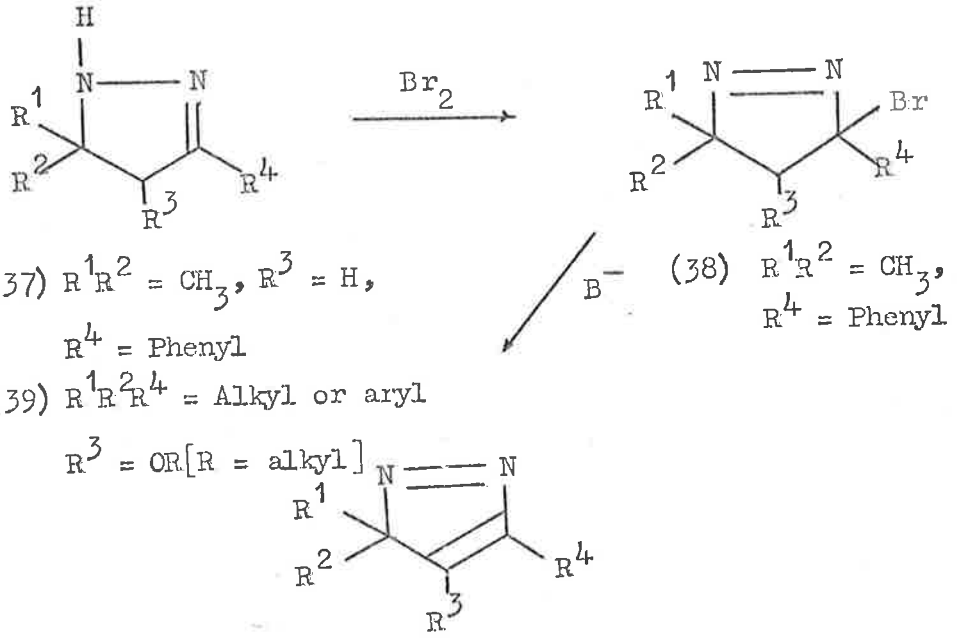
(36)

$R^1R^2R^4$ = Alkyl or aryl

R^3 = Alkyl

phenyl-1-pyrazoline (38) which on treatment with base afforded the 3H-pyrazole 30. If compounds of the type 39 could be synthesised it was anticipated that bromination, followed by dehydrobromination could lead to the required 4-alkoxy-3H-pyrazoles.

A possible route to compounds of the type 39 utilizes a 5-disubstituted-4-hydroxy-2-pyrazoline (40). Examples of these compounds were unknown at the initiation of this project. If compounds of the type 40 could be synthesised and selective protection of the amino group effected then subsequent ether formation followed by removal of the amino protective group could realise compounds of the



(37) $R^1R^2 = CH_3$, $R^3 = H$,

R^4 = Phenyl

(38) $R^1R^2 = CH_3$, $R^3 = H$

R^4 = Phenyl

(39) $R^1R^2R^4$ = Alkyl or aryl

R^3 = OR[R = alkyl]

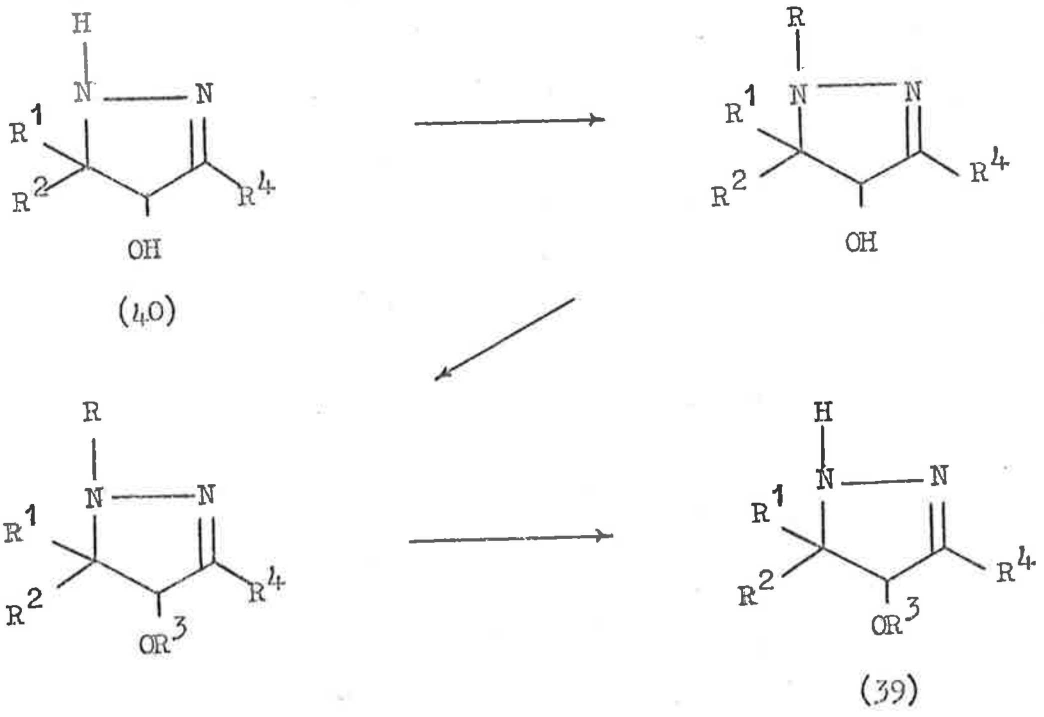
(30) $R^1R^2 = CH_3$, $R^3 = H$, R^4 = Phenyl

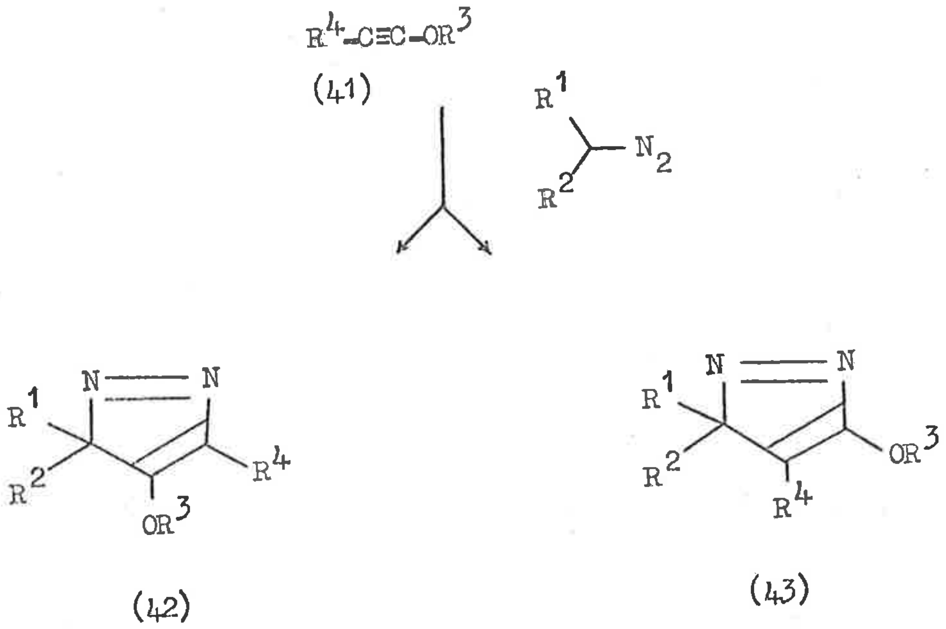
(28) $R^1R^2R^4$ = Alkyl or aryl; R^3 = OR[R = alkyl]

general type 39 (see Scheme below).

A third possible route to 4-alkoxy-3H-pyrazoles makes use of a 1,3-dipolar cycloaddition reaction between a disubstituted diazo compound and an alkynyl ether (41). Cycloadditions between disubstituted diazo compounds to both carbonyl conjugated[27] and non-carbonyl conjuated[27,28,29] acetylenes are known.

It was anticipated that the ether group in an alkynyl ether should facilitate cycloaddition as conjugation of multiple bonds with electron attracting or electron releasing substituents increases the


(40)
(39)


(41)
(42)
(43)

dipolarophilic activity of that bond.[30] This is manifested in the increased rate of cycloaddition shown by these systems. Huisgen[30] has explained this phenomenon by two effects which may be interrelated. Conjugation leads to an increased polarisability of the π-system. If in the transition state the two new o-bonds are formed to a different extent then the residual partial charges can be stabilised by the substituents with a consequent lowering of the activation energy for the reaction.

On electronic grounds it is impossible to predict whether isomer 42 or 43 should predominate. Polarisation of the alkynyl ether would lead to 44 and nucleophilic attack by the diazo compound would favour the α-carbon atom. Huisgen,[30] however, stresses that due to mesomerism it is impossible to identify unequivocally an electrophilic and nucleophilic centre in a diazo compound. As a result either the outer nitrogen or the central carbon atom might link with the α-carbon atom.

$$\underset{\beta\ \ \alpha}{R{-}C{\equiv}C{-}O{-}R'} \longleftrightarrow R{-}\bar{C}{=}C{=}\overset{+}{O}{-}R$$

(41) (44)

CHAPTER II

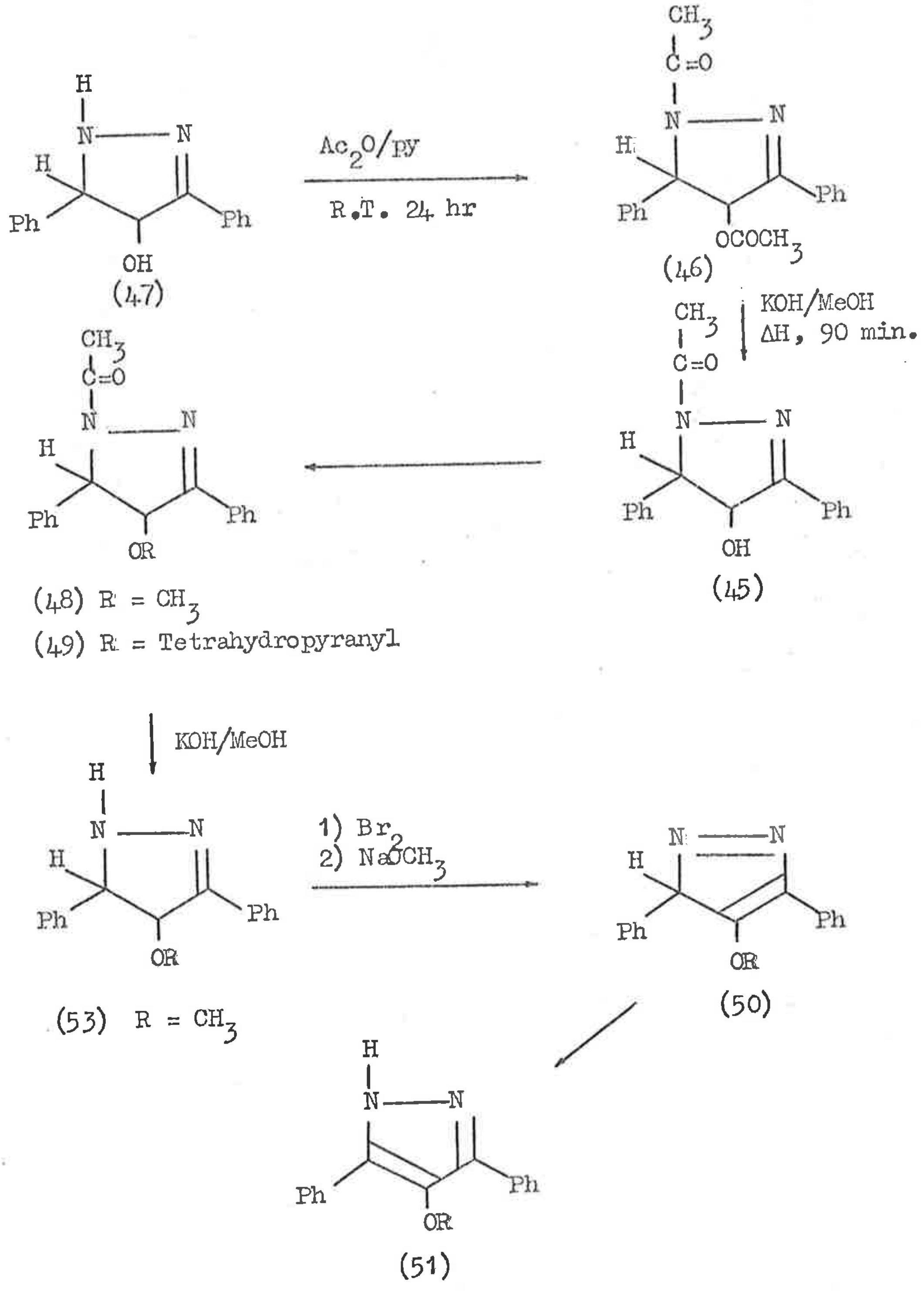
Approaches towards the synthesis of 4-alkoxy-3H-pyrazoles.

(a) Studies directed towards the synthesis of 4-alkoxy-2-pyrazolines, unsubstituted on nitrogen.

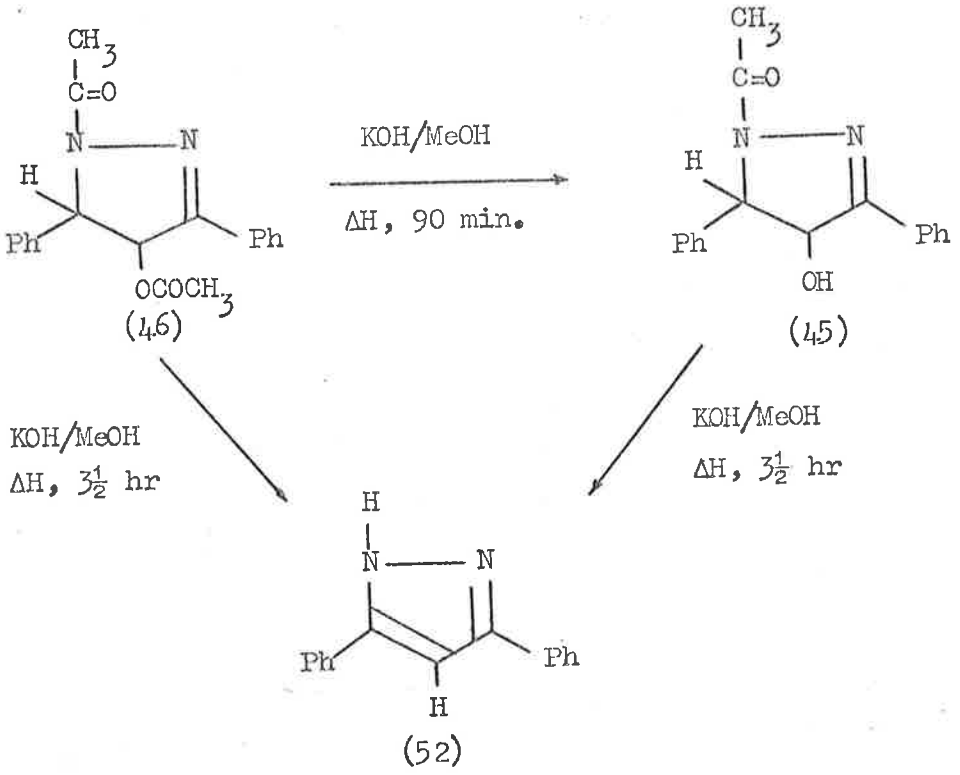
Soon after the commencement of this project, 1-acetyl-4-hydroxy-3,5-diphenyl-2-pyrazoline (45) became available.[31] This seemed an ideal compound to test one of the proposed routes to 4-alkoxy-3H-pyrazoles (see Scheme 1, page 21). Although the final product in this scheme is not a 4-alkoxy-3H-pyrazole, compound 50 is. This route to 4-alkoxy-3H-pyrazoles would be tested because the tautomerism of the 3H-pyrazole 50 to the isomeric 1H-pyrazole 51 can be prevented when the 5-position of the initial 4-hydroxy-2-pyrazoline is disubstituted.

The amido-alcohol 45 was formed on hydrolysis of the acetate group of 4-acetoxy-1-acetyl-3,5-diphenyl-2-pyrazoline (46). The latter compound resulted from the action of acetic anhydride in pyridine on 4-hydroxy-3,5-diphenyl-2-pyrazoline (47). Sinclair[31] found that treatment of the amido-acetate 46 with 10% potassium hydroxide in methanol under reflux for 90 min gave the amido alcohol 45, while refluxing for $3\frac{1}{2}$ hr afforded 3,5-diphenylpyrazole (52). He was also able to show that the amido-alcohol 45 could be converted to the pyrazole 52 by the action of 10% potassium hydroxide in methanol under reflux for $3\frac{1}{2}$ hr.

The conversion of the amido alcohol 45 to the pyrazole 52 can be explained by two mechanisms. The first involves initial dehydration followed by hydrolysis of the amide function (see Mechanism 1).

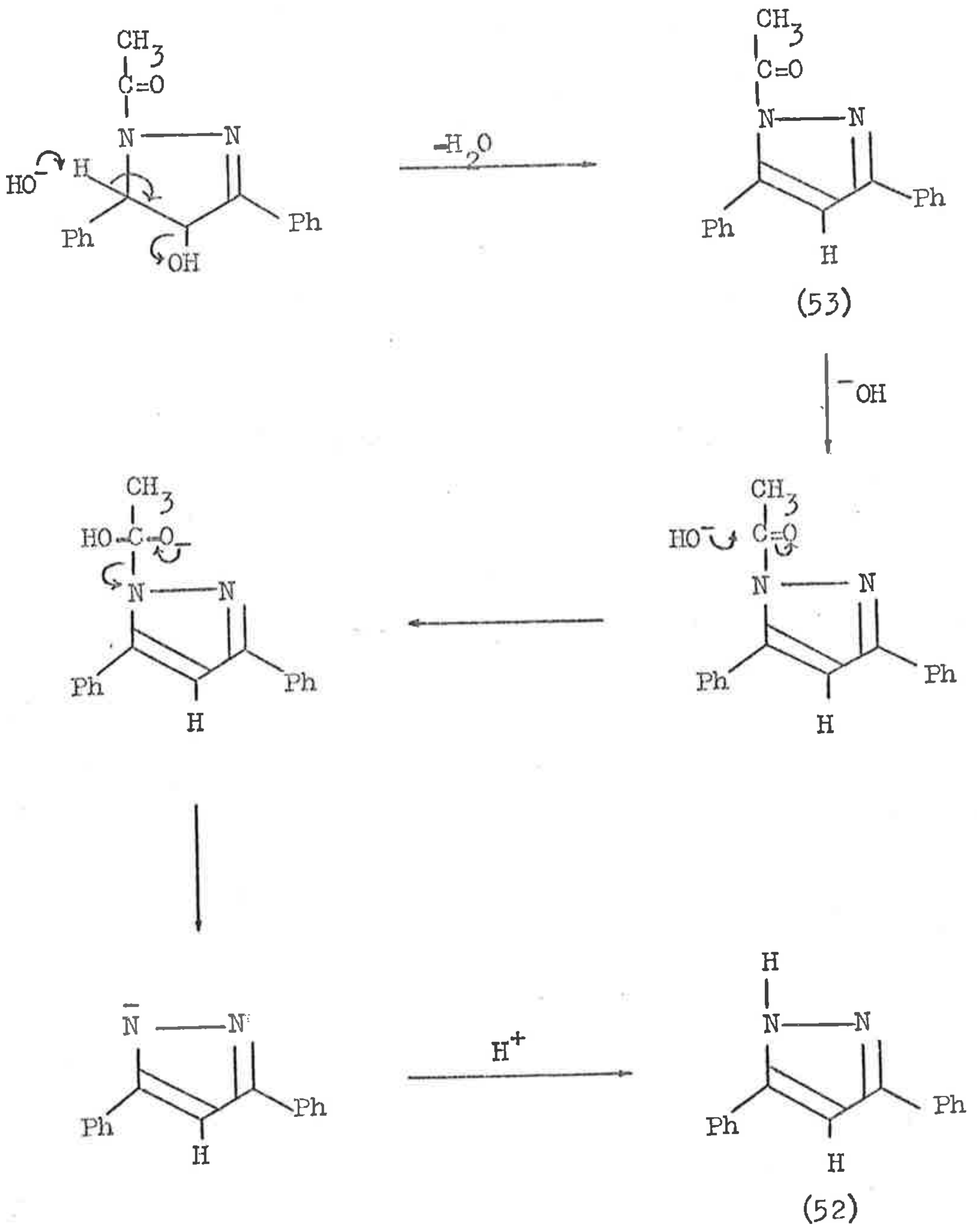

Ac$_2$O/py
R.T. 24 hr
(47)
(46)
KOH/MeOH
ΔH, 90 min.
(45)
(48) R = CH$_3$
(49) R = Tetrahydropyranyl
KOH/MeOH
(53) R = CH$_3$
1) Br$_2$
2) NaOCH$_3$
(50)
(51)

Scheme 1.

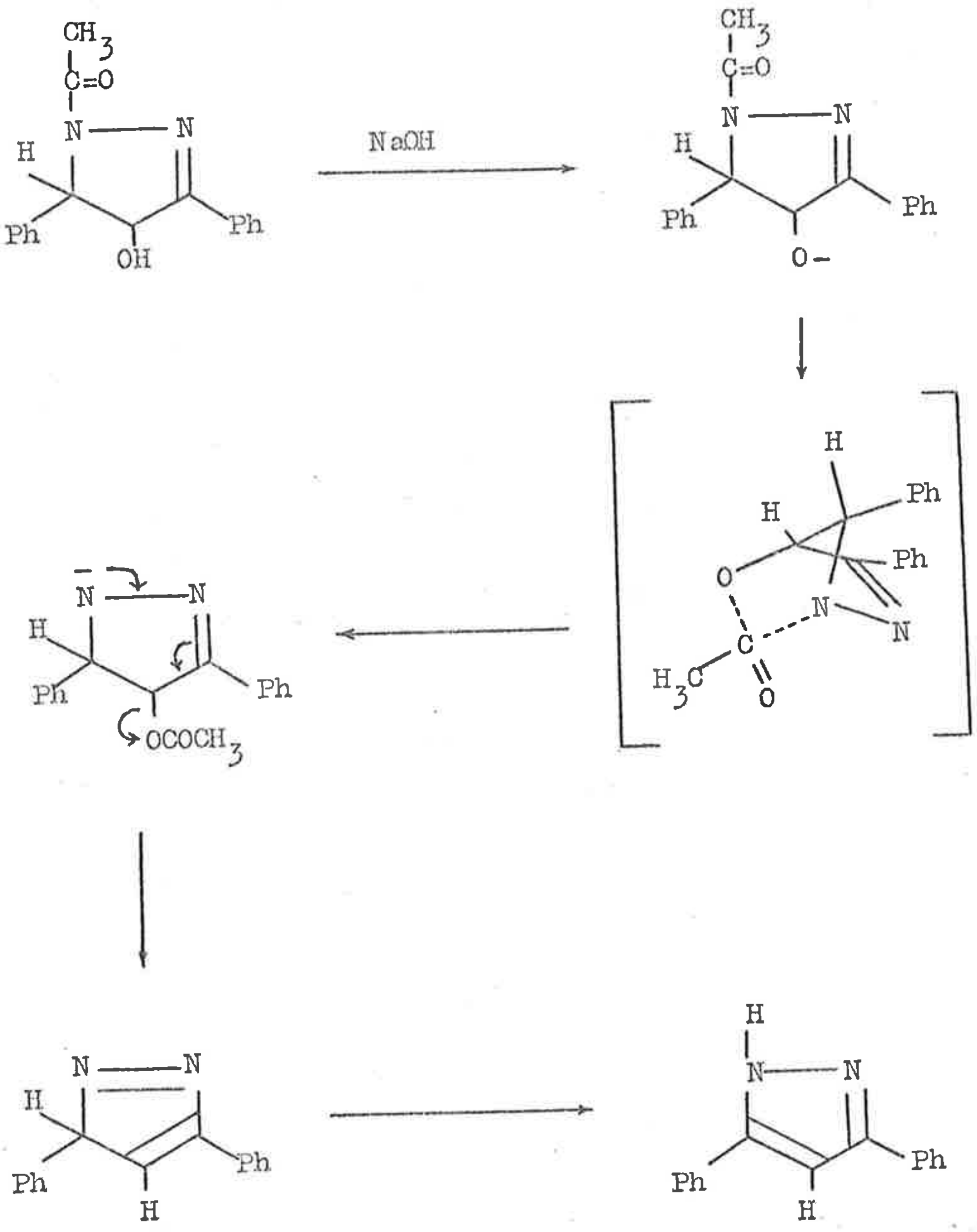


The second mechanism is based on work by Padwa.[26] He showed that treatment of 4-hydroxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline with sodium hydride in boiling tetrahydrofuran gave 3,5-diphenylpyrazole. The mechanism proposed incorporates the transfer of the p-toluenesulphinyl group from nitrogen to oxygen and subsequent elimination as the p-toluenesulphonyl anion. In the case of compound 45 the acetyl group may be transferred from nitrogen to oxygen followed by subsequent elimination as the acetate anion (see Mechanism 2).

Although several attempts were made to determine which of the two mechanisms operate, no definite conclusions have been drawn.[31]



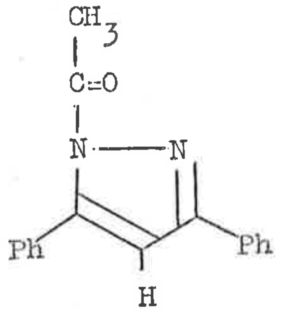
Mechanism 1.



(52)

Mechanism 2.

In Mechanism 1 the N-acetyl pyrazole 53 is postulated as an intermediate. It was shown that this compound was hydrolysed to 3,5-diphenylpyrazole under similar conditions as those employed in the conversion of the amido-alcohol 45 to 3,5-diphenylpyrazole. Evidence in favour for the exclusion of the first mechanism was provided by the absence of any N-acetylpyrazole (53) during the course of the reaction, the reaction being monitored by thin-layer chromatography. Although this result suggested that Mechanism 1 could be discounted, no evidence in support of the alternative mechanism could be forwarded.



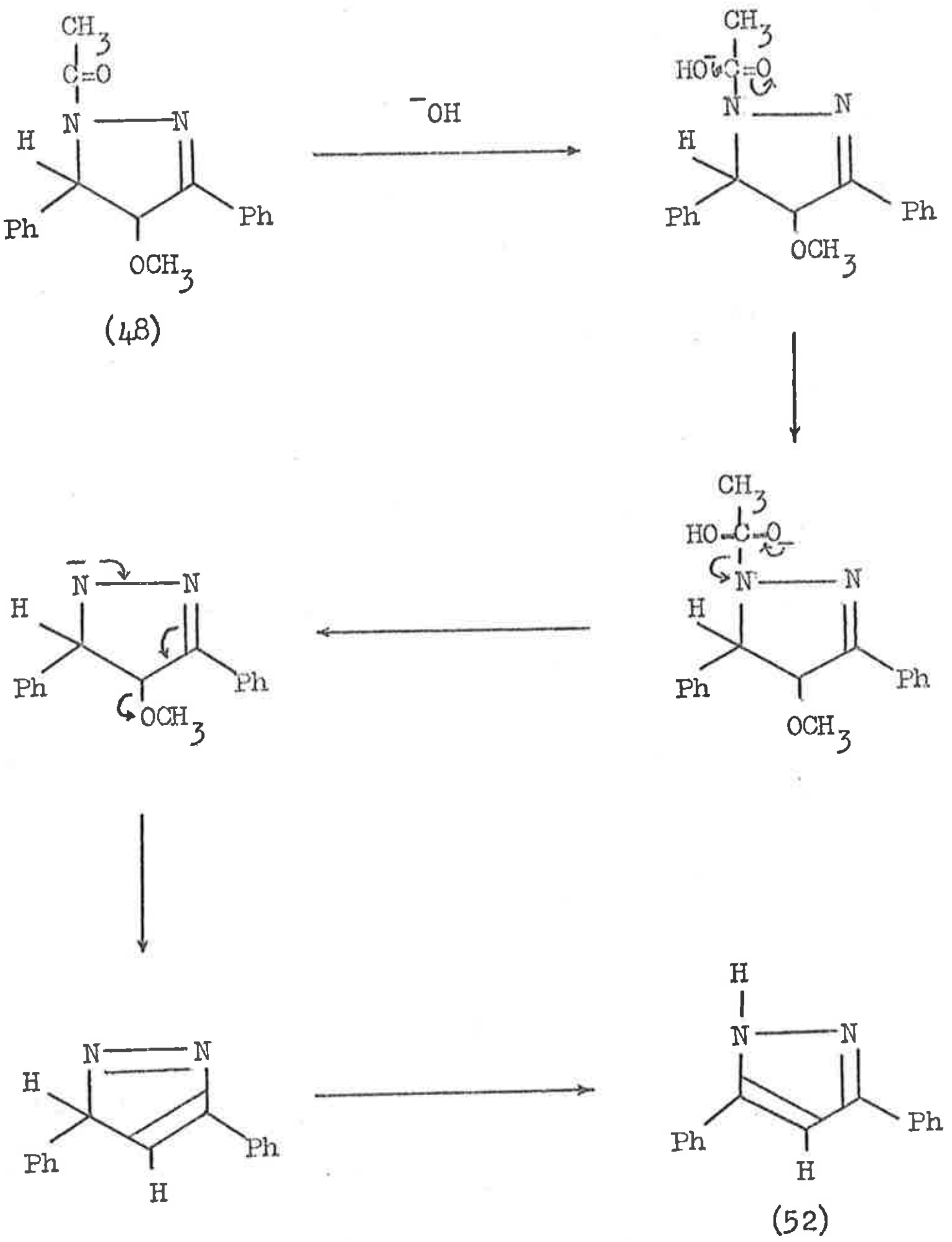
(53)

The initial step in Scheme 1 was the conversion of the hydroxyl function of compound 45 to an ether function. It was found that 1-acetyl-3,5-diphenyl-4-tetrahydropyranyloxy-2-pyrazoline (49) could be readily obtained on dissolving the amido-alcohol 45 in 2,3-dihydropyran in the presence of a crystal of p-toluenesulphonic acid. A second ether, the methyl ether 48, was synthesised by addition of compound 45 to a mixture of sodium hydride and methyl iodide in dimethoxyethane✓ at room temperature.

It was anticipated that hydrolysis of the amide functions of the amido-ethers 48 and 49 would lead to 4-alkoxy-2-pyrazolines, unsubstituted on nitrogen. These compounds were key intermediate in one of the proposed routes to 4-alkoxy-3H-pyrazoles (see Introduction, page 16). The amido ether 48 was dissolved in a 10% potassium hydroxide in methanol solution and heated under reflux for 4 hr. Instead of the expected product, compound 53 (see Scheme 1, page 21) the compound isolated was identified as 3,5-diphenylpyrazole. The same result was obtained using compound 49.

Two separate mechanisms could account for the formation of 3,5-diphenylpyrazole from the amido-ethers 48 and 49. The first mechanism involves the initial elimination of methanol, in the case of compound 48, followed by hydrolysis of the amide group. Mechanism 3 is therefore, similar to mechanism 1 (see page 23) except methanol instead of water is eliminated in the initial step. The second mechanism could also account for the observed product (see Mechanism 4). In an effort to distinguish between these two mechanisms the reaction was monitored by thin-layer chromatography. Very strong evidence that the first mechanism (Mechanism 3, page 23) did not operate was provided by the fact that no N-acetyl pyrazole 53 could be detected during the hydrolysis of the amido-ether 48. In view of this result it seems likely that the transformation occurs by way of Mechanism 4.

✓ In this thesis 1,2-dimethoxyethane is referred to as dimethoxyethane.

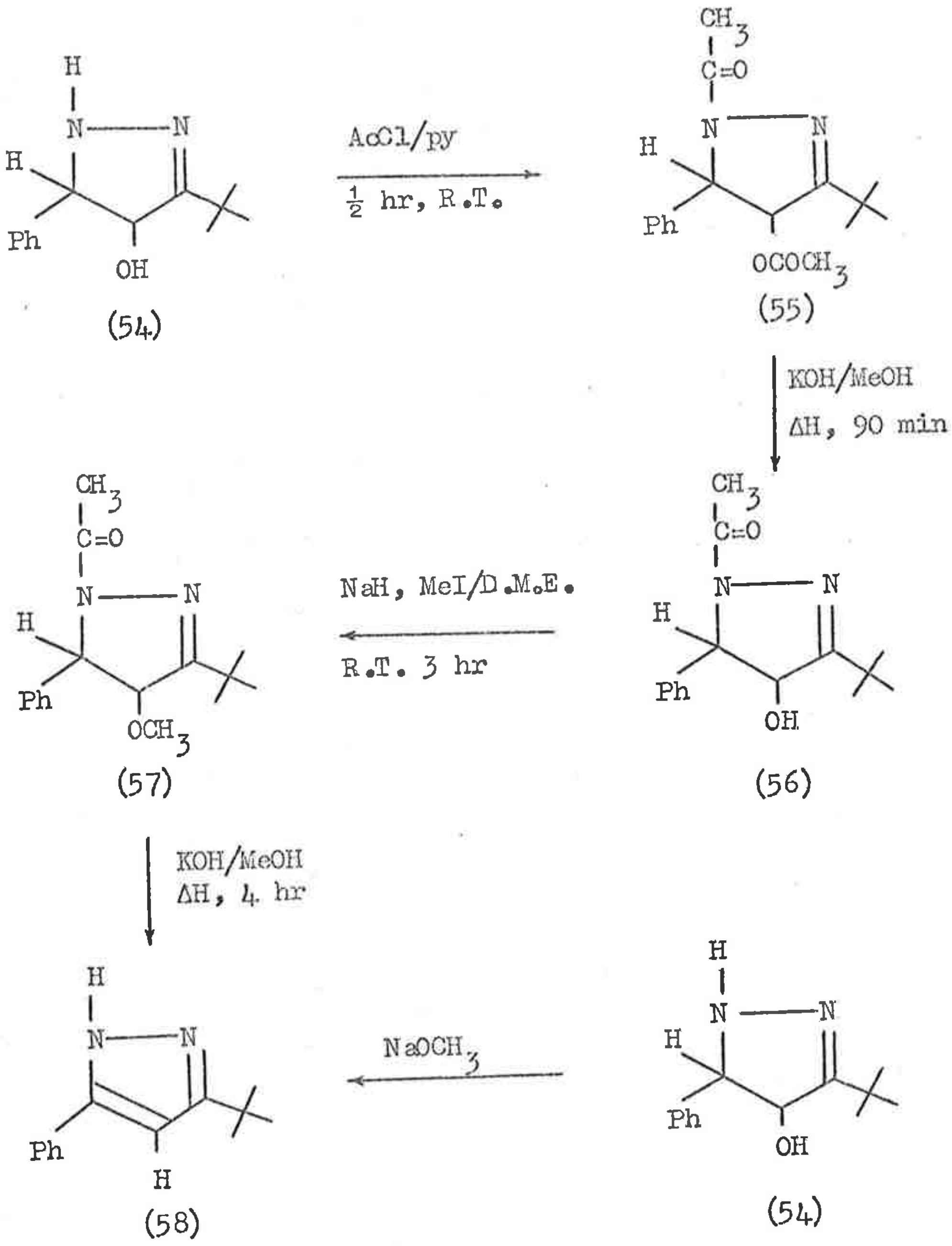


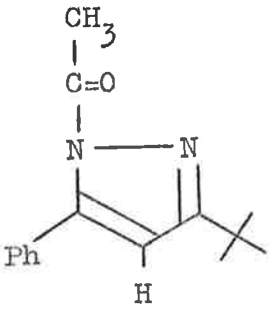
Mechanism 4.

At this stage it was decided to synthesise a new 4-hydroxy-2-pyrazoline. After suitable modification to this pyrazoline the generality of Mechanism 4 could be tested.

The new 4-hydroxy-2-pyrazoline synthesised was 3-*tert*-butyl-4-hydroxy-5-phenyl-2-pyrazoline (54) and this compound was produced in excellent yield (95%) on heating under reflux in ethanol a mixture of *trans*-benzalpinacolone oxide and hydrazine hydrate. This compound was conveniently converted to the amido-acetate 55 by the action of acetyl chloride in pyridine at room temperature for ½ hr. The selective hydrolysis of the ester group of compound 55, to give the amido-alcohol 56, was achieved by boiling the amido-acetate 55 in a 10% potassium hydroxide in methanol solution for 90 min. The synthesis of the methyl ether 57 was then smoothly carried out by the addition of sodium hydride and methyl iodide to a solution of the amido-alcohol 56 in dimethoxyethane at room temperature.

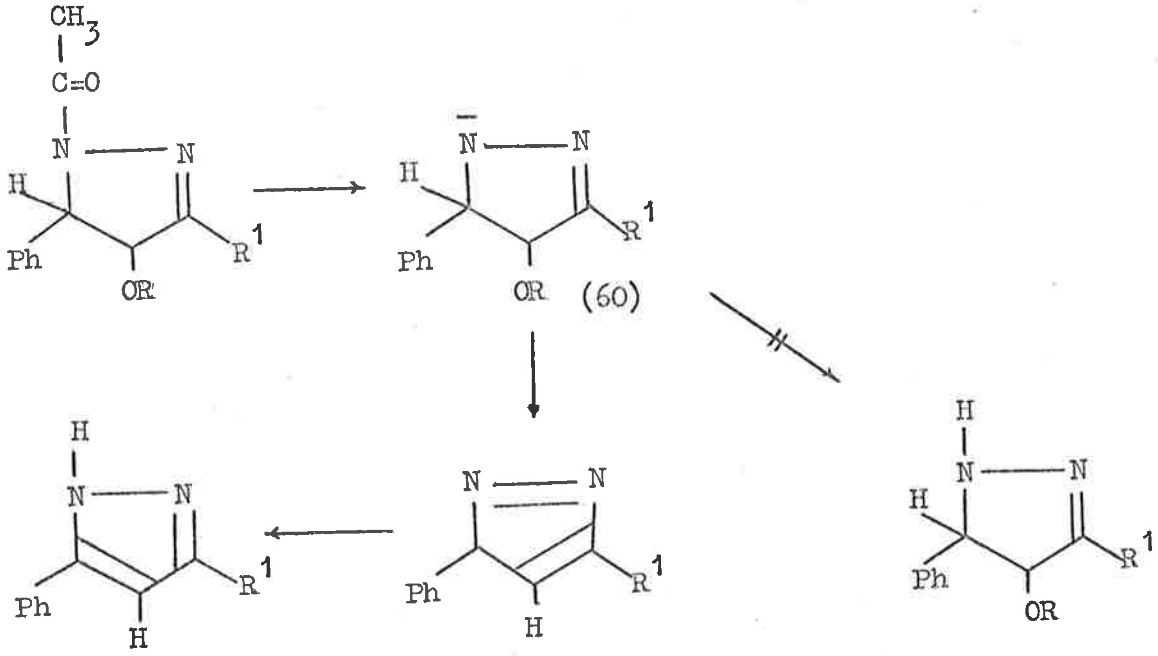
When the amido-ether 57 was heated under reflux in a solution of potassium hydroxide in methanol the product was 3-*tert*-butyl-5-phenylpyrazole (58). The identity of the product was confirmed by comparison with the compound obtained on base-catalysed dehydration of the 4-hydroxy-2-pyrazoline 54. Once again no N-acetyl pyrazole (59) could be detected during the reaction, therefore the mechanism for the conversion of the amido-ether 57 to the pyrazole 58 was thought to be the same as outlined in Mechanism 4 (see page 27).


(54)
AcCl/py
½ hr, R.T.
(55)
KOH/MeOH
ΔH, 90 min
(56)
NaH, MeI/D.M.E.
R.T. 3 hr
(57)
KOH/MeOH
ΔH, 4 hr
(58)
NaOCH3
(54)

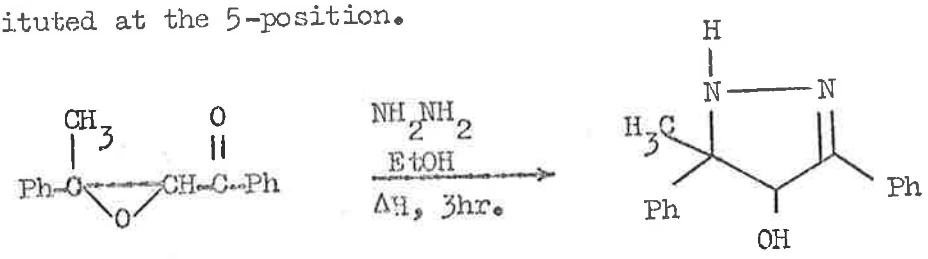


(59)

No 4-alkoxy-2-pyrazolines were formed on hydrolysis of the amido-ethers 48, 49, and 57 indicating that the formation of the pyrazole products from the anion 60 occurs to the exclusion of protonation (see below).



During the course of the work mentioned above, Sinclair[31] found that treatment of *trans*-dypnone oxide (61) with boiling hydrazine hydrate in ethanol gave 4-hydroxy-5-methyl-3,5-diphenyl-2-pyrazoline (62) in 30% yield. This compound is the first 4-hydroxy-2-pyrazoline disubstituted at the 5-position.



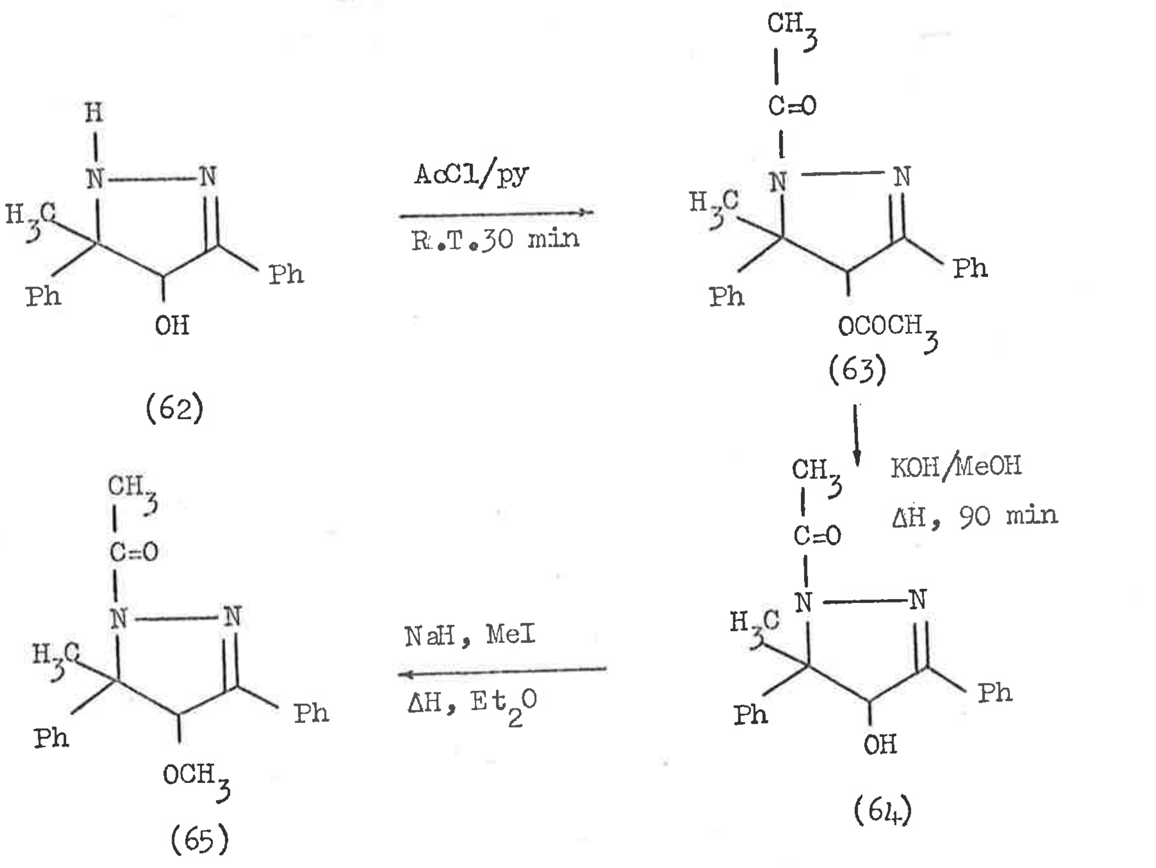
(61)

(62)

It was decided to employ the 4-hydroxy-2-pyrazoline 62 in the same reaction sequence as outlined in Scheme 1 (see page 21). This was undertaken to determine whether Mechanism 4 could be extended to cover the case of a 1-acetyl-4-alkoxy-2-pyrazoline, disubstituted at the 5-position.

Acetylation of the 4-hydroxy-2-pyrazoline 62 to the amido-acetate 63 proceeded smoothly using acetyl chloride in pyridine at room temperature. The next step, the hydrolysis of the ester group of the amido-acetate 63 to give the amido-alcohol 64 was carried out using boiling 10% potassium hydroxide in methanol. Compound 64 was then smoothly converted to the methyl ether 65 by treatment with a mixture of sodium hydride and methyl iodide in boiling ether.

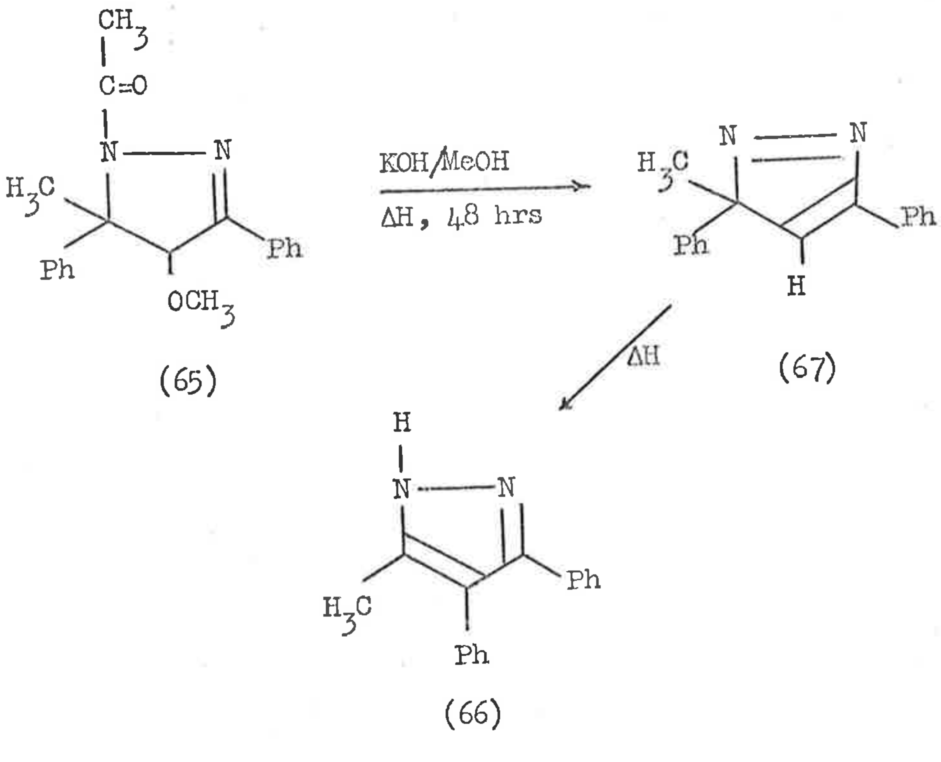
Since treatment of the amido-ether 65 with boiling 10% potassium hydroxide in methanol for 4 hr resulted in no change, severe conditions were required to cleave the amide group. 5-Methyl-3,4-diphenylpyrazole (66) was obtained on refluxing the amido-ether 65 in a 40% potassium hydroxide in methanol mixture, in an atmosphere of nitrogen, for 2 days. The product was thought to result from the isomerisation of 3-methyl-3,5-diphenyl-3H-pyrazole (67) under the reaction conditions. Huttel et al.[32] have reported the isomerisation of the 3H-pyrazole 67 to the 1H-pyrazole 66 in the presence of either acid or heat. The formation of the 3H-pyrazole 67 from the amido-ether



65 can be explained by mechanism 4 (see page 27) and therefore, this mechanism can be extended to 1-acetyl-4-alkoxy-2-pyrazolines, disubstituted at the 5-position.

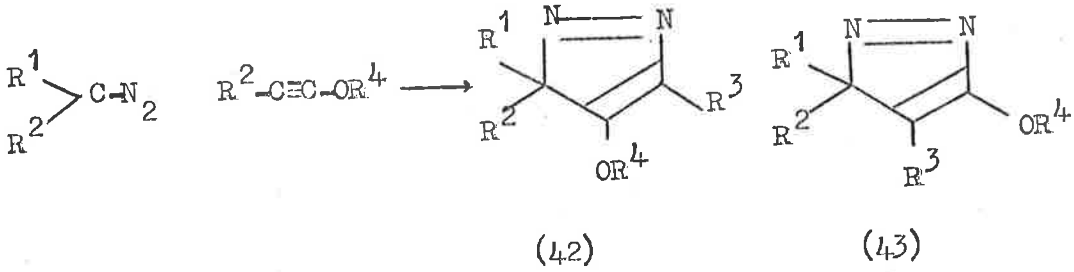
The difference in reactivity of the amide group in compound 65 and the compounds 48, 49, and 57 may be attributed to steric hindrance. While examination of molecular models of the amido-ethers 65 and 48, 49 and 57 indicate that the carbonyl group in compound 65 is more sterically hindered than those in the other compounds, the severe conditions of hydrolysis necessary in the case of the amido-ether 65 are surprising as the amount of steric hindrance does not appear extremely severe.

At this stage this route to 4-alkoxy-3H-pyrazoles was abandoned.



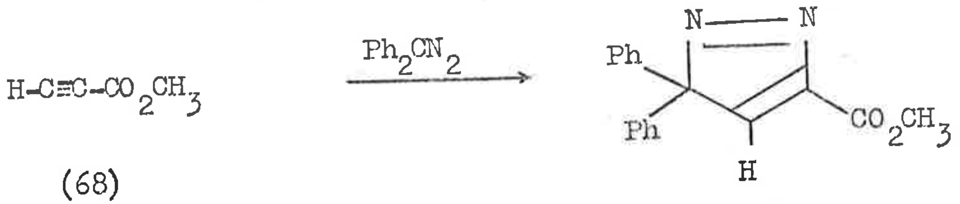
(b) Attempted 1,3-dipolar cycloaddition reactions between 1-ethoxyprop-1-yne and disubstituted diazocompounds.

As 4-alkoxy-3H-pyrazoles could not be prepared by the route discussed in section (a), a second route which involved in the key step, a 1,3-dipolar cycloaddition reaction between a disubstituted diazocompound and an alkynyl ether was investigated. On electronic grounds, it is impossible to predict whether isomer 42 or 43 would



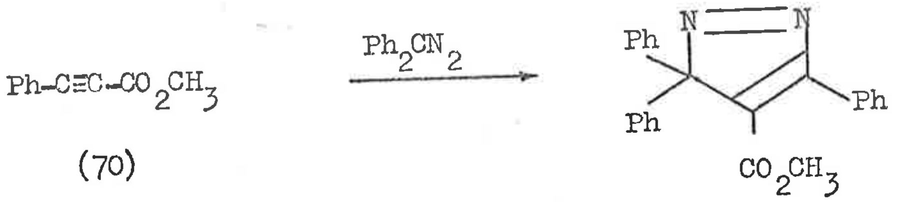
$R^1R^2R^3$ = alkyl or aryl; R^4 = alkyl.

predominate and so the importance of steric factors on these reactions had to be considered. Huisgen[33] in an excellent review on the mechanism and kinetics of 1,3-dipolar cycloadditions outlines several examples where steric factors alone determine the orientation of addition. While diphenyldiazomethane adds to the triple bond of methyl propiolic ester (68) in one direction only to give the 3H-pyrazole 69, the direction is reversed when the diazocompound adds to methyl phenyl propiolic ester (70). This reversal in orientation is due to the greater steric requirements of the phenyl group compared with the methoxy carbonyl group. When compound 70 is treated with the sterically



(68)

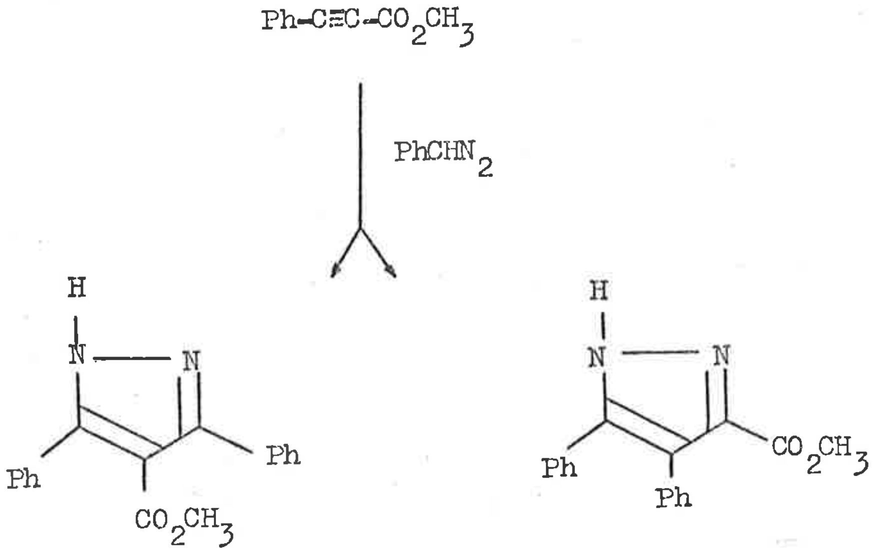
(69)



(70)

less demanding phenyl diazomethane, a mixture of the two possible isomers 71 and 72[†] is obtained, in which the isomer which is favoured on steric grounds (compound 71) is again dominant. Steric effects, therefore, can play an important role in concerted cycloadditions.

[†] These 1H-pyrazoles result on tautomerism of the corresponding 3H-pyrazoles.



(71) (72)

The rate of cycloaddition between the disubstituted diazocompound and the alkynyl ether was anticipated to be slow even though the ether group increases the electron density of the triple bond. It has been found that diphenyldiazomethane adds to acetylene when acetylene is added to the diazocompound under a partial pressure of 20 atmospheres.[34] The addition of the same diazocompound to phenylacetylene occurs after stirring for several days at room temperature[35] while addition to methyl phenyl propiolic ester occurs readily.[28] The relative rates of addition of diphenyldiazomethane to phenylacetylene and methyl phenyl propiolic ester at 40° in dimethylformamide are 1.18 to 1065.[33] It was anticipated that the reactivity of the alkynyl ether would lie close to that of phenylacetylene.

The choice of the alkynyl ether was important. As steric effects have been shown to influence, and sometimes control, the orientation of addition, the presence of a bulky group attached to the β-carbon atom of the alkynyl ether seemed desirable. This situation would favour the formation of the 4-alkoxy-3H-pyrazole (42) over the isomeric 5-alkoxy-3H-pyrazole (43). Ideally phenylmethoxyacetylene (73) would be the acetylenic ether of choice. This compound, however, has the distinct disadvantage of readily undergoing polymerisation.[36] Instead 1-ethoxyprop-1-yne (74) was selected as it is known to be stable at ordinary temperatures. In the case of compound 73, the phenyl group increases the polarisability of the triple bond but in compound 74 the methyl group has a much less significant

$Ph{-}C{\equiv}C{-}O\ CH_3$

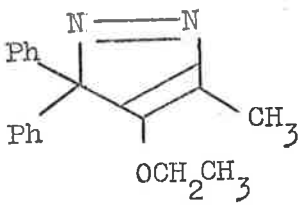
(73)

$CH_3{-}C{\equiv}C{-}OCH_2CH_3$

(74)

effect. However, in cycloaddition reactions it is suspected that the polar effects of a methyl group is less significant than its steric influence.[33]

The first 1,3-dipolar cycloaddition was attempted between diphenyldiazomethane and 1-ethoxyprop-1-yne. The two possible products are 4-ethoxy-5-methyl-3,3-diphenyl-3H-pyrazole (75) and 5-ethoxy-4-methyl-3,3-diphenyl-3H-pyrazole(76) with compound 75 favoured on steric grounds. A mixture of diphenyldiazomethane and 1-ethoxyprop-1-yne in light petroleum was stirred for several days at room temperature. An infrared spectrum of the reaction mixture indicated the presence of unchanged acetylene. Neither of the expected products were produced in this reaction. The products obtained from this reaction were benzophenone azine and a 1:1 molecular complex of benzophenone azine and sym tetraphenylethane, known decomposition products of diphenyldiazomethane.[37] When benzene was used as the solvent benzophenone azine was the only product. Once again an infrared spectrum of the reaction mixture indicated the presence of unchanged acetylene. A similar reaction employing a Carius tube at 80° for 24 hr was undertaken, however, this modification to the reaction conditions failed to alter the course of the reaction.



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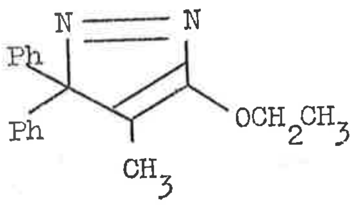
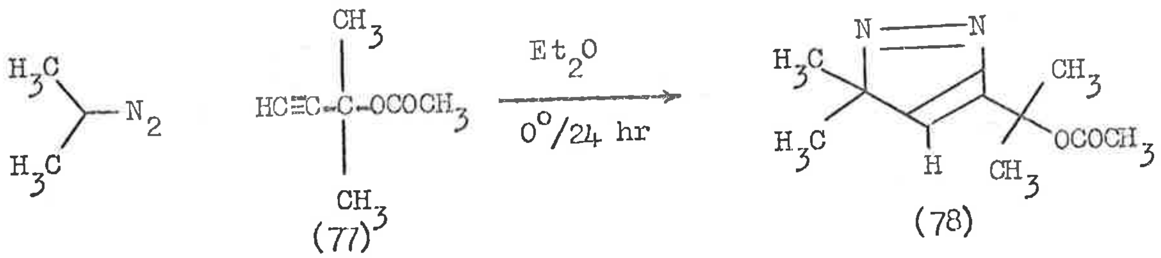
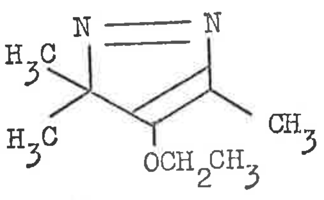


(76)

The possibility of a cycloaddition employing a more reactive diazocompound, 2-diazopropane, was then investigated. Whiting and Day[38] have successfully added 2-diazopropane to 3-methylbutyn-3-yl propionate (77) to give the 3H-pyrazole 78. In this case the high reactivity of 2-diazopropane more than compensates for the weakly active dipolarophile. A cycloaddition reaction was then attempted between 1-ethoxyprop-1-yne and 2-diazopropane, the two possible products being 4-ethoxy-3,3,5-trimethyl-3H-pyrazole (79) and 5-ethoxy-3,3,4-trimethyl-3H-pyrazole (80). Compound 79 is favoured on consideration of steric effects. A mixture of 2-diazopropane and 1-ethoxyprop-1-yne in ether, initially at 0°, was allowed to reach room temperature overnight. Neither of the expected products were produced in this reaction, the only product being acetone azine, a known decomposition product of



(77) (78)



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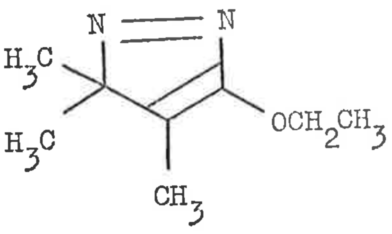


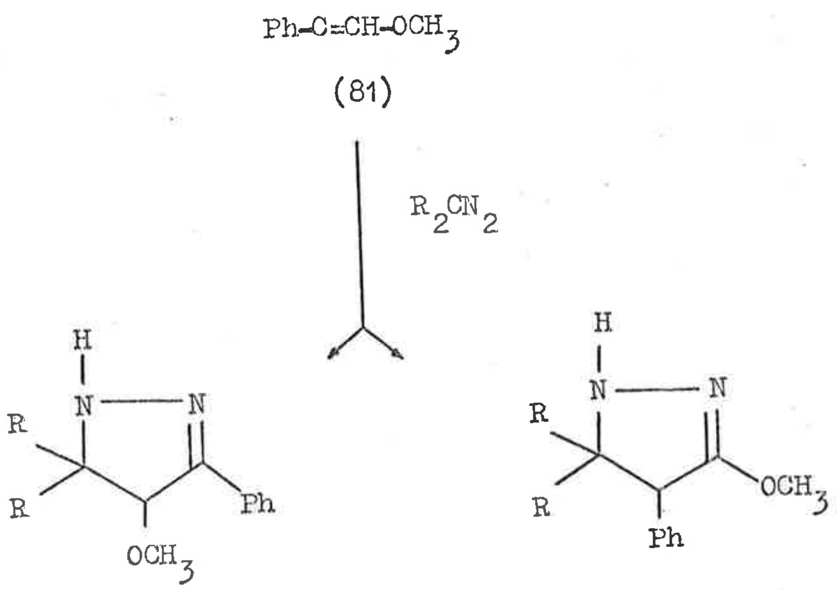
(80)

2-diazopropane.[39] No reactions were attempted at higher temperatures due to the instability of 2-diazopropane.

It appears, therefore, that, under the conditions outlined above, diphenyldiazomethane and 2-diazopropane do not add to 1-ethoxyprop-1-yne. Apparently, the rate of decomposition of the diazocompounds is greater than the rate of addition in all cases. Although 1,3-dipolar cycloadditions have been shown to be reversible,[30] it is more likely in this case that the ether group is not sufficiently activating to ensure cycloaddition. It has been stated above (see Introduction, page 17) that groups increasing or decreasing the electron density in multiple bonds increase the rate of 1,3-dipolar cycloaddition. It has been found, however, that double bonds bearing fluorine or chlorine substituents are especially poor dipolarophiles.[33] In this case, the decrease in electron density of the double bond cannot, therefore be the controlling factor and no explanation for the difference in dipolarophilicity has been forwarded.

Bearing in mind that the dipolarophilic character of a carbon-carbon double bond is almost identical to that of a triple bond,[33] it was of interest to determine whether the ether group also has a deactivating effect on the addition of diazocompounds to double bonds.

As diazocompounds, in particular diphenyldiazomethane,[27] have been added to styrene, the 1,3-dipolar cycloaddition between β-methoxystyrene (81) and diphenyldiazomethane and 2-diazopropane should indicate the effect of the ether group on such additions with olefins. Outlined below are the expected products resulting on the addition of diphenyldiazomethane and 2-diazopropane to β-methoxystyrene. Compounds 82 and 83 are favoured on consideration of steric factors. In all cases the only products isolated were those resulting from decomposition of the diazocompound.



(82) R = Ph
(83) R = CH$_3$

(84) R = Ph
(85) R = CH$_3$

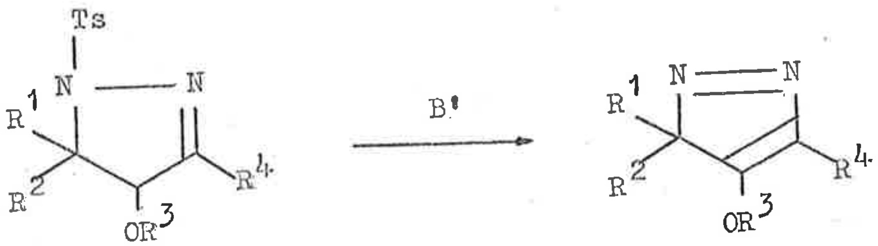
This aspect of the work was abandoned at this stage. It appears that the presence of an ether group attached to either a triple or double bond deactivates that bond to such an extent as to prevent it entering in 1,3-dipolar cycloadditions with disubstituted diazocompounds. No explanation for this effect can be forwarded at this stage.

CHAPTER III.

Elimination of p-toluenesulphinic acid from 4-alkoxy-1-p-toluenesulphonyl-2-pyrazolines.

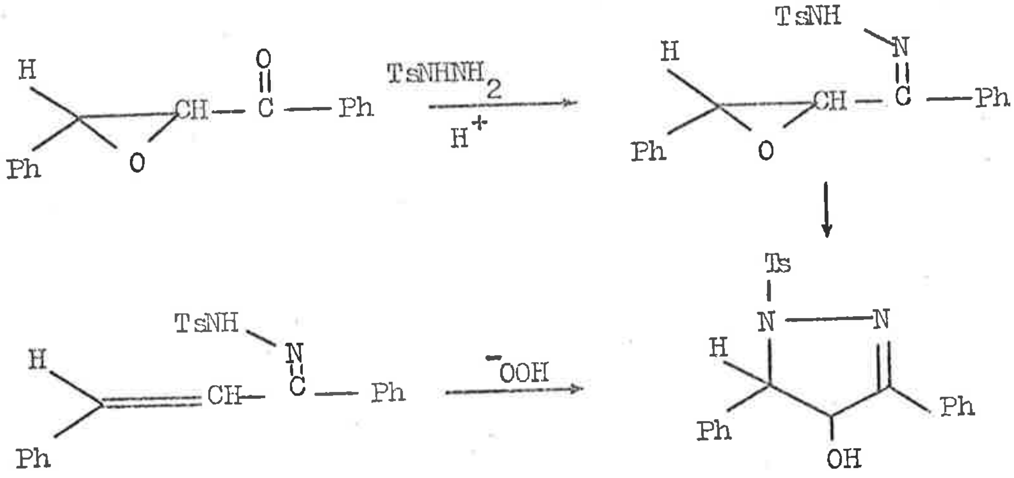
(a) Elimination of p-toluenesulphinic acid from 4-alkoxy-3,5-diphenyl-1-p-toluenephonyl-2-pyrazolines.

The third possible route to 4-alkoxy-3H-pyrazoles (28) was then explored. This route has as its key step the elimination of p-toluenesulphinic acid from suitably substituted 4-alkoxy-1-p-toluenesulphonyl-2-pyrazolines (31) (See Introduction, page 14).



(31) (28)

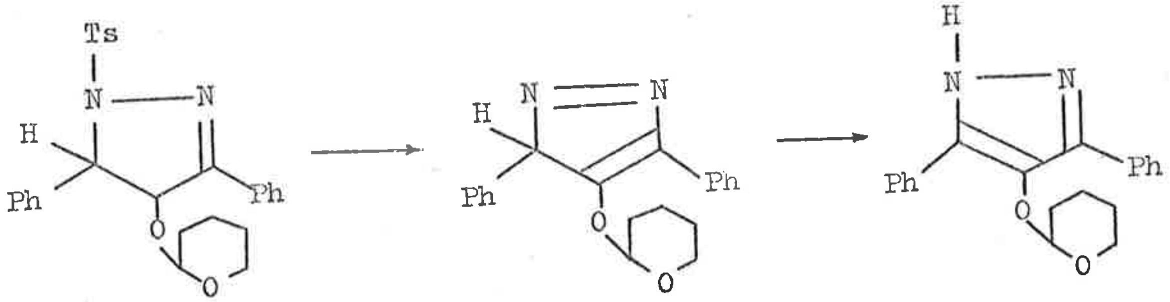
As 4-hydroxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (34) was readily available,[26] it was decided to use it as a model compound in a sequence of reactions which would test the possibility of obtaining compounds of the type 28 from suitably substituted 4-alkoxy-1-p-toluenesulphonyl-2-pyrazolines. Compound 34 is synthesised under acidic conditions by the action of p-toluenesulphonylhydrazine on benzalacetophenone oxide in a reaction in which the syn-p-toluenesulphonylhydrazone 86 is believed to be an intermediate. Compound 34 can also be synthesised by the addition of alkaline hydrogen



(34)

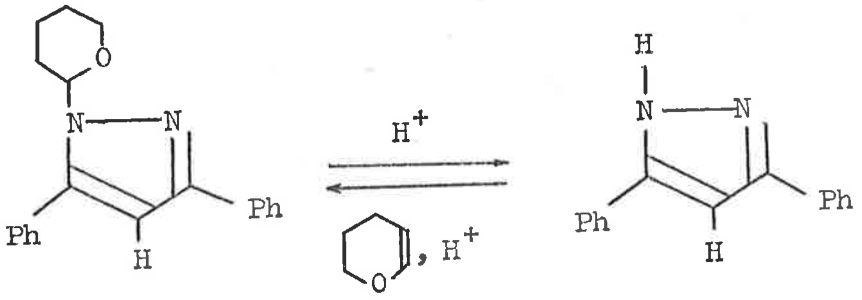
peroxide to the *p*-toluenesulphonylhydrazone derivative of chalcone.

The conversion of the 4-hydroxy-2-pyrazoline 34 to its tetrahydropyranyl ether 87 (a 1:1 mixture of diastereoisomers, by n.m.r.) was smoothly effected using 2,3-dihydropyran in chloroform in the presence of acid. It was expected that treatment of the tetrahydropyranyl ether 87 with base would lead to the elimination of *p*-toluenesulphinic acid to give the 3H-pyrazole 88 which would then tautomerise



(87) (88) (89)

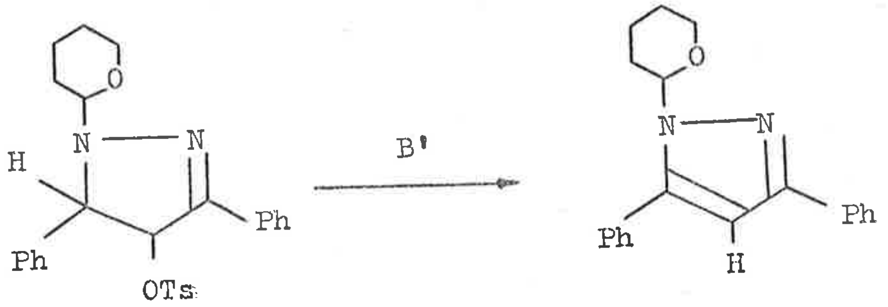
to the more stable 1H-pyrazole 89. The base-catalysed elimination would test the proposed route to 4-alkoxy-3H-pyrazoles as the tautomerism of compound 88 to compound 89 can be prevented if the 3-position is disubstituted. It must also be emphasised that the driving force for the reaction would be the elimination of p-toluenesulphinic acid and not the conversion to an aromatic compound. When the tetrahydropyranyl ether 87 was heated with sodium hydride in dimethoxyethane the expected product was not obtained. Instead, a compound $C_{20}H_{20}N_2O$, in which the tetrahydropyranyl group was still present and which on acidic hydrolysis gave 3,5-diphenylpyrazole (52) was obtained. That the product was the tetrahydropyranyl derivative (90) of 3,5-diphenylpyrazole was confirmed by comparison with the product obtained from treatment of 3,5-diphenylpyrazole with 2,3-dihydropyran under acidic conditions. If treatment of the 4-hydroxy-2-pyrazoline 34 with acid resulted in the migration of the p-toluenesulphonyl group from nitrogen to oxygen, then subsequent reaction with



(90)

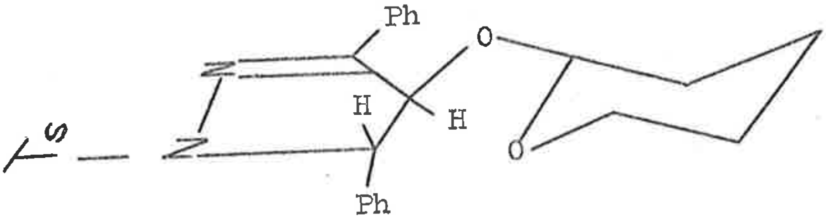
(52)

2,3-dihydropyran would give compound 91. Base-catalysed elimination of p-toluenesulphonic acid from compound 91 would give the observed



(91) (90)

product. However, comparison of the n.m.r. spectra of compounds 87 and 90 provided definite proof that in compound 87 the tetrahydropyranyl group is fixed on oxygen and not on nitrogen. In the n.m.r. spectrum of compound 87 the hydrogen at the 2-position in the tetrahydropyranyl ring appears as a broad signal, while the hydrogens at the 3,4- and 5-positions in the tetrahydropyranyl ring resonate as a fairly sharp peak. This indicates that the tetrahydropyranyl ring is not in a fixed conformation but is rapidly interconverting, relative to the n.m.r. time scale, between two chair forms. In the n.m.r. spectrum of compound 90 the hydrogens at the 2- and 3-positions in the tetrahydropyranyl ring form an ABX system. The X part of the system, which resonates as a doublet-of-doublets, is observed while the AB part is concealed beneath other resonances. As J_{AB} could not



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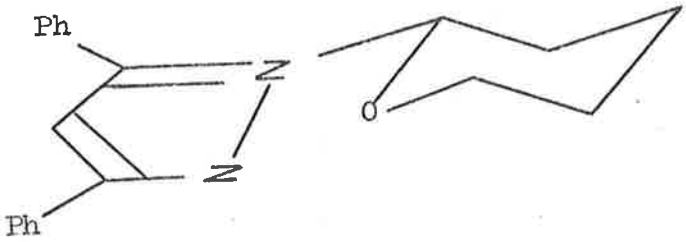
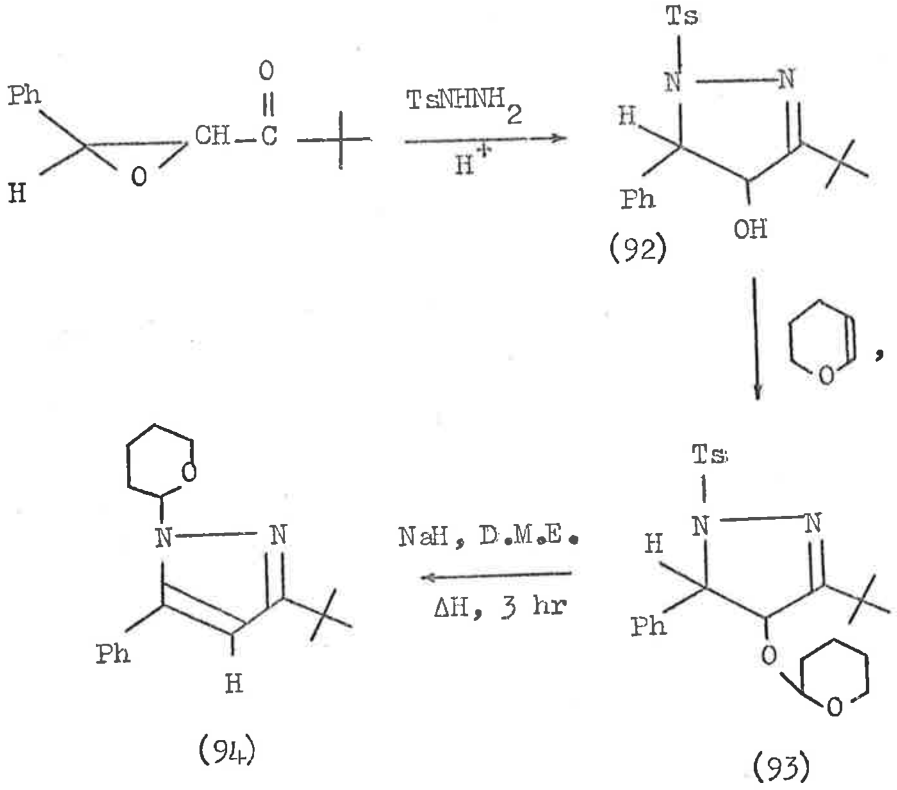


(90)

be observed values of J_{AX} and J_{BX} could not be determined.[40] Another feature of the n.m.r. spectrum is that the hydrogens at the 3,4- and 5-positions in the tetrahydropyranyl ring exhibit very broad absorption and the absorptions cannot be resolved with certainty. The above evidence indicates that the bulky pyrazole ring locks the tetrahydropyranyl ring into a chair conformation in which the bulky substituent occupies an equatorial configuration. It would be expected that the n.m.r. resonances of the tetrahydropyranyl group of compound 91 would be similar to those of compound 90. Additional evidence for structure 87 was provided by the infrared spectrum of the product. The infrared spectrum exhibited an absorption at 1166 cm^{-1} which is indicative of a p-toluenesulphonyl group attached to nitrogen.[41] If the p-toluenesulphonyl group had been attached to oxygen, as in structure 91, then characteristic absorptions at 1170 and 1190 cm^{-1} would have been evident.[42] The above physical evidence for structure 87 was further supported by some chemical evidence. It was found that the tetrahydropyranyl ether 87 could be smoothly hydrolysed by acid to the 4-hydroxy-2-pyrazoline 34.

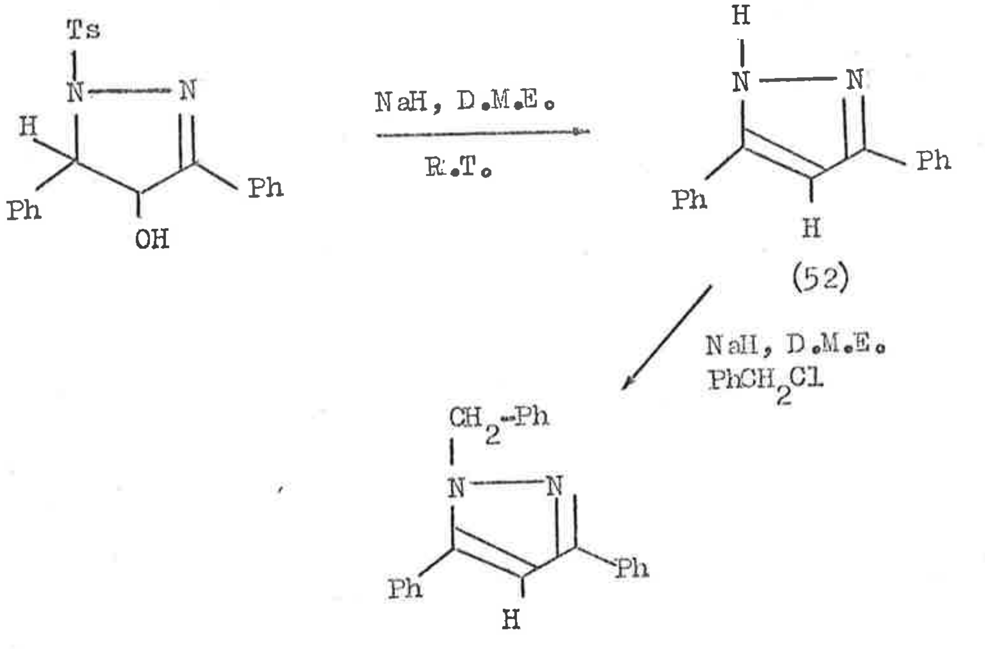
A new 4-hydroxy-1-p-toluenesulphonyl-2-pyrazoline was prepared to test the generality of the above result. When trans-benzalpinacolone oxide and p-toluenesulphonylhydrazine were dissolved in a mixture of chloroform and acetic acid and heated under reflux for 3 hr, 3-tert-butyl-4-hydroxy-5-phenyl-1-p-toluenesulphonyl-2-pyrazoline (92) was obtained. This compound was then smoothly converted to its tetrahydropyranyl ether 93 (a 1:1 mixture of diastereoisomers, by n.m.r.). When the tetrahydropyranyl ether 93 was treated with sodium hydride in



boiling dimethoxyethane 3-tert-butyl-5-phenyl-1-tetrahydropyranylpyrazole (94) was formed. As was expected, the n.m.r. spectrum of this compound was very similar to that of compound 90. Therefore the formation of 1-tetrahydropyranylpyrazoles by the base-catalysed elimination of p-toluenesulphinic acid from the tetrahydropyranyl ethers of 4-hydroxy-1-p-toluenesulphonyl-2-pyrazolines, mono-substituted at the 5-position, seems general.

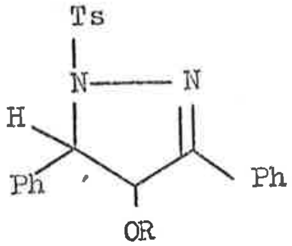
At this stage the work on the tetrahydropyranyl ethers was discontinued and an attempt to synthesise the benzyl and methyl ethers of compound 34 was initiated. It was planned to eliminate p-toluenesulphinic acid from these ethers to determine whether these ethers also underwent the above rearrangement. A complication in the synthesis of the ethers is that when compound 34 is treated with sodium hydride in boiling tetrahydrofuran p-toluenesulphonic acid is eliminated and this results in the formation of 3,5-diphenylpyrazole (see Chapter II, page 22). It was hoped that ether formation would compete favourably with the elimination at low temperatures. It was found that when compound 34 was stirred in a mixture of sodium hydride and benzyl bromide in dimethoxyethane at room temperature the product was 1-benzyl-3,5-diphenylpyrazole (95). This product presumably arises from the benzylation of 3,5-diphenylpyrazole which arises from the elimination of p-toluenesulphonic acid from compound 34. However, when benzyl bromide was added to the anion derived from compound 34 at -30°, a compound, assigned structure 96, was isolated in good yield (71%). Inspection of the infrared spectrum of the benzyl ether 96 indicated that the p-toluenesulphonyl group was attached to the nitrogen (absorption at 1166 cm^{-1}, see page 48). When the anion derived from compound 34 was methylated at -30°, a compound, assigned structure 97 was isolated in good yield (64%).

Attempts were then made to substantiate beyond doubt the structures of the benzyl and methyl ethers mentioned above. Padwa[26]



(52)

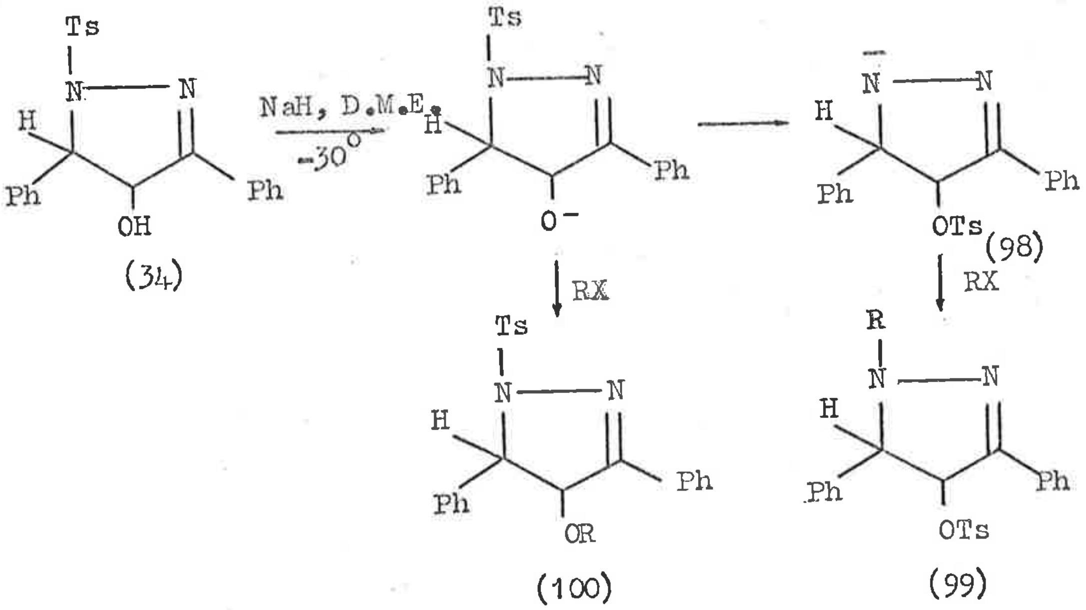
(95)



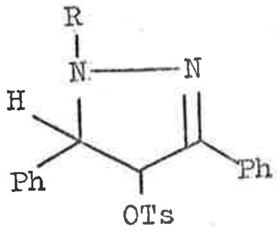
(96) R = $PhCH_2$

(97) R = CH_3

has shown that on treatment of compound 34 with sodium hydride in boiling tetrahydrofuran the *p*-toluenesulphonyl group is transferred from nitrogen to oxygen and subsequently eliminated as *p*-toluenesulphonic acid (see Chapter II, page 22). It is therefore possible that treatment of the 4-hydroxy-2-pyrazoline 34 at -30° with base and an alkylating agent results in the transfer of the p-toluenesulphonyl group from nitrogen to oxygen to give the anion 98. The anion 98, instead of eliminating p-toluenesulphonic acid, may be alkylated on nitrogen to give compounds of the general type 99. If the transfer of the p-toluenesulphonyl group did not occur at this temperature then alkylation would give compounds of the general type 100. Two attempts were

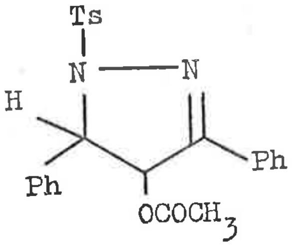


then made to trap the possible intermediate anion 98. In the first experiment the anion of compound 34 was generated at -30° and protonated (with acetic acid) at this temperature in an attempt to form the compound 101. However, the 4-hydroxy-2-pyrazoline 34 was recovered.



(101) R = H

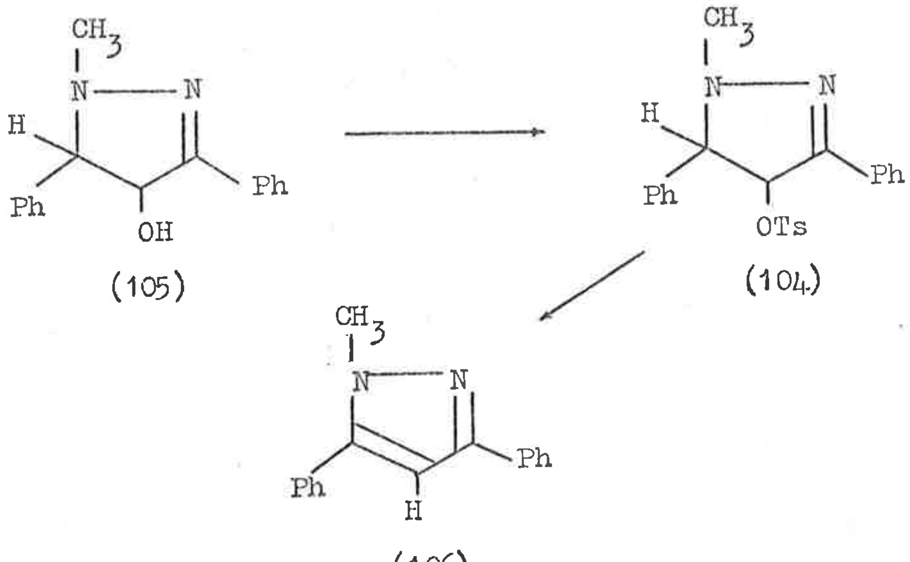
(102) R = CH_3CO



(103)

In the second experiment the anion of compound 34 was generated at -30° and acetic anhydride was added at this temperature in an attempt to form the amide 102. The reaction product was identified as the acetate 103 by comparison with the compound obtained on treatment of compound 34 with acetic anhydride in pyridine. These two experiments verify that treatment of compound 34 with base at -30° does not result in the transfer of the p-toluenesulphonyl group from nitrogen to oxygen.

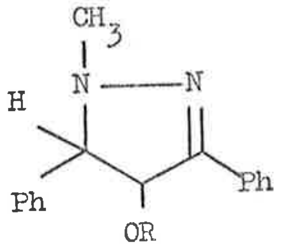
An attempt was then made to synthesise unambiguously compound 104 in order to compare it with the product obtained on methylation of the 4-hydroxy-2-pyrazoline 34 at -30°. Chalcone oxide was readily converted into 4-hydroxy-1-methyl-3,5-diphenyl-2-pyrazoline (105) by treatment with methylhydrazine under acidic conditions. All attempts to prepare 1-methyl-3,5-diphenyl-4-p-toluenesulphonyloxy-2-pyrazoline (104) were unsuccessful. In all cases the product isolated was 1-methyl-3,5-diphenylpyrazole (106). Apparently under the reaction conditions p-toluenesulphonic acid is eliminated from compound 104 to give the



(105) (104) (106)

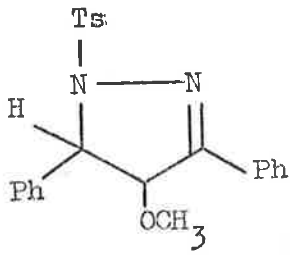
observed product. When an attempt to acetylate the 4-hydroxy-2-pyrazoline 105 was made, the infrared spectrum of the crude product exhibited an absorption at 1760 cm^{-1} which suggests the presence of an ester function. However, crystallisation of the crude product gave only compound 106.

Although compound 104 could not be synthesised, comparison of the n.m.r. spectra of compounds 105 and 97 added support to the structure 97 assigned to the product obtained on methylation of the 4-hydroxy-2-pyrazoline 34 at -30°. The methyl group of compound 105 exhibits resonance at δ2.8 while the methoxyl group of compound 97 absorbs at δ3.05. While the resonance at δ2.8 in the n.m.r. spectrum of compound 105 is in the region attributed to a methyl group attached to nitrogen it must be pointed out that the absorption at δ3.05 attributed to the methoxyl group of compound 97 occurs at a slightly lower



(104) R = Tosyl

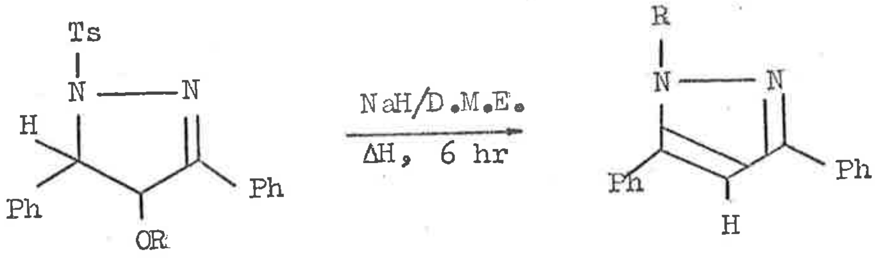
(105) R = H



(97)

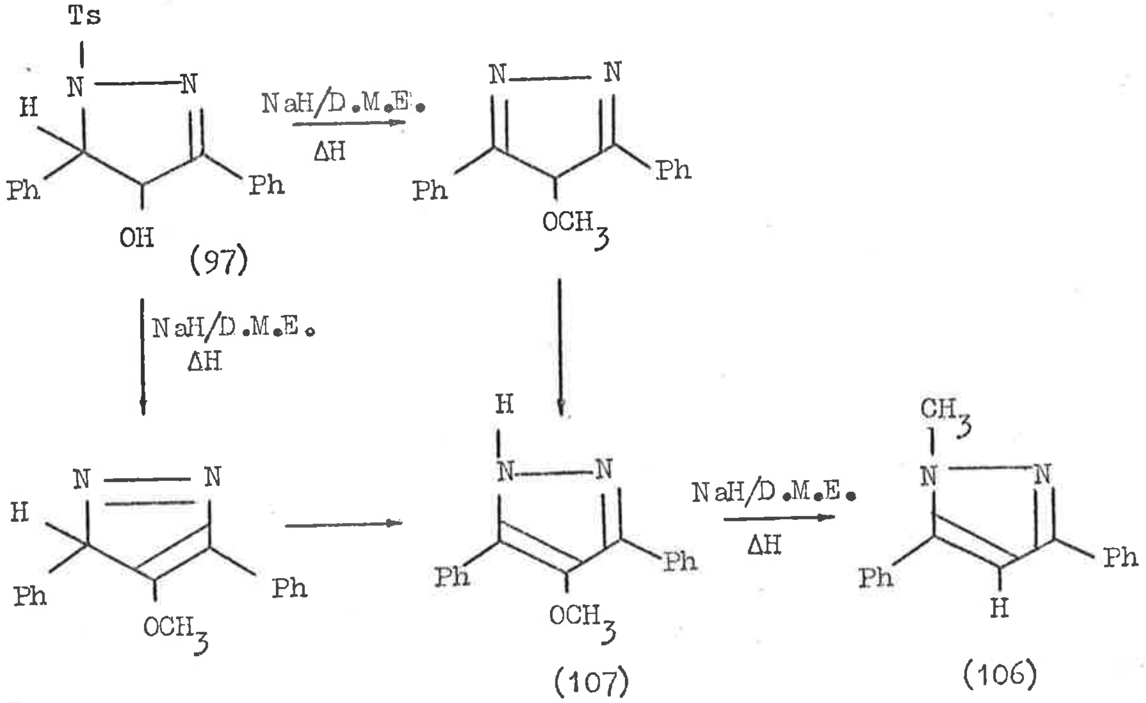
value than anticipated for a methyl group attached to oxygen.[43] However, it is doubtful whether the presence of a p-toluenesulphonyloxy group at the 4-position in compound 105, would alter the methyl resonance appreciably and so this n.m.r. evidence adds support to structure 97.

Having established that the structures of compounds 96 and 97 are as shown, these compounds were then subjected to sodium hydride in boiling dimethoxyethane. The respective products were 1-benzyl-3,5-diphenylpyrazole (95) and 1-methyl-3,5-diphenylpyrazole (106) and they were isolated in reasonable yield. The above rearrangement constitutes the loss of p-toluenesulphinic acid and an atom of oxygen or alternatively the loss of p-toluenesulphonic acid. In an effort to determine the mechanism of this rearrangement it was decided to synthesise 4-methoxy-3,5-diphenylpyrazole (107), a possible reaction intermediate (see below), and subject it to the elimination conditions. It must be

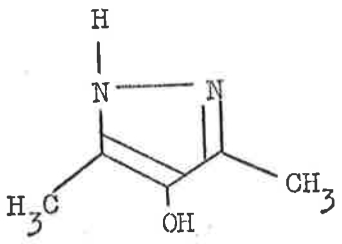


(96) R = $PhCH_2$, (97) R = CH_3; (95) R = $PhCH_2$, (106) R = CH_3

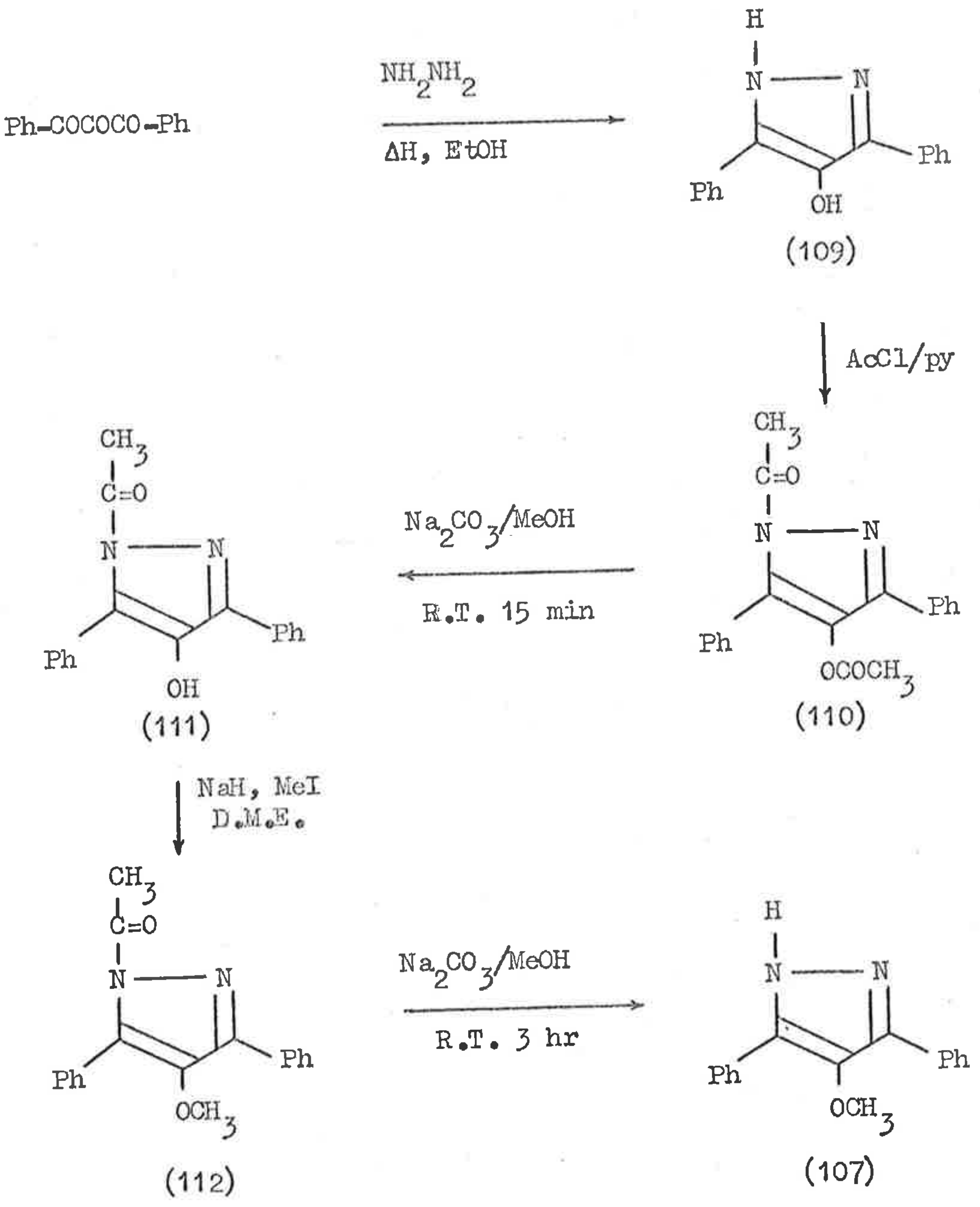
emphasised that the transformation of compound 107 to compound 106 constitutes the loss of an atom of oxygen and this seems unlikely.



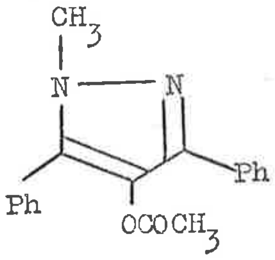
Early workers[44] had shown that treatment of dimethyltriketone (pentane-2,3,4-trione) with hydrazine hydrate gave 4-hydroxy-3,5-dimethylpyrazole (108) in good yield. When the reaction with hydrazine hydrate was applied to diphenyltriketone an almost quantitative yield of 4-hydroxy-3,5-diphenylpyrazole (109) was obtained. Compound 109 was converted into the amido-acetate 110 when treated with either acetic anhydride or acetyl chloride in pyridine. After the synthesis of compounds 109 and 110 had been completed an identical route to these compounds was reported.[45] When the amido-acetate 110 was boiled in a 10% potassium hydroxide in methanol solution for 30 min, both the ester and amide groups were hydrolysed to give the 4-hydroxypyrazole 109. It was found that the selective hydrolysis of the ester group could be effected by stirring the amido-acetate 110 with sodium carbonate in methanol for 15 min. The conversion of the amido-alcohol 111 to the methyl ether 112 was smoothly achieved using a mixture of sodium hydride and methyl iodide in dimethoxyethane at room temperature. Evidence for the



(108)


Ph-COCOCO-Ph
NH2NH2
ΔH, EtOH
(109)
AcCl/py
(110)
Na2CO3/MeOH
R.T. 15 min
(111)
NaH, MeI
D.M.E.
(112)
Na2CO3/MeOH
R.T. 3 hr
(107)

proposed structure 112 was provided by examination of physical data and this data clearly distinguished between the proposed structure and structure 113 which could have arisen by rearrangement on treatment



(113)

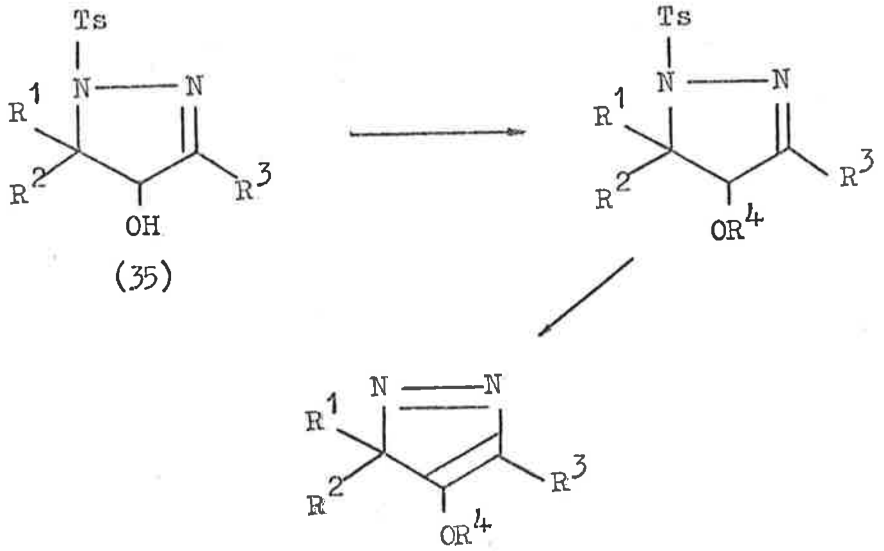
of the amido-alcohol with base and an alkylating agent. The infrared spectrum of the product exhibited an absorption at 1740 cm^{-1} and this is in good agreement with the value of 1745 cm^{-1} reported for the amide group in the amido-acetate 110.[45] Resonances at δ2.1 and δ3.8 in the n.m.r. spectrum of the product were attributed to the N-acetyl and methoxyl groups respectively. The value of δ2.1 obtained for the N-acetyl group in the amido-ether 112 is in good agreement with a value of δ2.0 obtained for the N-acetyl group in the amido-acetate 110. Furthermore the methoxyl group in compound 112 resonates at δ3.80 while the N-methyl group in 1-methyl-3,5-diphenylpyrazole (106) resonates at δ3.85. Subsequent hydrolysis of the amide group of compound 112 gave 4-methoxy-3,5-diphenylpyrazole (107) in high yield

(83%). Since compound 107 was not affected by treatment with sodium hydride in boiling dimethoxyethane it is unlikely that the elimination of p-toluenesulphinic acid from compound 97 to give 1-methyl-3,5-diphenylpyrazole involves compound 107 as an intermediate.

At this stage work on the rearrangement was discontinued as further work on this problem would have deviated from the main objectives of this thesis.

(b) Elimination of *p*-toluenesulphinic acid from 4-methoxy-3,5,5-trimethyl-1-*p*-toluenesulphonyl-2-pyrazoline.

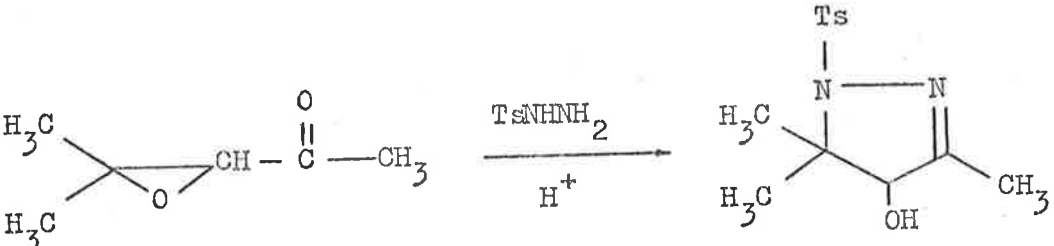
At this stage the work was directed towards the synthesis of a 4-hydroxy-1-*p*-toluenesulphonyl-2-pyrazoline, disubstituted at the 5-position (35). Elimination of *p*-toluenesulphinic acid from an ether of the compound of general type 35 should give a 4-alkoxy-3H-pyrazole (28). It has been predicted in the Introduction that 2-pyrazolines of the general type 35 mentioned above would result from the condensation of *p*-toluenesulphonylhydrazine with β,β-disubstituted α,β-epoxy ketones under acidic conditions. In fact, 4-hydroxy-3,5,5-trimethyl-1-*p*-toluenesulphonyl-2-pyrazoline (114, 46% yield) was formed



(35)

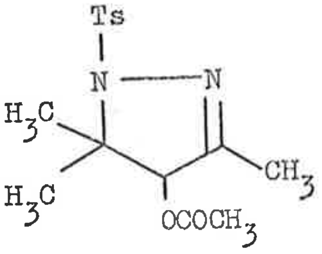
(28)

when mesityl oxide epoxide was treated with p-toluenesulphonylhydrazine under acidic conditions. The infrared spectrum of the product exhibited

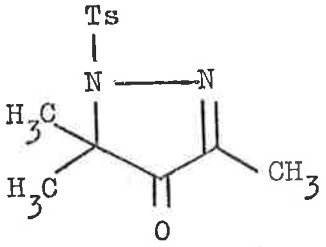


(114)

an absorption at 3300 cm^{-1} which was attributed to the hydroxyl group. A resonance at δ3.2 in the n.m.r. spectrum of the product was attributed to the hydrogen of the hydroxyl group. Compound 114 formed an acetate (115) and could be oxidized to the ketone (116).

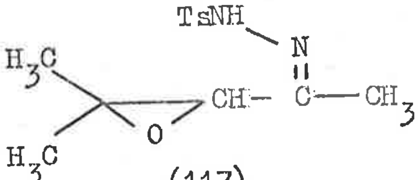


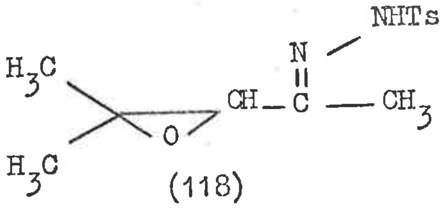
(115)

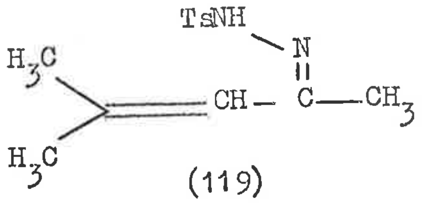


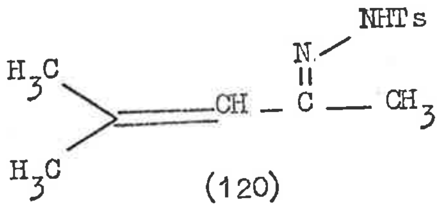
(116)

As compound 114 was formed in only low yield, it seemed of interest to ascertain whether it was only the syn-p-toluenesulphonylhydrazone of mesityl oxide epoxide (117) that underwent cyclisation to

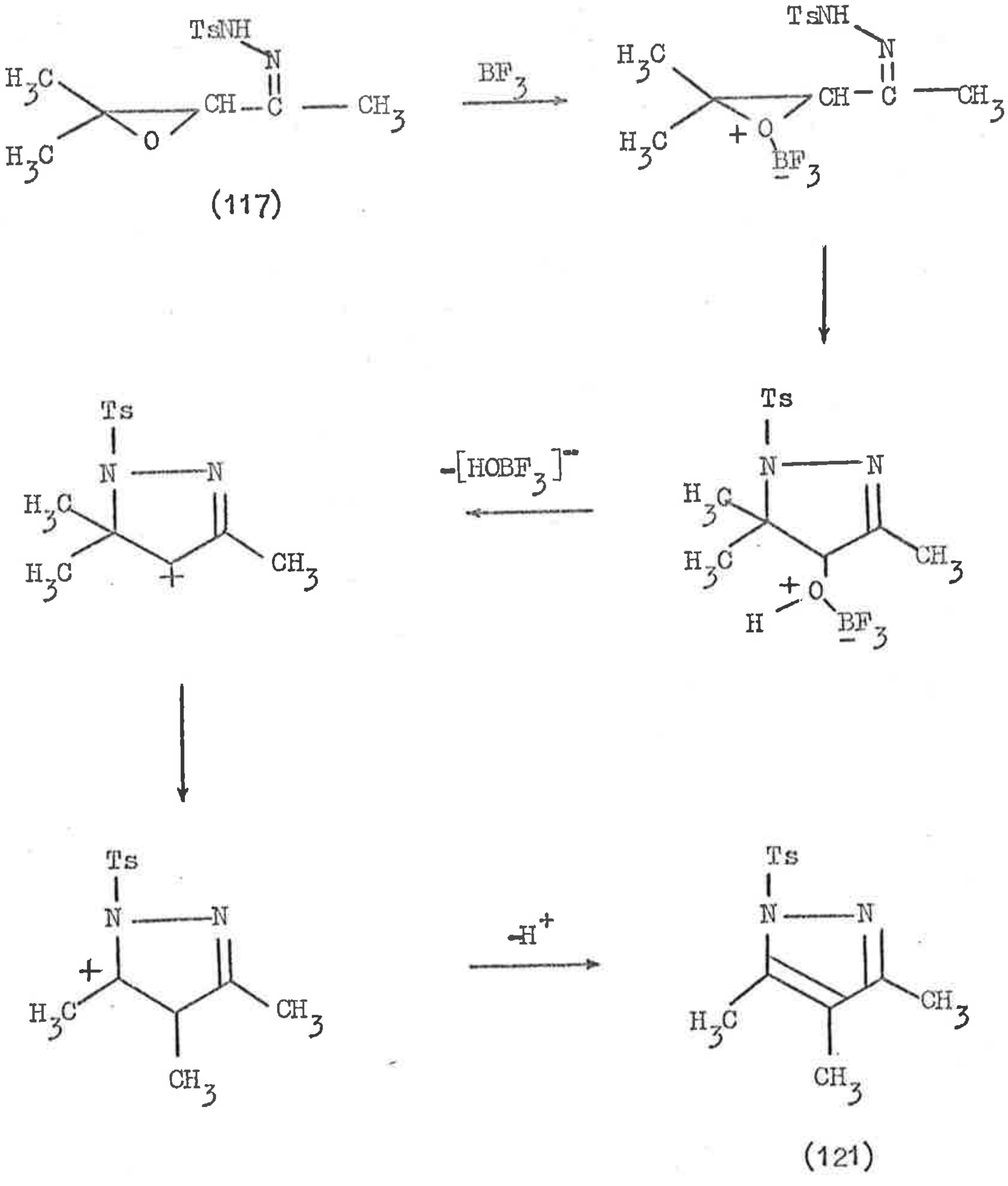

(117)

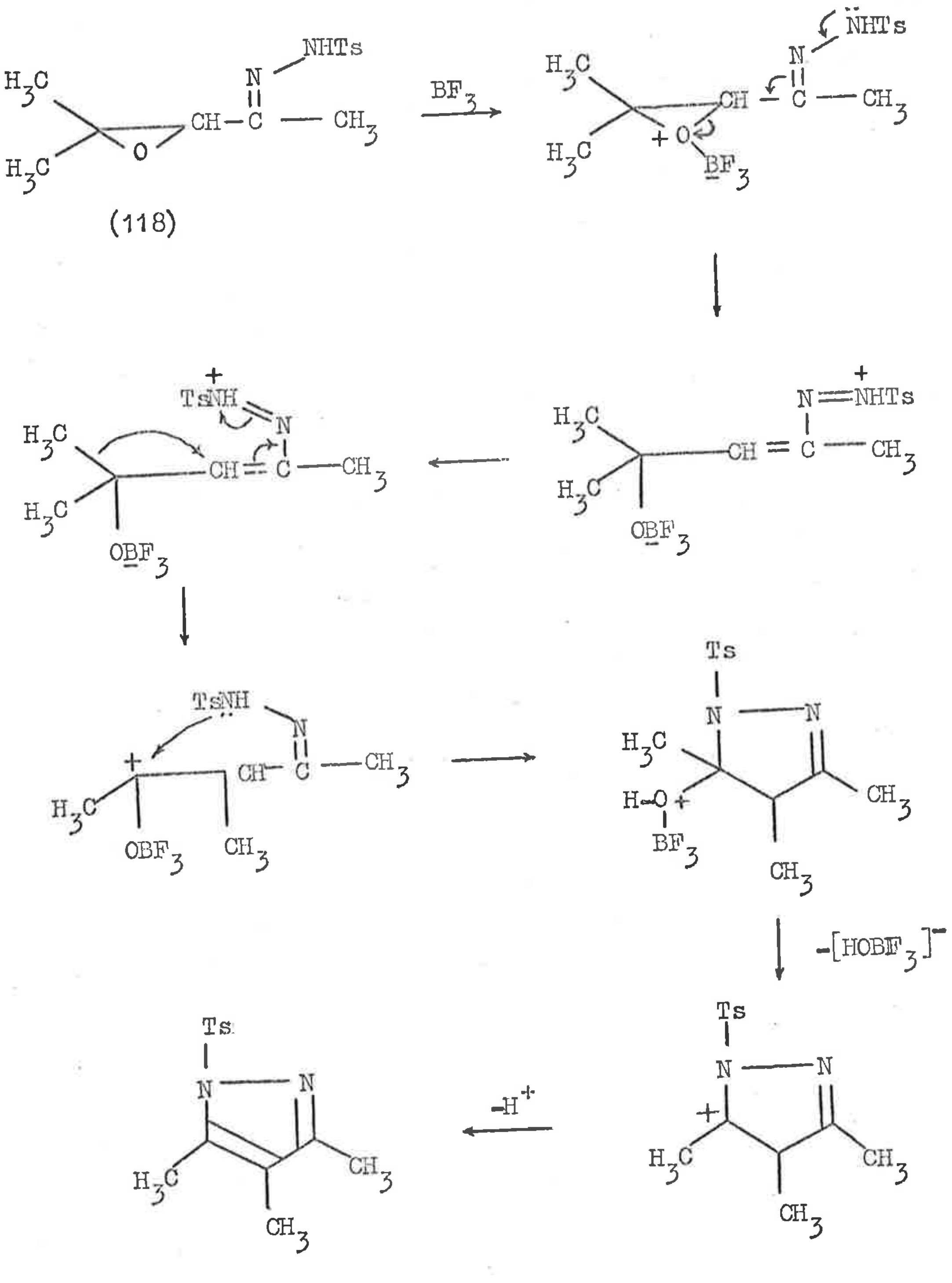

(118)


(119)


(120)

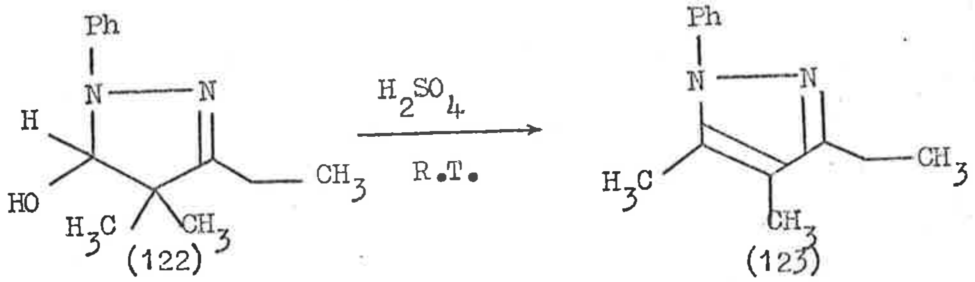
compound 114 (see Chapter III, page 43). It was decided to synthesise both the syn- (117) and anti-isomers (118) and subject them to the same conditions used in the synthesis of the 4-hydroxy-2-pyrazoline 114. As both the syn- (119) and anti-isomers (120) of the p-toluenesulphonylhydrazone of mesityl oxide have been synthesised[12] the initial attempt to synthesise the two epoxides 117 and 118 involved epoxidation of these two isomers. It was found, however, that both isomers were recovered unchanged when treated with either alkaline hydrogen peroxide or m-chloroperbenzoic acid. Apparently the presence of the gem-dimethyl group in the p-toluenesulphonylhydrazones 119 and 120 prevents attack by the reagents. The successful syntheses of the two epoxides was accomplished by treatment of mesityl oxide epoxide with p-toluenesulphonylhydrazine in chloroform at room temperature. Separation of the two isomers (A, m.p. 115-116°, B, m.p. 96-97°) was effected by fractional crystallisation. The two epoxides exhibited different physical properties (see Experimental, page 133). When isomer A was treated under acidic conditions, a good yield (71%) of the cyclic alcohol 114 was realised. However, only a poor yield (5%) of the cyclic alcohol 114 was obtained when isomer B was treated under similar conditions. This result was presumably due to contamination of isomer B with isomer A. On the basis of this chemical evidence compound A was assigned structure 117. An interesting result was obtained when either the _syn_- (117) or _anti_-epoxide (118) was treated with boron trifluoride diethyl etherate. The product, in both cases, was identified as 3,4,5-trimethyl-1-_p_-toluenesulphonylpyrazole (121) on the basis of physical evidence. One possible mechanism for the formation of the pyrazole 121 from the _syn_-epoxide (117) is outlined below. This mechanism, however, must be discounted as compound 114 is recovered unchanged when treated with boron trifluoride diethyl etherate. The mechanism outlined below also cannot explain the formation of the pyrazole 121 from the _anti_-epoxide 118. It has been mentioned above that the _anti_-epoxide 118 is not cyclised to the alcohol 114 on treatment with acid. A possible mechanism to account for the observed product from both the _syn_- and _anti_-epoxides is outlined on page 66. It is of interest to note that the 5-hydroxy-2-pyrazoline 122 undergoes rearrangement to the pyrazole 123 on treatment with sulphuric


TsNH
H_3C
H_3C
CH
C
CH_3
O
(117)
BF_3
BF_3
-$[HOBF_3]^-$
Ts
N
N
+
H
-H^+
(121)


(118)

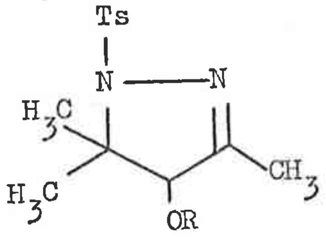
(121)

acid at room temperature.[46]



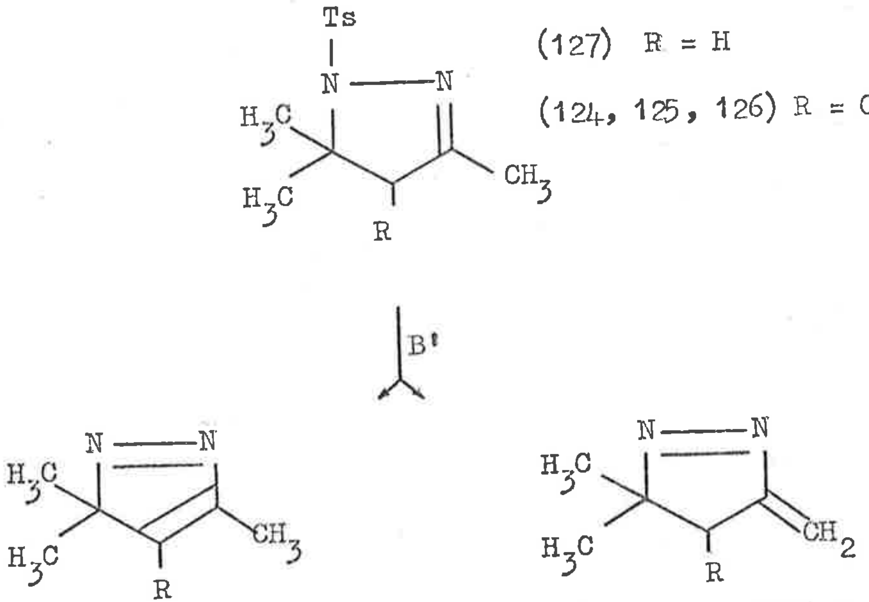
(122) (123)

Compound 114 was then smoothly converted to the methyl ether 124 when treated with a mixture of sodium hydride and methyl iodide in dimethoxyethane at room temperature. In anticipation of later work two other ethers, the benzyl (125) and tetrahydropyranyl (126, a 1:1 mixture of diastereoisomers, by n.m.r.) ethers were also synthesised.



(124) R = CH_3
(125) R = $PhCH_2$
(126) R = Tetrahydropyranyl

Closs[23] has shown that treatment of 3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (127) with base gave a mixture of the 3H-pyrazole 128 and the isomeric 3-methylene-1-pyrazoline 129. He was able to separate the 3H-pyrazole isomer from the mixture by chemical means. It was therefore anticipated that elimination of p-toluenesulphinic acid from the ethers 124, 125, and 126 should give a mixture of the 4-alkoxy-3H-pyrazole 130 and the isomeric 3-methylene-1-pyrazoline 131.



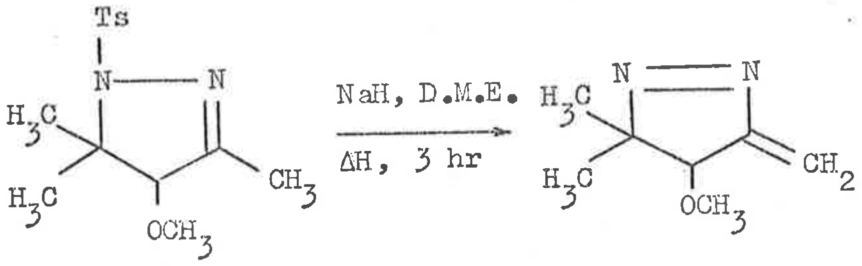
(127) R = H

(124, 125, 126) R = OR'

(128) R = H (130) R = OR'

(129) R = H (131) R = OR'

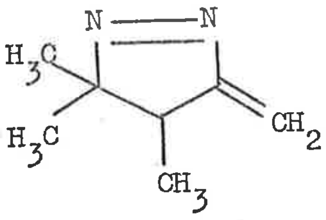
When the methyl ether 124 was treated with sodium methoxide in boiling tetrahydrofuran it gave an unstable product, consisting of at least three compounds which were not further investigated. However, when compound 124 was treated with either the anion of dimethylsulphoxide or sodium hydride in boiling dimethoxyethane, a colourless liquid which was homogeneous and whose structure was shown to be 4-methoxy-5,5-dimethyl-3-methylene-1-pyrazoline (132) on the basis of spectral data, was obtained. Infrared absorptions were observed at



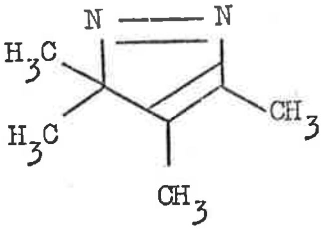
(124) (132)

3090, 1640, and 930 cm^{-1} which are consistent with the presence of an exocyclic double bond in the product. The n.m.r. spectrum exhibited resonances at δ1.3 (singlet, 6H), 3.35 (singlet, 3H), 4.5 (doublet, Jc 1.5 Hz, 2H), and δ6.55 (triplet, Jc 1.7, 1.9 Hz, 1H). The absorptions at δ1.3 and δ3.35 can be attributed to the *gem*-dimethyl group and the methoxy group respectively, while the signal at δ4.5 can be attributed to the hydrogens of the exocyclic double bond. Clear evidence for the presence of the exocyclic double bond was provided by the signal at δ6.55. This absorption can be attributed to the hydrogen at the 4-position and as a result of allylic coupling to the exocyclic double bond hydrogens this signal is split into a triplet. Further support for the proposed structure 132 was provided by the ultraviolet spectrum of the product. Absorptions at λ_{max} (ethanol) 248 (ε 2,000) and 345 (ε 150) n.m. are close to those of λ_{max} (ethanol) 244 (ε 6,400) and 352 (ε 250) n.m. exhibited by 4,5,5-trimethyl-3-methylene-1-pyrazoline (133).[23] It is of interest to note that the values for 3,3,4,5-tetramethyl-3H-pyrazole (134) are λ_{max} (ethanol) 269 (ε 6,900) and 339 (ε 250) n.m.[23] Since no 4-methoxy-3,3,5-trimethyl-3H-pyrazole (135) was produced on elimination of p-toluenesulphinic acid from compound 124 it indicates that the hydrogens of the methyl group at the 3-position are more accessible than the hydrogen at the 4-position. The formation of only one isomer was surprising as it was thought that the hydrogen at the 4-position would probably be more acidic than the methyl hydrogens at the 3-position.

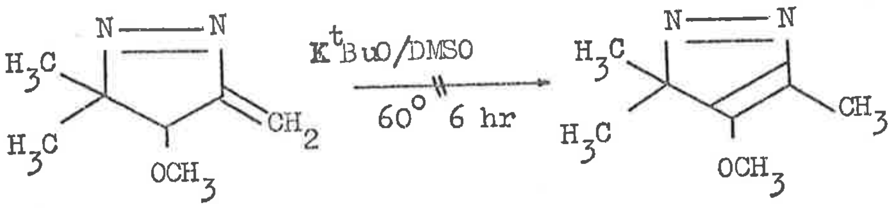
Attempts to isomerise compound 132 to the 4-alkoxy-3H-pyrazole 135 using potassium tert-butoxide in dimethylsulphoxide were unsuccessful as starting material was recovered unchanged.



(133)



(134)



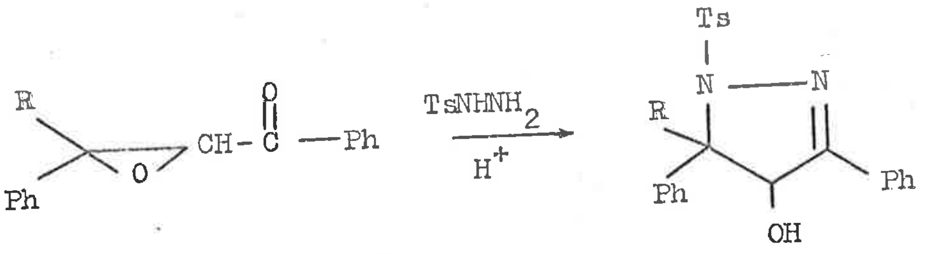
(132) (135)

The benzyl (125) and tetrahydropyranyl (126) ethers were not further investigated.

This aspect of the work indicated that a 4-alkoxy-3H-pyrazole was likely to be formed on elimination of p-toluenesulphinic acid from a 4-alkoxy-1-p-toluenesulphonyl-2-pyrazoline, disubstituted at the 5-position, provided the 3-position is blocked with a group which cannot lose a hydrogen on treatment with base.

(c) Studies directed towards the synthesis of 4-hydroxy-5-methyl-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline.

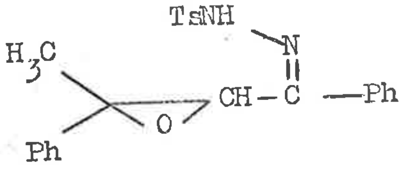
It was then decided to use trans-dypnone oxide in an attempt to synthesise 4-hydroxy-5-methyl-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (136). In this pyrazoline the 3-position is blocked by a phenyl substituent and the importance of this has been discussed above (Chapter III, page 71). Several acids, including acetic, sulphuric, p-toluenesulphonic, and perchloric acid were used in the attempts to synthesise compound 136 by condensation of p-toluenesulphonylhydrazine with trans-dyprione oxide. However, in all cases there was obtained a mixture, chromatography of which gave only gums which after preliminary spectral studies were not further investigated. It is noteworthy that recently Padwa[47] has isolated 4-hydroxy-3,5,5-triphenyl-1-p-toluenesulphonyl-2-pyrazoline (137), in poor yield (10%), from the reaction of



(136) $R = CH_3$
(137) $R = Ph$

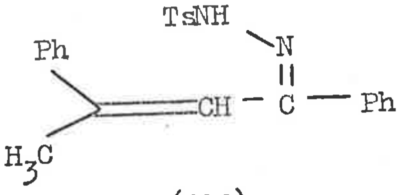
β,β-diphenyl acrylophenone oxide with p-toluenesulphonylhydrazine under acidic conditions.

Another approach to compound 136 was attempted through the synthesis of the syn-p-toluenesulphonylhydrazone of trans-dypnone oxide (138). It was anticipated that subsequent treatment of compound 138 with acid should give compound 136 (see Chapter III, page 64).

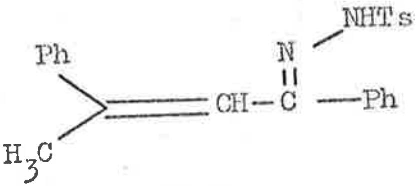


(138)

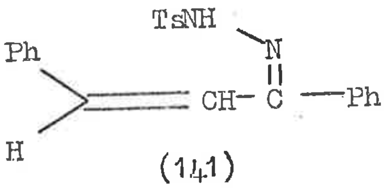
The initial attempt to synthesise the epoxide 138 involved the addition of p-toluenesulphonylhydrazine to a methanolic solution of trans-dypnone oxide. However, no addition took place. This is in contrast to the case of mesityl oxide where the p-toluenesulphonylhydrazone was readily formed. It was found, however, that p-toluenesulphonylhydrazine condensed with dypnone to give two products, A (m.p. 152°) and B (m.p. 112°). Although spectral data indicated that the products were p-toluenesulphonylhydrazones of dypnone, no structural assignments to



(139)



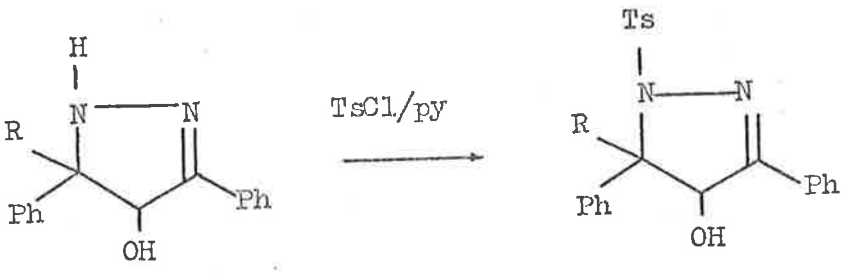
(140)



(141)

the *syn*- (139) and *anti*-structures (140) could be made. All attempts to epoxidise these isomers, either by addition of alkaline hydrogen peroxide or *m*-chloroperbenzoic acid, failed. In all cases unchanged material was recovered. Apparently the presence of the extra methyl group in compounds 139 and 140, in contrast to compound 141, prevents attack by the reagents. Compound 141 has been shown to react with alkaline hydrogen peroxide (Chapter III, page 43).

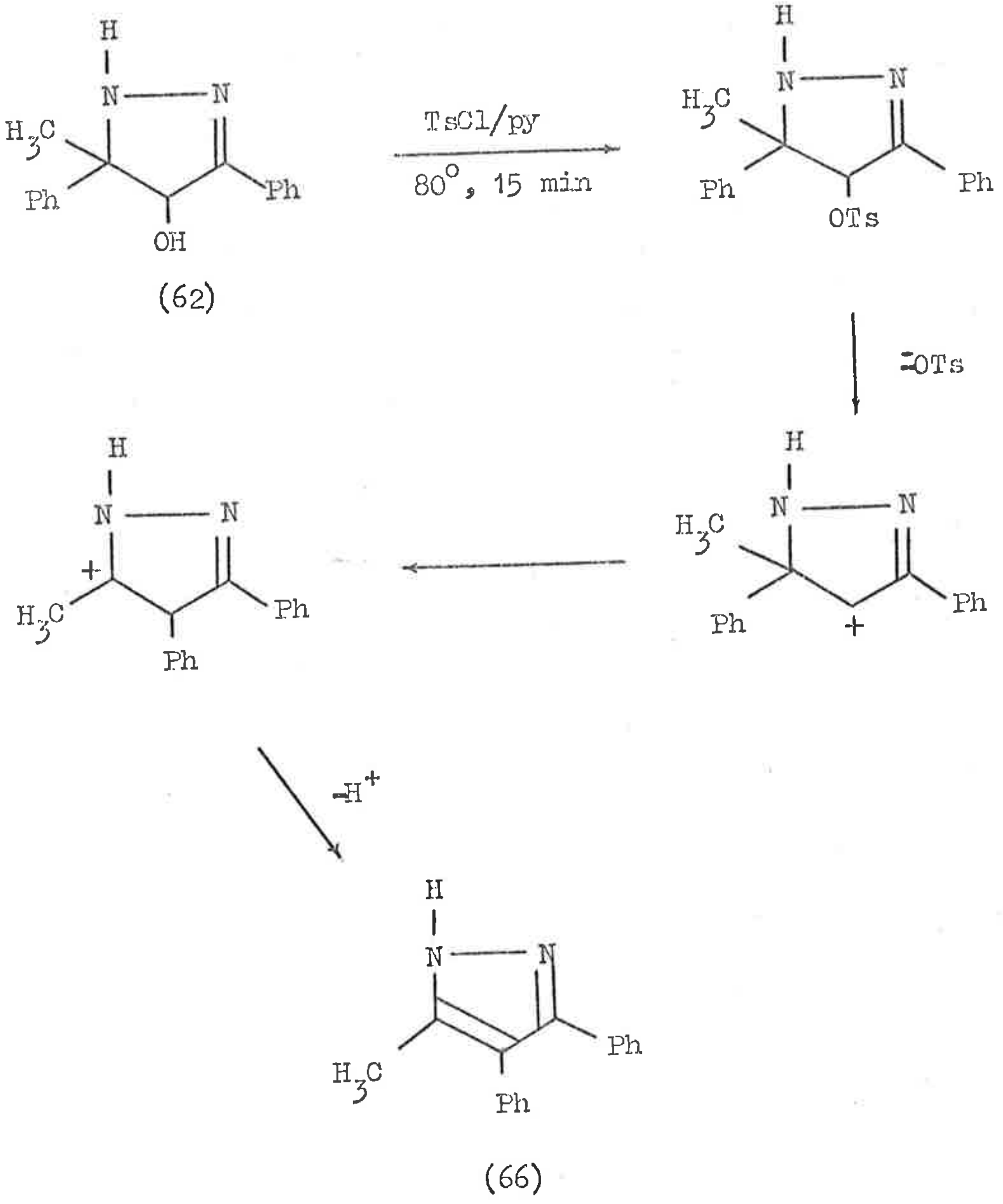
One more approach to the synthesis of compound 136 was then tried. It would be possible to synthesise the 4-hydroxy-2-pyrazoline 136 if the nitrogen of compound 62 (see Chapter II, page 31) reacted selectively with *p*-toluenesulphonyl chloride. In an initial study the 4-hydroxy-2-pyrazoline 47 was treated with *p*-toluenesulphonyl chloride in pyridine at room temperature. It was found that the *p*-toluenesulphonyl chloride reacted preferentially on the nitrogen to



(47) R = H
(62) R = CH_3

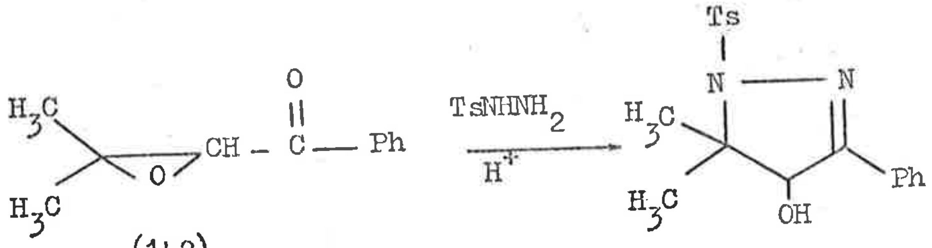
(34) R = H
(136) R = CH_3

give a good yield of compound 34. However, when compound 62 was subjected to similar conditions, no reaction took place. At a higher temperature (25-30°, 12 hr) there was obtained a mixture, chromatography of which gave only gums which after preliminary spectral studies were not further investigated. An interesting product, 5-methyl-3,4-diphenylpyrazole (66), was obtained on heating compound 62 with p-toluenesulphonyl chloride in pyridine at 80° for 15 min. It is thought that initially p-toluenesulphonyl chloride reacts with the hydroxyl function of compound 62. A subsequent solvolysis, accompanied by a phenyl migration could account for the observed product (see below). At this stage all work directed towards the synthesis of compound 136 was discontinued.


TsCl/py
80°, 15 min
⁻OTs
-H⁺
(62)
(66)

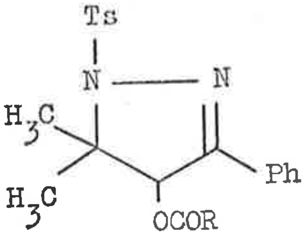
(d) Synthesis of 4-methoxy-3,3,-dimethyl-5-phenyl-3H-pyrazole and 4-benzyloxy-3,3-dimethyl-5-phenyl-3H-pyrazole.

As the reaction of trans-dypnone oxide with p-toluenesulphonylhydrazine under acidic conditions gave only gums, it was decided to substitute β,β-dimethylacrylophenone oxide (142) in the reaction to determine if the replacement of a phenyl group by a methyl group in the epoxy-ketone would have the desired effect on the course of the reaction. Indeed, when a mixture of p-toluenesulphonylhydrazine and β,β-dimethylacrylophenone oxide was heated under reflux in a mixture of acetic acid and chloroform, 4-hydroxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline (143) was formed (30% yield). Evidence supporting structure 143 was provided by an absorption at 3480 cm^{-1} in the infrared spectrum which suggested the presence of a hydroxyl function. Compound 143 formed an acetate (144) and a m-dinitrobenzoate (145), and could be oxidized to the ketone (146).



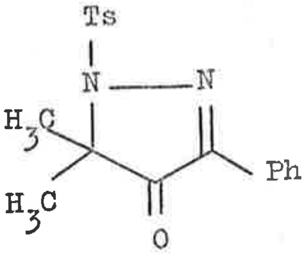
(142)

(143)



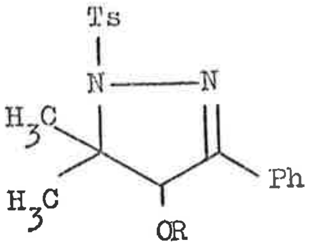
(144) R = CH_3

(145) R = m-dinitrobenzene



(146)

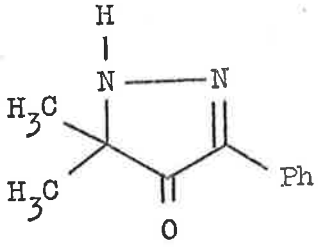
The methyl (147) and benzyl (148) ethers were also readily obtained when the sodium salt of compound 143 was treated with the appropriate alkyl halide in dimethoxyethane at room temperature.



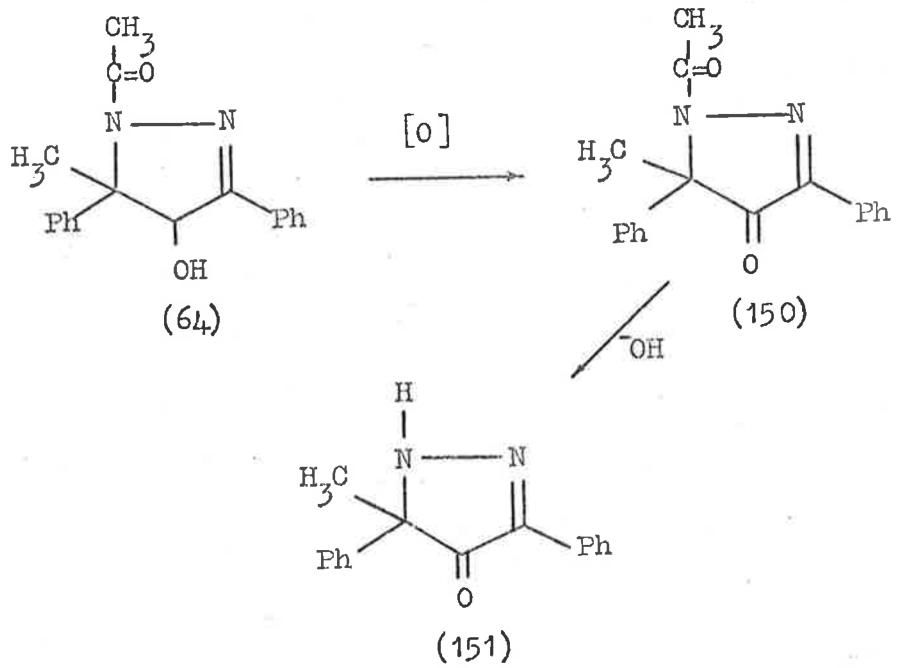
(147) R = CH_3

(148) R = $PhCH_2$

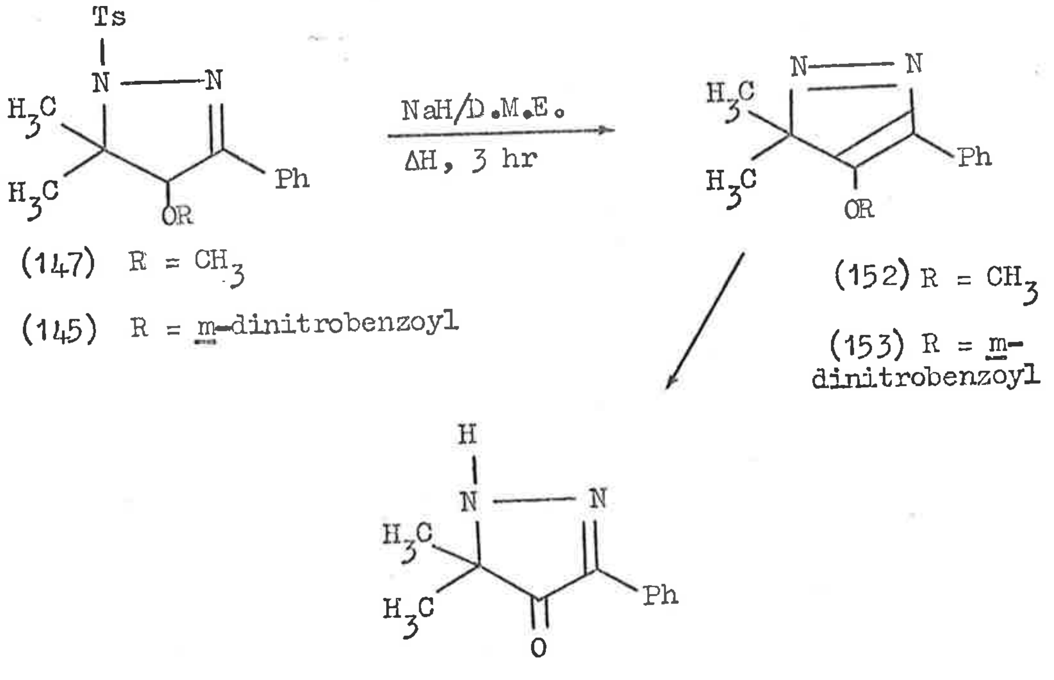
The elimination of p-toluenesulphinic acid from the methyl ether 147 was then studied. When compound 147 was subjected to sodium hydride in boiling dimethoxyethane for 3 hr, followed by aqueous work-up, a yellow crystalline solid was the only product. Although the product exhibited absorptions at 3300 and 1680 cm^{-1} in the infrared spectrum, these values corresponded to the N-H and the conjugated carbonyl group of the proposed structure 149, no signal attributable to a hydrogen on a nitrogen could be detected in the n.m.r. spectrum. However, it must be emphasised that it is not unusual that such a signal could not be detected.[48] In order to confirm that the product was 4-keto-5,5-dimethyl-3-phenyl-2-pyrazoline (149) it was decided to synthesise an analogue of compound 149 in order to compare the physical properties of the two compounds. Accordingly, the hydroxy-amide 64, available from earlier work (Chapter II, page 31), was oxidized to the ketone 150. Subsequent base-catalysed hydrolysis of the amide function of compound 150 gave 4-keto-5-methyl-3,5-diphenyl-2-pyrazoline (151) as a yellow



(149)



crystalline solid. Comparison of the infrared and ultraviolet absorption values of compounds 149 and 151 clearly established that the product obtained an elimination of p-toluenesulphinic acid from the methyl ether 147 was in fact compound 149. Infrared absorption values of 3300 and 1680 cm^{-1} obtained for compound 149, corresponding to the N-H and unsaturated ketone groups respectively, were in good agreement with those of 3280 and 1680 cm^{-1} obtained for compound 151. The ultravuilet values of λ_{max} (ethanol) 257 (ε 11,400) and 372 (ε 4,000) n.m. obtained for compound 149 were also close to those of λ_{max} (ethanol) 264 (ε 12,700) and 382 (ε 4,800) n.m. obtained for compound 151. As was observed for the keto-pyrazoline 149 the hydrogen on the nitrogen of compound 151 could not be detected in the n.m.r. spectrum. To account for the product 149 it was postulated that the enol-ether function of the 4-alkoxy-3H-pyrazole 152 underwent base-catalysed hydrolysis on work-up. However, as enol-ethers are usually hydrolysed in acidic media, this result is not easy to understand. The isolation of compound 149 therefore provided evidence for the existence of the 4-alkoxy-3H-pyrazole 152.



(147) R = CH_3

(145) R = m-dinitrobenzoyl

(152) R = CH_3

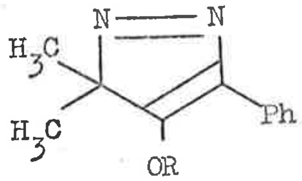
(153) R = m-dinitrobenzoyl

(149)

When the *m*-dinitrobenzoate ester 145 was subjected to sodium hydride in boiling dimethoxyethane, and the product isolated by aqueous work-up, it was found that the ketone 149 was the only product. Again it is likely that the product arose from the hydrolysis of the enol-ester 153. The importance of such a pyrazole as compound 153, especially with an acetate group at the 4-position, has been mentioned in the Introduction (see pages 7 and 9).

The conditions for elimination were then modified in order to avoid an aqueous work-up. In the modified procedure, the methyl ether 147 was heated with sodium hydride in dimethoxyethane under reflux for 1 hr and the product was isolated by filtration of the reaction mixture, followed by evaporation of the solvent *in vacuo*. The product was rather unstable and was identified as 4-methoxy-3,3-dimethyl-5-phenyl-3H-pyrazole (152) by physical methods only. An absorption at 1630 cm^{-1} in the infrared spectrum of the product was assigned to the conjugated enol-ether function. Resonances at δ1.40 (singlet, 6H), 3.74 (singlet, 3H), and δ7.5 (multiplet, 5H) in the n.m.r. spectrum were attributed to the hydrogens of the *gem*-dimethyl, methoxyl, and phenyl groups respectively. The mass spectrum of the product showed a parent ion peak at m/e 202, which is the expected molecular weight for the compound. The compound absorbed at λ_{max} (ethanol) 237 (ε 8,200) and 293 (ε 2,000) n.m. in the ultraviolet region.

When the benzyl ether 148 was treated with sodium hydride in



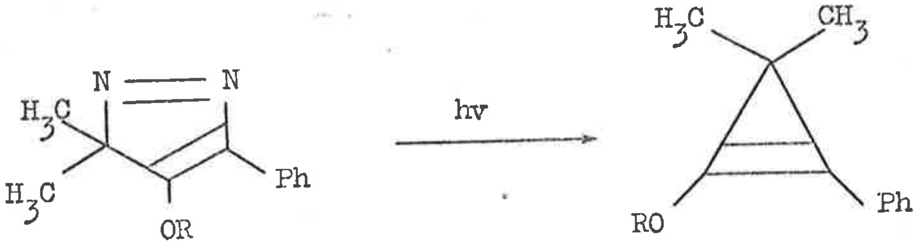
(152) R = CH_3

(154) R = $PhCH_2$

boiling dimethoxyethane and the product isolated using a non-aqueous work-up 4-benzyloxy-3,3,-dimethyl-5-phenyl-3H-pyrazole (154) was isolated in good yield (81%). An absorption at 1640 cm^{-1} in the infrared spectrum was assigned to the conjugated enol-ether function, while signals at δ1.42 (singlet, 6H), 4.93 (singlet, 2H), and δ7.5 (multiplet,10H) in the n.m.r. spectrum were attributed to the hydrogens of the gem-dimethyl, benzylic methylene, and phenyl groups respectively. Compound 154 absorbed at λ_{max} (ethanol) 236 (ε 8,900) and 297 (ε 3,500) n.m. in the ultraviolet region. This compound proved to be more stable than the methyl analogue.

(e) Preparation of 1-methoxy-3,3-dimethyl-2-phenylcyclopropene and 1-benzyloxy-3,3,-dimethyl-2-phenylcyclopropene.

The next step in the scheme to cyclopropenyl ethers was the irradiation of the 4-alkoxy-3H-pyrazoles 152 and 154. It can be seen from the ultraviolet spectrum of compounds 152 and 154 (see Figure 1) that these compounds exhibit considerable absorption above 300 n.m. and so it was hoped that these compounds would undergo a photochemical reaction when irradiated in a Pyrex apparatus which allows light of wavelength longer than 300 n.m. to enter the solution. It was hoped that, by analogy with the work of Closs (see Introduction, page 13), on irradiation, compounds 152 and 154 would eliminate a molecule of nitrogen to give the corresponding cyclopropenyl ethers 155 and 156.



(152) R = CH_3 (155) R = CH_3

(154) R = $PhCH_2$ (156) R = $PhCH_2$

After several unsuccessful attempts (see Experimental, page 157) to convert compound 152 to the cyclopropenyl ether 155, the transformation was finally achieved. Of critical importance was the use of thin-walled Pyrex photochemical reactors and of very dilute solutions. It was found that when a very dilute solution of the 3H-pyrazole 152 was irradiated for 1 hr and the reaction mixture subjected to chroma-

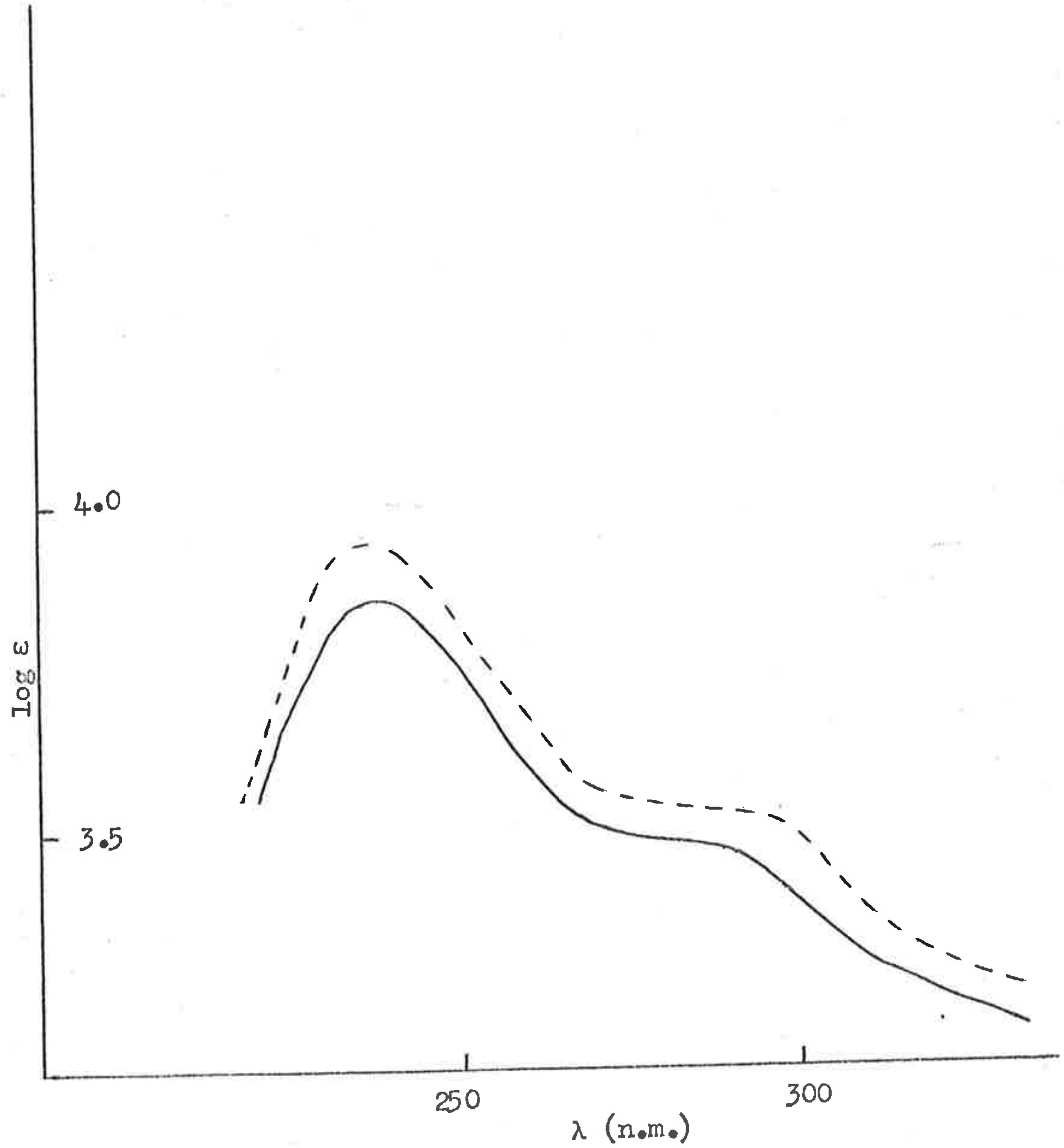
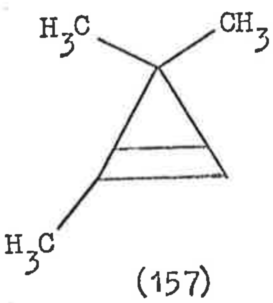
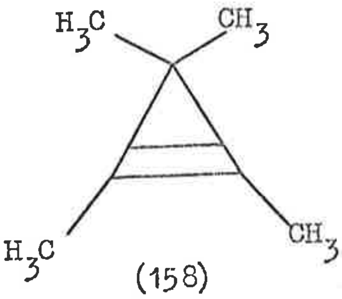


Figure 1. - Ultraviolet absorption spectrum of 4-methoxy-3,3-dimethyl-5-phenyl-3H-pyrazole (152) (———) and of 4-benzyloxy-3,3-dimethyl-5-phenyl-3H-pyrazole (154) (-------).

tography, 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (155) was obtained in low yield (5-10%). The product was obtained as an oil and was stable at room temperature. It was characterised on the basis of physical data. The infrared spectrum (liquid film) of the product is shown in Figure 2. Of particular note is a strong absorption at 1840 cm^{-1}. Closs[5] has found that the absorption value of the ring skeleton vibrations* in cyclopropenes depends almost entirely on the number of substituents attached to the double bond and not on the nature of the substituents. For instance a considerable shift to higher wavenumber occurs on increasing the methyl substitution on the double bond. 1,3,3-Trimethylcyclopropene (157) has been found to absorb at 1768 cm^{-1} in the infrared region as compared with an absorption at 1641 cm^{-1} for cyclopropene.[5] An increase of over one hundred wavenumbers occurs on


(157)


(158)

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* This band has sometimes been incorrectly referred to as "the double bond stretching vibration".

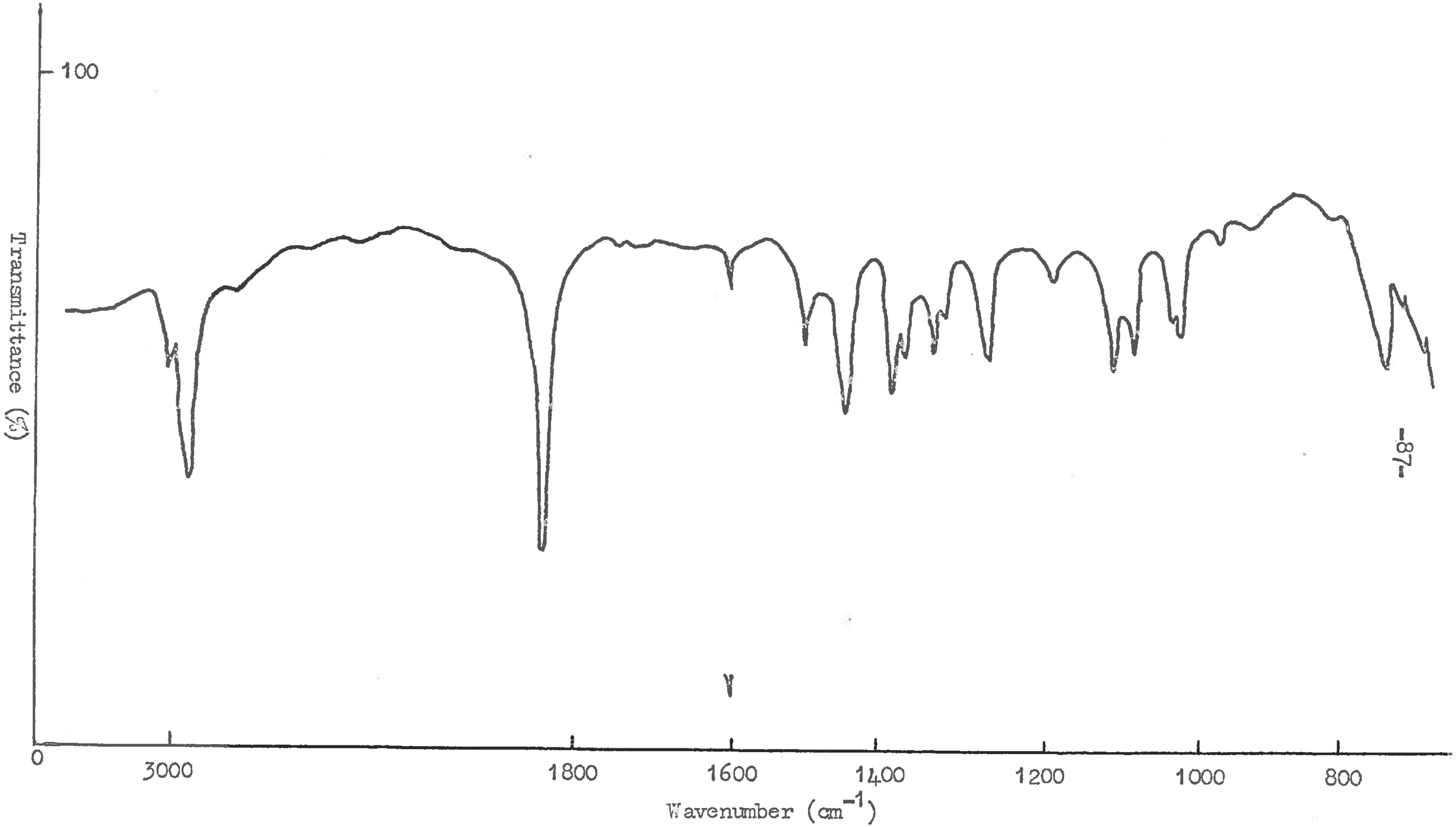
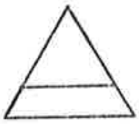


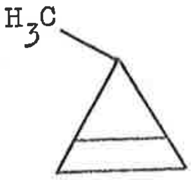
Figure 2. - Infrared absorption spectrum of 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (155).

substitution of the second methyl group on the double bond, 1,2,3,3-tetramethylcyclopropene (158) absorbing at 1877 cm^{-1} in the infrared region.[5] In contrast, substitution at C-3 in cyclopropene causes little change in the infrared absorption values of the skeletal vibrations. Outlined below are the values obtained for cyclopropene (1), 3-methylcyclopropene (159), and 3,3-dimethylcyclopropene (160).[5] It



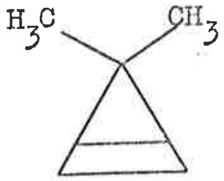
(1)

1641 cm^{-1}



(159)

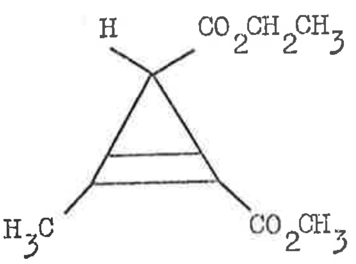
1638 cm^{-1}



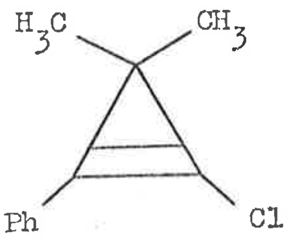
(160)

1632 cm^{-1}

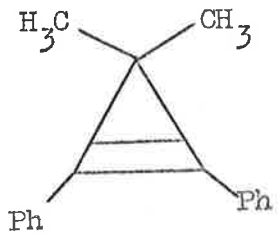
has been mentioned above that the nature of the substituents attached to the double bond in 1,2-disubstituted cyclopropenes have little effect on the absorption value of the skeletal vibrations in the infrared region. In the cyclopropenes 161, 162, and 163 shown below, the chromophoric groups are derivatives of methyl crotonate, <u>cis</u>-β-chlorostyrene and <u>cis</u>-stilbene respectively. In the parent compounds the double bond absorb at 1713,[49] 1620,[50] and 1594[51] cm^{-1} respectively, yet when these compounds are incorporated in the cyclopropene system they all exhibit skeletal absorption at 1840 cm^{-1}.[5] From this, therefore, it could be likely that 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (155) would also absorb at 1840 cm^{-1} and this, in fact, is found



(161)



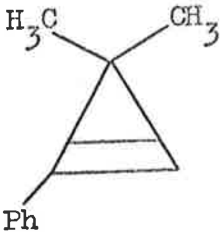
(162)



(163)

to occur. The infrared spectrum of the product exhibits two absorptions between 1000 and 1025 cm^{-1} and these absorptions were attributed to a ring deformation mode.[52] Derfer, Pickett, and Boord[53] have established that absorption between 1000 and 1020 cm^{-1} is typical of the cyclopropane structure. It has also been found[71] that if two methyl groups are substituted around the ring the infrared spectrum exhibits absorption at 1100 cm^{-1}. A band at this wavenumber was present in the spectrum. It was considered likely that the absorption at 1100 cm^{-1} may also contain an absorption attributable to the C-O stretching vibrations of the ether group. The presence of the phenyl group was substantiated by absorptions at 1600, 690, and 750 cm^{-1} in the infrared spectrum, the two latter values being indicative of a monosubstituted benzene compound.

Additional support for the proposed structure 155 was provided by the n.m.r. spectrum of the product. Absorptions at δ1.37 (singlet, 6H), 3.98 (singlet, 3H), and δ7.0-7.3 (multiplet, 5H) in the n.m.r. spectrum were attributed to the gem-dimethyl, methoxyl, and phenyl groups respectively. The values obtained for the gem-dimethyl and phenyl groups are in close agreement with those of δ1.38 (singlet, 6H) and δ7.4-7.7 (multiplet, 5H) obtained for 3,3-dimethyl-1-phenylcyclopropene (27).[20]



(27)

The ultraviolet spectrum (see Figure 3) of the product exhibited a maximum at 277 (ε 2,100) n.m. The low value obtained for the extinction coefficient was unexpected as Closs[5] has found that the electronic spectra of cyclopropenes are not significantly different from those of more conventional systems.

The mass spectrum exhibited a parent ion peak at m/e 174, which is the expected molecular weight for this compound, with peaks at m/e 159 and 144 due to losses of one and two methyl radicals respectively (see Figure 4). The presence of a phenyl group in the product was

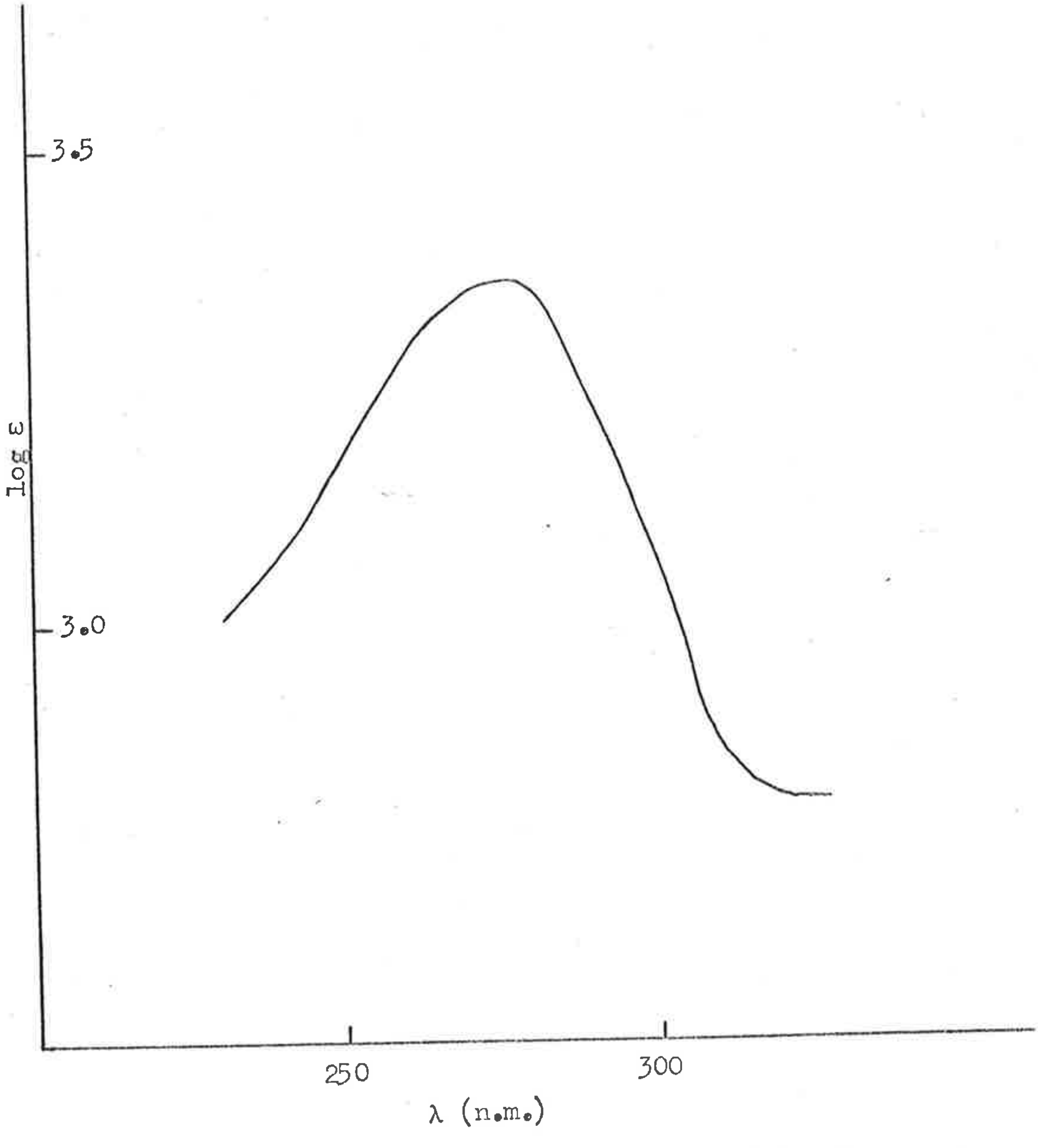


Figure 3. - Ultraviolet absorption spectrum of 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (155).

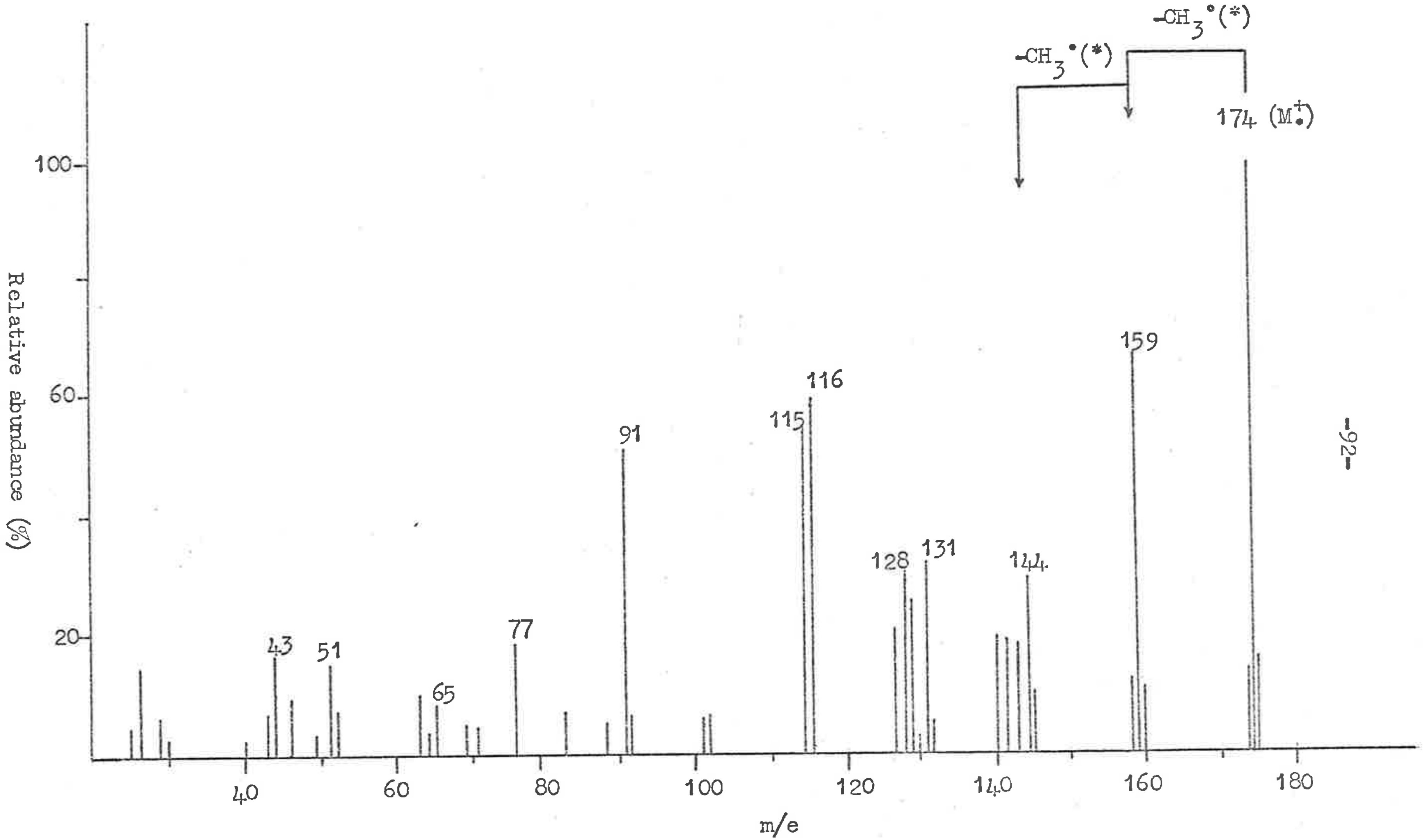


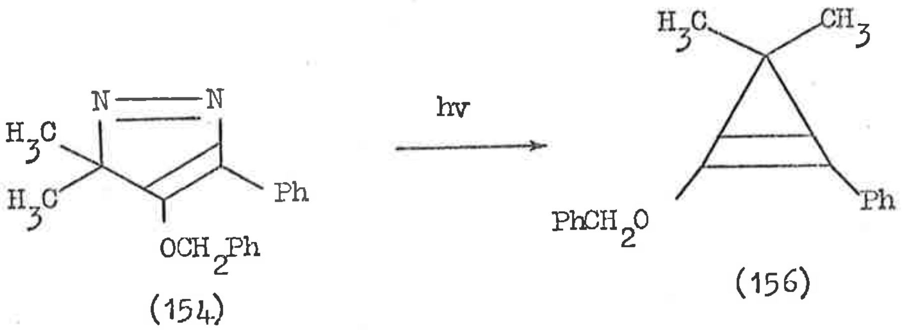
Figure 4. - Mass spectrum of 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (155).

(*) This loss is supported by the appropriate metastable peak.

substantiated by peaks at m/e 77, 65, 51, and 43, these peaks being characteristic of a phenyl group.

The poor yields in the final step are presumed to be due to absorption of radiation by the product with subsequent decomposition. It is interesting to note that the extinction coefficient of the cyclopropenyl ether 155 at 300 nm is 1,196 which is comparable with that of 1,720 for the starting material.

When 4-benzyloxy-3,3,-dimethyl-5-phenyl-3H-pyrazole (154) was irradiated under similar conditions to those used for the methyl analogue 152, 1-benzyloxy-3,3,-dimethyl-2-phenylcyclopropene (156) was produced in low yield (5-10%). The product, an oil, was identified on the basis of physical data. An absorption at 1840 cm^{-1} in the



(154)

(156)

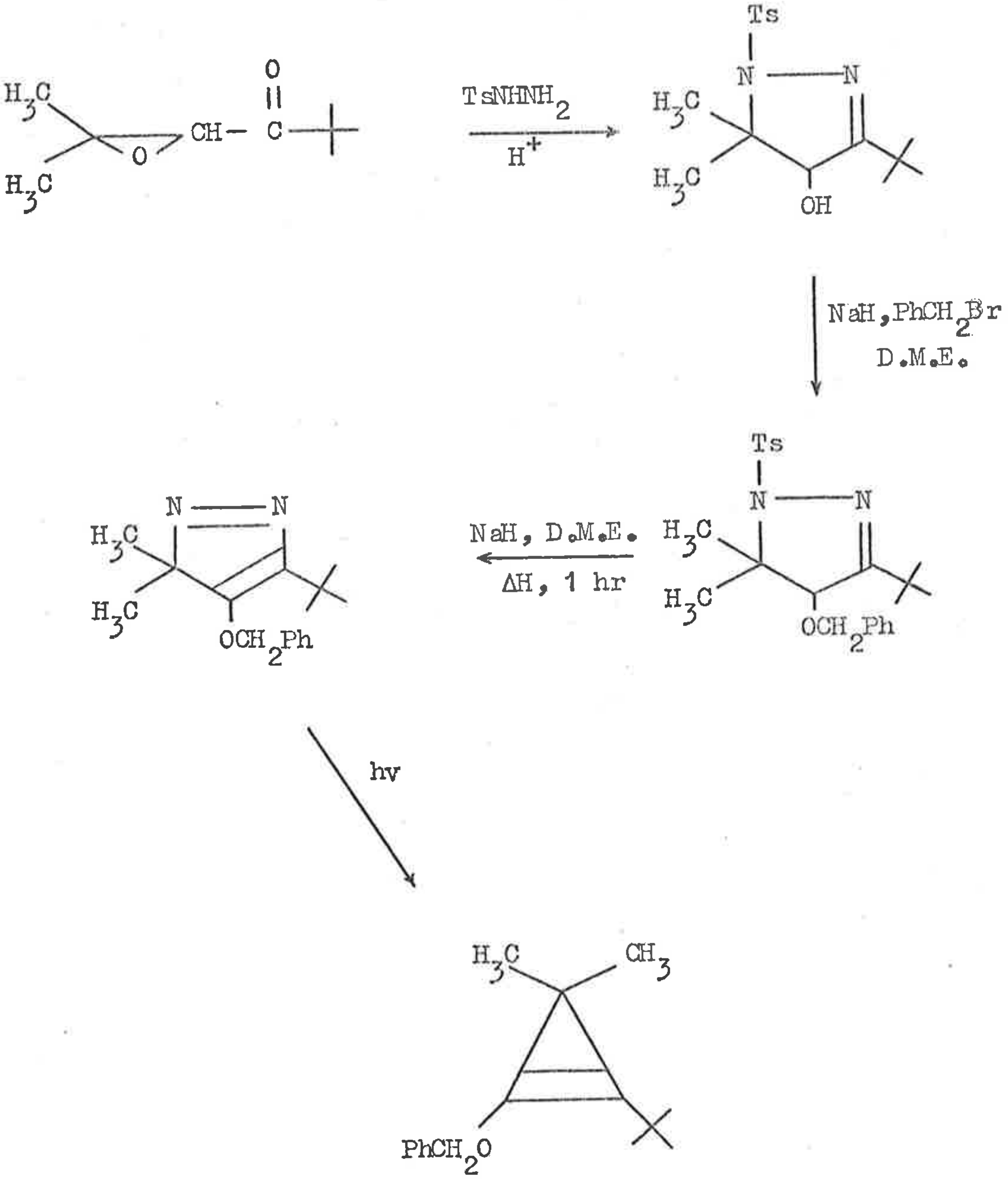
infrared spectrum was attributed to the skeletal vibration, while signals at δ1.33 (singlet, 6H), 5.18 (singlet, 2H), and δ7.2-7.3 (multiplet, 10H) in the n.m.r. spectrum were attributed to the <u>gem</u>-

dimethyl, benzylic methylene, and phenyl groups respectively. The mass spectrum showed a parent ion peak at m/e 250, which is the expected molecular weight for the compound. The compound absorbed at λ_{max} (pentane) 277 (ε 2,000) n.m. in the ultraviolet region.

Once again the yield of the cyclopropenyl ether was low (5-10%) and it was thought that the reason for this was the same as outlined for the methyl analogue, i.e. absorption by the product of the incident light with subsequent decomposition.

At this stage the synthetic work described in this thesis was concluded and no attempts to cleave the benzyl group of the cyclopropenyl ether 156 were made.

Hamon[54] has now used the experience gained by this work to synthesise 1-benzyloxy-2-*tert*-butyl-3,3-dimethylcyclopropene (164) by the general method outlined below. The infrared absorption value of the ring skeleton vibration was 1860 cm^{-1} which is in agreement with Closs' work.[5] Although this compound was produced in better yield (20%) than the cyclopropenyl ethers 155 and 156 the product was contaminated with an unknown compound.


H3C
H3C
O
CH—
C
O
TsNHNH2
H+
Ts
N
N
H3C
H3C
OH
NaH, PhCH2Br
D.M.E.
Ts
N
N
H3C
H3C
OCH2Ph
NaH, D.M.E.
ΔH, 1 hr
N
N
H3C
H3C
OCH2Ph
hv
H3C
CH3
PhCH2O

(164)

EXPERIMENTAL.

General.

Melting points were determined using a Koffler hot stage, and are uncorrected.

Microanalyses were carried out by the Australian Microanalytical Service, Melbourne.

Organic extracts were dried over anhydrous magnesium sulphate.

Spectroscopic Measurements.

Infrared spectra were determined in Nujol mulls (unless stated otherwise) with Perkin-Elmer 237 and 337 Grating Spectrophotometers and a Unicam SP200 Spectrophotometer. Mass spectra were recorded using a Hitachi Perkin-Elmer RMU-6D spectrometer, fitted with a double focussing device. Nuclear magnetic resonance spectra were recorded with Varian DP60 and T60 spectrometers at 60 mc/s and chemical shifts were measured relative to tetramethylsilane as the internal standard.

Work described in Chapter II

(part a)

Benzalacetophenone.

Benzalacetophenone, m.p. 56-57° (lit.[55] 56-57°), was prepared by the base-catalysed condensation of acetophenone with benzaldehyde.[55]

Benzalacetophenone oxide (32).

Benzalacetophenone oxide, m.p. 88-89° (lit.[56] 90°), was prepared by the action of alkaline hydrogen peroxide on benzalacetophenone.[56]

4-Hydroxy-3,5-diphenyl-2-pyrazoline (33).

4-Hydroxy-3,5-diphenyl-2-pyrazoline, m.p. 208-209° (lit.[25] 209°), was prepared by the action of hydrazine hydrate on benzalacetophenone oxide (32).[25]

4-Acetoxy-1-acetyl-3,5-diphenyl-2-pyrazoline (46).

4-Acetoxy-1-acetyl-3,5-diphenyl-2-pyrazoline, m.p. 177-178° (lit.[31] 177-178°), was prepared by the action of an acetic anhydride-pyridine mixture on 4-hydroxy-3,5-diphenyl-2-pyrazoline (33).[31]

1-Acetyl-4-hydroxy-3,5-diphenyl-2-pyrazoline (45).

1-Acetyl-4-hydroxy-3,5-diphenyl-2-pyrazoline, m.p. 128-129° (lit.[31] 128-129°), was prepared by the method of Sinclair[31] in which 4-acetoxy-1-acetyl-3,5-diphenyl-2-pyrazoline (46) was heated under reflux in 10% potassium hydroxide in methanol solution for 90 min.

1-Acetyl-3,5-diphenyl-4-tetrahydropyranyloxy-2-pyrazoline (49).

1-Acetyl-4-hydroxy-3,5-diphenyl-2-pyrazoline (45; .20 g, 0.5 mmole) was added to freshly distilled 2,3-dihydropyran (5 ml) and the mixture was acidified by the addition of a crystal of p-toluenesulphonic acid. After the reaction mixture had been stirred for 1 hr, it was neutralised by the addition of aqueous sodium hydroxide. The organic material was extracted into ether, which was washed several times with water, dried, and evaporated. The residue, an oil, was triturated with hexane and the resulting solid was recrystallised from a hexane-ether mixture to give 1-acetyl-3,5-diphenyl-4-tetrahydropyranyloxy-2-pyrazoline (.18 g, 69%) as colourless prisms, m.p. 138-145° (Found: C, 72.4; H, 6.5; N, 7.8. $C_{22}H_{24}N_2O_3$ requires C, 72.5; H, 6.6; N, 7.7%). ν_{max} 1675 cm^{-1} (N-CO-CH_3), n.m.r. (CCl_4): δ1.6 (multiplet, 6 methylene, H), δ2.4 (singlet, 3H, $\underline{H}_3$-$\overset{O}{\overset{\|}{C}}$-), δ3.8 (multiplet, 2H, -C$\underline{H}_2$-O-), δ4.9 (overlapping doublets, J_C 1.0 Hz, 2H, O-C$\underline{H}$-O, and Ph-C$\underline{H}$-), δ5.2 (doublet, J_C 1.0 Hz, 1H, Ph-C$\underline{H}$-), δ5.4 (doublet, J_C 1.0 Hz, 1H, -C$\underline{H}$-O-), δ5.6 (doublet, J_C 1.0 Hz, 1H, -C$\underline{H}$-O), and δ7.5 (multiplet, 10 aromatic protons). Integration of the signals at δ5.4 and δ5.6 indicated a mixture of diastereoisomers in the ratio of 2:1.

1-Acetyl-4-methoxy-3,5-diphenyl-2-pyrazoline (48).

Sodium hydride (.02 g, 0.9 mmole) was added to a solution of 1-acetyl-4-hydroxy-3,5-diphenyl-2-pyrazoline (45; .20 g, 0.5 mmole) in anhydrous dimethoxyethane (10 ml) and the solution was then stirred at room temperature for 2 min. Methyl iodide (5 ml, 0.08 mmole) was then added and the stirring was continued at room temperature for 4 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. The ethereal layer was washed with water, dried, and evaporated. Recrystallisation of the residue from hexane gave 1-acetyl-4-methoxy-3,5-diphenyl-2-pyrazoline (.18 g, 87%) as colourless prisms, m.p. 92-93° (Found: C, 73.8; H, 6.2; N, 9.2. $C_{18}H_{18}N_2O_2$ requires C, 73.5; H, 6.2; N, 9.5%). ν_{max} 1665 cm^{-1} ($N-CO-CH_3$), n.m.r. (CCl_4): δ2.3 (singlet, 3H, $C\underline{H}_3-\overset{O}{\overset{\|}{C}}-$), δ3.4 (singlet, 3H, $-O-C\underline{H}_3$), δ4.75 (doublet, J_C 2.0 Hz, 1H, $Ph-C\underline{H}-$), δ5.3 (doublet, J_C 2.0 Hz, 1H, $-C\underline{H}-O-$) and δ7.2 (multiplet, 10 aromatic protons).

Hydrolysis of 1-acetyl-4-methoxy-3,5-diphenyl-2-pyrazoline (48).

1-Acetyl-4-methoxy-3,5-diphenyl-2-pyrazoline (48; .06 g, 2 mmole) was dissolved in a solution of potassium hydroxide in methanol (10%, 10 ml) and the solution was heated under reflux for 4 hr. The cooled solution was poured into water and the organic material was extracted into ether. After the ethereal layer had been washed thoroughly with water, it was dried and evaporated. The residue was recrystallised from ethanol to give 3,5-diphenylpyrazole (.03 g, 70%) as colourless prisms, m.p. and mixed m.p. 200-201° (lit.[57] 200-201°). The infrared spectrum was identical with that of an authentic sample.

A similar result was obtained using 1-acetyl-3,5-diphenyl-4-tetrahydropyranyloxy-2-pyrazoline (49).

1-Acetyl-3,5-diphenylpyrazole (53).

1-Acetyl-3,5-diphenylpyrazole, m.p. 86-87° (lit.[58] 87°), was prepared by the action of an acetic anhydride-pyridine mixture on 3,5-diphenylpyrazole (52).[58]

Benzalpinacolone.

Benzalpinacolone, m.p. 40-41° (lit.[59] 41°), was prepared by the base-catalysed condensation between pinacolone and benzaldehyde.[59]

trans-Benzalpinacolone oxide.

A solution of sodium hydroxide in methanol (8%, 30 ml) and 30% hydrogen peroxide (40 ml) was added to benzalpinacolone (18 g, .096 mole) in methanol (200 ml) in small portions over ½ hr. The temperature was not allowed to exceed 40°, and the stirring was continued for 2 hr. The solution was then poured into water and the precipitate (16.5 g, 81%) was removed by filtration, dissolved in ethanol (100 ml), and kept at 0°. *trans*-Benzalpinacolone oxide (8 g, 42%) was obtained as colourless needles, m.p. 80-81° (lit.[60] 81°). Concentration of the mother liquor gave a further quantity (2 g) of the *trans*-isomer.

3-tert-Butyl-4-hydroxy-5-phenyl-2-pyrazoline (54).

Hydrazine hydrate (1 ml, 20 mmole) was added to a solution of *trans*-benzalpinacolone oxide (2 g, 9.8 mmole) in ethanol (20 ml) and the solution was heated under reflux for 4 hr. The solvent and excess hydrazine hydrate were then removed *in vacuo* to yield a solid which was recrystallised from hexane-ether. 3-tert-Butyl-4-hydroxy-5-phenyl-2-pyrazoline (2.0 g, 95%) was obtained as colourless needles, m.p. 116-117° (Found: C, 71.6; H, 8.3; N, 12.8. $C_{13}H_{18}N_2O$ requires C, 71.5; H, 8.3; N, 12.8%). ν_{max} 3250 and 3125 cm^{-1} (-OH and N-H respectively), n.m.r. ($CCl_4/CDCl_3$): δ1.2 (singlet, 9H, tert-butyl group), δ4.4 (doublet, J_C 4.5 Hz, 1H, Ph-C$\underline{H}$-), δ4.65 (doublet, J_C 4.5 Hz, 1H, -C$\underline{H}$-O-) and δ7.2 (multiplet, 5 aromatic protons). The hydroxylic and amino protons could not be detected.

4-Acetoxy-1-acetyl-3-tert-butyl-5-phenyl-2-pyrazoline (55).

Acetyl chloride (1 ml) was added to a solution of 3-tert-butyl-4-hydroxy-5-phenyl-2-pyrazoline (54; 1 g, 4.6 mmole) in pyridine (10 ml) and the reaction mixture kept at room temperature for 30 min. After the reaction mixture had been diluted with water, the organic material was extracted into ether and the ether extract was washed with 10% aqueous hydrochloric acid and dried. Evaporation of the solvent gave a solid which was recrystallised from hexane to give 4-acetoxy-1-acetyl-3-tert-butyl-5-phenyl-2-pyrazoline (1.2 g, 86%) as colourless prisms, m.p. 103-104° (Found: C, 67.6; H, 7.4; N, 9.3. $C_{17}H_{22}N_2O_3$ requires C, 67.5; H, 7.3; N, 9.3%). ν_{max} 1740 and 1680 cm^{-1} (-$OCOCH_3$ and N-CO-CH_3 respectively), n.m.r. ($CCl_4/CDCl_3$): δ1.2 (singlet, 9H, tert-butyl group), δ2.1 (singlet, 3H, N-CO-C$\underline{H}_3$), δ2.3 (singlet, 3H, O-CO-C$\underline{H}_3$), δ5.2 (doublet, J_C 2.0 Hz, 1H, Ph-C$\underline{H}$-O), δ5.5 (doublet, J_C 2.0 Hz, 1H, -C$\underline{H}$-O-) and δ7.3 (multiplet, 5 aromatic protons).

1-Acetyl-3-tert-butyl-4-hydroxy-5-phenyl-2-pyrazoline (56).

4-Acetoxy-1-acetyl-3-*tert*-butyl-5-phenyl-2-pyrazoline (55; .40 g, 1.3 mmole) was dissolved in a solution of potassium hydroxide in methanol (10%, 10 ml) and the reaction mixture was heated under reflux for 90 min. The cooled solution was poured into water and the organic material was extracted into ether. After the ether extract had been washed thoroughly with water, it was dried and evaporated. Recrystallisation of the residue from hexane gave 1-acetyl-3-tert-butyl-4-hydroxy-5-phenyl-2-pyrazoline (.23 g, 67%) as a colourless solid, m.p. 133-134° (Found: C, 69.3; H, 7.9; N, 11.1. $C_{15}H_{20}N_2O_2$ requires C, 69.2; H, 7.7; N, 10.8%). ν_{max} 3400 and 1640 cm^{-1} (-OH and $N-CO-CH_3$ respectively), n.m.r. ($CCl_4/CDCl_3$): δ1.2 (singlet, 9H, *tert*-butyl group), δ2.25 (singlet, 3H, $-N-CO-C\underline{H}_3$), δ4.5 (doublet, J_C 1.0 Hz, 1H, $Ph-C\underline{H}-$), δ5.1 (doublet, J_C 2.0 Hz, 1H, $-C\underline{H}-O-$), and δ7.3 (multiplet, 5 aromatic protons). The hydroxylic proton could not be detected.

1-Acetyl-3-tert-butyl-4-methoxy-5-phenyl-2-pyrazoline (57).

Sodium hydride (0.2 g, 0.9 mmole) was added to a solution of 1-acetyl-3-*tert*-butyl-4-hydroxy-5-phenyl-2-pyrazoline (56; .20 g, 0.5 mmole) in anhydrous dimethoxyethane (10 ml) and the solution was then stirred at room temperature for 2 min. Methyl iodide (5 ml, .08 mole) was then added and the stirring was continued at room temperature for 4 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. The ethereal layer was washed with water, dried, and evaporated. The residue, an oil, was crystallised from hexane to give 1-acetyl-3-tert-butyl-4-methoxy-5-phenyl-2-pyrazoline (.10 g, 91%) as colourless needles, m.p. 93.5-94.5° (Found: C, 70.2; H, 8.2; N, 10.4. $C_{16}H_{22}N_2O_2$ requires C, 70.1; H, 8.1; N, 10.2%). ν_{max} 1665 cm^{-1} (N-CO-CH_3), n.m.r. (CCl_4): δ1.2 (singlet, 9H, tert-butyl group), δ2.3 (singlet, 3H,N-CO-C$\underline{H}_3$), δ3.4 (singlet, 3H, -O-C$\underline{H}_3$), δ4.3 (doublet, J_C 1.4 Hz, 1H, Ph-C$\underline{H}$-), δ5.25 (doublet, J_C 1.2 Hz, 1H, -C$\underline{H}$-O-), and δ7.3 (multiplet, 5 aromatic protons).

3-tert-Butyl-5-phenylpyrazole (58).

(a) 1-Acetyl-3-tert-butyl-4-methoxy-5-phenyl-2-pyrazoline (57; .20 g, .73 mmole) was dissolved in a solution of potassium hydroxide in methanol (10%, 20 ml) and heated under reflux for 4 hr. The cooled solution was poured into water and the organic material was extracted into ether. After the ether extract had been washed thoroughly with water, it was dried and evaporated. The residue, an oil, was crystallised from petroleum ether (b.p. 30-40°) to give 3-tert-butyl-5-phenylpyrazole (.10 g, 66%) as colourless plates, m.p. 120.5-121.5° (Found: C, 77.7; H, 8.1. $C_{13}H_{16}N_2$ requires C, 77.9; H, 8.1%); n.m.r. ($CDCl_3$): δ1.2 (singlet, 9H, tert-butyl group), δ6.4 (singlet, 1H, proton at the 4-position), δ7.3 (multiplet, 5 aromatic protons), and

δ10.45 (broad singlet, 1H, N-H).

(b) Sodium (.01 g, 4.4 mmole) was added to a solution of 3-*tert*-butyl-4-hydroxy-5-phenyl-2-pyrazoline (54; .50 g, 1.8 mmole) in anhydrous methanol (20 ml) and the solution was heated under reflux for 3 hr. The cooled solution was poured into water and the organic material was extracted into ether. After the ethereal layer had been washed with water, it was dried and evaporated. The residue, an oil, was crystallised from petroleum ether (b.p. 30-40°) to give 3-*tert*-butyl-5-phenylpyrazole (.41 g, 89%) as colourless plates, m.p. and mixed m.p. 120.5-121.5°. The infrared and n.m.r. spectra were identical with those of the product isolated from the hydrolysis of compound 57.

1-Acetyl-3-tert-butyl-5-phenylpyrazole (59).

Acetic anhydride (4 ml) was added to a solution of 3-*tert*-butyl-5-phenylpyrazole (58; 4g, 12 mmole) in pyridine (10 ml) and the reaction mixture was kept at room temperature for 24 hr. After the reaction mixture had been diluted with water, the organic material was extracted into ether. The ether extract was then washed thoroughly with water and dried. Evaporation of the solvent gave an oil which crystallised from petroleum ether (b.p. 30-40°) to afford 1-acetyl-3-tert-butyl-5-phenylpyrazole (3.6 g, 78%) as colourless prisms, m.p. 85-86° (Found: C, 74.4; H, 7.4; N, 11.4. $C_{15}H_{18}N_2O$ requires C, 74.7;

H, 7.5; N, 11.6%). ν_{max} 1740 (N-CO-CH_3), n.m.r. (CCl_4/$CDCl_3$): δ1.2 (singlet, 9H, tert-butyl group), δ2.7 (singlet, 3H, N-CO-CH_3), δ6.13 (singlet, 1H, proton at the 4-position), and δ7.3 (multiplet, 5 aromatic protons).

Dypnone.

Dypnone, b.p. 160-165°/2 mm (lit.[61] 150-155°/1 mm), was prepared by the method of Wayne and Adkins.[61]

trans-Dypnone Epoxide (61).

Dypnone was epoxidised by treatment with alkaline hydrogen peroxide and the two isomers, cis- m.p. 158-159° (lit.[62] 159.6°), trans- m.p. 91-92° (lit.[62] 93°) were separated by fractional crystallisation.[62]

4-Hydroxy-5-methyl-3,5-diphenyl-2-pyrazoline (62).

4-Hydroxy-5-methyl-3,5-diphenyl-2-pyrazoline, m.p. 207-208° (lit.[31] 207-208°), was prepared by the action of hydrazine hydrate on trans-dypnone oxide (61).[31]

4-Acetoxy-1-acetyl-5-methyl-3,5-diphenyl-2-pyrazoline (63).

Acetyl chloride (1 ml) was added to a solution of 4-hydroxy-5-methyl-3,5-diphenyl-2-pyrazoline (62; .12 g, 0.45 mmole) in pyridine (3 ml) and the reaction mixture kept at room temperature for 30 min.

After the reaction mixture had been diluted with water, the organic material was extracted into ether and the ether extract was washed with 10% aqueous hydrochloric acid and dried. Evaporation of the solvent gave a solid which was recrystallised from ethanol to give 4-acetoxy-1-acetyl-5-methyl-3,5-diphenyl-2-pyrazoline (.13 g, 82%) as colourless needles, m.p. 196-197° (Found: C, 71.1; H, 5.9; N, 8.3. $C_{20}H_{20}N_2O_3$ requires C, 71.4; H, 6.0; N, 8.3%). ν_{max} 1730 and 1660 cm^{-1} (-OCOCH$_3$ and -N-CO-CH$_3$ respectively), n.m.r. ($CDCl_3$) : δ1.9 (singlet, 3H, N-C-C$\underline{H}_3$), δ2.15 (singlet, 3H, N-CO-C$\underline{H}_3$), δ2.50 (singlet, 3H, O-CO-C$\underline{H}_3$), δ6.3 (singlet, 1H, -C$\underline{H}$-O), and δ7.3 (multiplet, 10 aromatic protons).

1-Acetyl-4-hydroxy-5-methyl-3,5-diphenyl-2-pyrazoline (64).

4-Acetoxy-1-acetyl-5-methyl-3,5-diphenyl-2-pyrazoline (63; .08 g, 0.22 mmole) was dissolved in a solution of potassium hydroxide in methanol (10%, 10 ml) and the reaction mixture was heated under reflux for 90 min. The cooled solution was poured into water and the organic material was extracted into ether. After the ether extract had been washed thoroughly with water, it was dried and evaporated. Recrystallisation of the solid from carbon tetrachloride gave 1-acetyl-4-hydroxy-5-methyl-3,5-diphenyl-2-pyrazoline (.05 g, 73%) as a colourless solid, m.p. 161-162° (Found: C, 73.1; H, 6.2; N, 9.4. $C_{18}H_{18}N_2O_2$ requires C, 73.4; H, 6.2; N, 9.5%). ν_{max} 3250 and 1665 cm^{-1} (-OH and -N-CO-CH$_3$ respectively), n.m.r. ($CDCl_3$): δ1.9 (singlet, 3H, -C-C$\underline{H}_3$), δ2.2 (singlet, 3H, N-CO-$C\underline{H}_3$), δ4.9 (singlet, 1H, -C$\underline{H}$-O), and δ7.3 (multiplet, 10 aromatic protons). The hydroxylic proton could not be detected.

1-Acetyl-4-methoxy-5-methyl-3,5-diphenyl-2-pyrazoline (65).

Sodium hydride[≠] (0.020 g, .9 mmole) was added to a solution of 1-acetyl-4-hydroxy-5-methyl-3,5-diphenyl-2-pyrazoline (64; .16 g, .55 mmole) in anhydrous ether (20 ml) and the solution was heated under reflux for 10 min. Methyl iodide (5 ml, .08 mmole) was then added and the reaction mixture was heated under reflux for 3 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. The ethereal layer was washed with water, dried, and evaporated. The residue, an oil, was crystallised from petroleum ether (b.p. 40-60°)-methylene chloride to give 1-acetyl-4-methoxy-5-methyl-3,5-diphenyl-2-pyrazoline (0.156 g, 93%) as colourless needles, m.p. 101-102° (Found: C, 74.2; H, 6.4; N, 9.0. $C_{19}H_{20}N_2O_2$ requires C, 74.0; H, 6.5; N, 9.1%). ν_{max} 1665 cm^{-1} (N-CO-CH_3), n.m.r. ($CDCl_3$): δ2.05 (singlet, 3H, -C-$C\underline{H}_3$), δ2.4 (singlet, 3H, N-CO-$C\underline{H}_3$), δ3.45 (singlet, 3H, -O-$C\underline{H}_3$), δ4.7 (singlet, 1H, -C$\underline{H}$-O), and δ7.3 (multiplet, 10 aromatic protons).

5-Methyl-3,4-diphenylpyrazole (66).

1-Acetyl-4-methoxy-5-methyl-3,5-diphenyl-2-pyrazoline (65; .10 g,

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[≠] The sodium hydride mineral oil dispersion was repeatedly washed with hexane and heated under reflux in hexane (20 ml) for 2 hr.

.33 mmole) was dissolved in a solution of potassium hydroxide in methanol (40%, 20 ml), and the system was placed under an atmosphere of nitrogen. The solution was then heated under reflux for 2 days. The cooled solution was poured into water and the organic material was extracted into ether. After the ether extract had been washed thoroughly with water, it was dried and evaporated. The residue, an oil, was purified by sublimation (200°, .1 mm) to give 5-methyl-3,4-diphenylpyrazole (.05 g, 65%) as colourless prisms, m.p. 174-175° (lit.[32] 175°), n.m.r. ($CDCl_3$): δ2.1 (singlet, 3H, $-C\underline{H}_3$) and 7.3 (multiplet, 10 aromatic protons). The amino proton could not be detected. The mass spectrum showed an m/e 234, requires 234.

Work described in Chapter II

(part b).

1-Ethoxyprop-1-yne (74).

1-Ethoxyprop-1-yne, b.p. 86-88° (lit.[64] 88-90.5°), was prepared by the method of Farnum, Heybrey, and Webster.[63]

Diphenyldiazomethane.

Diphenyldiazomethane was obtained from the oxidation of benzophenone hydrazone using yellow mercuric oxide.[65]

2-Diazopropane.

2-Diazopropane was prepared by the oxidation of acetone hydrazone with yellow mercuric oxide in the presence of base.[66]

β-Methoxystyrene (81).

β-Methoxystyrene, b.p. 210-212° (lit.[67] 210-213°), was prepared by heating a mixture of phenylacetylene and potassium hydroxide in methanol.[67]

Attempted 1,3-dipolar cycloaddition between diphenyldiazomethane and 1-ethoxyprop-1-yne (74).

(a) A solution of diphenyldiazomethane (1.2 g, 6.2 mmole) in petroleum ether (b.p. 40-60°, 10 ml) was added to a solution of 1-ethoxyprop-1-yne (75; .5 g, 5.9 mmole) in petroleum ether (b.p. 40-60°, 10 ml). The reaction mixture was protected from light, and stirred at room temperature for 4 days. An absorption at 2300 cm^{-1} in the infrared spectrum of the reaction mixture indicated the presence of 1-ethoxyprop-1-yne. After the reaction mixture had been cooled, the precipitate was removed by filtration. Recrystallisation of the precipitate gave a 1:1 molecular complex of benzophenone azine and _sym_-tetraphenylethane (.52 g, 47%) as yellow needles, m.p. 176-177° (lit.[37] 177-177.5°). Evaporation of the filtrate gave a solid which was recrystallised from ethanol to afford benzophenone azine (.47 g, 40%) as a yellow crystalline solid, m.p. 162-163° (lit.[37] 163-163.5°). No other products could be detected using thin-layer chromatography.

(b) A mixture of diphenyldiazomethane (1.2 g, 6.2 mmole) and 1-ethoxyprop-1-yne (74; .5 g, 5.9 mmole) in benzene (20 ml) was stirred in the dark, at room temperature for 4 days. An absorption at 2300 cm^{-1} in the infrared spectrum of the reaction mixture indicated the presence of 1-ethoxyprop-1-yne. Evaporation of the solvent and 1-ethoxyprop-1-yne gave a yellow solid which was recrystallised from ethanol to give benzophenone azine (.83 g, 71%) as a yellow crystalline solid, m.p. 162-163° (lit.[37] 163-163.5°). No other product could be detected using thin-layer chromatography.

A similar result was obtained on heating the above mixture under reflux for 4 hr or by heating the reaction mixture in a Carius tube at 80° for 12 hr.

Attempted 1,3-dipolar cycloaddition between 2-diazopropane and 1-ethoxyprop-1-yne (74).

A mixture of 1-ethoxyprop-1-yne (74; 1 g, 12 mmole) and 2-diazopropane (1 g, 14 mmole) in ether (20 ml), initially at 0°, was stirred at room temperature for 24 hr. The solvent was then carefully removed to yield an oil, which was identified as a mixture of 1-ethoxyprop-1-yne and acetone azine by comparison of the infrared spectrum of the oil with those of the authentic compounds. Carbon tetrachloride (20 ml) was then added and the solvent removed *in vacuo*. After this process had been repeated several times, a small amount of residue remained. This residue was identified as acetone azine by comparison of the infrared spectrum with that of authentic material.

Attempted 1,3-dipolar cycloaddition between diphenyldiazomethane and β-methoxystyrene (81).

A mixture of diphenyldiazomethane (2 g, 10 mmole) and β-methoxystyrene (81; 1.4 g, 10 mmole) in benzene (15 ml) was stirred in the dark, at room temperature for 4 days. After the solvent had been evaporated, the residue, an oil, was dissolved in ethanol and set aside at 0°. Benzophenone azine (1.1 g, 56%) was obtained as yellow crystals, m.p. 162-163° (lit.[37] 163-163.5°). The residue was identified as a mixture of β-methoxystyrene and benzophenone azine on the basis of spectral data and thin-layer chromatography. No other products could be detected using thin-layer chromatography.

A similar result was obtained on heating the above mixture under reflux for 4 hr or by heating the reaction mixture in a Carius tube at 80° for 12 hr.

Attempted 1,3-dipolar cycloaddition between 2-diazopropane and β-methoxystyrene.

A mixture of 2-diazopropane (3 g, 43 mmole) and β-methoxystyrene (81; 5.7 g, 42 mmole) in ether (30 ml), initially at 0°, was stirred at room temperature for 24 hr. The solvent was then removed to yield an oil, which was identified as a mixture of β-methoxystyrene and acetone azine on the basis of spectral data and thin-layer chromatography. No other products could be detected using thin-layer chromatography.

Work described in Chapter III

(part a).

p-Toluenesulphonylhydrazine.

p-Toluenesulphonylhydrazine, m.p. 103-106° (lit.[68] 104-107°), was prepared by the action of p-toluenesulphonyl chloride on hydrazine hydrate.[68]

4-Hydroxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (34).

4-Hydroxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline, m.p. 224-225° (lit.[26] 225-226°), was prepared by the method of Padwa[26] in which benzalacetophenone oxide and p-toluenesulphonylhydrazine were heated under reflux in acidic methanol.

3,5-Diphenyl-4-tetrahydropyranyloxy-1-p-toluenesulphonyl-2-pyrazoline (87).

Freshly distilled 2,3-dihydropyran (2 ml) was added to a solution of 4-hydroxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (34; .80 g, 2.1 mmole) in chloroform (100 ml) and the mixture was acidified by the addition of three drops of concentrated hydrochloric acid. After the reaction mixture had been kept at room temperature for 3 hr, it was neutralised by the addition of aqueous sodium hydroxide. The organic layer was then separated, washed several times with water, dried, and evaporated. Crystallisation of the residue from methanol gave 3,5-diphenyl-4-tetrahydropyranyloxy-1-p-toluenesulphonyl-

2-pyrazoline (0.72 g, 75%) as colourless prisms, m.p. 152-164° (Found: C, 68.0; H, 6.1; N, 5.8. $C_{27}H_{28}N_2O_4S$ requires C, 68.0; H, 5.9; N, 5.9%), n.m.r. ($CDCl_3$): δ1.45 (multiplet, 6 methylene H), δ2.37 (singlet, 3H, methyl protons of *p*-toluenesulphonyl group), δ3.62 (broad multiplet, 2H, $-OC\underline{H}_2-$), δ4.72 (singlet, 1H, $O-C\underline{H}-O$), δ4.75 (doublet, J_C 5.1 Hz, 1H, $Ph-C\underline{H}-$), δ4.95 (doublet, J_C 4.9 Hz, 1H, $Ph-C\underline{H}-$), δ5.06 (doublet, J_C 5.2 Hz, 1H, $-C\underline{H}-O-$), δ5.32 (doublet, J_C 5.4 Hz, 1H, $-C\underline{H}-O-$), δ7.13 (multiplet, 10 aromatic protons), and δ7.65, 7.75 (AB quartet, J_{AB} 9.0 Hz, 4H, aromatic protons of *p*-toluenesulphonyl group). Integration of the signals at δ5.06 and δ5.32 indicated a mixture of diastereoisomers in the ratio of 1:1.

Acid hydrolysis of 3,5-diphenyl-4-tetrahydropyranyloxy-1-p-toluenesulphonyl-2-pyrazoline (87).

A solution of 3,5-diphenyl-4-tetrahydropyranyloxy-1-*p*-toluenesulphonyl-2-pyrazoline (87; .20 g, .52 mmole) in ethanol (15 ml) was acidified by the addition of a drop of dilute hydrochloric acid. After the reaction mixture had been kept at room temperature for 1 hr, it was neutralised by the addition of aqueous sodium bicarbonate. The organic material was extracted into ether, which was washed with water, dried, and evaporated. Recrystallisation of the residue from ethanol gave a quantitative yield of 4-hydroxy-3,5-diphenyl-1-*p*-toluenesulphonyl-2-pyrazoline, m.p. and mixed m.p. 224-225°. The infrared spectrum was identical with that of an authentic sample.

3,5-Diphenyl-1-tetrahydropyranylpyrazole (90).

(a) Sodium hydride (0.15 g, 6.2 mmole) was added to a solution of 3,5-diphenyl-4-tetrahydropyranyloxy-1-p-toluenesulphonyl-2-pyrazoline (87; 1 g, 2.1 mmole) in anhydrous dimethoxyethane (20 ml) and the solution was heated under reflux for 6 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. After the ether extract had been washed thoroughly with water, it was dried and evaporated. The residue was crystallised from ethanol to give 3,5-diphenyl-1-tetrahydropyranylpyrazole (0.32 g, 48%) as colourless prisms, m.p. 136.5-137.5° (Found: C, 78.9; H, 6.8; N, 9.4. $C_{20}H_{20}N_2O$ requires C, 78.9; H, 6.6; N, 9.2%), n.m.r. (CCl_4): δ1.6 (multiplet, 6 methylene H), δ3.4-4.3 (complex multiplet, 2H, $-OC\underline{H}_2-$), δ5.2 (doublet of doublets, J_C 3.0 Hz, 1H, $O-C\underline{H}-N$), δ6.5 (singlet, 1H, proton at 4-position), and δ7.4 (multiplet, 10 aromatic protons).

(b) 3,5-Diphenylpyrazole (52; .10 g, .45 mmole) was added to freshly distilled 2,3-dihydropyran (10 ml) and the mixture was acidified by the addition of a crystal of p-toluenesulphonic acid. After the reaction mixture had stirred for 20 min, it was neutralised by the addition of aqueous sodium hydroxide. The organic material was extracted into ether, which was washed several times with water, dried, and evaporated. Crystallisation of the residue from ethanol gave 3,5-diphenyl-1-tetrahydropyranylpyrazole (.10 g, 70%), m.p. and mixed m.p. 136.5-137.5°.

The infrared and n.m.r. spectra were identical with those of the elimination product.

3-tert-*Butyl-4-hydroxy-5-phenyl-1*-p-*toluenesulphonyl-2-pyrazoline (92)*.

To a solution of *trans*-benzalpinacolone oxide (1 g, 5 mmole) in a chloroform-acetic acid mixture (1:1, 30 ml) was added *p*-toluenesulphonylhydrazine (1 g, 5.4 mmole) and the solution was heated under reflux for 3 hr. The cooled solution was poured into water and additional chloroform (50 ml) was added. After the chloroform layer had been thoroughly washed with water, aqueous sodium bicarbonate, and aqueous sodium hydroxide, it was dried and evaporated. Crystallisation of the residue from ethanol gave 3-tert-*butyl-4-hydroxy-5-phenyl-1-*p-*toluenesulphonyl-2-pyrazoline* (.84 g, 46%) as colourless needles, m.p. 188-189° (Found: C, 64.5; H, 6.7; N, 7.6. $C_{20}H_{24}N_2O_3S$ requires C, 64.5; H, 6.5; N, 7.5%). ν_{max} 3400 cm^{-1} (O-H), n.m.r. ($CDCl_3$): δ1.2 (singlet, 9H, *tert*-butyl group), δ2.2 (broad singlet, 1H, O-H), δ2.4 (singlet, 3H, methyl protons of *p*-toluenesulphonyl group), δ4.4 (doublet, J_C 6.0 Hz, 1H, Ph-C*H*-), δ4.7 (broad doublet, 1H, -C*H*-O), and δ7.3 (multiplet, 9 aromatic protons).

3-tert-*Butyl-5-phenyl-4-tetrahydropyranyloxy-1*-p-*toluenesulphonyl-2-pyrazoline (93)*.

Freshly distilled 2,3-dihydropyran (1 ml) was added to a solution of 3-*tert*-butyl-4-hydroxy-5-phenyl-1-*p*-toluenesulphonyl-2-pyrazoline

(92; .50 g, 1.3 mmole) in chloroform (25 ml) and the mixture was acidified by the addition of three drops of concentrated hydrochloric acid. After the reaction mixture had been kept at room temperature for 3 hr, it was neutralised by the addition of aqueous sodium hydroxide. The organic layer was then separated, washed several times with water, dried, and evaporated. Crystallisation of the residue from petroleum ether (b.p. 40-60°)-ether gave 3-tert-*butyl-5-phenyl-4-tetrahydropyranyloxy-1*-p-*toluenesulphonyl-2-pyrazoline* (.49 g, 86%) as colourless prisms, m.p. 129.5-133.0° (Found: C, 65.4; H, 7.1; N, 6.3. $C_{25}H_{32}N_2O_4S$ requires C, 65.7; H, 7.1; N, 6.1%), n.m.r. ($CDCl_3$): δ1.2 (two singlets, 9H, *tert*-butyl group), δ1.4 (multiplet, 6 methylene protons), δ2.4 (singlet, 3H, methyl protons of *p*-toluenesulphonyl group), δ3.5 (multiplet, 2H, $-C\underline{H}_2-O$), δ4.5 (singlet, 1H, $-O-C\underline{H}-O$), δ4.35 (doublet, J_C 2.7 Hz, 1H, $Ph-C\underline{H}-$), δ4.5 (doublet, J_C 6.5 Hz, 1H, $Ph-C\underline{H}-$), δ4.7 (doublet, J_C 7.0 Hz, 1H, $-C\underline{H}-O-$), δ4.9 (doublet, J_C 3.0 Hz, 1H, $-C\underline{H}-O-$), and δ7.3 (multiplet, 9 aromatic protons). Integration of the signals at δ4.7 and δ4.9 indicated a mixture of diastereoisomers in the ratio of 1:1.

3-tert-*Butyl-5-phenyl-1-tetrahydropyranylpyrazole (94)*.

Sodium hydride (0.15 g, 6.2 mmole) was added to a solution of 3-*tert*-butyl-5-phenyl-4-tetrahydropyranyloxy-1-*p*-toluenesulphonyl-2-pyrazoline (93; 1 g, 2.1 mmole) in anhydrous dimethoxyethane (20 ml) and the solution was heated under reflux for 6 hr. After ethanol

(5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. The ethereal layer was washed with water, dried, and evaporated. Crystallisation of the residue from petroleum ether (b.p. 30-40°) gave 3-tert-butyl-5-phenyl-1-tetrahydropyranylpyrazole (.35 g, 57%) as a colourless solid, m.p. 59-60° (Found: C, 76.2; H, 8.4; N, 9.8. $C_{18}H_{24}N_2O$ requires C, 76.0; H, 8.5; N, 9.9%), n.m.r. (CCl_4): δ1.25 (singlet, 9H, tert-butyl group), δ1.4 (multiplet, 6 methylene protons), δ3.4-4.2 (complex multiplet, 2H, -O-C$\underline{H}_2$), δ5.0 (doublet of doublets, J_C 3.0 Hz, N-C$\underline{H}$-O), δ6.3 (singlet, 1H, proton at the 4-position), and δ7.3 (multiplet, 5 aromatic protons).

4-Benzyloxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (96).

4-Hydroxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (34; 1 g, 2.6 mmole) was added to a suspension of sodium hydride (.08 g, 3.3 mmole) in anhydrous dimethoxyethane (20 ml) at -30° and the mixture was stirred at this temperature for 5 min. Benzyl bromide (1 ml, 8.5 mmole) was then added and the mixture was stirred at room temperature for 12 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. The ethereal layer was washed with water, dried, and evaporated. Crystallisation of the residue from hexane-ether gave 4-benzyloxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (.88 g, 71%) as colourless prisms, m.p. 124.5-125.5° (Found: C, 71.8; H, 5.4; N, 5.7. $C_{29}H_{26}N_2O_3S$

requires C, 72.1; H, 5.4; N, 5.8%), n.m.r. ($CCl_4/CDCl_3$): δ2.3 (singlet, 3H, methyl protons of p-toluenesulphonyl group), δ4.2 (doublet, J_C 3.0 Hz, 1H, Ph-C<u>H</u>-), δ4.95 (singlet, 1H, -C<u>H</u>-O-), δ7.5 (multiplet, 14 aromatic protons).

<u>4-Methoxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (97).</u>

4-Hydroxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (34; 1 g, 2.6 mmole) was added to a suspension of sodium hydride (.08 g, 3.3 mmole) in anhydrous dimethoxyethane (20 ml) at -30° and the mixture was stirred at this temperature for 5 min. Methyl iodide (5 ml, .08 mmole) was then added and the mixture was stirred at room temperature for 12 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. The ethereal layer was washed with water, dried, and evaporated. Crystallisation of the residue from hexane-ether gave <u>4-methoxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline</u> (.67 g, 64%) as colourless prisms, m.p. 127-128° (Found: C, 68.1; H, 5.7; N, 7.1. $C_{23}H_{22}N_2O_3S$ requires C, 68.0; H, 5.5; N, 7.0%), n.m.r. (CCl_4): δ2.3 (singlet, 3H, methyl protons of p-toluenesulphonyl group), δ3.0 (singlet, 3H, -O-C<u>H</u>$_3$), δ4.85 (broad singlet, 2H, -C<u>H</u>-O and Ph-C<u>H</u>-), δ7.5 (multiplet, 14 aromatic protons).

Protonation of the anion of 4-hydroxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (34), at -30°.

Sodium hydride (.08 g, 3.3 mmole) was added to a solution of 4-hydroxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (34, 1 g, 2.6 mmole) in dimethoxyethane (40 ml) at -30° and the mixture was stirred at this temperature for 1 hr. Acetic acid (2 ml) was then added and the mixture was stirred at -30° for 3 hr. Ethanol (5 ml) was then carefully added and the resulting solution was poured into water and the organic material was extracted into ether. After the ethereal layer had been washed with sodium bicarbonate, it was dried and an equal volume of petroleum ether (b.p. 40-60°) was added. The solution was then kept at 0° for several days. The product deposited was identified as 4-hydroxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (.83 g, 83%) m.p. and mixed m.p. 224-225°. The infrared spectrum was identical with that of an authentic sample.

4-Acetoxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (103).

(a) Acetic anhydride (1 ml) was added to a solution of 4-hydroxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (34; .20 g, .52 mmole) in pyridine (4 ml) and the reaction mixture was kept at room temperature for 24 hr. After the reaction mixture had been diluted with water, the organic material was extracted into ether. The ether extract was then washed with dilute hydrochloric acid, and water. The dried ethereal layer was evaporated to yield an oil, which was crystallised from hexane-ether to yield *4-acetoxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline* (.20 g, 86%) as colourless needles, m.p. 166-167° (Found: C, 66.4; H, 4.8; N, 6.3. $C_{24}H_{26}N_2O_4S$ requires C, 66.4; H, 5.1; N, 6.5%). ν_{max} 1735 cm^{-1} (O-CO-CH_3), n.m.r. (CCl_4): δ1.80 (singlet, 3H, -O-CO-C$\underline{H}_3$), δ2.35 (singlet, 3H, methyl protons of *p*-toluenesulphonyl group), δ5.05 (doublet, J_C 2.0 Hz, Ph-C$\underline{H}$-), δ6.05 (doublet, J_C 2.0 Hz, -C$\underline{H}$-O-), and δ7.5 (multiplet, 14 aromatic protons).

(b) Sodium hydride (.08 g, 3.3 mmole) was added to a solution of 4-hydroxy-3,5-diphenyl-1-*p*-toluenesulphonyl-2-pyrazoline (34; 1 g, 2.6 mmole) in dimethoxyethane (40 ml) at -30° and the mixture was stirred at this temperature for 1 hr. Acetic anhydride (2 ml) was then added and the mixture was stirred at -30° for 3 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. The ethereal layer was washed thoroughly with water, dried, and evaporated. Recrystallisation of the residue from hexane-ether gave 4-acetoxy-3,5-diphenyl-1-*p*-toluenesulphonyl-2-pyrazoline (.19 g, 85%), m.p. and mixed m.p. 166-167°. The infrared spectrum was identical with that of an authentic sample.

4-Hydroxy-1-methyl-3,5-diphenyl-2-pyrazoline (105).

A mixture of methylhydrazine (3 ml, 5.1 mmole) and benzalacetophenone oxide (1 g, 4.5 mmole) in acidic ethanol (1% H_2SO_4, 40 ml) was heated under reflux for 30 min. The mixture was then poured into water and the organic material was extracted into ether. After the ethereal layer had been washed with water, and aqueous sodium hydroxide, it was dried and evaporated. After the residue had been dissolved in a petroleum ether (b.p. 40-60°)-ether mixture (1:1, 20 ml) it was cooled in a dry ice-acetone bath. After the mixture had been scratched, a solid was precipitated. Recrystallisation of the solid from petroleum ether (b.p. 40-60°) gave *4-hydroxy-1-methyl-3,5-diphenyl-2-pyrazoline* (.43 g, 38%) as a colourless solid, m.p. 109-110° (Found: C, 76.2; H, 6.5; N, 11.3. $C_{16}H_{16}N_2O$ requires C, 76.2; H, 6.4; N, 11.1%). ν_{max} 3200 cm^{-1} (O-H), n.m.r. ($CDCl_3$): δ2.80 (broad singlet, 1H, -O-$\underline{H}$), δ2.83 (singlet, 3H, -N-C$\underline{H}_3$), δ4.0 (doublet, J_C 5.0 Hz, 1H, Ph-C$\underline{H}$-), δ5.2 (broad doublet, J_C 4.0 Hz, 1H, -C$\underline{H}$-O-), and δ7.3 (multiplet, 10 aromatic protons).

Attempted preparation of 1-methyl-3,5-diphenyl-4-p-toluenesulphonyloxy-2-pyrazoline (104).

p-Toluenesulphonyl chloride (.48 g, 2.5 mmole) was added to a solution of 4-hydroxy-1-methyl-3,5-diphenyl-2-pyrazoline (105; .50 g, 1.9 mmole) in pyridine (10 ml) at 0° and the reaction mixture was kept at room temperature for 24 hr. After the reaction mixture had been diluted with water, the organic material was extracted into ether. The ethereal layer was washed with dilute hydrochloric acid and water. After the ethereal solution had been dried, the solvent was evaporated at room temperature *in vacuo* to yield a yellow oil. Crystallisation of the oil from petroleum ether (b.p. 30-40°) gave 1-methyl-3,5-diphenylpyrazole (.35 g, 74%), m.p. 67-68° (lit.[70] 69°). When the reaction mixture was kept at 0° for 24 hr, starting material was recovered.

Attempted preparation of 4-acetoxy-1-methyl-3,5-diphenyl-2-pyrazoline.

Acetic anhydride (1 ml) was added to a solution of 4-hydroxy-1-methyl-3,5-diphenyl-2-pyrazoline (105; .50 g, 1.9 mmole) in pyridine (5 ml) and the reaction mixture was kept at room temperature for 24 hr. After the reaction mixture had been diluted with water, the organic material was extracted into ether. After the ether extract had been washed with water, it was dried and evaporated. An infrared spectrum of the resultant oil showed absorption at 1750 cm^{-1}. Crystallisation of the oil from petroleum ether (b.p. 38-40°) gave 1-methyl-3,5-diphenylpyrazole (.32 g, 68%), m.p. 67-68° (lit.[70] 69°). A similar result was obtained using acetyl chloride in pyridine.

1-Benzyl-3,5-diphenylpyrazole (95).

(a) Sodium hydride (.08 g, 3.3 mmole) was added to a solution of 4-hydroxy-3,5-diphenyl-1-*p*-toluenesulphonyl-2-pyrazoline (34; 1 g, 2.6 mmole) in anhydrous dimethoxyethane (20 ml) and the mixture was stirred at room temperature for 2 min. Benzyl chloride (1 ml, 8.7 mmole) was then added and the mixture was stirred at room temperature for 12 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. The ethereal layer was washed with water, dried, and evaporated. Crystallisation of the residue from hexane gave 1-benzyl-3,5-diphenylpyrazole (.62 g, 78%), m.p. 112-113° (lit.[69] 113-114°), n.m.r. ($CDCl_3$): δ5.3 (singlet, 2H, $-O-C\underline{H}_2-Ph$), δ6.6 (singlet, 1H, proton at the 4-position), and δ7.3 (multiplet, 15 aromatic protons).

(b) Sodium hydride (0.15 g, 6.2 mmole) was added to a solution of 4-benzyloxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (96; 1 g, 2.1 mmole) in anhydrous dimethoxyethane (20 ml) and the solution was heated under reflux for 6 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. After the ether extract had been washed with water, it was dried and evaporated. Crystallisation of the residue from hexane-benzene gave 1-benzyl-3,5-diphenylpyrazole (.44 g, 48%) m.p. 112-113° (lit.[69] 113-114°).

1-Methyl-3,5-diphenylpyrazole (106).

Sodium hydride (0.15 g, 6.2 mmole) was added to a solution of 4-methoxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (97; 1 g, 2.4 mmole) in anhydrous dimethoxyethane (20 ml) and the solution was heated under reflux for 6 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. The ethereal layer was washed with water, dried, and evaporated. Crystallisation of the residue from hexane gave 1-methyl-3,5-diphenylpyrazole (.45 g, 76%) m.p. 68-69° (lit.[70] 69°), n.m.r. ($CDCl_3$): δ3.9 (singlet, 3H, N-$C\underline{H}_3$), δ6.6 (singlet, 1H, proton at the 4-position), and δ7.4 (multiplet, 10 aromatic protons).

4-Hydroxy-3,5-diphenylpyrazole (109).

4-Hydroxy-3,5-diphenylpyrazole, m.p. 234-235° (lit.[45] 235°), was prepared by the action of hydrazine hydrate on diphenyltriketone.[45]

4-Acetoxy-1-acetyl-3,5-diphenylpyrazole (110).

4-Acetoxy-1-acetyl-3,5-diphenylpyrazole, m.p. 147-148° (lit.[45] 149°) was prepared by the action of an acetic anhydride or acetyl chloride-pyridine mixture on 4-hydroxy-3,5-diphenylpyrazole (109).[45]

1-Acetyl-4-hydroxy-3,5-diphenylpyrazole (111).

Sodium carbonate (1 g, .01 mole) was added to a solution of 4-acetoxy-1-acetyl-3,5-diphenylpyrazole (110; .96 g, 3.0 mmole) in methanol (20 ml) and the mixture was stirred at room temperature for 15 min. The mixture was then poured into water and the organic material was extracted into ether. After the ethereal layer had been washed with water, it was dried, and evaporated. Recrystallisation of the residue from cyclohexane gave 1-acetyl-4-hydroxy-3,5-diphenylpyrazole

(.70 g, 83%) as colourless plates, m.p. 180-181° (Found: C, 73.4; H, 5.2; N, 10.3. $C_{17}H_{14}N_2O$ requires C, 73.4; H, 5.1; N, 10.1%). ν_{max} 3180 and 1740 cm^{-1} (O-H and N-CO-CH_3 respectively), n.m.r. ($CDCl_3$): δ2.2 (singlet, 3H, -N-CO-C<u>H</u>$_3$), δ7.4 (multiplet, 10 aromatic protons), and δ9.2 (singlet, 1H -O-<u>H</u>).

<u>1-Acetyl-4-methoxy-3,5-diphenylpyrazole (112)</u>.

Sodium hydride (.03 g, 1.2 mmole) was added to a solution of 1-acetyl-4-hydroxy-3,5-diphenylpyrazole (111, .25 g, .9 mmole) in anhydrous dimethoxyethane (10 ml) and the mixture was then stirred at room temperature for 1 min. Methyl iodide (3 ml, .05 mmole) was then added and the mixture was stirred at room temperature for 3 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. The ethereal layer was washed with water, dried, and evaporated. Crystallisation of the residue from hexane afforded <u>1-acetyl-4-methoxy-3,5-diphenylpyrazole</u> (.24 g, 81%) as colourless needles, m.p. 109-110° (Found: C, 73.7; H, 5.4; N, 9.6. $C_{18}H_{16}N_2O$ requires C, 73.9; H, 5.5; N, 9.6%). ν_{max} 1750 cm^{-1} (N-CO-CH_3), n.m.r. ($CCl_4/CDCl_3$): δ2.1 (singlet, 3H, N-CO-C<u>H</u>$_3$), δ3.8 (singlet, 3H, -O-C<u>H</u>$_3$), and δ7.4 (multiplet, 10 aromatic protons).

4-Methoxy-3,5-diphenylpyrazole (107).

Sodium carbonate (1 g, .10 mmole) was added to a solution of 1-acetyl-4-methoxy-3,5-diphenylpyrazole (112; .70 g, 2.4 mmole) in methanol (15 ml) and the mixture was stirred under an atmosphere of nitrogen for 3 hr. The mixture was then poured into water and the organic material was extracted into ether. After the ether extract had been washed with water, it was dried, and evaporated. Recrystallisation of the residue from petroleum ether (b.p. 30-40°) gave 4-methoxy-3,5-diphenylpyrazole (.51 g, 83%) as a colourless solid, m.p. 176-177° (Found: C, 76.8; H, 5.9; N, 11.1. $C_{16}H_{14}N_2O$ requires C, 76.8; H, 5.6; N, 11.2%), n.m.r. ($CDCl_3$): δ3.8 (singlet, 3H, $-O-C\underline{H}_3$) and δ7.6 (multiplet, 10 aromatic protons). The hydrogen at the 1-position could not be detected.

Action of sodium hydride on 4-methoxy-3,5-diphenylpyrazole (107).

Sodium hydride (0.15 g, 6.2 mmole) was added to a solution of 4-methoxy-3,5-diphenylpyrazole (107; 1 g, 4.0 mmole) in anhydrous dimethoxyethane (25 ml) and the mixture was heated under reflux in an atmosphere of nitrogen for 6 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. The ethereal layer was washed with water, dried, and evaporated. Crystallisation of the residue from petroleum ether (b.p. 30-40°) gave a nearly quantitative yield of starting material, m.p. and mixed m.p. 176-177°. The infrared spectrum was identical with that of an authentic sample.

Work described in Chapter III

(part b).

Mesityl oxide epoxide.

Mesityl oxide epoxide, b.p. 59-60°/17 mm (lit.[72] 61-62°/20 mm), was prepared by the action of alkaline hydrogen peroxide on mesityl oxide.[72]

4-Hydroxy-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (114).

To a solution of mesityl oxide epoxide (25 g, .22 mole) in a chloroform-acetic acid mixture (1:1, 200 ml) was added p-toluenesulphonylhydrazine (43 g, .23 mole) and the solution was heated under reflux for 3 hr. The cooled solution was poured into water and the chloroform layer separated. After the chloroform layer had been thoroughly washed with water, aqueous sodium bicarbonate, and aqueous sodium hydroxide, it was dried and evaporated. Crystallisation of the residue from hexane-carbon tetrachloride gave 4-hydroxy-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (28.3 g, 46%) as a colourless solid, m.p. 129.5-130.5° (Found: C, 55.2; H, 6.5; N, 9.8. $C_{13}H_{18}N_2O_3S$ requires C, 55.3; H, 6.4; N, 9.9%). ν_{max} 3300 cm^{-1} (O-H), n.m.r. ($CDCl_3/CCl_4$): δ1.32, 1.45 (two singlets, 6 gem-dimethyl protons), δ2.0 (singlet, 3H, N=C-$\underline{CH_3}$), δ2.4 (singlet, 3H, methyl protons of p-toluenesulphonyl group), δ4.5 (singlet, 1H, -$\underline{CH}$-O), δ3.2 (broad singlet, 1H, -O-$\underline{H}$), and δ7.4, 7.8 (AB quartet, J_{AB} 8.5 Hz, 4H, aromatic protons of p-toluenesulphonyl group).

4-Acetoxy-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (115).

Acetic anhydride (1 ml) was added to a solution of 4-hydroxy-3,5,5-trimethyl-1-*p*-toluenesulphonyl-2-pyrazoline (114, 0.10 g, 0.35 mmole) in pyridine (3 ml) and the reaction mixture was kept at room temperature for 24 hr. After the reaction mixture had been diluted with water, the organic material was extracted into ether and the extract was washed with dilute hydrochloric acid and dried. Evaporation of the solvent gave an oil which was crystallised from ethanol to give 4-acetoxy-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (0.09 g, 83%) as colourless needles, m.p. 102.5-103.5° (Found: C, 55.4; H, 6.3; N, 8.5. $C_{15}H_{20}N_2O_4S$ requires C, 55.6; H, 6.2; N, 8.6%). ν_{max} 1750 cm^{-1} ($O-CO-CH_3$), n.m.r. ($CDCl_3$): δ1.47, 1.45 (two singlets, 6 *gem*-dimethyl protons), δ2.0 (singlet, 3H, $N=C-C\underline{H}_3$), δ2.15 (singlet, 3H, $-O-CO-C\underline{H}_3$), δ2.4 (singlet, 3H, methyl protons of *p*-toluenesulphonyl group), δ5.45 (singlet, 1H, $-C\underline{H}-O$), and δ7.3, 7.8 (AB quartet, J_{AB} 9.0 Hz, 4H, aromatic protons of *p*-toluenesulphonyl group).

4-Keto-3,5,5'-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (116).

Jones' reagent[73] (1.1 equivalents) was added to a solution of 4-hydroxy-3,5,5-trimethyl-1-*p*-toluenesulphonyl-2-pyrazoline (114; 0.28 g, 1 mmole) in purified acetone (10 ml) and the reaction mixture was stirred at room temperature, in an atmosphere of nitrogen, for 5 min. After the reaction mixture had been diluted with water, the organic material was extracted into ether. The ether extract was dried and the solvent was evaporated to yield a solid. Recrystallisation of the solid from hexane gave 4-keto-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (0.26 g, 91%) as a colourless solid, m.p. 98-99° (Found: C, 55.8; H, 5.7; N, 10.0. $C_{13}H_{16}N_2O_3S$ requires C, 55.7; H, 5.8; N, 10.0%). λ_{max} (ethanol) 232 (ε 11,200), and 304 (ε 6,900) nm; ν_{max} 1720 cm^{-1} (C=O), n.m.r. ($CDCl_3$): δ1.5 (singlet, 6 gem-dimethyl protons), δ2.2 (singlet, 3H, N=C-CH_3), δ2.4 (singlet, 3H, methyl protons of p-toluenesulphonyl group), and δ7.3, 7.8 (AB quartet, J_{AB} 8.0 Hz, 4H, aromatic protons of p-toluenesulphonyl group).

Mesityl oxide p-toluenesulphonylhydrazone.

Mesityl oxide p-toluenesulphonylhydrazone, m.p. 106-111° (lit.[12] 105-110°), was prepared by the addition of p-toluenesulphonylhydrazine to a solution of mesityl oxide in methanol.

Separation of the syn- and anti-isomers of mesityl oxide p-toluenesulphonylhydrazone.

The separation of the syn- and anti-isomers of mesityl oxide p-toluenesulphonylhydrazone, m.p. 121-123° (lit.[12] 122-123°) and m.p. 106-110° (lit.[12] 106-110°) was carried out according to the method of Closs.[12]

Attempted epoxidation of the syn- and anti-isomers of mesityl oxide p-toluenesulphonylhydrazone.

(a) m-Chloroperbenzoic acid (.32 g, 1.9 mmole) was added to a solution of the higher melting point isomer of mesityl oxide p-toluenesulphonylhydrazone (.50 g, 1.9 mmole) in chloroform (15 ml), and the reaction mixture was kept at room temperature for 24 hr. Additional chloroform (30 ml) was then added and the reaction mixture was diluted with water. After the chloroform layer had been washed with aqueous sodium bicarbonate, it was dried and evaporated. Crystallisation of the residue from ethanol gave a nearly quantitative yield of starting material.

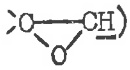
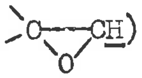
A similar result was obtained using the lower melting point isomer.

(b) Aqueous sodium hydroxide (8%, 1 ml) and 30% hydrogen peroxide (1.5 ml) were added to a solution of the higher melting point isomer of mesityl oxide p-toluenesulphonylhydrazone (.50 g, 1.9 mmole) in methanol (15 ml) and the reaction mixture was stirred at room temperature for 12 hr. Further aqueous sodium hydroxide (8%, 1 ml) and 30% hydrogen peroxide (1.5 ml) were added to the reaction mixture, and the reaction mixture was stirred at room temperature for an additional 12 hr. After the reaction mixture had been diluted with water, the organic material was extracted into ether. The ether extract was washed with aqueous sodium thiosulphate solution, dried, and evaporated.

The residue (.47 g, 94%), an oil, could not be induced to crystallise. The infrared spectrum of the residue was identical with that of the starting material.

A similar result was obtained using the lower melting point isomer.

Syn- (117) and anti-isomers (118) of the *p*-toluenesulphonylhydrazone of mesityl oxide epoxide.

p-Toluenesulphonylhydrazine (1.56 g, 8.4 mmole) was added to a solution of mesityl oxide epoxide (1 g, 8.7 mmole) in chloroform (20 ml) and the reaction mixture was placed over calcium chloride. After the reaction mixture had been kept at room temperature for 24 hr, the calcium chloride was removed by filtration and the solvent was removed *in vacuo* at 0°. The residue was dissolved in the minimum amount of ether and was set aside at 0°. Recrystallisation of the precipitate from ether gave syn-*mesityl oxide epoxide p-toluenesulphonylhydrazone* (.53 g, 21%) as a colourless crystalline solid, m.p. 115-116° (Found: C, 55.5; H, 6.6; N, 10.2. $C_{13}H_{18}N_2O_3S$ requires C, 55.3; H, 6.4; N, 10.0%). ν_{max} 3150 cm^{-1} (N-H), n.m.r. (CCl_4): δ1.05, 1.40 (two singlets, 6 *gem*-dimethyl protons), δ1.80 (singlet, 3H, N=C-$C\underline{H}_3$), δ2.40 (singlet, 3H, methyl protons of *p*-toluenesulphonyl group), δ3.35 (singlet, 1H, ) and δ7.2, 7.8 (AB quartet, J_{AB} 8.0 Hz, 4 aromatic protons of *p*-toluenesulphonyl group), and δ9.6 (singlet, 1H, N-H). The mother liquor was then diluted with an equal volume of petroleum ether (b.p. 30-40°) and the solution was set aside at 0°. The resulting precipitate was recrystallised from petroleum ether (b.p. 30-40°) to afford anti-*mesityl oxide epoxide*-p-*toluenesulphonylhydrazone* (.41 g, 16%) as a colourless crystalline solid, m.p. 96-97° (Found: C, 55.4; H, 6.4; N, 10.2. $C_{13}H_{18}N_2O_3S$ requires C, 55.3; H, 6.4; N, 10.0%). ν_{max} 3150 cm^{-1} (N-H), n.m.r. (CCl_4): δ1.05, 1.35 (two singlets, 6 *gem*-dimethyl protons), δ1.80 (singlet, 3H, N=C-CH_3), δ2.4 (singlet, 3H, methyl protons of *p*-toluenesulphonyl group), δ3.20 (singlet, 1H, ), δ7.2, 7.7 (AB quartet, J_{AB} 8.0 Hz, 4 aromatic protons of *p*-toluenesulphonyl group), and δ9.1 (singlet, 1H, N-H).

Action of acetic acid on syn- *(117) and* anti-*(118) mesityl oxide epoxide*-p-*toluenesulphonylhydrazone.*

syn-Mesityl oxide epoxide-*p*-toluenesulphonylhydrazone (117; .40 g, 1.4 mmole) was added to an acetic acid-chloroform mixture (1:1, 20 ml) and the solution was heated under reflux for 3 hr. After the reaction mixture had been diluted with water, additional chloroform (30 ml) was added. After the chloform extract had been thoroughly washed with water, aqueous sodium bicarbonate, and aqueous sodium hydroxide, it was dried and evaporated. Recrystallisation of the residue gave 4-hydroxy-3,5,5-trimethyl-1-*p*-toluenesulphonyl-2-pyrazoline (.28 g, 71%), m.p. and mixed m.p. 129.5-130.5°. The infrared spectrum was identical with that of an authentic sample.

When the *anti*-isomer (118) of mesityl oxide epoxide-*p*-toluenesulphonylhydrazone was subjected to similar conditions a low yield (ca. 5%) of 4-hydroxy-3,5,5'-trimethyl-1-*p*-toluenesulphonyl-2-pyrazoline, m.p. and mixed m.p. 129.5-130.5°, was obtained.

3,4,5-Trimethyl-1-p-toluenesulphonylpyrazole (121).

A couple of drops of boron trifluoride diethyl etherate were added to a solution of the *syn*-isomer of mesityl oxide epoxide-*p*-toluenesulphonylhydrazone (117; .20 g, 0.71 mmole) in ether (10 ml) and the reaction mixture was kept at room temperature for 12 hr. After the reaction mixture had been diluted with water, the organic material was extracted into ether. After the ether extract had been washed with water, it was dried and evaporated. Recrystallisation of the residue from ethanol gave *3,4,5-trimethyl-1-p-toluenesulphonylpyrazole* (.14 g, 77%) as colourless plates, m.p. 145.5-146.5° (Found: C, 59.0; H, 6.1; N, 10.5. $C_{13}H_{16}N_2O_2S$ requires C, 69.1; H, 6.1; N, 10.6%), n.m.r. ($CDCl_3$): δ1.8, 2.05 (two singlets, 6H, two methyl groups attached to ring), δ2.4 (two overlapping singlets, 6H, methyl group attached to ring and methyl group of *p*-toluenesulphonyl group), and δ7.3, 7.7 (AB quartet, J_{AB} 8.0 Hz, aromatic protons of *p*-toluenesulphonyl group).

Action of boron trifluoride diethyl etherate on 4-hydroxy-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (114).

A couple of drops of boron trifluoride diethyl etherate were added to a solution of 4-hydroxy-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (114; .10 g, .35 mmole) in ether (10 ml) and the reaction mixture was kept at room temperature for 24 hr. After the reaction mixture had been diluted with water, the organic material was extracted into ether. After the ether extract had been washed with sodium bicarbonate and water, it was dried, and evaporated. Recrystallisation of the residue from hexane-carbon tetrachloride gave a quantitative yield of starting material, m.p. and mixed m.p. 129.5-130.5°.

3,5,5-Trimethyl-4-tetrahydropyranyloxy-1-p-toluenesulphonyl-2-pyrazoline (126).

Freshly distilled 2,3-dihydropyran (6 ml) was added to a solution of 4-hydroxy-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (114; 4 g, 14 mmole) in chloroform (15 ml) and the mixture was acidified by the addition of three drops of concentrated hydrochloride acid. After the reaction mixture had been kept at room temperature for 2 hr, it was neutralised by the addition of aqueous sodium hydroxide. Additional chloroform was then added and the chloroform extract was washed thoroughly with water and dried. Evaporation of the solvent gave an oil which was dissolved in carbon tetrachloride and set aside at 0° for several days. Recrystallisation of the precipitate from hexane-carbon tetrachloride gave 3,5,5-trimethyl-4-tetrahydropyranyloxy-1-p-toluenesulphonyl-2-pyrazoline (4.8 g, 92%) as colourless prisms, m.p. 95-99° (Found: C, 58.9; H, 7.1; N, 7.7. $C_{18}H_{26}N_2O_4S$ requires C, 59.0; H, 7.2;

N, 7.6%), n.m.r. ($CDCl_3$): δ1.3, 1.35, 1.45, 1.6 (singlets, 6 gem-dimethyl protons), δ1.5 (broad multiplet, 6 methylene protons), δ2.0 (two singlets, 3H, $N{=}C{-}C\underline{H}_3$), δ2.4 (singlet, 3H, methyl protons of p-toluenesulphonyl group), δ3.65 (broad multiplet, 2H, $-O-C\underline{H}_2$), δ4.3 (singlet, 1H, $-C\underline{H}-O$), δ4.55 (broad singlet, 1H, $O-C\underline{H}-O$), and δ7.3, 7.8 (AB quartet, J_{AB} 8.0 Hz, 4H, aromatic protons of p-toluenesulphonyl group). Integration of the signals at δ2.0 indicated a mixture of diastereoisomers in the ratio of 1:1.

4-Methoxy-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (124).

Sodium hydride (.60 g, 25 mmole) was added to a solution of 4-hydroxy-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (114; 6 g, 21 mmole) in anhydrous dimethoxyethane (50 ml) and the reaction mixture was stirred at room temperature for 5 min. Methyl iodide (10 ml) was then added and the reaction mixture was stirred at room temperature for 6 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. After the ether extract had been washed with water, it was dried and evaporated. Crystallisation of the residue from hexane-benzene gave 4-methoxy-3,5,5-methyl-1-p-toluenesulphonyl-2-pyrazoline (4.9 g, 63%) as chunky crystals, m.p. 82-83° (Found: C, 56.9; H, 7.0; N, 9.7. $C_{14}H_{20}N_2O_3S$ requires C, 56.7; H, 6.8; N, 9.5%), n.m.r. ($CDCl_3/CCl_4$): δ1.35, 1.63 (two singlets, 6 gem-dimethyl protons), δ2.0 (singlet, 3H, N=C-C$\underline{H}_3$), δ2.45 (singlet, 3H, methyl protons of p-toluenesulphonyl group), δ3.45 (singlet, 3H, -O-C$\underline{H}_3$), δ3.95 (singlet, 1H, -C$\underline{H}$-O), and δ7.3, 7.8 (AB quartet, J_{AB} 8.0 Hz, 4H, aromatic protons of p-toluenesulphonyl group).

4-Benzyloxy-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (125).

Sodium hydride (.03 g, 1.4 mmole) was added to a solution of 4-hydroxy-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (114; .28 g, 1.0 mmole) in anhydrous dimethoxyethane (15 ml) and the reaction mixture was stirred at room temperature for 5 min. Benzyl bromide (.5 ml) was then added and the reaction mixture was stirred at room temperature for 12 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. After the ether extract had been washed with water, it was dried, and evaporated. Crystallisation of the residue from hexane-benzene gave 4-benzyloxy-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (0.18 g, 48%) as a colourless solid, m.p. 114.5-115.5° (Found: C, 64.5; H, 6.5; N, 7.6. $C_{20}H_{24}N_2O_3S$ requires C, 64.5; H, 6.5; N, 7.5%), n.m.r. ($CDCl_3$): δ1.32, 1.55 (singlets, 6 gem-dimethyl protons), δ1.92 (singlet, 3H, -N=C-C$\underline{H}_3$), δ2.4 (singlet, 3H, methyl protons of p-toluenesulphonyl group), δ4.15 (singlet, 1H, -C$\underline{H}$-O), δ4.6 (singlet, 2H, -O-C$\underline{H}_2$-Ph), δ7.3 (multiplet, 5 aromatic protons), and δ7.3, 7.8 (AB quartet, J_{AB} 8.0 Hz, 4H, aromatic protons of p-toluenesulphonyl group).

4-Methoxy-5,5-dimethyl-3-methylene-1-pyrazoline (132).

Sodium hydride (.5 g, 21 mmole) was added to a solution of 4-methoxy-3,5,5-trimethyl-1-p-toluenesulphonyl-2-pyrazoline (124; 3.8 g, 13 mmole) in dimethylsulphoxide (30 ml) and the reaction mixture was stirred in an atmosphere of nitrogen, at room temperature for 12 hr. After the mixture had been diluted with a brine solution, the organic material was extracted into ether. The ether extract was separated, dried, and concentrated to give a residue which was chromatographed on neutral alumina. Elution with light petroleum (b.p. 40-60°) containing ether (1%, 200 ml) gave only mineral oil. Elution with ether gave 4-methoxy-5,5-dimethyl-3-methylene-1-pyrazoline (1.2 g, 62%) as a colourless liquid. An analytical sample was prepared by evaporative distillation, 85°/12 mm (Found: C, 60.2; H, 8.6; N, 20.3. $C_7H_{12}N_2O$ requires C, 60.0; H, 8.6; N, 20.0). λ_{max} (ethanol) 243 (ε 1,875) and 345 (ε 145) nm. ν_{max} 3090, 1640, and 930 cm^{-1} ($C=CH_2$), n.m.r. (CCl_4): δ1.3 (singlet, 6 gem-dimethyl protons), δ3.35 (singlet, 3H, $-OC\underline{H}_3$), δ4.5 (doublet, J_C 1.0 Hz, 2H, $C=C\underline{H}_2$), and δ6.55 (triplet, J_C 1.7, 1.9 Hz, 1H, $-C\underline{H}-O$).

Attempted isomerisation of 4-methoxy-5,5-dimethyl-3-methylene-1-pyrazoline (132) to 4-methoxy-3,5,5'-trimethyl-3H-pyrazole (135).

Freshly sublimed potassium tert-butoxide (.008 g, .07 mmole) was added to a solution of 4-methoxy-5,5-dimethyl-3-methylene-1-pyrazoline

(.20 g, 1.3 mmole) in dimethylsulphoxide (20 ml) and the reaction mixture was heated in an atmosphere of nitrogen, at 60° for 6 hr. After the reaction mixture had been diluted with brine solution, the organic material was extracted into ether. The ether extract was separated, dried, and the solvent evaporated to give a pale yellow oil (.15 g, 77%) which was identified as starting material by comparison of the infrared spectrum with that of the starting material.

Work described in Chapter III.

(part c)

Attempted synthesis of 4-hydroxy-5-methyl-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (136) by the action of p-toluenesulphonylhydrazine on trans-dypnone oxide.

In a typical experiment a mixture of p-toluenesulphonylhydrazine (2 g, 11 mmole) and trans-dypnone oxide (2.2 g, 9 mmole) in acidic methanol (1% H_2SO_4, 30 ml) was heated under reflux for 30 min. On cooling, the reaction mixture was poured into water and the organic material was extracted into ether. After the organic layer had been washed with aqueous sodium hydroxide it was dried, and evaporated. The residue, a gum, was chromatographed on silica gel. After preliminary spectral studies the gums which were eluted from the column were not further investigated. A similar mixture of gums was obtained on using acetic acid in chloroform (1:1), 1% p-toluenesulphonic acid, or 1% perchloric acid in methanol as the solvent.

Attempted preparation of the p-toluenesulphonylhydrazone of trans-dypnone oxide.

p-Toluenesulphonylhydrazine (2 g, 11 mmole) was added to a solution of trans-dypnone oxide (2.2 g, 9 mmole) in methanol (30 ml) and the reaction mixture was kept at room temperature for 24 hr. After the mixture had been diluted with water the organic material was extracted into ether. After the ether extract had been washed with dilute acetic acid it was dried, and evaporated. Crystallisation of the residue from methanol-water gave a nearly quantitative yield of starting material, m.p. and mixed m.p. 91-92°.

A similar result was obtained when the above mixture was heated under reflux for 6 hr or when the above mixture was acidified by the addition of a couple of drops of acetic acid and the reaction mixture kept at room temperature for 24 hr.

Syn- and anti-isomers of the p-toluenesulphonylhydrazone of dypnone.

p-Toluenesulphonylhydrazine (2 g, 11 mmole) was added to a solution of dypnone (1.8 g, 8 mmole) in methanol (40 ml) and the reaction mixture was kept at room temperature for 48 hr. After this time the reaction mixture was concentrated to 20 ml and set aside at 0° for 24 hr. The crystals which were deposited were removed by filtration and were recrystallised from methanol to give the higher melting point isomer of the p-toluenesulphonylhydrazone of dypnone (.343 g,11%) as colourless crystals, m.p. 151-152° (Found: C, 70.8; H, 5.8; N, 7.2. $C_{23}H_{22}N_2O_2S$ requires C, 70.8; H, 5.7; N, 7.2%). ν_{max} 3300 cm^{-1} (N-H).

The mother liquor was then diluted with water and set aside at 0°. The crystals which were deposited were removed by filtration and were recrystallised from methanol-water to give the lower melting point isomer of the p-toluenesulphonylhydrazone of dypnone (.95 g, 31%) as colourless crystals, m.p. 111-112° (Found: C, 70.5; H, 5.9; N, 7.0. $C_{23}H_{22}N_2O_2S$, requires C, 70.8; H, 7.5; N, 7.2%). ν_{max} 3300 cm^{-1} (N-H).

The n.m.r. spectra were not measured due to the poor solubility of the compounds in normal n.m.r. solvents.

Attempted epoxidation of the *syn*- and *anti*-isomers of the *p*-toluenesulphonylhydrazone of dypnone.

(a) *m*-Chloroperbenzoic acid (.34 g, 2 mmole) was added to a solution of the higher melting point isomer of dypnone *p*-toluenesulphonylhydrazone (.78 g, 2 mmole) in chloroform (50 ml) and the reaction mixture was kept at room temperature for 24 hr. After the reaction mixture had been diluted with water, the organic layer was separated, washed with aqueous sodium bicarbonate, dried, and evaporated. Crystallisation of the residue from ethanol gave a nearly quantitative yield of starting material, m.p. and mixed m.p. 151-152°.

A similar result was obtained using the lower melting point isomer.

(b) Aqueous sodium hydroxide (8%, 2 ml) and 30% hydrogen peroxide (3 ml) were added to a solution of the higher melting point isomer of dypnone p-toluenesulphonylhydrazone (.78 g, 2 mmole) in methanol (20 ml) and the reaction mixture was stirred at room temperature for 12 hr. Further aqueous sodium hydroxide (8%, 2 ml) and 30% hydrogen peroxide (3 ml) were added to the reaction mixture, and the reaction mixture was stirred at room temperature for an additional 12 hr. After the reaction mixture had been diluted with water, the organic material was extracted into ether. The ethereal extract was washed with aqueous sodium thiosulphate solution, dried, and evaporated. Crystallisation of the residue from ethanol gave a nearly quantitative yield of starting material, m.p. and mixed m.p. 151-152°.

A similar result was obtained using the lower melting point isomer.

Reaction of p-toluenesulphonyl chloride with 4-hydroxy-3,5-diphenyl-2-pyrazoline (33).

p-Toluenesulphonyl chloride (.50 g, 2.6 mmole) was added to a solution of 4-hydroxy-3,5-diphenyl-2-pyrazoline (33; .48 g, 2 mmole) in pyridine (15 ml) and the reaction mixture was kept at room temperature for 24 hr. After the reaction mixture had been diluted with water, the organic material was extracted into ether and the extract was washed with dilute hydrochloric acid and dried. Evaporation of the solvent gave an oil which was crystallised from ethanol to give

4-hydroxy-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (.51 g, 63%), m.p. and mixed m.p. 224-225°. The infrared spectrum was identified with that of an authentic sample.

Attempted preparation of 4-hydroxy-5-methyl-3,5-diphenyl-1-p-toluenesulphonyl-2-pyrazoline (136) by the action of p-toluenesulphonyl chloride on 4-hydroxy-5-methyl-3,5-diphenyl-2-pyrazoline (62).

(a) p-Toluenesulphonyl chloride (.50 g, 2.6 mmole) was added to a solution of 4-hydroxy-5-methyl-3,5-diphenyl-2-pyrazoline (62; .5 g, 2 mmole) in pyridine (10 ml) and the reaction mixture was kept at room temperature for 24 hr. After the reaction mixture had been diluted with water, the organic material was extracted into ether and the extract was washed with dilute hydrochloric acid and dried. Evaporation of the solvent gave an oil which was crystallised from ethanol to give starting material (67%), m.p. and mixed m.p. 207-208°.

(b) When the above reaction mixture was heated at 25-30° for 12 hr there was obtained a mixture, chromatography of which gave only gums which after preliminary spectral studies were not further investigated.

(c) When the above reaction mixture was heated at 80° for 15 min there was obtained a mixture which was adsorbed onto a column of silica gel. Elution of the column with chloroform gave a gum which after a preliminary spectral study was not further investigated. Elution of the column with ethanol gave a solid which was purified by sublimation (200°, .1 mm) to give 5-methyl-3,4-diphenylpyrazole (.34 g, 73%) as colourless prisms, m.p. 174-175° (lit.[32] 175°).

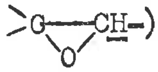
Work described in Chapter III.

(part d)

β,β-Dimethylacrylophenone.

β,β-Dimethylacrylophenone, b.p. 118-120°/12 mm (lit.[74] 104-106°/5mm), was prepared by the method of Smith and Engelhardt.[74]

β,β-Dimethylacrylophenone oxide (142).

To a solution of β,β-dimethylacrylophenone (4 g) in methanol (50 ml) was added 2N sodium hydroxide (6 ml) and 30% hydrogen peroxide (6 ml). The solution was stirred for 12 hr and then diluted with an equal volume of saturated sodium chloride solution. After the solution had been thoroughly extracted with ether the extracts were combined, washed with saturated aqueous sodium thiosulphate solution, and dried. Evaporation of the solvent gave an oil which crystallised from hexane. β,β-Dimethylacrylophenone oxide (3 g, 68%) was obtained as colourless prisms, m.p. 53-54° (Found: C, 74.7; H, 6.8; N, 18.1. $C_{11}H_{12}O_2$ requires C, 74.9; H, 6.9; N, 18.2%). ν_{max} 1705 cm^{-1} (C=O); n.m.r. ($CDCl_3$): δ0.91, 1.3 (two singlets, 6 *gem*-dimethyl protons), δ3.85 (singlet, 1H,  $>C\underset{O}{—}CH-$) and δ7.5 (multiplet, 5 aromatic protons).

4-Hydroxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline (143).

To a solution of β,β-dimethylacrylophenone oxide (142; 2 g, .01 mole) in a chloroform-acetic acid mixture (1:1, 200 ml) was added p-toluenesulphonylhydrazine (2 g, .01 mole) and the solution was heated under reflux for 3 hr. The cooled solution was then poured into water and the chloroform layer was separated, washed thoroughly with water, aqueous sodium bicarbonate, and aqueous sodium hydroxide. Removal of the solvent from the dried chloroform layer gave an oil which was crystallised from a petroleum ether- (b.p. 40-60°) carbon tetrachloride mixture to give 4-hydroxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline (1.1 g, 30%) as a colourless solid, m.p. 173-174° (Found: C, 62.5; H, 5.9; N, 8.2. $C_{18}H_{20}N_2O_3S$ requires C, 62.8; H, 5.9; N, 8.1%). ν_{max} 3480 cm^{-1} (O-H), n.m.r. ($CDCl_3$): δ1.3, 1.6 (two singlets, 6 gem-dimethyl protons), δ2.3 (singlet, 3H, methyl protons of p-toluenesulphonyl group), δ4.6 (singlet, 1H, proton at the 4-position), and δ7.3 (multiplet, 9 aromatic protons). The hydroxylic proton could not be detected.

4-Acetoxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline (144).

Acetic anhydride (2 ml) was added to a solution of 4-hydroxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline (143; .20 g, .6 mmole) in pyridine (10 ml) and the reaction mixture was kept at room temperature for 24 hr. After the reaction mixture had been diluted with water, the organic material was extracted into ether and the extract was washed with dilute hydrochloric acid, and dried. Evaporation of the solvent gave an oil which was crystallised from hexane-methylene chloride to give *4-acetoxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline* (.197 g, 88%) as colourless prisms, m.p. 124-125° (Found: C, 62.4; H, 5.9; N, 7.2. $C_{20}H_{22}N_2O_4S$ requires C, 62.2; H, 5.7; N, 7.3%). ν_{max} 1760 cm^{-1} (O-CO-CH_3), n.m.r. ($CDCl_3$): δ1.4, 1.6 (two singlets, 6 *gem*-dimethyl protons), δ2.1 (singlet, 3H, methyl protons of *p*-toluenesulphonyl group), δ2.4 (singlet, 3H, -O-CO-C$\underline{H}_3$), δ6.0 (singlet, 1H, proton at the 4-position), and δ7.3 (multiplet, 9 aromatic protons).

5,5-Dimethyl-4-m-dinitrobenzocarbonyloxy-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline (145).

3,5-Dinitrobenzoyl chloride (.34 g, 1.5 mmole) was added to a solution of 4-hydroxy-5,5-dimethyl-3-phenyl-1-*p*-toluenesulphonyl-2-pyrazoline (143; .50 g, 1.4 mmole) in pyridine (20 ml) and the reaction mixture was then heated under reflux for 12 hr. On cooling, the reaction mixture was diluted with water and the organic material was extracted into ether. The ethereal extract was then washed with dilute hydrochloric acid and dried. Evaporation of the solvent gave an oil which was crystallised from a petroleum ether- (b.p. 40-60°) carbon tetrachloride mixture to give *5,5-dimethyl-4-m-dinitrobenzocarbonyloxy-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline* (.61 g, 79%) as a pale yellow crystalline solid, m.p. 123.5-124.5° (Found: C, 56.9; H, 4.3; N, 10.1. $C_{25}H_{22}N_4O_8S$ requires C, 56.8; H, 4.1; N, 10.4%). ν_{max} 1725 (O-CO-Ph$(NO_2)_2$), n.m.r. ($CDCl_3$): δ1.5, 1.6 (two singlets, 6 gem-dimethyl protons), δ2.4 (singlet, 3H, methyl protons of p-toluenesulphonyl group), δ6.3 (singlet, 1H, proton at the 4-position), and δ7.4, 9.1 (multiplets, 12 aromatic protons).

4-Keto-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline (146).

Jones' reagent (1-1 equivalents) was added to a solution of 4-hydroxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline (143; .07 g, .2 mmole) in purified acetone (10 ml) and the reaction mixture was then stirred at room temperature for 10 min. After the reaction mixture had been diluted with water, the organic material was extracted into ether. The ethereal extract was dried and the solvent was evaporated to yield a solid. Recrystallisation of the solid from petroleum ether- (b.p. 40-60°) ether gave 4-keto-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline (.06 g, 79%) as colourless plates, m.p. 119-120° (Found: C, 63.2; H, 5.4; N, 7.9. $C_{18}H_{18}N_2O_3S$ requires C, 63.2; H, 5.3; N, 8.2%). λ_{max} (ethanol) 237 (ε 14,800) and 337 (ε 7,300) nm; ν_{max} 1720 cm^{-1} (C=O), n.m.r. ($CDCl_3$): δ1.5 (singlet, 6 gem-dimethyl protons), δ2.3 (singlet, 3H, methyl protons of p-toluenesulphonyl group), and δ7.3 (multiplet, 9 aromatic protons).

4-Methoxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline (147).

Sodium hydride (.06 g, 2.5 mmole) was added to a solution of 4-hydroxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline (143; .55 g, 1.2 mmole) in anhydrous dimethoxyethane (20 ml) and the reaction mixture was stirred at room temperature for 2 min. Methyl iodide (3 ml) was then added and the reaction mixture was stirred at room temperature for 4 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. After the ethereal extract had been washed with water, it was dried, and evaporated. Crystallisation of the residue from hexane-carbon tetrachloride gave 4-methoxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline (.48 g, 92%) as colourless prisms, m.p. 93-94° (Found: C, 63.7; H, 6.3; N, 7.7. $C_{19}H_{22}N_2O_3S$ requires C, 63.7; H, 6.2; N, 7.8%). n.m.r. (CCl_4): δ1.3, 1.6 (two singlets, 6 gem-dimethyl protons), δ2.3 (singlet, 3H, methyl protons of p-toluenesulphonyl group), δ4.3 (singlet, 1H, proton at the 4-position), and δ7.3 (multiplet, 9 aromatic protons).

4-Benzyloxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline (148).

Sodium hydride (.08 g, 3.3 mmole) was added to a solution of

4-hydroxy-5,5-dimethyl-3-phenyl-1-*p*-toluenesulphonyl-2-pyrazoline (143; 1 g, 2.7 mmole) in anhydrous dimethoxyethane (30 ml) and the reaction mixture was stirred at room temperature for 2 min. Benzyl bromide (1 ml) was then added and the reaction mixture was stirred at room temperature for 12 hr. After ethanol (5 ml) had been carefully added, the resulting solution was poured into water and the organic material was extracted into ether. After the ethereal extract had been washed with water, it was dried, and evaporated. Crystallisation of the residue from hexane-carbon tetrachloride gave *4-benzyloxy-5,5-dimethyl-3-phenyl-1-p-toluenesulphonyl-2-pyrazoline* (.98 g, 78%) as colourless needles, m.p. 133-134° (Found: C, 69.0; H, 6.0; N, 6.8. $C_{25}H_{26}N_2O_3S$ requires C, 69.1; H, 6.0; N, 6.5%). n.m.r. (CCl_4/$CDCl_3$): δ1.4, 1.7 (two singlets, 6 *gem*-dimethyl protons), δ2.3 (singlet, 3H, methyl protons of *p*-toluenesulphonyl group), δ4.4 (singlet, 2H, benzylic methylene protons), δ4.6 (singlet, 1H, proton at the 4-position), and δ7.3 (multiplet, 14 aromatic protons).

4-Keto-5,5-dimethyl-3-phenyl-2-pyrazoline (149).

Sodium hydride[†] (0.15 g, 6.2 mmole) was added to a solution of 4-methoxy-5,5-dimethyl-3-phenyl-1-*p*-toluenesulphonyl-2-pyrazoline

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[†] The sodium hydride mineral oil dispersion was repeatedly washed with hexane and heated under reflux in hexane (20 ml) for 1 hr.

(147; 2g, 5.5 mmole) in anhydrous dimethoxyethane (30 ml) and the mixture was then heated under reflux in an atmosphere of nitrogen for 3 hr. Water was cautiously added to the cooled solution until the excess sodium hydride had been destroyed. The mixture was then poured into water and the organic material was extracted into ether. After the ether extract had been washed with water, it was dried, and evaporated. Crystallisation of the residue from petroleum ether (b.p. 30-40°) gave 4-keto-5,5-dimethyl-3-phenyl-2-pyrazoline (.51 g, 48%) as golden plates, m.p. 116-117° (Found: C, 70.2; H, 6.5; N, 14.9. $C_{11}H_{12}N_2O$ requires C, 70.2; H, 6.4; N, 14.9%). λ_{max} (ethanol) 257 (ε 11,400) and 372 (ε 4,000) nm; ν_{max} 3300 and 1680 cm^{-1} (N-H and C=O respectively), n.m.r. ($CDCl_3$): δ1.3 (singlet, 6 gem-dimethyl protons) and δ7.5 (multiplet, 5 aromatic protons). The amino proton at the 1-position could not be detected.

A similar result was obtained when compound 145 was subjected to similar conditions.

1-Acetyl-4-keto-5-methyl-3,5-diphenyl-2-pyrazoline (150).

Jones' reagent (1.1 equivalents) was added to a solution of 1-acetyl-4-hydroxy-5-methyl-3,5-diphenyl-2-pyrazoline (64; .14 g, .5 mmole) in purified acetone (10 ml) and the reaction mixture was stirred at room temperature for 10 min. After the reaction mixture had been diluted with water, the organic material was extracted into ether. The ethereal extract was dried and the solvent was evaporated to yield a solid. Recrystallisation of the solid from petroleum ether (b.p. 40-60°)-ether gave 1-acetyl-4-keto-5-methyl-3,5-diphenyl-2-pyrazoline (.11 g, 79%) as colourless prisms, m.p. 108-109° (Found: C, 74.2; H, 5.7; N, 9.7. $C_{18}H_{16}N_2O_2$ requires C, 74.0; H, 5.5; N, 9.6%). λ_{max} (ethanol) 249 (ε 14,600) and 343 (ε 11,400)nm; ν_{max} 1720 and 1700 cm^{-1} (C=O and N-CO-CH_3 respectively), n.m.r. ($CDCl_3$): δ1.9 (singlet, 3H, methyl group at the 5-position), δ2.5 (singlet, 3H, N-CO-$C\underline{H}_3$), and δ7.3 (multiplet, 10 aromatic protons).

4-Keto-5-methyl-3,5-diphenyl-2-pyrazoline (151).

1-Acetyl-4-keto-5-methyl-3,5-diphenyl-2-pyrazoline (150; 1 g, 3.4 mmole) was dissolved in a solution of potassium hydroxide in methanol (10%, 25 ml) and the solution was heated under reflux for 30 min. The cooled solution was poured into water and the organic material was extracted into ether. After the ethereal layer had been washed thoroughly with water, it was dried, and evaporated. The residue was crystallised from hexane to give 4-keto-5-methyl-3,5-diphenyl-2-pyrazoline (.61 g, 71%) as yellow needles, m.p. 104-105° (Found: C, 76.4; H, 5.7; N, 11.1. $C_{16}H_{14}N_2O$ requires C, 76.7; H, 5.6; N, 11.2%). λ_{max} (ethanol) 264 (ε 12,600) and 382 (ε 4,800) nm;

ν_{max} 3280 and 1680 cm^{-1} (N-H and C=O respectively), n.m.r. ($CDCl_3$): δ1.8 (singlet, 3H, methyl group at the 5-position) and δ7.3 (multiplet, 10 aromatic protons). The amino proton at the 1-position could not be detected.

4-Methoxy-3,3-dimethyl-5-phenyl-3H-pyrazole (152).

Sodium hydride[⸗] (0.15 g, 6.2 mmole) was added to a solution of 4-methoxy-5,5-dimethyl-3-phenyl-1-*p*-toluenesulphonyl-2-pyrazoline (147; 2 g, 5.5 mmole) in anhydrous dimethoxyethane (30 ml) and the mixture was heated under reflux in an atmosphere of nitrogen for 1 hr. On cooling the reaction mixture was filtered and the solvent removed *in vacuo* at 0°. The residue, an oil, was dissolved in petroleum ether (b.p. 30-40°) and cooled in a dry ice-acetone bath. A solid was deposited and this was removed by filtration. 4-Methoxy-3,3-dimethyl-5-phenyl-3H-pyrazole (.570 g, 52%) was obtained as a pale yellow solid, m.p. 39-40°. λ_{max} (ethanol) 237 (ε 8,200) and 293 (ε 2,000) nm; ν_{max} 1630 ($C=C-OCH_3$), n.m.r. (CCl_4): δ1.40 (singlet, 6 *gem*-dimethyl protons), δ3.74 (singlet, 3H, $-OCH_3$), and δ7.5 (multiplet, 5 aromatic protons). The mass spectrum showed a parent ion peak at m/e 202, which is the expected molecular weight for the compound.

[⸗] The sodium hydride mineral oil dispersion was freed of the mineral oil as outlined on page 107.

4-Benzyloxy-3,3-dimethyl-5-phenyl-3H-pyrazole (154).

Sodium hydride[≠] (0.075 g, 3.1 mmole) was added to a solution of 4-benzyloxy-5,5-dimethyl-3-phenyl-1-*p*-toluenesulphonyl-2-pyrazoline (148; 1 g, 2.3 mmole) in anhydrous dimethoxyethane (30 ml) and the mixture was heated under reflux in an atmosphere of nitrogen for 1 hr. On cooling the reaction mixture was filtered and the solvent removed *in vacuo* at 0°. The residue, an oil, (.48 g, 81%), was dissolved in petroleum ether (b.p. 30-40°) and set aside at 0° for 3 days. After filtration the solution was used in the irradiation experiments. An analytical sample was prepared by crystallisation of the oil from petroleum ether (b.p. 30-40°) at -20°. 4-Benzyloxy-3,3-dimethyl-5-phenyl-3H-pyrazole was obtained as colourless needles, m.p. 65-66° (Found: C, 77.6; H, 6.5; N, 10.1. $C_{18}H_{18}N_2O$ requires C, 77.7; H, 6.5; N, 10.1%). λ_{max} (ethanol) 236 (ε 8,900) and 297 (ε 3.500) nm; ν_{max} 1640 ($C{=}C{-}OCH_2Ph$), n.m.r. ($CCl_4/CDCl_3$): δ1.4 (singlet, 6 *gem*-dimethyl protons), δ4.9 (singlet, 2H, benzylic methylene protons), and δ7.5 (multiplet, 10 aromatic protons).

[≠] The sodium hydride mineral oil dispersion was freed of the mineral oil as outlined on page 107.

Work described in Chapter III.

(part e)

Unsuccessful attempts to convert 4-methoxy-3,3-dimethyl-5-phenyl-3H-pyrazole (152) to 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (155).

In the initial attempt, a solution of the 3H-pyrazole (152; 1 g) in pentane (50 ml) was irradiated under nitrogen in a Pyrex reactor, with a Rayonet Photochemical Reactor for 3 hr. An infrared solution spectrum indicated that no reaction had taken place. Irradiation for 6 hr produced the same result.

A similar result was obtained when the above solution was irradiated under similar conditions with either a Philips 125-W mercury-quartz lamp or a Hanovia UVS 220A high pressure lamp.

When a solution of the 3H-pyrazole (152; 1 g) in pentane (50 ml) was irradiated under nitrogen in a quartz reactor with a Hanovia UVS 220A high pressure lamp for 3/4 hr, a polymer was produced. Irradiations for a short duration produced the same result. No reaction took place when an aqueous nickel sulphate filter[75] was circulated between the lamp and the solution.

When the experiments above were repeated using a 1% solution of the 3H-pyrazole (152) in petroleum ether (b.p. 30-40°), similar results were obtained.

1-Methoxy-3,3-dimethyl-2-phenylcyclopropene (155).

A solution of 4-methoxy-3,3-dimethyl-5-phenyl-3H-pyrazole (152; .40 g) in petroleum ether (b.p. 30-40°) (200 ml) was irradiated in 50 ml fractions, under nitrogen, in a thin-walled Pyrex reactor[≁] with a Hanovia UVS 220A high pressure lamp for 1 hr. After the fractions had been combined, the volume was reduced to 20 ml by heating the reaction mixture on a hot water-bath, the excess solvent being removed through a column packed with glass helices. The solution was then passed down a column of neutral alumina which was eluted with petroleum ether (b.p. 30-40°). The eluant was collected until it became coloured. Careful removal of the solvent through a column packed with glass helices gave 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (.03 g, 10%) as a colourless oil, λ_{max} (pentane) 277 (ε 2,100) nm; ν_{max} (film) 1840, 1600, 1025, 1000, 690, and 750 cm^{-1} (see Chapter III, pages 88 and 89), n.m.r. (CCl_4): δ1.37 (singlet, 6H, *gem*-dimethyl group), δ3.98 (singlet, 3H, $-OC\underline{H}_3$), and δ7.0-7.3 (multiplet, 5 aromatic protons). The mass spectrum exhibited a parent ion peak at m/e 174, which is the expected molecular weight for this compound.

[≁] The reactor consisted of a 100 ml round-bottomed flask fitted with a reflux condenser. The solution was irradiated externally.

Elution of the column with benzene gave 4-keto-5,5-dimethyl-3-phenyl-2-pyrazoline (.140 g, 37%), m.p. and mixed m.p. 116-117°. On prolonged irradiation (greater than 5 hr) a product which absorbed at 1700 cm^{-1} in the infrared spectrum was obtained. The structure of this compound was not determined as it was found to be polymeric in nature. The conversion of the 3H-pyrazole (152) to 1-methoxy-3,3-dimethyl-2-phenylcyclopropene (155) was not always reproduceable and seemed to depend on the purity of the 3H-pyrazole (152). Solutions of unrecrystallised 3H-pyrazole (152) failed to undergo the desired conversion.

1-Benzyloxy-3,3-dimethyl-2-phenylcyclopropene (156).

A solution of 4-benzyloxy-3,3-dimethyl-5-phenyl-3H-pyrazole (154; .40 g) in petroleum ether (b.p. 30-40°) (200 ml) was irradiated in 50 ml fractions, under nitrogen, in a thin-walled Pyrex reactor with a Hanovia UVS 220A high pressure lamp for 3/4 hr. After the fractions had been combined, the volume was reduced to 20 ml by heating the reaction mixture on a hot water-bath, the excess solvent being removed through a column packed with glass helices. The solution was then passed down a column of Florosil which was eluted with petroleum ether (b.p. 30-40°) (20 ml). The eluant was rechromatographed until the eluant (20 ml) was colourless. Careful removal of the solvent through a column packed with glass helices gave 1-benzyloxy-3,3-dimethyl-2-phenylcyclopropene (.03 g, 10%) as a colourless oil, λ_{max} (pentane) 277 (ε 2,000) nm; ν_{max} 1840 cm^{-1} (skeletal vibration), n.m.r. ($CDCl_3$): δ1.33 (singlet, 6H, *gem*-dimethyl group), δ5.18 (singlet, 2H, benzylic methylene protons), and δ7.2-7.3 (multiplet, 10 aromatic protons). The mass spectrum showed a parent ion peak at m/e 250, which is the expected molecular weight for the compound.

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