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ACYLATION AND ALKYLATION REACTIONS OF
BIPHENYL- AND N-PHENYLPYRROLE-ALKANOIC
ACID DERIVATIVES.

by

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TO MY PARENTS

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Summary

This thesis is presented in four distinct chapters, necessary because of the apparent independence of the subjects studied.

The initial object was an investigation of the interaction of a series of biphenyl-2-oxyalkanoyl chlorides with aluminium chloride in benzene as solvent. Ring closure can occur at two distinct sites leading, in general, to the formation of five- or seven-membered-ring cyclic ketones and an attempt has been made to assess the steric and electronic factors affecting these cyclisations.

In some of these reactions decarbonylation of the acid chloride was found to occur and some alkylated products were isolated. Such reactions had previously been shown to involve an aryl benzyl ether as intermediate and the interactions of several biphenyl benzyl ethers with aluminium chloride in benzene were studied. These, generally, led to the same alkylated products formed in similar proportions to those in the cyclisations.

In the course of the initial study the cyclic ketone, dibenz[b,d]oxepin-7(6H)-one, was prepared by cyclisation of biphenyl-2-oxyacetyl chloride. From this several other derivatives, including the previously unknown parent compound, of the dibenz[b,d]oxepin ring system were prepared. Some reactions of dibenz[b,d]oxepin were investigated.

The study of cyclisation reactions was extended initially to ring closure of N-phenylpyrrole-propionic acids and subsequently to some other heterocyclic alkanolic acids, using polyphosphoric acid as condensing agent. In the course of this work, a rearrangement, leading to inversion of the cyclic ketone ring was discovered, which is thought to involve a four-membered-ring spirocyclic intermediate. Some S.C.F. molecular orbital calculations using the CNDO approximation and the computer program CNINDO were performed on the starting materials, products and proposed intermediates involved in these reactions.

CONTENTS

	<u>Page</u>
<u>Chapter One</u>	
<u>Cyclisations of Aryl- and Heterocyclic Alkanoic Acids</u>	1
<u>Section One</u>	
<u>Introduction</u>	2
1.1 Cyclisation of Arylalkanoic Acids	3
1.2 Cyclisation of Heterocyclic Alkanoic Acids	7
1.3 Rearrangement during Cyclisation	12
<u>Section Two</u>	
<u>Results and Discussion</u>	15
A 1.4 The Cyclisations of 2-Biphenylalkanoic Acids	16
B Cyclisations of Heterocyclic Alkanoic Acids	21
1.5 Propionic Acids	21
1.6 Mechanism of the Rearrangement	27
M.O. Calculations	31
1.7 The Cyclisations of 5-methylthiophene-2-propionic acid and 5-methylfuran-2-propionic acid	41
1.8 The Cyclisation of 5-methyl-1-(1-pyrrolyl)pyrrole-2- propionic acid	44
1.9 Attempted Cyclisation of 5-methyl-1-phenylpyrrole-2- acetic acid	45
1.10 Cyclisation of 1-methylpyrrole-2-butyric acid	46
<u>Chapter Two</u>	
<u>Reactions of Aryloxyalkanoyl chlorides and Arylthioacetyl chlorides with Aluminium chloride</u>	50
<u>Section One</u>	
<u>Introduction</u>	51
2.1 Purpose of the Investigation	52
2.2 Reactions of Aryloxyacetyl chlorides	53

2.3	The effect of the "ether" oxygen on cyclisation	61
2.4	Cyclisations of 3-Aryloxypropionic Acids	63
2.5	Reactions of Arylthioacetyl chlorides	64
<u>Section Two</u>		
<u>Results and Discussion</u>		66
2.6	The Preparation of Aryloxyalkanoic Acids	67
2.7	The reactions of Aryloxyalkanoylchlorides with Aluminium chloride	70
2.8	The effects of Side-Chain substituents	75
2.9	Other cyclisations	81
2.10	Cyclisation of 3-(2-biphenyloxy)propionyl chloride	87
2.11	Reaction of Biphenyl-2-thioacetyl chloride	88
<u>Chapter Three</u>		
<u>Rearrangements of Aryl Benzyl Ethers</u>		90
<u>Section One</u>		
<u>Introduction</u>		91
3.1	Scope of the Investigation	92
3.2	Historical Background	92
<u>Section Two</u>		
<u>Results and Discussion</u>		98
3.3	Rearrangements of Aryl Benzyl Ethers	99
3.4	Rearrangements of Cyclic Ethers	103
<u>Chapter Four</u>		
<u>The Dibenz [b,d]oxepin Ring system</u>		110
<u>Section One</u>		
<u>Introduction</u>		111
4.1	Dibenz [b,d]oxepin	112
4.2	Dibenz [b,d]thiepin and Dibenz [b,d]azepin	113
<u>Section Two</u>		
<u>Results and Discussion</u>		115

4.3	Reactions of Dibenz [b,d] oxepin-7(6H)-one	116
4.4	Preparation of Dibenz [b,d] oxepin system	123
4.5	Reactions of Dibenz [b,d] oxepin	124
	<u>EXPERIMENTAL SECTION</u>	130
	General Notes	131
	<u>Chapter One</u>	132
1.1	Preparation of 3-Arylpropionic Acids	132
1.2	Cyclisations of 3-Arylpropionyl chlorides with Aluminium Chloride	133
1.3	Preparation of Pyrrole-2-propionic Acids	136
1.4	Other propionic acids	141
1.5	5-Methyl-1-phenyl-pyrrole-2-acetic acid	142
1.6	Pyrrole-2-butyric Acids	143
1.7	Cyclisations of Heterocyclic Alkanoic Acids	147
	<u>Chapter Two</u>	156
2.1	Preparation of Phenols	156
2.2	Preparation of Aryloxyacetic Acids	157
2.3	2-(Biphenyl-2)oxypropionic acid	160
2.4	3-(Biphenyl-2)oxypropionic acid	161
2.5	Biphenyl-2-oxyisobutyric acid	161
2.6	Phenoxyisobutyric acid	162
2.7	Attempted preparation of 1-(biphenyl-2)oxycyclohexane- carboxylic acid	162
2.8	Biphenyl-2-thioacetic acid	163
2.9	The preparation of Aryloxyalkanyl chlorides	164
2.10	Reactions of Aryloxyacetyl chlorides with Aluminium Chloride in Benzene	165
	<u>Chapter Three</u>	176
3.1	Preparation of Acyclic Aryl Benzyl Ethers	176

3.2	Preparation of Cyclic Ethers	177
3.3	The reactions of Acyclic Aryl Benzyl Ethers with Aluminium Chloride in Benzene.	178
3.4	Reactions of Cyclic Ethers with Aluminium Chloride in Benzene	179
	<u>Chapter Four</u>	182
4.1	Preparation of Dibenz[b,d]oxepin-7(6H)-one	182
4.2	7-Hydroxy derivatives	182
4.3	Other Reduction reactions of Dibenz[b,d]oxepin-7(6H)-one	184
4.4	Other reactions of Dibenz[b,d]oxepin-7(6H)-one	187
4.5	Preparation of Dibenz[b,d]oxepin	189
4.6	7-Substituted Dibenz[b,d]oxepins	190
4.7	Reactions of Dibenz[b,d]oxepin	192
4.8	7-Bromodibenz[b,d]oxepin	194
4.9	Attempted preparation of 7-cyanodibenz[b,d]oxepin	195
	BIBLIOGRAPHY	196

Chapter One

Cyclisations of Aryl- and Heterocyclic

Alkanoic Acids

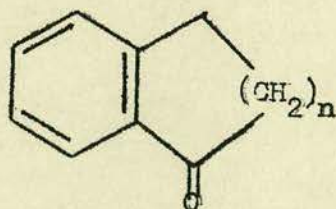
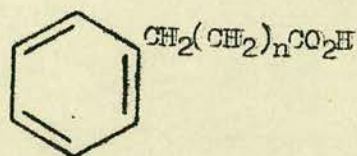
Section One

Introduction

1:1 Cyclisation of Arylalkanoic Acids.

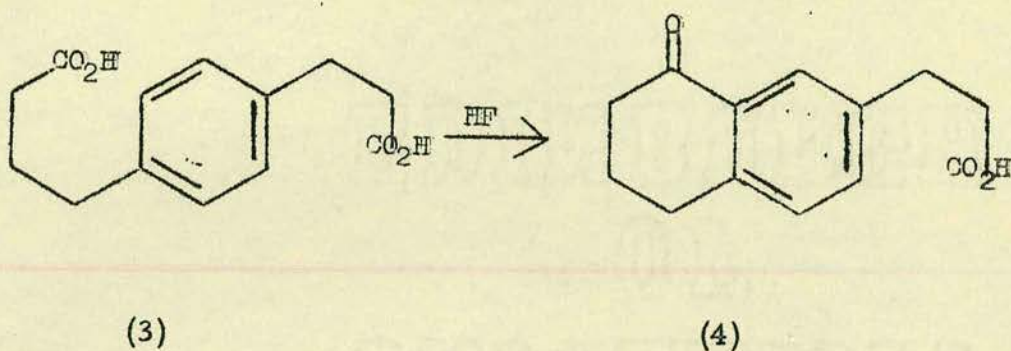
The ring closure of arylalkanoic acids and their derivatives is a well-established method for the preparation of hydroaromatic cyclic ketones^{1, 2}. The reactions are acid-catalysed and both Lewis and Brønsted-Lowry acids will effect cyclisation. Typical conditions involve heating the free acid with a suitable condensing agent such as sulphuric acid, hydrogen fluoride, polyphosphoric acid or stannic chloride, or the acid may be converted into its chloride and then treated with a typical Friedel-Crafts reagent such as aluminium chloride or stannic chloride.

Typical examples are the cyclisations of 3-phenylpropionic acid (1, $n = 1$) to give 1-indanone (2, $n = 1$) and of 4-phenylbutyric acid (1, $n = 2$) to give 1-tetralone (2, $n = 2$).

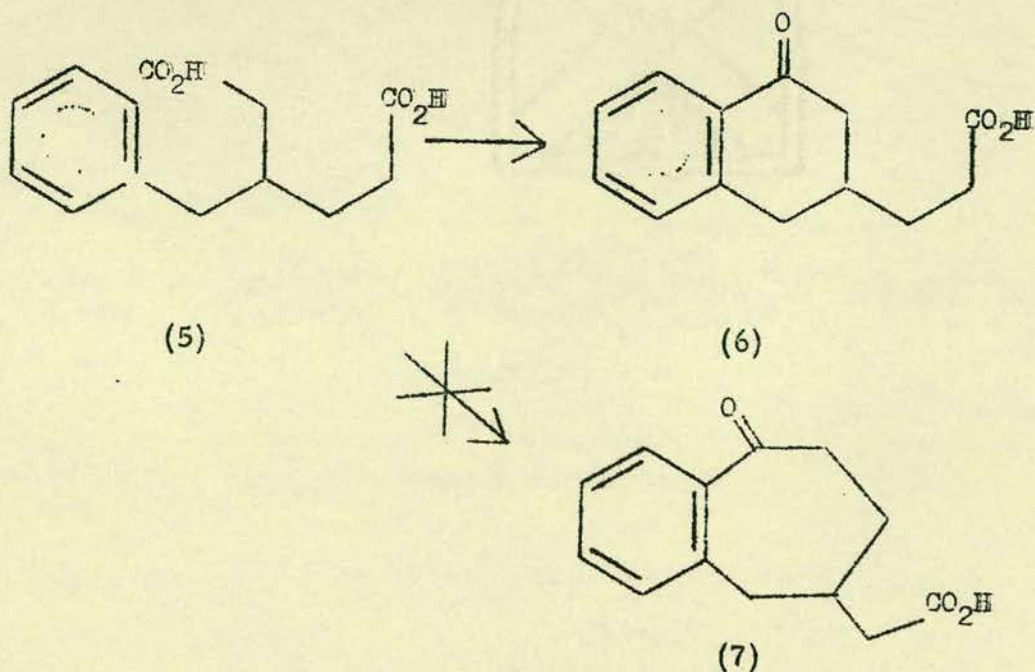


It has been found that the size of the ring to be formed has a great effect on the reaction. Three- and four-membered rings are not favoured as shown by the failure of benzoyl chloride and phenylacetyl chloride to cyclise in the presence of Friedel-Crafts reagents³.

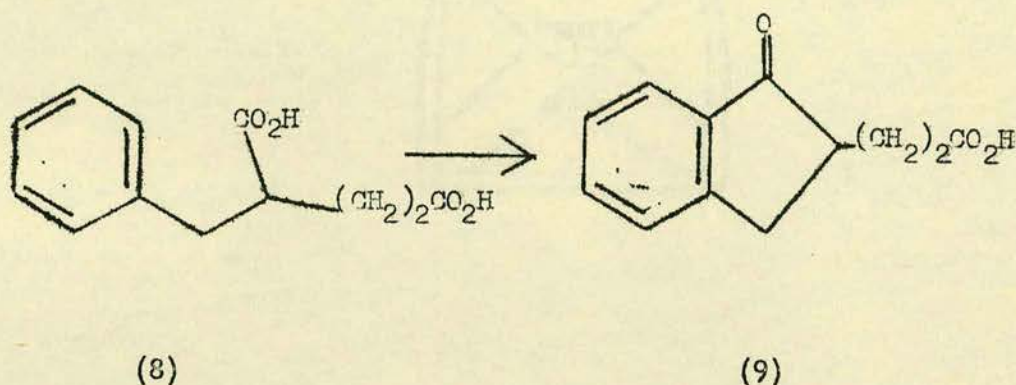
A six-membered ring is formed more readily and in better yield than a five- or a seven-membered ring. Whenever there is a choice between the formation of a five- and a six-membered ring the latter is generally favoured. This is demonstrated in the cyclisation of the diacid (3) to give the tetralone derivative (4) as the sole product⁴.



That a six-membered ring is formed more readily than a seven-membered ring is shown in the cyclisation of 3-benzyl adipic acid (5) which gives only the tetralone derivative (6) and none of the benzosuberone (7)⁵.



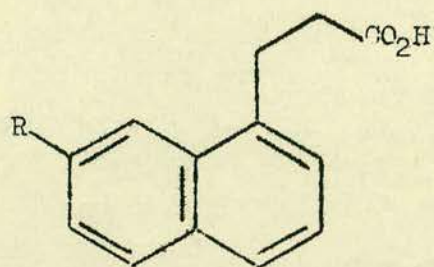
Similarly the preference for five-membered ring formation over seven-membered is demonstrated in the cyclisation of 2-benzylglutaric acid (8) which gives exclusively the indanone derivative (9) rather than the 7-membered ring.⁶



Diacid cyclisations of this type do not imply that certain ring systems are inherently more stable than others but are illustrative only of rates of reaction, assuming, of course that both acyl groups are equally reactive i. e. that the reactive intermediate is the di-acylium ion, or that the rate of inter-conversion of the mono-ions is faster than cyclisation.

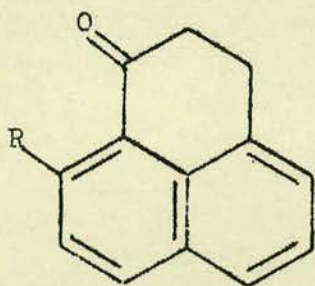
Other factors than ring size may also influence the course of ring-closure. The nature of the products can depend on steric and electronic influences in the molecule and also on reaction conditions.

Cyclisation of a series of β -(1-naphthyl)propionic acids (10, a - d) gave the six-membered ring cyclic ketones (11) formed by attack at the 8-position. In the case of (10, a, R = H) a trace

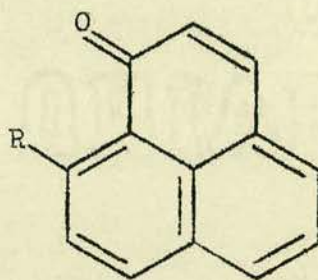


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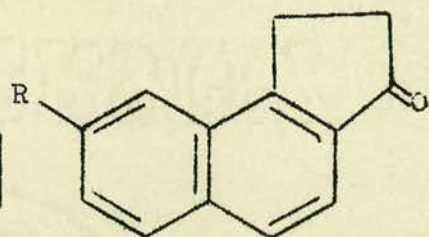
- (a) R = H
- (b) R = Me
- (c) R = Et
- (d) R = i - Pr
- (e) R = t - Bu



(11)



(12)



(13)

of the isomeric benzindanone (13, R = H) was also formed⁷. Under vigorous reaction conditions some dehydrogenation of (11) took place giving the phenalenones (12). With the 7-tert-butyl substituted acid (10 e), however, the benzindanone (13, R = t - Bu) was the sole product, showing the dominant steric effect in this case⁸.

In contrast to these results, both 1-naphthyloxyacetyl chloride⁹ and β -(1-naphthyl)ethanesulphonyl chloride¹⁰ cyclise exclusively to the five-membered ring products (10) and benzo(e)-2,3-dihydro-thianaphthene-1-dioxide.

As can be seen in cyclisations where alternative sites for ring-closure are available, ring-size of the product is only one factor to be considered along with steric and electronic

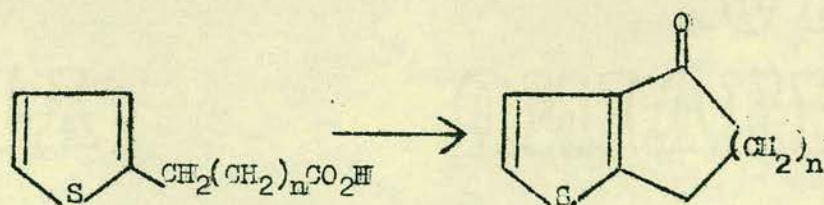
effects in the molecule.

1:2 Cyclisation of Heterocyclic Alkanoic Acids.

Alkanoic acid derivatives of 5-membered ring heterocycles and their benzologues undergo cyclisation reactions analogous to those in the carbocyclic series. These " π -excessive" heterocycles are very susceptible to electrophilic attack and cyclisation occurs readily under mild conditions although this is often accompanied by some decomposition (generally by polymerisation of the protonated rings) which lowers the yields.

Most of the examples reported in the literature involve cyclisations of alkanolic acid derivatives of thiophene, benzothiophene and indole. These reactions may be regarded as typical examples.

Thiophene-2-alkanoic acids (16) or acid chlorides cyclise readily with the exception of the propionic acid (16, $n = 1$) which cyclises only with difficulty and in low yield¹¹, to give the cyclic ketones formed by attack at the 3- position (17)^{12, 13}.

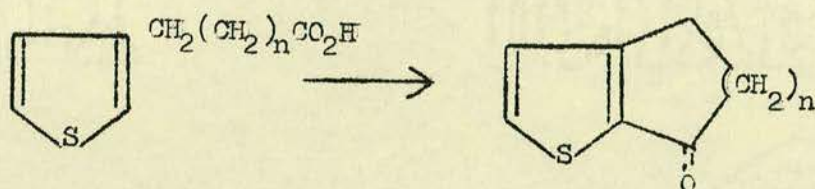


(16)

(17)

Typically the conditions used involve heating the free acid with polyphosphoric acid or treating the acid chloride with stannic chloride in carbon disulphide.

The isomeric thiophene-3-alkanoic acids (18) also cyclise readily, and in the case of propionic acid (18, $n = 1$) more readily than the 2-isomer¹¹ to give the cyclic ketones formed by attack at the 2-position (19)^{14, 15}.

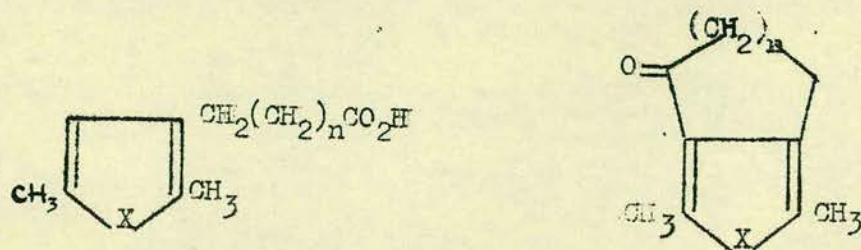


(18)

(19)

Although the 4-position is also free, the 2- is very much more reactive towards electrophilic attack and ring-closure occurs exclusively there.

With the 2-position blocked as in 2,5-dimethylthiophen-3-propionic acid (20, $X = S$, $n = 1$)¹⁵ and 2,5-dimethylpyrrole-3-propionic (20, $X = NH$, $n = 1$)^{16, 17} and 3-butyric acids

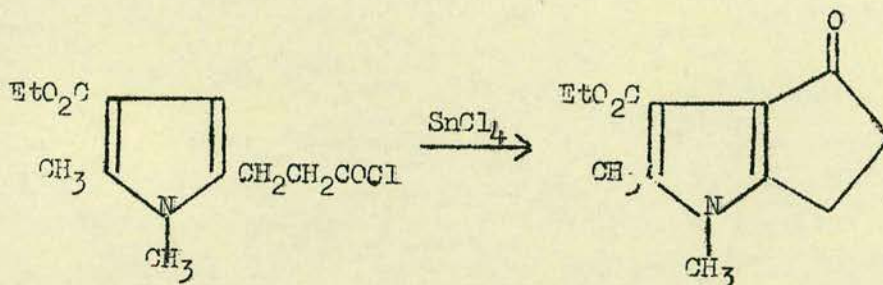


(20)

(21)

(20, X = NH, n = 2)¹⁷ cyclisation readily occurs giving the 3,4-cyclic ketone (21).

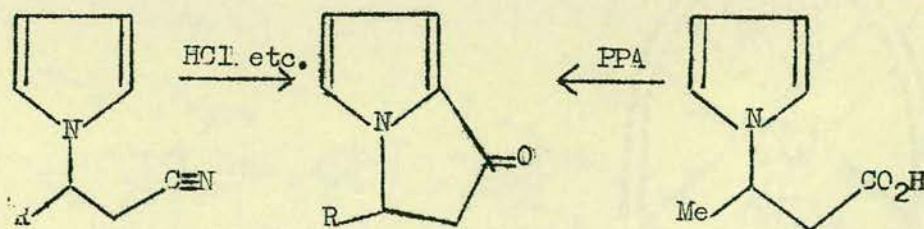
In the pyrrole series, only one example of a cyclisation of a 2-propionic acid is recorded, that of 1,5-dimethyl-4-ethoxycarbonylpyrrole-2-propionyl chloride (22) to give the ketone (23)¹⁸.



(22)

(23)

Pyrrole-1-propionic acid decomposes under cyclising conditions when treated with polyphosphoric acid but the nitrile (24, R = H) undergoes the Houben reaction forming the cyclic ketone in the 2-position (26, R = H) and the β -methyl acid (25) cyclises with polyphosphoric acid¹⁹.

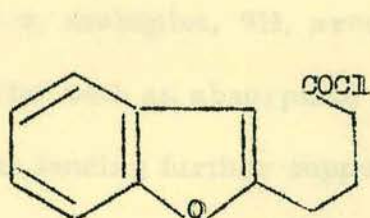


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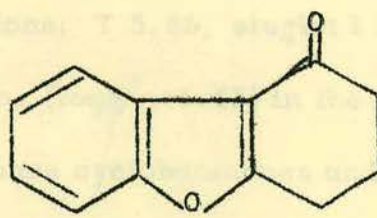
(26)

(25)

There are no recorded examples of ring-closure of furan alkanolic acids on the furan ring although this is known in the benzofuran series as exemplified in the stannic chloride-catalysed cyclisation of the acid chloride of benzo [b] furan-2-butylric acid (27) to the cyclic ketone (28)²⁰.

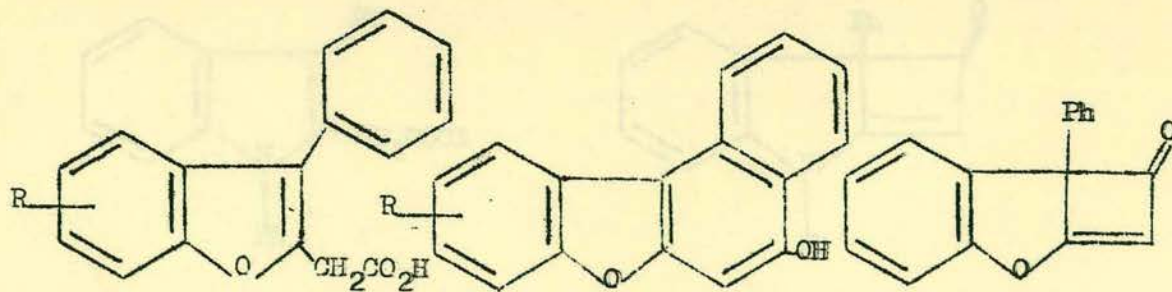


(27)



(28)

An interesting and most unusual example of a cyclisation forming a four-membered ring has been reported in the reaction of 3-arylbenzo[b]furan-2-acetic acids (29) with phosphoric anhydride in benzene. In an earlier report²¹ the



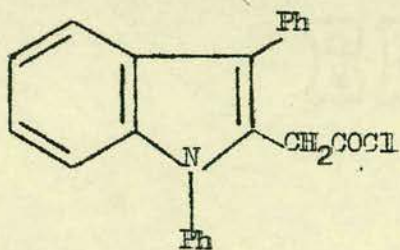
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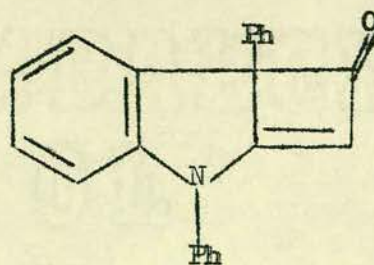
(31)

products of these cyclisations are claimed to be 5-hydroxybenzo[b]naphtho[1,2-d]furans (30) but ⁱⁿmore recent work²² it has been shown that the products are, in fact, the isomeric cyclobutenones (31). This structure has been assigned on the basis of the I. R. ($\bar{\nu}_{C=O} = 1750 - 1765 \text{ cm}^{-1}$) and N.M.R. (τ 2.4, multiplet, 9H, aromatic protons; τ 5.66, singlet 1 H) spectra with an absorption at 248 n.m. ($\log \epsilon$, 4.43) in the ultra-violet lending further support. These cyclobutenones undergo base-catalysed rearrangement to the naphthols (30) when treated with lithium aluminium hydride or Grignard reagents.

Very recently, a similar cyclisation to a four-membered, cyclobutenone ring has been observed in the reaction of 1,3-diphenylindole-2-acetyl chloride (32) with aluminium chloride in benzene forming (33)²³. The spectral characteristics of this product are very similar to those of (31).



(32)



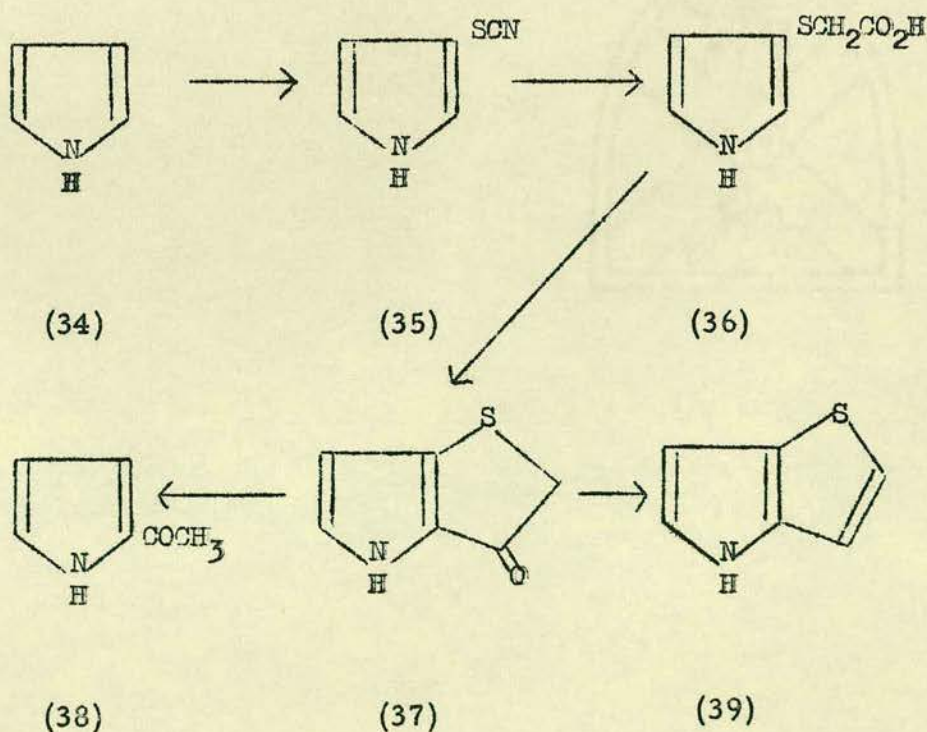
(33)

In both benzofurans and indoles the 3-position is highly activated to electrophilic attack and normally, when this position

is free, substitution occurs there. In the cases of (29) and (32), although these positions are, in fact, already substituted, they still prove to be the most favourable for cyclisation.

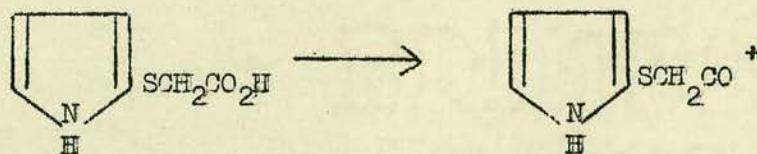
1: 3 Rearrangement during Cyclisation.

In an investigation of the thiocyanation of pyrrole (34), using either methanolic thiocyanogen at low temperature (-75°) or cupric thiocyanate at 0° , Matteson and Snyder²⁴ obtained a monothiocyanatopyrrole which they converted to the thioacetic acid and cyclised giving a cyclic ketone which was positively identified as (37) by desulphurisation with Raney nickel which gave the known 2-acetylpyrrole (38) and by conversion to thieno[3,2-b]pyrrole (39) which was also synthesised from thiophene



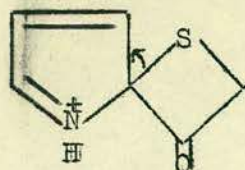
derivatives. From this they concluded that the product must have arisen from cyclisation of pyrrole-3-thioacetic acid (36). Hence the mono-thiocyanato pyrrole must be the 3- isomer (35). This meant that thiocyanation of pyrrole, an electrophilic substitution, had occurred, unusually, in the 3-position, whereas the 2-position is normally attacked in such reactions.

The reaction was re-investigated by Gronowitz and co-workers²⁵ who, using ¹H N.M.R. spectroscopy, identified both the thiocyanatopyrrole and the thioacetic acid (40) as the much more probable 2- isomers. The original structure proposed for the cyclic ketone was correct so a rearrangement must have occurred during the cyclisation. They proposed the following mechanism for this rearrangement where the acylium ion (41)

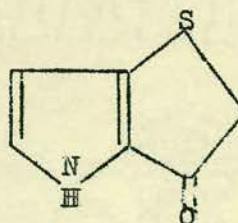


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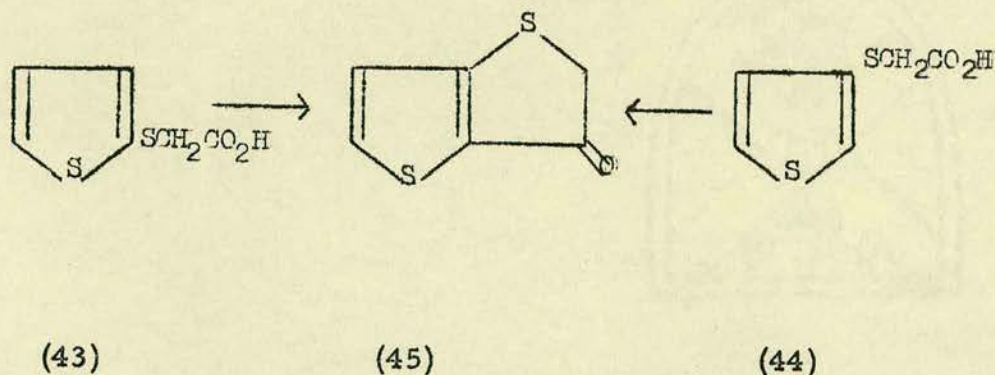
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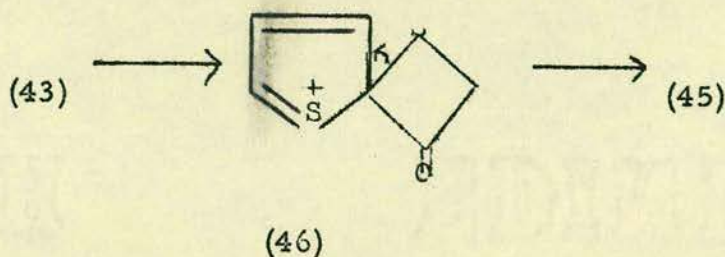
(37)

attacks the already-substituted but more reactive 2-position giving the spirocyclic intermediate (42) which rearranges and loses a proton forming (37).

Subsequently Gronowitz and Moses²⁶ discovered a similar rearrangement in the reaction of 2-thienylthioacetic acid (43) which cyclises to give 2H-thieno[3,2-b]thiophen-3-one (45), identical to the product obtained from cyclisation of 3-thienylthioacetic acid (44). Around 10% of a second component



was also formed in the cyclisation of (43). This was never fully identified but is probably the unrearranged cyclic ketone. A similar mechanism also involving a spirocyclic intermediate (46) is proposed for this reaction.



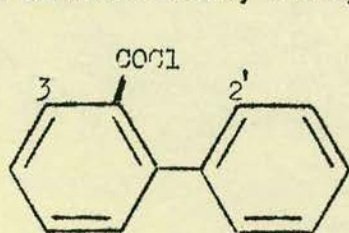
Rearrangements of this type are probably connected with the considerably greater reactivity of the 2-position over the 3-position in electrophilic substitution reactions.

Section Two

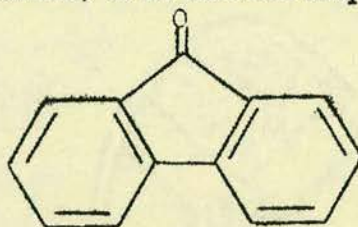
Results and Discussion.

A 1:4 The Cyclisations of 2-Biphenylalkanoic Acids.

The ready cyclisation of biphenyl-2-carbonyl chloride (47) to form fluorenone (48) is well-known. The reaction can occur in the absence of any catalyst and, indeed, it is almost impossible



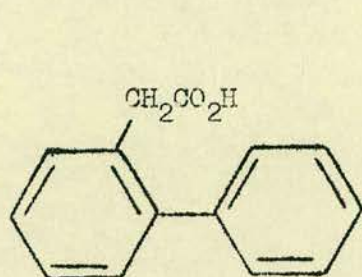
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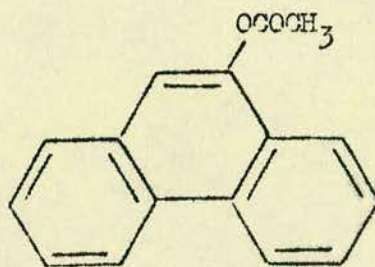
(48)

to prepare the acid chloride uncontaminated by fluorenone. In this case cyclisation to the 2'-position of the second ring forms a five-membered-ring cyclic ketone and cyclisation to the 3-position of the same ring is excluded since a three-membered ring would have to be formed.

Biphenyl-2-acetic acid (49) also readily cyclises to the 2-position of the second ring even under the mild conditions of warming with acetic anhydride, acetic acid and zinc chloride, when the product is 9-acetoxyphenanthrene (50), the enol acetate of phenanthrene²⁷. In this case cyclisation on to the same ring would necessitate the formation of a four-membered-ring cyclic ketone and is therefore highly improbable.

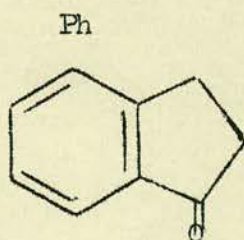


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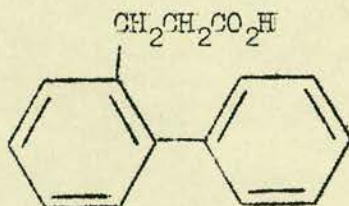


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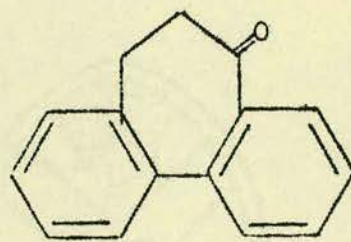
The case of 3-(2-biphenyl)propionic acid (51) is the first where cyclisation at both the 3- and 2'-positions is possible, the former leading to 4-phenylindanone (52) and the latter to dibenzocycloheptadienone (53). In an early report of the



(52)



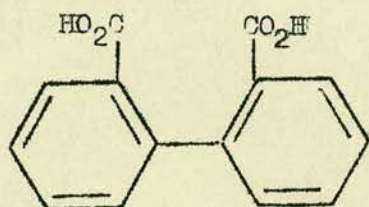
(51)



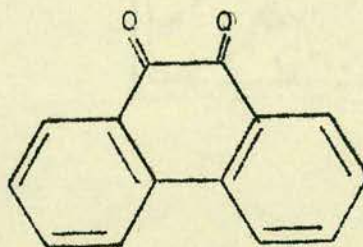
(53)

cyclisation²⁸ it was claimed that (52) was the sole product of cyclisation. However, the evidence presented is not very convincing. A subsequent investigation by Cook and his co-workers²⁹ of the cyclisation of the acid chloride using aluminium chloride in carbon disulphide showed that while (52) was the major product, a small amount of (53) was also formed. They did not succeed in isolating any of this ketone but did obtain a little of the

phenylhydrazone. They also identified phenanthraquinone (54) and diphenic acid (55) amongst the products of oxidation of the crude cyclisation mixture. These must have come from oxidation of (53).



(55)



(54)

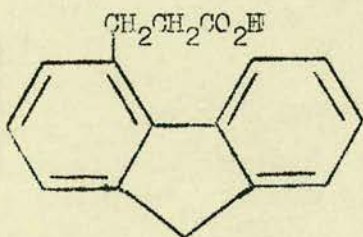
They could not accurately estimate the amount of (53) present but estimated it to be less than 10%. A similar result was obtained from cyclisation of the free acid with hydrogen fluoride as catalyst.

In this investigation the cyclisation of the acid chloride of (51) using aluminium chloride as catalyst was studied in both benzene and sym-tetrachloroethane as solvents. A similar result was obtained in each case. From the ^1H n. m. r. spectrum of the crude cyclisation products it was possible to confirm that both (52) and (53) were present and also to estimate fairly accurately the relative amounts of each from the integration of the methylene region of the spectrum. The methylene groups of 4-phenylindanone (52) gave rise to two quite-well-resolved triplets ($J = 7$ Hz) centred on 6.82 τ and 7.36 τ respectively while those of dibenzocycloheptadienone were degenerate and gave a singlet at

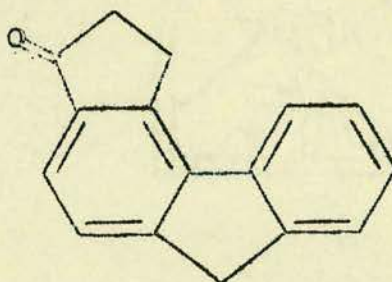
7.03 T. The estimated amounts of (52) and (53) present were 80% and 20% respectively.

Again it proved impossible to obtain a pure sample of (53) even using chromatographic techniques. 4-Phenylindanone (52) was obtained pure and characterised.

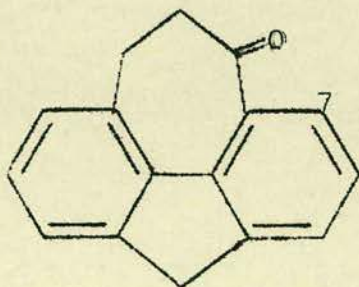
A compound which is structurally closely related to biphenyl-2-propionic acid (51) is 3-(4-fluorenyl)propionic acid (56). In this case the geometry of the molecule is much more rigid and the aromatic rings are held coplanar. Again there is the



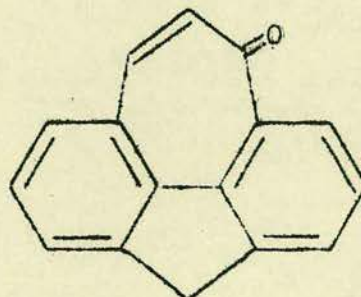
(56)



(57)



(58)



(59)

possibility of five- or seven-membered ring formation. When the acid chloride of (56) was treated with aluminium chloride in benzene, one product was formed. This was identified as the seven-membered ring ketone, 9,10-dihydrocyclohepta[def]fluoren-8

(4H)one, (58) on the basis of the I.R. ($\bar{\nu}_{\text{C=O}} = 1675 \text{ cm}^{-1}$ and $^1\text{H n.m.r.}$ spectra (2.10 τ , quartet, H-7). The n.m.r. spectrum also showed the two methylene groups as a singlet (6.94 τ) which was also found in (53). None of the isomeric five-membered ring ketone (57) was detected.

Shortly after this reaction had been studied a report was published reporting the cyclisation of fluorene-4-propionic acid (56) using polyphosphoric acid to effect ring closure³⁰. When the reaction was carried out at 180° two products were formed which were identified as 9,10-dihydrocyclohepta[def]fluoren-8(4H)one (58), the same cyclic ketone as is formed in the aluminium chloride catalysed reaction on the acid chloride, and the unsaturated derivative (59). At higher temperatures (200°) they found that (59) was formed almost exclusively while at lower temperatures (120°) the dihydro-compound predominated.

This observation finds a parallel in the cyclisations of β -(1-naphthyl)propionic acid (10a)⁸ and its acid chloride³¹ when dehydrogenation of the initially formed perinaphthenone (11a) to phenalenone (12a) under vigorous reaction conditions occurs.

The reason for such a difference in behaviour during cyclisation of the biphenyl and fluorene propionic acids is difficult to see. The electronic effects in the two molecules are not significantly different at the cyclisation sites and so the explanation

probably lies in a steric effect. It is possible that the 5-position of the fluorene nucleus is held just at the correct distance for attack by a propionyl side-chain while the 2'-position in biphenyl is less favourably placed.

The Dreiding model of the fluorene-4-propionyl acylium ion shows that the 5-position of the fluorene nucleus is just at the correct distance for attack by the $-\overset{+}{\text{C}}\equiv\text{O}$ group which can easily approach above this site while cyclisation to the five-membered-ring ketone would involve much more strain in the transition state. The model of the biphenyl-2-propionyl acylium ion shows that attack at the 2'-position of the second ring is possible. However this ring is able to rotate freely and attack there introduces an unfavourable entropy factor compared to five-membered-ring formation.

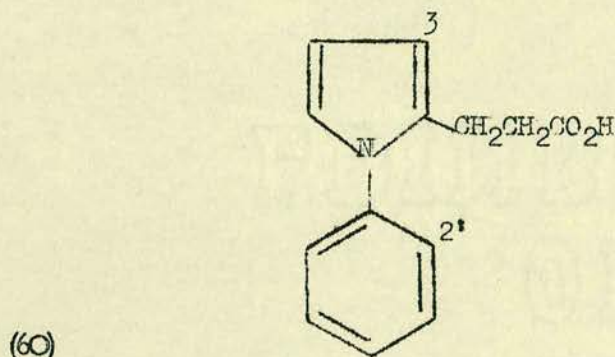
B Cyclisations of Heterocyclic Alkanoic Acids.

1:5 Propionic Acids.

The study of cyclisations of propionic acids where there is a possibility of cyclisation to a five- or a seven-membered ring product was extended to the heterocyclic series.

These reactions were all carried out by stirring a mixture of the free acid (one part) and polyphosphoric acid (one hundred parts by weight) at 100° . The usual time for the reaction was three hours unless the acid was suspected to be unstable, or the reaction mixture darkened noticeably, when a shorter time was allowed.

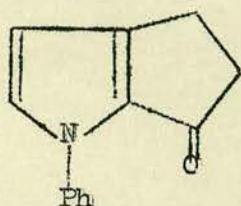
The first cyclisation studied was that of 1-phenylpyrrole-2-propionic acid (60). In this case, a five-membered ring would



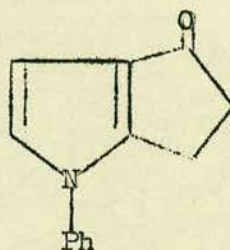
result from attack at the 3-position and a seven-membered ring from attack at the 2'-position of the phenyl ring. Although the 3-position is quite strongly activated towards electrophilic substitution the product of cyclisation there will have two fused five-membered rings and will be quite strained. So the possibility of cyclisation at the less activated 2'-position cannot be excluded since this would lead to a strain-free product.

Unexpectedly, the thin-layer chromatogram of the crude product after hydrolysis showed the presence of three components, all with similar R_F values. The ¹H n.m.r. spectrum of the crude product also suggested three components. The separation of these components proved to be difficult. Chromatography on silica-gel did not give any separation. However on alumina it proved possible to separate the two major components in a pure state although the third was not recovered. The first fraction eluted

gave a crystalline white solid which was shown to be 5,6-dihydro-1-phenyl-4H-cyclopenta[b]pyrrol-6-one (61) on the basis of its ¹H n.m.r. spectrum which showed absorptions at 7.12 τ (singlet, 4H, 4-CH₂ and 5-CH₂), 3.74 τ (doublet, J = 2.7 Hz,



(61)



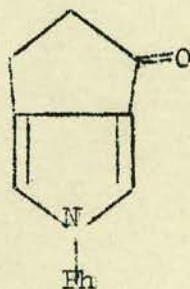
(62)

1H, H-3), 2.28 - 2.77 τ (multiplet, 6H, 1-phenyl plus H-2). The second component isolated was identified as

5,6-dihydro-1-phenyl-4H-cyclopenta[b]pyrrol-4-one (62). Its ¹H n.m.r. spectrum showed absorptions at 7.02 τ (singlet, 4H, 5-CH₂ and 6-CH₂), 3.53 τ (doublet, J = 3.2 Hz, 1H, H-3), 2.90 τ (doublet, J = 3.2 Hz, 1H, H-2) and 2.58 τ (singlet, 5H, 1-phenyl).

When the cyclisation was repeated on a larger scale, the third component was isolated after very lengthy chromatography on alumina. The 60 MHz n.m.r. spectrum showed that this also was a cyclic ketone with singlet peaks at 7.07 τ and 2.57 τ for the methylenes and phenyl groups respectively. In addition there was a poorly-resolved multiplet at 3.11 τ which integrated for one proton. The spectrum at 100 MHz was more informative. Expansion of the peak at 7.07 τ showed it to be a quartet and

irradiation of this caused the multiplet at 3.11 τ to collapse to a clean doublet ($J = 0.4$ Hz). Also revealed was a doublet ($J = 0.4$ Hz) at the upfield edge of the phenyl resonance at 2.64 τ . On this basis, the structure of this product was assigned as 5,6-dihydro-2-phenyl-4H-cyclopenta[c]pyrrol-4-one (63) with the resonances being designated 3.11 τ as H-1 and 2.64 τ as H-3.

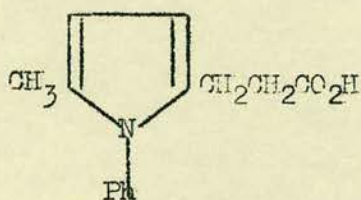


(63)

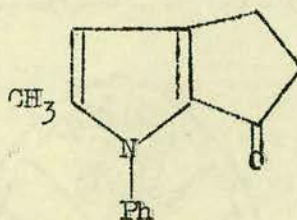
An interesting variation in the ratios of the three products was observed in the two reactions which were performed at the same temperature for a similar time and with a similar ratio of polyphosphoric acid to starting material. In the first experiment the yields of (61), (62) and (63) as estimated from the integrated n. m. r. spectrum of the reaction product were 45%, 35% and 20% while in the second experiment they were 50%, 25% and 25% respectively. In the second case there is a higher proportion of "abnormal" products compared with the unrearranged cyclic ketone (62). It was also shown that when (62) is heated with polyphosphoric acid at 100° (the temperature of the cyclisation reaction) for 5.5

hours (twice the time of the cyclisation) it does not rearrange and is recovered unchanged. Thus the rearrangement must take place at some intermediate stage in the reaction and not by rearrangement of the expected product (62). The differences in product ratios must presumably be due to slightly different acidities of the polyphosphoric acid used as catalyst.

Several other cyclisations gave similar rearrangement reactions. From the cyclisation of 5-methyl-1-phenylpyrrole-2-propionic acid (64) only one product was formed, in excellent yield.



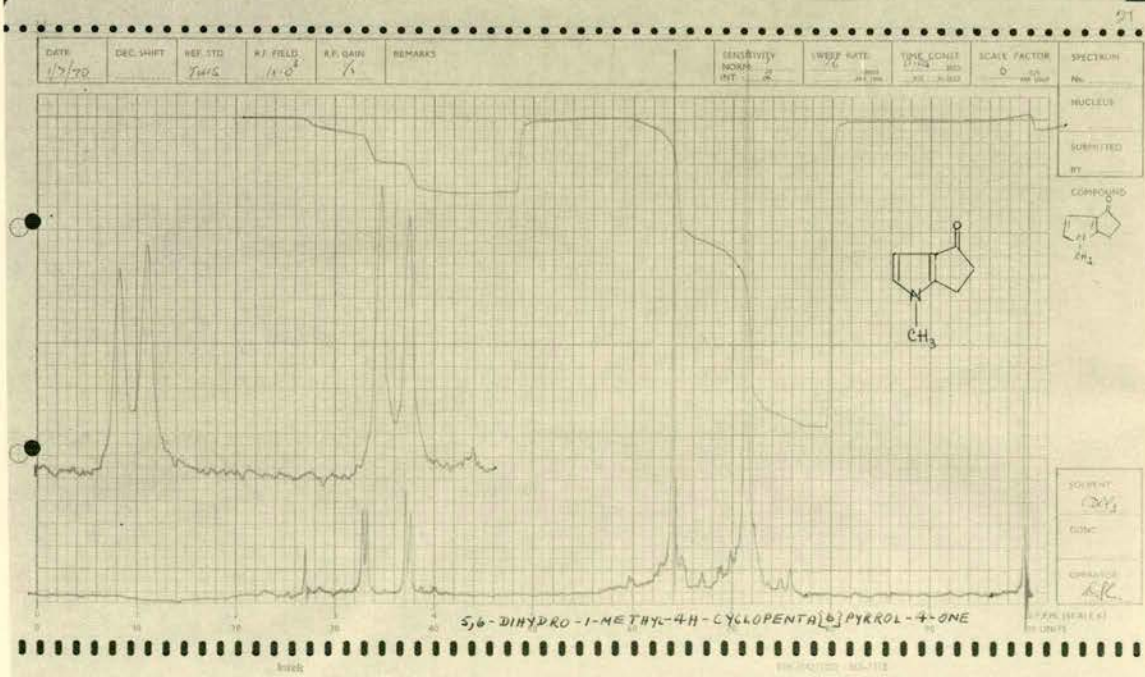
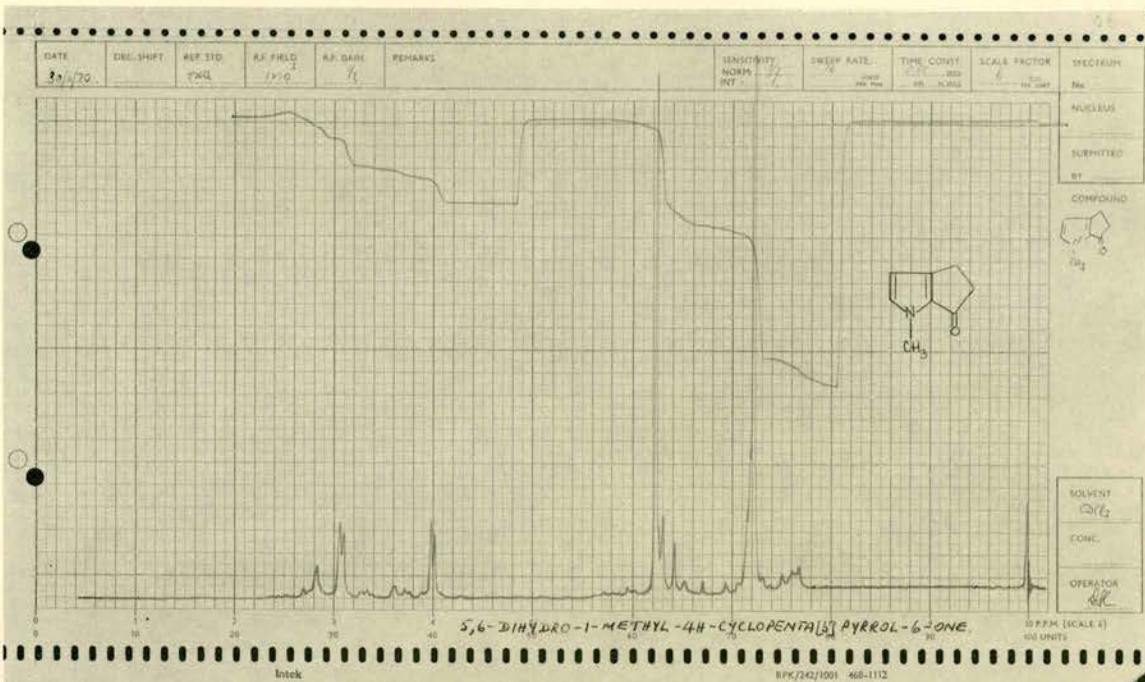
(64)

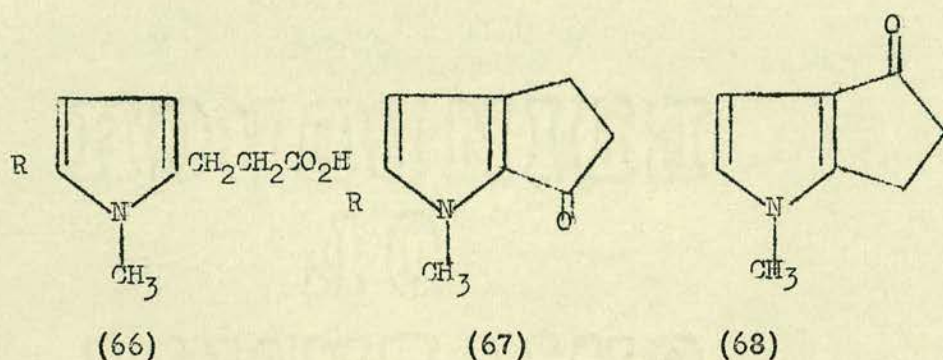


(65)

This was shown to be 5,6-dihydro-2-methyl-1-phenyl-4H-cyclopenta[b]pyrrol-6-one (65). In this case there had been total rearrangement.

The 1-phenyl group did not appear to play an important part in the reaction and so the cyclisations of 1-methylpyrrole-2-propionic acid (66, R=H) and 1,5-dimethylpyrrole-2-propionic acid (66, R=CH₃) were examined.





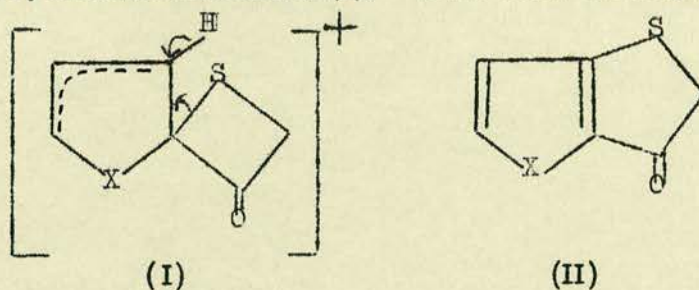
In the former case, both the rearranged cyclic ketone (67, R=H) and the "normal" product (68) were formed. Again the ratios of these products differed in two cyclisations apparently under the same conditions. This is also, presumably, an effect of different acidities of polyphosphoric acid used. The first reaction gave (67, R=H) as 78% and (68) as 22% of the product and in the second the isomers were formed in equal amounts. There was no sign of any product of the type (63) which must have been formed by a double rearrangement.

In similar fashion to (64), cyclisation of 1,5-dimethylpyrrole-2-propionic acid (66, R=CH₃) gave only the rearranged ketone, 5,6-dihydro-1,2-dimethyl-4H-cyclopenta[b]pyrrol-6-one (67, R=CH₃).

Thus in both the 1-phenyl and the 1-methyl series the acid without a 5-methyl substituent has given both rearrangement and normal cyclisation products and the acid with a 5-methyl substituent has given only the rearranged cyclic ketone.

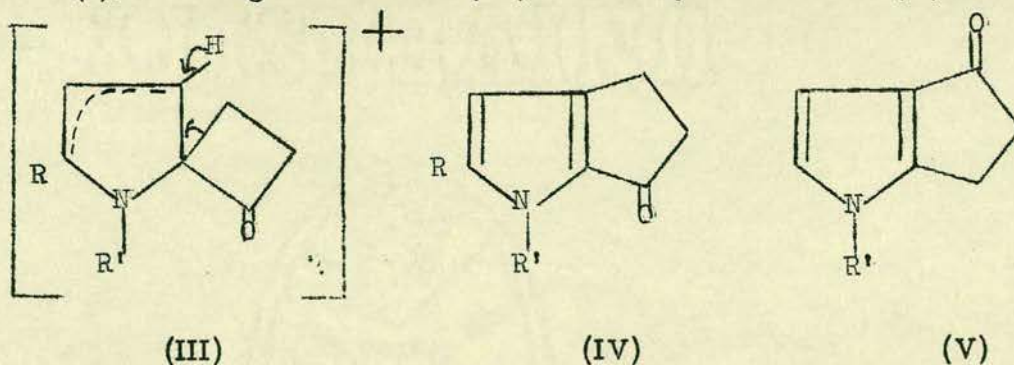
1:6 Mechanism of the Rearrangement.

There are obvious similarities between this rearrangement and those observed in the cyclisations of pyrrole-2-thioacetic acid (40) and thiophene-2-thioacetic acid (43). The 2-positions of the pyrrole and thiophene nuclei are very much more activated to electrophilic attack than the 3-positions and ring closure is thought to occur initially at the 2-position forming the four-membered ring spirocyclic intermediate (I). This then rearranges and loses



a proton to form the cyclic ketone (II).

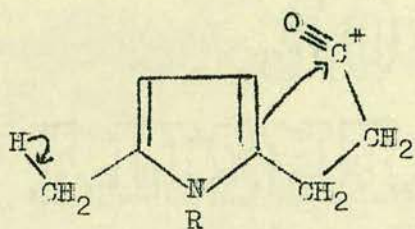
A similar process is thought to occur in the cyclisations of pyrrole-2-propionic acids. Attack at the 2-position leads to the spirocyclic ions (III) which rearrange, in an analogous fashion to (I), forming the ketones (IV). The cyclic ketones (V) form by



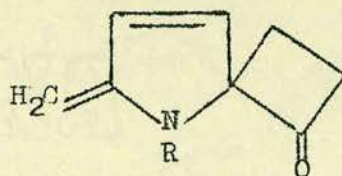
direct cyclisation to the 3-position of the acids without a

5-methyl-substituent. The reason for the formation of the 'normal' cyclic ketones (V) in these reactions compared with complete rearrangement during cyclisations of the thioacetic acids is probably that when the propionyl side-chain adopts the *cis*-conformation to cyclise to the spirocyclic ion (III, R = H), the hydrogen atoms of the methylene groups become eclipsed leading to strong non-bonded interactions and hence a high activation energy. These non-bonded interactions are, of course, absent in the thioacetyl case. In addition, it is possible that the fairly diffuse d-orbitals of the electronegative sulphur atom may attract the positively-charged acylium ion towards the cyclisation site, facilitating formation of the ion (I). Thus direct cyclisation to the 3-position can more readily occur in the case of the propionic acids.

The only products from the cyclisations of pyrrole-2-propionic acids with a 5-methyl substituent are the rearranged ketones (IV, R = Me). There are two possible reasons for this. The inductive effect of the 5-methyl substituent will further activate the 2-position making the formation of the spirocyclic ion (IV, R = Me) more probable. Another possibility is that attack of the acylium ion on the 2-position is accompanied by loss of a proton from the methyl group (VI) leading to a series of the type (VII) which then rearranges to (IV, R = Me).



(VI)

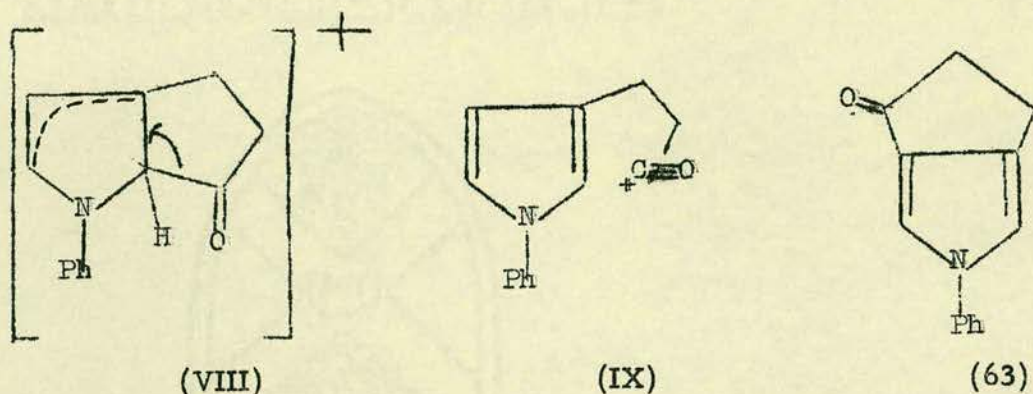


(VII)

Species analogous to (VII) have been proposed for some electrophilic substitution reactions of furan derivatives where an existing substituent is expelled by the attacking group.

A possibility existed that the ketones (IV) could have arisen by rearrangement of the normal products (V). This was discounted when the 'normal' ketone (V, $R' = \text{Ph}$) was heated with polyphosphoric acid at 100° for 5.5 hours (twice the normal time of a cyclisation reaction) and no rearrangement took place.

The formation of the 3,4- cyclic ketone was observed only in the cyclisation of 1-phenylpyrrole-2-propionic acid and this may provide the clue to the mechanism of its formation. In the cyclic ketone (IV, $R = \text{H}$, $R' = \text{Ph}$), the bulky phenyl substituent will cause considerable steric overcrowding in the region of the carbonyl group. This could be relieved to some extent by protonation of the 2-position which will push the carbonyl group out-of-plane as in (VIII). If the bond joining the carbonyl group



to the pyrrole ring cleaved this would lead, formally, to a pyrrole-3-propionyl acylium ion which would normally cyclise at the 2-position but, in view of the steric hindrance there, might also cyclise at the 4-position to (63).

This was shown to be the case. When 5,6-dihydro-1-phenyl-4H-cyclopenta[b]pyrrol-6-one (IV, $R = H$, $R' = Ph$) was heated with polyphosphoric acid for 4.5 hours (1.5 times the length of the cyclisation reaction time) at $100^{\circ}C$, the n. m. r. spectrum of the product showed the presence of 5,6-dihydro-2-phenyl-4H-cyclopenta[c]pyrrol-4-one (63) as 19% of the total with starting material accounting for the remainder. The structure was confirmed using nuclear magnetic double resonance which gave the same result as with the material isolated from the cyclisation reaction.

The thin-layer chromatogram of the product showed two bands with the minor component having the correct R_F value for (63). Although the reaction was performed on a very small scale

such that isolation of the products was not possible, there is no doubt that (63) is formed by rearrangement of (IV, R = H, R' = Ph) under cyclising conditions.

M. O. Calculations

LCAO-molecular orbital calculations were performed on the isomeric cyclic ketones formed in these cyclisations using the CNDO approximation and the computer program CNINDO which was already in use by other members of this group. This approach uses the semi-empirical Pople SCMO method which is superior to the empirical Huckel-type calculations in that both σ - and π -electron densities are considered. In Huckel-type calculations only the π -electrons are considered and the method is only successful for alternant aromatic hydrocarbons.

The Pople method works best for first row elements. Only electrons in the valency shell are considered in the calculations and the effective nuclear charge is the atomic number reduced by two to compensate for the 1s electrons which are considered to form part of the core.

The CNDO approximation introduces a further simplification into the calculations by complete neglect of differential overlap (CNDO). This means that the product $\phi_\mu \phi_\nu$, where ϕ_μ and ϕ_ν are assumed to be two different atomic orbitals, always vanishes, whether the orbitals μ and ν are centred on the same atom or on different atoms. All

two-centre overlap integrals and many of the Coulomb and repulsion integrals will vanish. Only electron repulsion integrals involving no more than two orbitals are retained.

The basis functions used to describe the atomic orbitals are Slater-type orbitals (STO). These are identical to hydrogenic orbitals except that the radial nodes are omitted. This introduces considerable simplification into the calculation of the integrals. If functions having radial nodes are required, these can be constructed from linear combinations of STO's. The orbitals most commonly used in applications of MO theory to organic π -systems, the 2p orbitals, are also nodeless in the hydrogenic case. Consequently Slater-type and hydrogenic 2p orbitals are identical.

Although the electron-electron repulsion, nuclear-nuclear repulsion and electron-nucleus attraction energies when calculated by this method are not correct in comparison with non-empirical calculations, the overall differences are reasonably correct. Hence the calculated binding energies, although much too large (probably by around a factor of five), do preserve the correct relative order in almost all cases.

To simplify the calculation of the molecular geometries, the N-methyl compounds only were considered. These geometries are shown in figs 1 - 3. The results of these calculations show that the rearranged ketone (IV, $R = H$, $R' = Me$) should be

5,6-dihydro-1-methyl-4H-cyclopenta[b]pyrrol-6-one

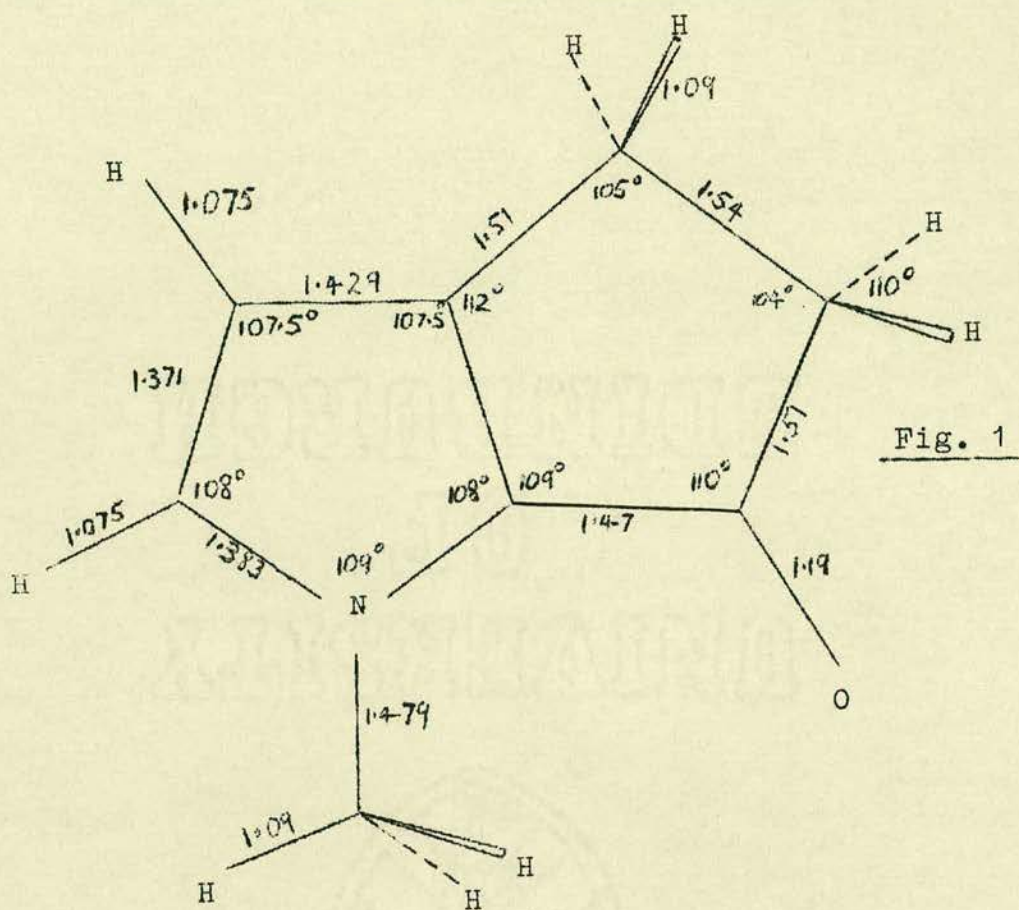


Fig. 1

5,6-dihydro-1-methyl-4H-cyclopenta[b]pyrrol-4-one

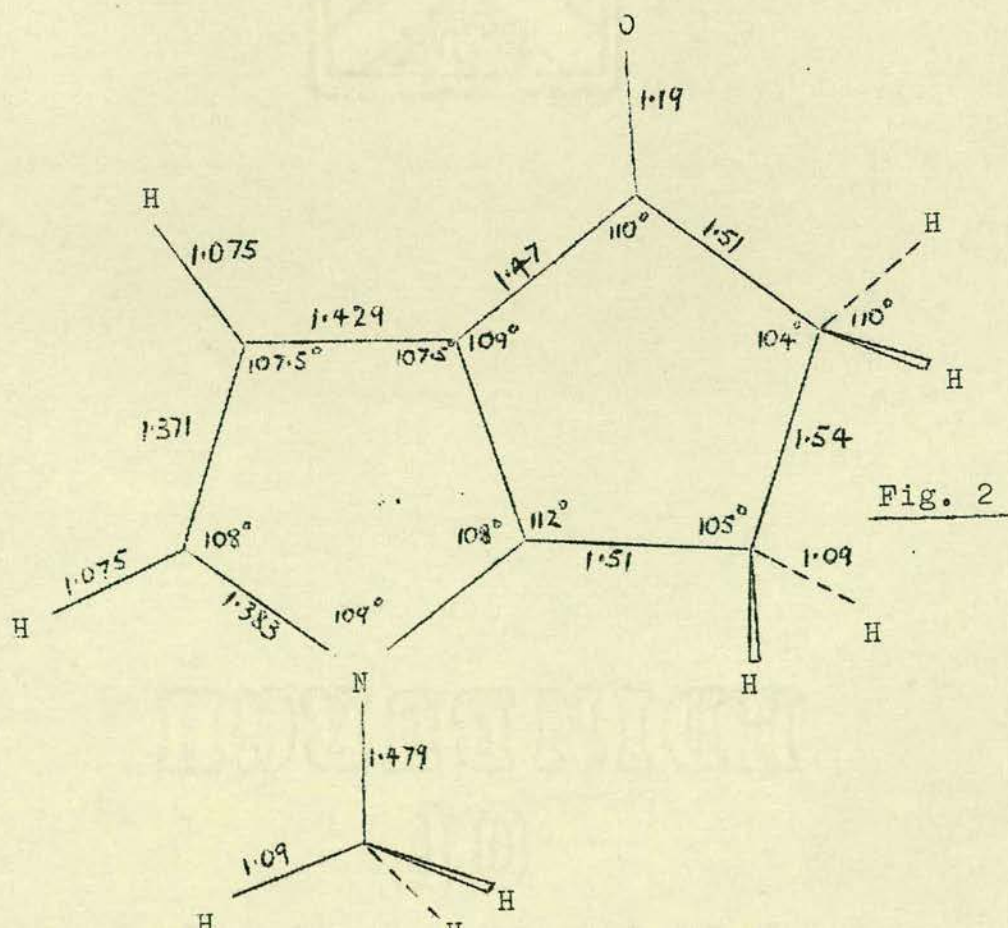


Fig. 2

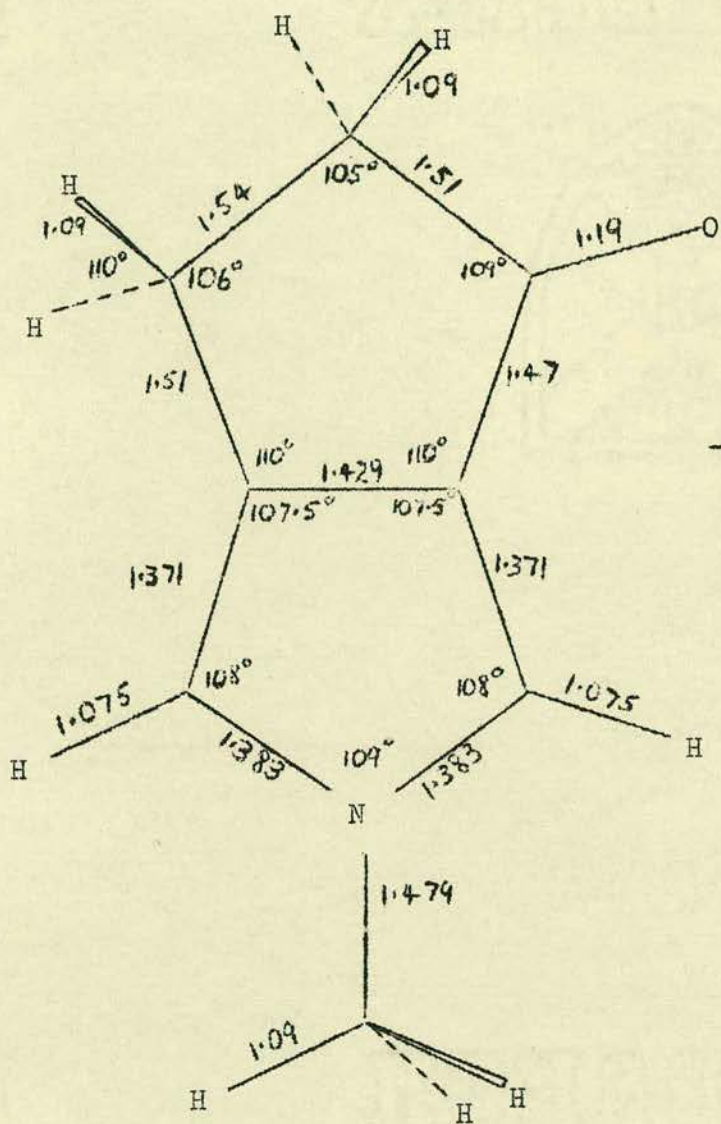


Fig. 3

5,6-dihydro-2-methyl-4H-cyclopenta[c]pyrrol-4-one

thermodynamically more stable than its unrearranged isomer (V, R' = Me) by approximately $50.1 \text{ Kcal.mole}^{-1}$. More surprisingly, the 3,4-cyclic ketone (63, Me for Ph) was shown to be more stable than (IV) although by only $2.3 \text{ Kcal mole}^{-1}$.

The results of these calculations were shown to be qualitatively correct in the 1-phenyl series. Heating the 'normal' ketone (V, R' = Ph) with polyphosphoric acid produced no rearrangement at all as predicted above while heating the rearranged ketone (IV, R = H, R' = Ph) with polyphosphoric acid resulted in the formation of a small amount of the 3,4-isomer (63).

In the calculations on the ketones (IV) and (V) it was found that the best, i. e. lowest, energy was obtained when the length of the bond common to the two fused rings was kept as it is in N-methylpyrrole. Increasing or decreasing this length (1.37 \AA) by 0.02 \AA with corresponding minor adjustments to the geometries of the cyclopentenone rings raised the calculated energies of the molecules by around $300 \text{ Kcal.mole}^{-1}$ in each case.

In all cases the orientation of the N-methyl group was taken with one hydrogen atom in the plane of the pyrrole ring and the other two out-of-plane, one above and the other below. The in-plane hydrogen atom pointed away from the cyclopentenone ring. Reversing this orientation and repeating the calculations gave a marginal energy difference which should be equated with the

barrier to rotation of the methyl group. This was found to be of the order of 2.5×10^{-2} Kcal.mole⁻¹ and quite insignificant.

The main criterion used to calculate a geometry for the fused cyclopentenone rings was that the internal angles of the two methylene groups should be approximately equal. This was done by varying the angles at the points of fusion of the ketone ring, within the limits $108^\circ - 115^\circ$, till that condition was satisfied.

Similar calculations were carried out on the starting material, 1-methylpyrrole-2-propionic acid, and the 3-propionic acid and also on several possible intermediates in the cyclisation reactions. For the acids and acylium ions the side-chain was taken in the fully extended conformation with the minimum number of non-bonded interactions and for the spirocyclic ions at the 2- and 3-positions the two rings were assumed to be at right angles to each other. The results of all these calculations and those on the cyclic ketones are shown in the table overleaf. The binding energies are quoted in atomic units (1 a. u. = 627.501 Kcal.mole⁻¹).

Geometries used in Calculations

For all cases, the geometry of the pyrrole ring was that of pyrrole itself as shown in fig 1. The dimensions of the N-methyl group were those of toluene.

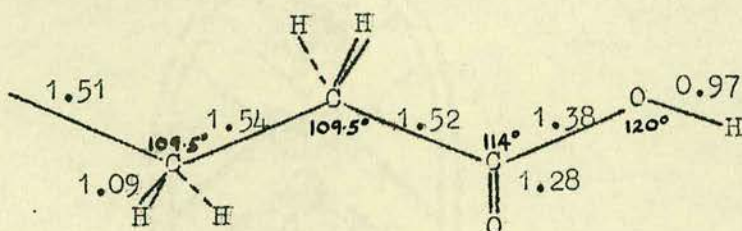
(a) Cyclic Ketones

These are shown in figs 1 - 3.

(b) Propionic Acids

The bond joining the side-chain to the pyrrole ring was taken as bisecting the external angle at the point of substitution.

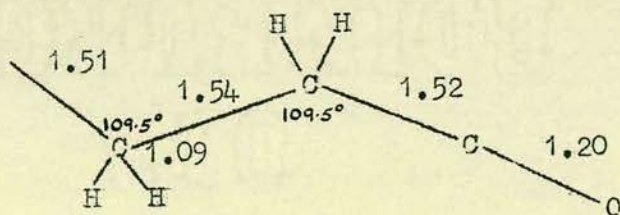
The geometry of the side-chain was



for the 2-propionic acid and the mirror-image of this for the 3-isomer.

(c) Acylium ions

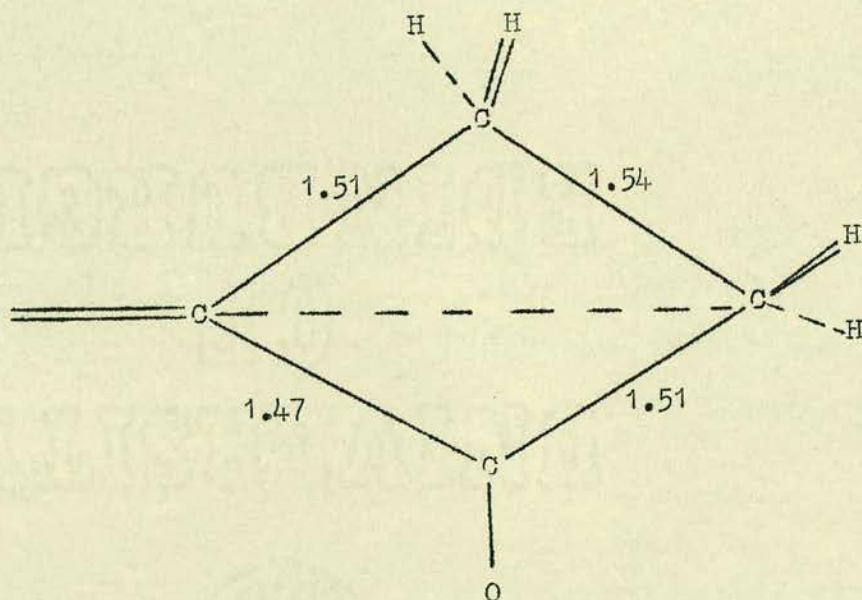
Again the bond joining the side-chain to the pyrrole ring was taken as bisecting the external angle. The geometry of the side-chain was



for the 2-propionyl acylium ion and the mirror-image of this for the 3-isomer.

(d) Spirocyclic Intermediates

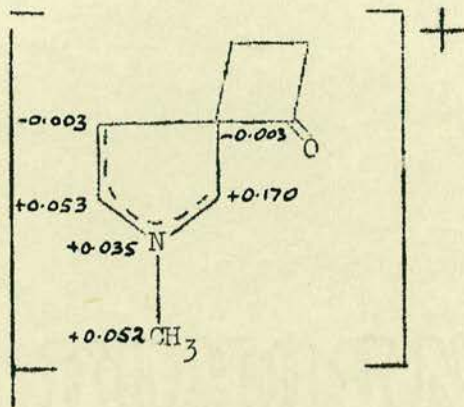
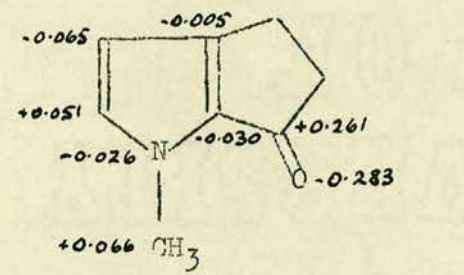
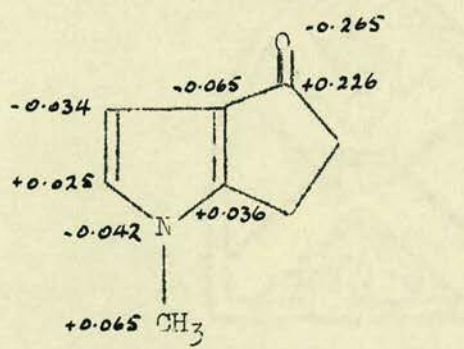
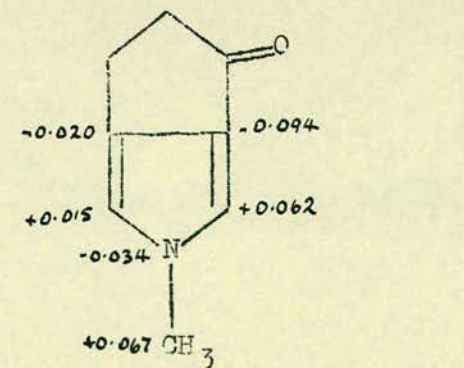
The plane of the four-membered ring was taken as perpendicular to that of the pyrrole ring and to bisect the external angle at the point of substitution. The geometry of the spiro-ring was as shown with carbon atom 'C' in the plane of the pyrrole ring



and with atoms B and D having identical x and y co-ordinates.

Results of CNDO Calculations

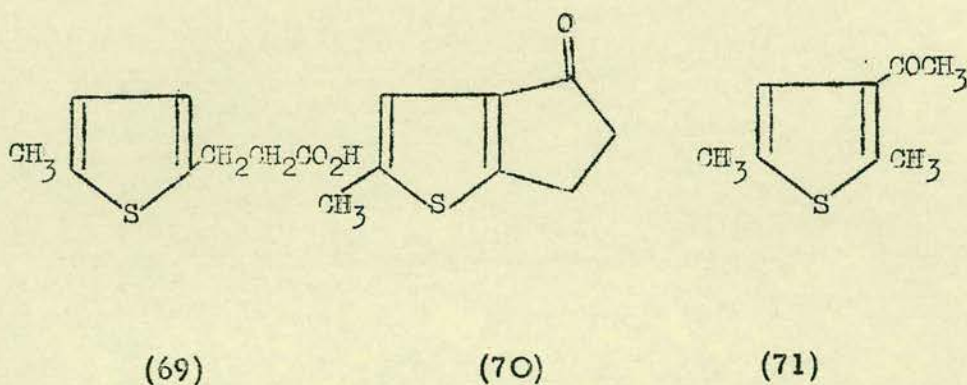
	<u>Binding Energy(a.u.)</u>	<u>Dipole Moment(Debyes)</u>
	-10.18003	0.31690 D
	-10.17543	3.31005 D
	-9.21999	18.34190 D
	-9.22421	17.93384 D
	-9.42133	4.16292 D

	<u>Binding Energy(a.u.)</u>	<u>Dipole Moment(Debyes)</u>
	-9.42334	4.22903 D
	-9.60991	2.06513 D
	-9.52999	4.71158 D
	-9.61358	4.02720 D

The calculated electron distributions in the pyrrole rings are shown in the diagrams.

1:7 The cyclisations of 5-methylthiophene-2-propionic acid and 5-methylfuran-2-propionic acid.

To discover if this rearrangement occurred in cyclisations of propionic acids of other five-membered ring heterocycles (although thiophene-2-propionic acid had been reported to cyclise normally), first 5-methylthiophene-2-propionic acid (69) was reacted with polyphosphoric acid. (69) reacted normally and cyclised at the 3- position giving 5,6-dihydro-2-methyl-4H-cyclopenta[b]thiophene-4-one (70). This was apparent from the ¹H n.m.r. spectrum of the product which showed peaks at 7.56 τ (singlet, CH₃), 7.17 τ (multiplet 2H, 6-CH₂), 6.92 τ (triplet, J = 6 Hz, 2H, 5-CH₂) and 3.28 τ (broad singlet showing some fine-structure, 1H, H-3). The lack of rearrangement



in this case is not surprising. The difference in reactivities between the 2- and 3- positions of the thiophene ring is much less than in pyrrole and although rearrangement occurs with the thioacetic acid the 2- position in that case is being activated by

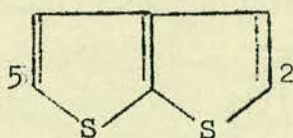
the sulphur atom of the side-chain and rearrangement of the spirocycle is aided by sulphur being a fairly good leaving group.

The 100 MHz n. m. r. spectrum of (70) showed some interesting features. Expansion of the peak at 3.28 τ from the 3-H showed it to be a quartet ($J = 1.2$ Hz) showing coupling between the 3- proton and the 2- methyl group which one might expect. However, on expansion, the peak from the methyl group at 7.56 τ was found to be, not a doublet as expected, but a 1:2:2:2:1 quintet arising from the doublet due to coupling with H-3 being further split into two overlapping triplets ($J = 0.6$ Hz). Decoupling the 6-CH₂ group caused this resonance to collapse to a doublet ($J = 1.2$ Hz). Thus, in this case, a coupling of 0.6 Hz exists between the protons of the 2- methyl group and those of the 6- methylene group (0.6 Hz) although these are separated by six bonds. No coupling between H-3 and the 6- methylene group was observed.

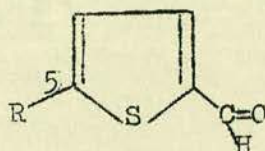
For comparison purposes 3-acetyl-2,5-dimethylthiophene (71) was prepared and its ¹H n. m. r. spectrum recorded at 100 MHz. This showed absorptions at 7.68 τ (broadened singlet, 3H, 5-CH₃), 7.66 τ (singlet, 3H, 3-acetyl), 7.44 τ (broadened singlet, 3H, 2-CH₃) and 3.11 τ (quartet, $J = 1.2$ Hz, 1H, H-4). Expansion of the broad singlet at 7.68 τ revealed it, in fact, as approximately a septet. Irradiation at 7.44 τ caused this to collapse to a doublet ($J = 1.2$ Hz) showing that a coupling exists between the

protons of the 2- and 5- methyl groups with the coupling constant estimated to be 0.3 Hz. Here we have another example of coupling extending across six bonds in a thiophene derivative.

A coupling constant of greater magnitude ($J = 1.20$ Hz) has been observed between the 2- and 5- protons of thieno[2,3-b]-thiophene (72)³⁴ and also between the aldehydic proton and H-5 ($J = 0.9$ Hz) in thiophen-2-aldehyde (73, R=H) although this was found to vanish when a 5- methyl substituent (73, R=CH₃)



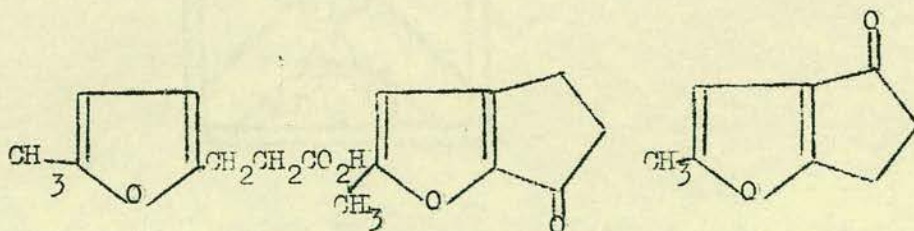
(72)



(73)

was introduced³⁵ i.e. there was no coupling between the protons of the methyl group and the aldehyde proton.

When 5-methylfuran-2-propionic acid (74) was heated with



(74)

(75)

(76)

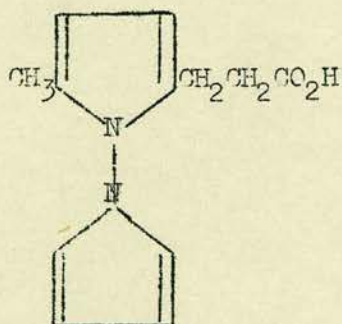
polyphosphoric acid, the product appeared to be a complex mixture. From the n.m.r. spectrum of the crude product it appeared that considerable hydrolysis of the furan ring had occurred. The spectrum

did show peaks at 4.34 τ and 3.67 τ (in the ratio of 3:1) which may have been due to the cyclic ketones (75) and (76) respectively.

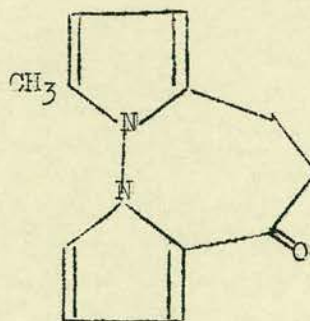
However chromatography on neutral alumina gave no separation and recrystallisation of the reaction product from petroleum ether gave a white amorphous solid which melted with decomposition over the range 140 - 170 $^{\circ}$ and appeared to be polymeric in nature.

1:8 The cyclisation of 5-methyl-1-(1-pyrrolyl)pyrrole-2-propionic acid.

The last cyclisation of a propionic acid to be attempted was that of 5-methyl-1-(1-pyrrolyl)pyrrole-2-propionic acid (77). This acid is a derivative of the 1,1'-bipyrrolyl ring system reported only recently by some German workers³⁶ who prepared some 2, 5 disubstituted derivatives. The n.m.r. spectrum of the product



(77)



(78)

suggested that the cyclic ketone (78) formed by attack of the 2'-position of the second ring represented around 75% of the total.

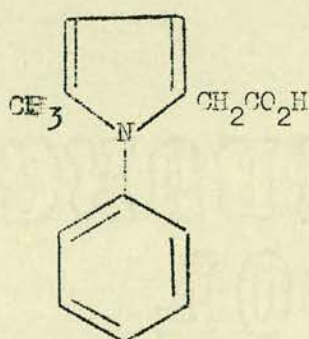
Thin-layer chromatography on silica-gel showed three components: a major band at R_F 0.7 and two minor bands at R_F s 0.2 and 0.3 respectively. These last two are characteristic values for 5-

membered ring cyclic ketones derived from pyrrole propionic acids.

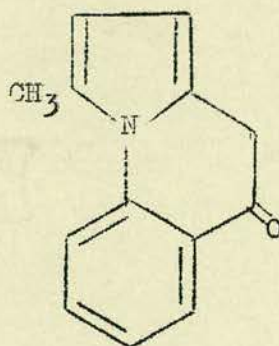
However the reaction was performed on such a small scale that chromatographic isolation of the components was not even possible and an attempt to isolate the major component by crystallisation also met with no success.

1:9 Attempted Cyclisation of 5-methyl-1-phenylpyrrole-2-acetic acid.

The cyclisation of 5-methyl-1-phenylpyrrole-2-acetic acid (79) on to the phenyl substituent to form (80) was attempted by two methods. In the first the acid was heated with polyphosphoric



(79)



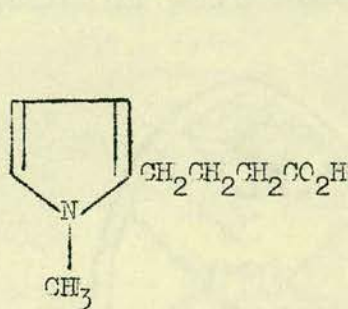
(80)

acid at 100° for three hours. The product of this reaction was an intractable brown gum from which no identifiable products could be isolated. The n.m.r. spectrum of this product also showed no resonances from pyrrole protons. The reaction was repeated this time using the conditions developed by J. F. Batchelor³⁷ for the cyclisation of indole acetic acids on to phenyl-substituents which involves refluxing the acid in acetic anhydride in the presence

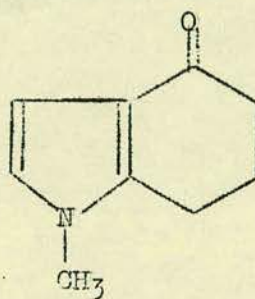
of anhydrous sodium acetate. The product of such reactions is normally the enol acetate of a six-membered ring cyclic ketone. In this case also no identifiable products could be isolated and the n.m.r. spectrum of the product again showed a total absence of pyrrole protons. The reaction was not pursued further.

1:10 Cyclisation of 1-methylpyrrole-2-butyric acid.

This acid (81) cyclised when heated with polyphosphoric acid to give one product only which was identified as 6,7-dihydro-1-methylindol-4(5H)-one (82). Clearly cyclisation to



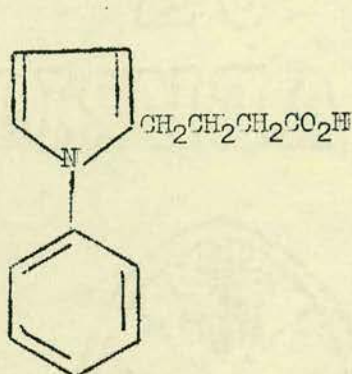
(81)



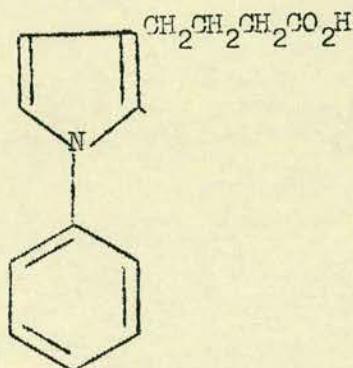
(82)

a six-membered ring is more favoured than attack of the more activated 2- position with subsequent rearrangement.

It was desired to perform the cyclisation of 1-phenylpyrrole-2-butyric acid (83) but separation of the mixture of this with the 3- isomer (84) formed by hydrolysis and reduction of the keto-esters produced by treatment of 1-phenylpyrrole with 3-ethoxycarbonylpropionyl chloride and stannic chloride proved impossible. Indeed the ¹H n.m.r. spectrum of this mixture



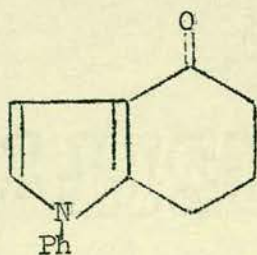
(83)



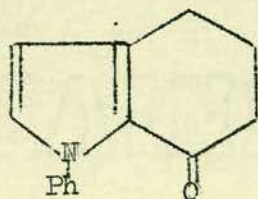
(84)

showed the proportion of 2-acid to be present in only approximately 41%.

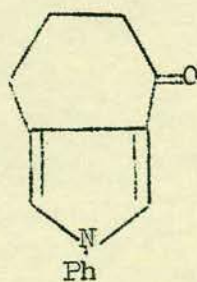
This mixture of acids was cyclised, and gave a mixture of three products. From the 100 MHz n.m.r. spectrum it was possible to estimate accurately, with the aid of double resonance, the proportions of each product formed. The products formed were 6,7-dihydro-1-phenylindol-4(5H)-one (85) (39%), 4,5-dihydro-1-phenylindol-7(6H)-one (86) (30%) and 4,5,6,7-tetrahydro-2-phenylbenzo[c]pyrrol-4-one (87) (30%). This mixture was subsequently separated by chromatography on alumina



(85)



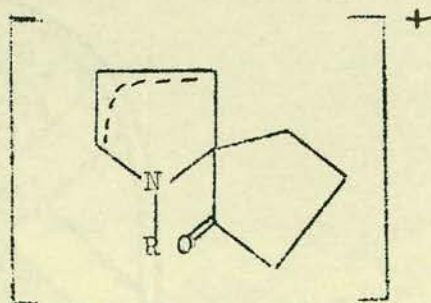
(86)



(87)

and the compounds characterised. From the ratio of the products it appears that the 2- acid (83) has cyclised without rearrangement into the 3- position forming (85) while the 3- acid (84) cyclises in equal amounts to the 2- and 4- positions forming (86) and (87) respectively. This is very unusual since, normally, pyrrole-3-alkanoic acids with a free 2- position cyclise there exclusively as this position is highly activated to electrophilic attack. However in the case of (84) the bulky 1-phenyl substituent may hinder attack at the 2- position.

The absence of rearrangement during the cyclisations of pyrrole-2-butyric acids may be due to several factors. Firstly, direct cyclisation to a strain-free six-membered ring is a very favourable reaction. Secondly, the intermediate for such a rearrangement would have to be of the form (88) with a five-membered spiro-ring. Although the ring strain is less, there are



(88)

more non-bonded interactions in this species than in the corresponding four-membered ring postulated as the intermediate in the rearrangement during cyclisation of the propionic acids.

These may decrease the stability of such a ring although this effect may be offset by the lesser ring strain.

Probably the main influence will be the higher entropy of activation for the formation of (88) since the statistical chance of having the ends of a chain meet decreases markedly as the chain length increases³⁸.

For these reasons the formation of an intermediate of the type (88) does not appear to be a very probable reaction when compared with direct cyclisation to the 3- position.

Chapter Two

Reactions of Aryloxyalkanoyl chlorides and Arylthioacetyl
chlorides with aluminium chloride.

Section One

Introduction.



2:1 Purpose of the Investigation.

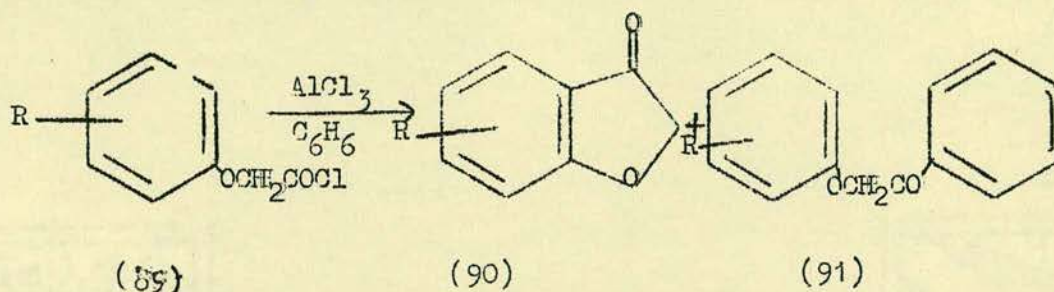
The object of this investigation was to study the reactions of some aryloxyalkanoyl chlorides with aluminium chloride in benzene where the aryl nucleus was biphenyl or a related system. In general ring-closure to a cyclic ketone was possible at two sites leading to either a five- or a seven-membered ring system. From the nature and ratios of products formed it was hoped to derive some information on the steric and electronic influences prevailing in the transition states involved.

The reaction of biphenyl-2-thioacetyl chloride was also investigated.

2:2 Reactions of aryloxyacetyl chlorides

Lewis-acid catalysed ring closure of phenoxyacetyl chlorides (89) has been a widely used method for the preparation of benzofuran-3(2H)ones (90). Most frequently the catalyst employed is aluminium chloride and the solvent benzene. Unless the aromatic nucleus is activated by an electron-donating substituent, the yield of cyclic ketone is only moderate and side-reactions occur giving rise to several products.

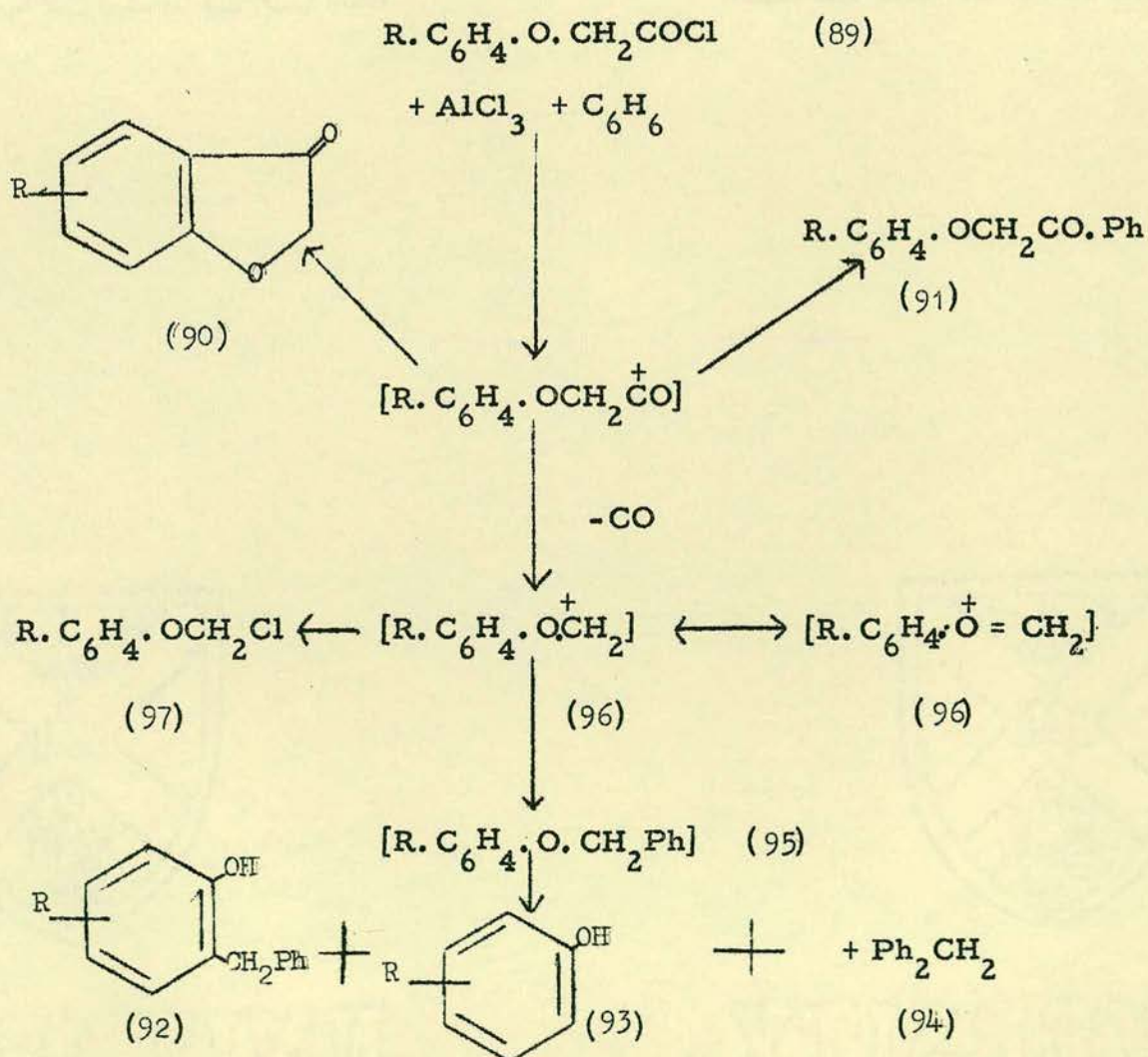
5-Methylbenzofuranone (90, R = 5-Me) was prepared³⁹ by cyclisation of 4-methylphenoxyacetyl chloride (89, R = 4-Me). Cyclisation of phenoxyacetyl chloride (89, R=H) was reported⁴⁰ to



give benzofuranone (90, R=H) and also some phenoxyacetophenone (91, R=H).

More recently, workers in this department have undertaken a detailed study of the reactions of aryloxyacetyl chlorides with aluminium chloride in both aromatic and non-aromatic (inert) solvents. Palmer and McVie showed⁴¹ that the reaction of phenoxyacetyl chloride (1 mole) (89, R=H) with aluminium chloride (1.1 mole) at 5 - 10°C for 1.5 hours in benzene (15 moles)

gave five products in addition to 10% recovered acid after hydrolysis. The major product was benzofuran-3(2H)one (90, R=H) formed by intramolecular acylation. A small amount of 2-phenoxyacetophenone (91, R=H) was also isolated. In addition to these acylation products, small amounts of phenol (93, R=H), O-benzylphenol (92, R=H) and diphenylmethane (94) were present.



The last three products are considered to arise from unimolecular loss of carbon monoxide from the acylium ion (or other reactive species) followed by alkylation of the solvent (benzene) by the resulting phenoxymethyl carbonium ion (96) and Fries-type rearrangement of the benzyl phenyl ether (95) formed to the observed products.

Benzyl phenyl ether (95) was shown to rearrange under these conditions giving the products (92), (93) and (94) in similar ratios to the acid chloride experiment. This justifies the postulate that benzyl phenyl ether is the initial decarbonylation product. Similar relationships were observed with nuclear substituted acid chlorides and the corresponding aryl benzyl ethers.

From a study of the reactions of nuclear substituted phenoxyacetyl chlorides under similar conditions, the effect of the substituent groups was determined. With strongly electron-attracting (-E, -M) groups in the 2- or 4-position (89, R = 2-NO₂, 4-NO₂, 2-CN) the only product formed was the corresponding phenoxyacetophenone (91, R = 2-NO₂, 4-NO₂, 2-CN) in 30 - 50% yield, the remaining material being accounted for as unreacted starting material isolated as the acid after hydrolysis. The low conversion is probably due to electron withdrawal from the aromatic nucleus decreasing the rate of formation of acylium ions by reducing the basicity of the chlorocarbonyl group. From this follows the implication that acylium ion formation is the rate-

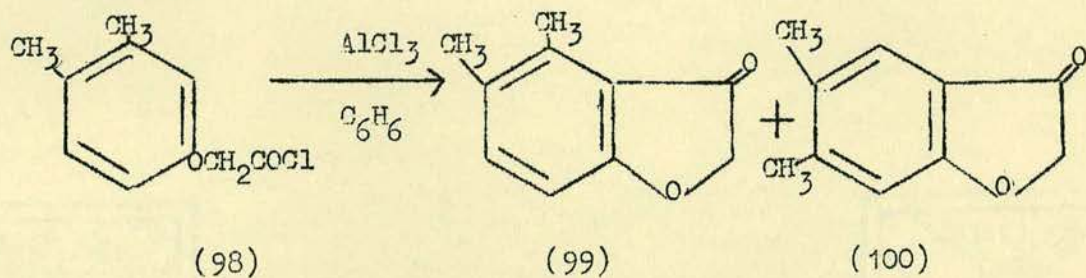
determining step in the reaction. The electron deficiency in the nucleus also accounts for the lack of decarbonylation since the aryloxymethyl cation (96) will be less stabilised by conjugation with the aromatic ring.

In inert, non-aromatic solvents it was found that phenoxyacetyl chlorides with -E, -M group, in the 2- or 4-positions lose carbon monoxide exclusively and the major product from these reactions is the chloromethyl ether (97, R = 2-NO₂, 4-NO₂, 2-CN etc.). The failure of 2,4-dinitrophenoxyisobutyryl chloride to form a similar product suggests that loss of carbon monoxide results from a bimolecular reaction involving attack by chloride or tetrachloroaluminate anion on the acylium ion.

2- and 4-Halogenphenoxyacetyl chlorides also gave the intermolecular aryloxyacetophenone as the major product in all cases (in yields of 30 - 80%). The cyclic ketones and decarbonylation products were also observed and the overall conversion to products was high as indicated by the low recovery of acid. In these cases net deactivation of the ring is still the dominant feature although offset to some extent by electron release from the halogen.

Alkyl substituted phenoxyacetyl chlorides give the cyclic ketones as the major products. In the cases of 3-alkyl and 3,4-dialkyl acid chlorides Palmer and Scollick⁴² generally found

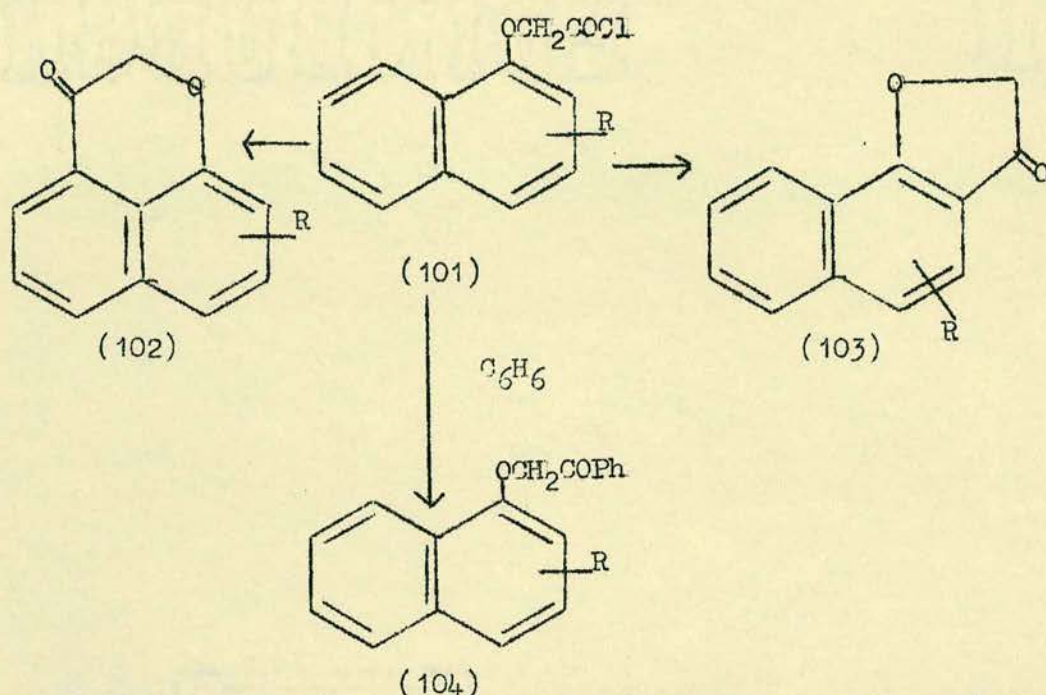
mixtures of the isomeric cyclic ketones resulting from ring closure at both of the available ortho-sites as in the reaction of 3,4-dimethylphenoxyacetyl chloride (98) which gave both 4,5-dimethylbenzofuranone (99) (24%) and 5,6-dimethylbenzofuranone (100) (76%).



Reaction of phenoxyacetyl chlorides with aluminium

chloride in aromatic solvents of greater nucleophilic character than benzene, such as p-xylene, anisole and m-dimethoxybenzene, resulted in a greater proportion of intermolecular ketoneformation over both cyclisation and decarbonylation when compared with reactions done in benzene. The more nucleophilic solvents have enhanced intermolecular acylation, as expected. These results imply that decarbonylation in aromatic solvents is a unimolecular process.

A similar study has also been undertaken ⁴³ of the reactions of a series of thirteen 1-naphthyloxyacetyl chlorides (10) with aluminium chloride in benzene. With only two exceptions, these gave an intramolecular cyclic ketone as the sole reaction product if the naphthalene nucleus was not strongly deactivated

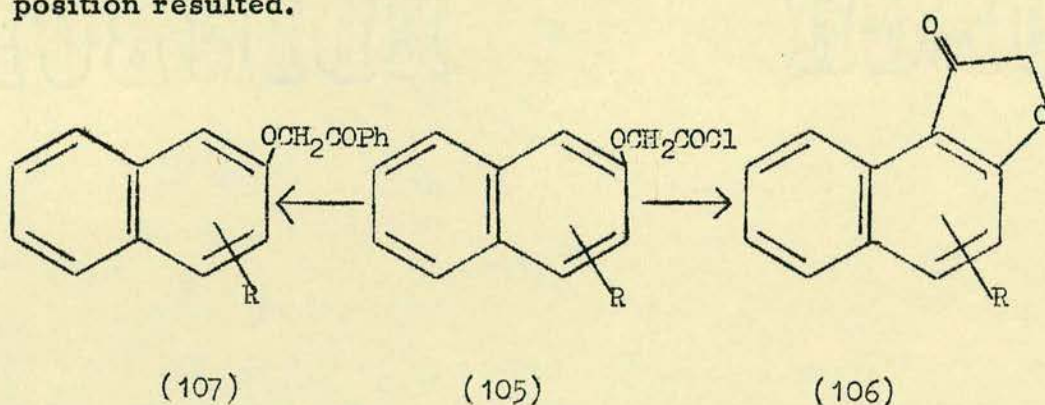


towards electrophilic attack. If the 2-position was free the cyclic ketone was always the naphtho[1,2-b]furan-3(2H)-one (103). Only when the 2-position was blocked as in 2-chloro-1-naphthyloxyacetyl chloride (101, R = 2-Cl) was the isomeric 1-oxaphenalen-3(2H) one (102, R = 9-Cl) formed. In the cyclisations of 5- and 7-methoxy-1-naphthyloxyacetyl chlorides (101, R = 5-OMe, 7-OMe) a small amount of the 2-(1-naphthyloxy)acetophenone (104, R = 5-OMe, 7-OMe) was formed in each case but the major products were the naphthofuranones (103, R = 6-OMe, 8-OMe).

When the aromatic nucleus of the acid chloride was deactivated towards electrophilic attack by a nitro-group (101, R = 3- NO_2 , 4- NO_2) cyclisation did not occur and the sole product formed was the 2-(1-naphthyloxy)acetophenone (104, R = 3- NO_2 , 4- NO_2) in low yield with the remainder of the material being

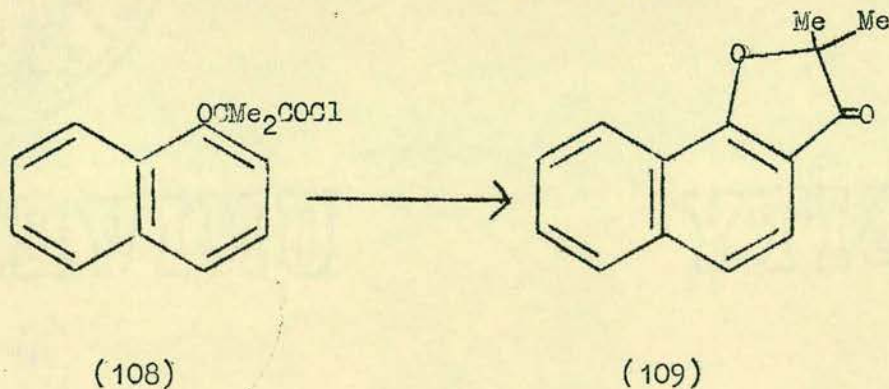
recovered as the acid after hydrolysis.

Investigation of the reactions of a series of 2-naphthyloxyacetyl chlorides (105) with aluminium chloride in benzene showed ⁴³ that if the 1-position was free then high yields of the cyclic ketones, naphtho[2,1-b]furan-1(2H)ones (106), formed by attack at that position resulted.



In a few cases a small amount (less than 10%) of the 2-(2-naphthyloxy)acetophenone (107) was also formed by acylation of the solvent. Attempted cyclisation of 1-chloro-2-naphthyloxyacetyl chloride (105, R = 1-Cl) gave the acetophenone (107, R = 1-Cl) as the only acylation product. Some decarbonylation also occurred.

2-(1-Naphthyloxy)isobutyryl chloride (108), the only side-chain substituted acid chloride investigated, gave as the only

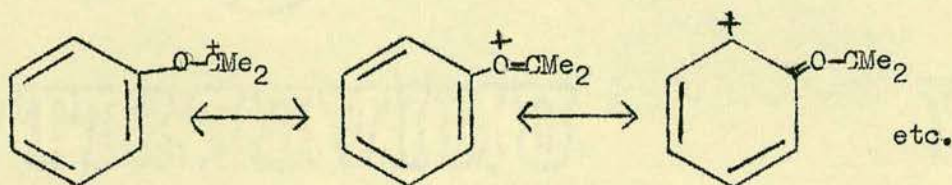


product 2,2-dimethylnaphtho-[1,2-b]furan-3(2H) one (109), the cyclic ketone formed by attack on the 2-position. No decarbonylation was observed although this might have been expected by analogy with the reaction of 2-phenoxyisobutyryl chloride which decarbonylates more readily than phenoxyacetyl chloride. Clearly the rate of decarbonylation, probably similar in the naphthyl and phenyl compounds is faster than cyclisation in the phenyl case but slower than cyclisation to the more reactive β -naphthyl position.

It has been shown by Rothstein⁴⁴ that increasing alkyl substitution of the side-chain in arylalkanoyl chlorides increases the rate of cyclisation compared to that of the less-substituted homologues. It is unlikely that this is solely an electronic effect with the side-chain substituents donating electrons into the ring and increasing the rate of cyclisation. The results appear to be more consistent with an increase in proximity effect with increasing side-chain substitution where restricted rotation allows the preferred conformation (resulting in the proximity of the acyl group to the cyclisation site) once formed to be more rigidly held in that conformation.

The rate of decarbonylation of tertiary acid chlorides is also increased. This is to be expected since a fairly stable tertiary carbonium ion will result. In the case of

aryloxyisobutryl chlorides the tertiary carbonium ion formed by decarbonylation of the acid chloride will be particularly stable since the positive charge is not only offset by the inductive effect of the methyl groups but can be delocalised throughout the aromatic ring (110).

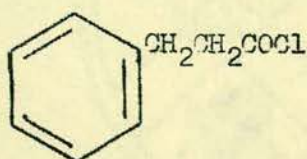


(110)

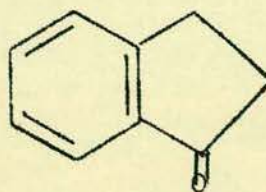
2:3 The effect of the "ether" oxygen on cyclisation

In general aryloxyacetyl chlorides containing electron-donating nuclear substituents readily cyclise in benzene without the formation of the corresponding intermolecular ketones (91)⁴², while those with electron-withdrawing nuclear substituents give the intermolecular ketones.

Comparison of the reactions of 3-phenylpropionyl chloride (111) and phenoxyacetyl chloride with aluminium chloride in benzene shows that the former gives indanone (112) as the only product in good (90%) yield while benzofuranone (90, R=H) is formed in only



(111)



(112)

44% yield along with a small amount of phenoxyacetophenone (91, R=H) the remaining products resulting from decarbonylation of the acylium ion.

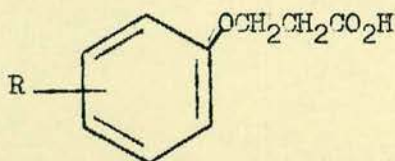
From these and other similar observations it appears that the "ether" oxygen of aryloxyacetyl chlorides does not exert any substantial effect to promote cyclisation relative to the 3-arylpropionyl analogues. This probably results from two effects.

The equilibrium conformation of aromatic ethers is in-plane with the oxygen atom approximately sp^2 hybridised. For cyclisation the $-O-CH_2-$ group must rotate out-of-plane and the hybridisation of the oxygen atom will change towards sp^3 with loss in conjugation with the ring. There is thus an overall loss in binding energy prior to the act of cyclisation i. e. a high activation energy.

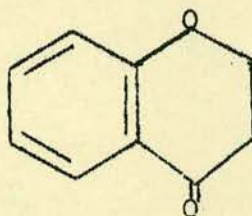
Also the electron-withdrawing effect of the positively-charged acylium ion on the aromatic nucleus will be greater in aryloxyacetyl chlorides than in 3-arylpropionyl chlorides possibly resulting in a slight relative deactivation of the ring towards cyclisation. It is unlikely that differences in proximity effect are significant since this is essentially a function of chain length and shape and the two are very similar in both respects.

2:4 Cyclisations of 3-Aryloxypropionic Acids

3-aryloxypropionic acids (113) can be cyclised to chromanones (114) in good yields under a variety of conditions. It has been



(113)



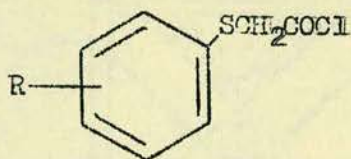
(114)

found^{45,46} that the most effective catalyst for these reactions is polyphosphoric acid, and indeed, ring closure of 3-aryloxypropionic acids containing strongly electron-withdrawing substituents e.g. nitro- has been achieved by this method⁴⁷.

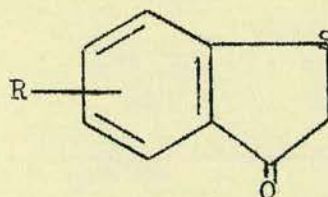
These acids cyclise much more readily than the corresponding aryloxyacetic acids and this fact can be rationalised on two accounts. Firstly the product of cyclisation is an almost strain-free six-membered ring. Secondly, in the transition state, the acylium ion can approach the site of cyclisation without causing the ether oxygen atom to distort much from the equilibrium in-plane conformation. This means there is little loss of conjugation with the aromatic ring and little loss in binding energy and, hence, a low activation energy for cyclisation. Furthermore, since the Ar-O-CH₂- portion of the molecule remains planar, the oxygen atom remains approximately sp² hybridised and, by electron release can activate the ortho-positions for cyclisation.

2:5 Reactions of Arylthioacetyl chlorides

The reactions of arylthioacetyl chlorides (115) with aluminium chloride have attracted little attention. Several groups of workers^{48, 49, 50, 51} have prepared thianaphthenones (116) by cyclisation of these compounds generally with methyl substituents but in each case have reported only moderate yields of cyclic ketones accompanied by side-products. However, no attempts were made to characterise these other products. The thianaphthenones (116) were reported to be unstable, undergoing



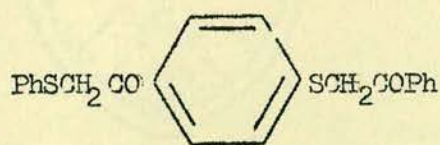
(115)



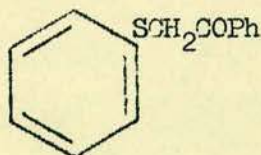
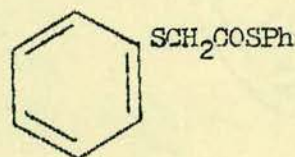
(116)

rapid air oxidation.

A recent investigation by Batchelor²³ of the reaction of phenylthioacetyl (115, R=H) chloride with aluminium chloride in benzene revealed a very complex process. After hydrolysis the products isolated were 4-(phenylthioacetyl)phenylthioacetophenone (117) (35%), phenylthioacetophenone (118) (25%), benzo[b]thiophenone (116, R=H) (11%), diphenyldisulphide (119) (4%) and phenyl phenylthiothiolacetate (120) (1%). In this case also benzothiophenone was found to be unstable with respect to air oxidation. (118) is the



(117)

(118)
Ph.S.S.Ph

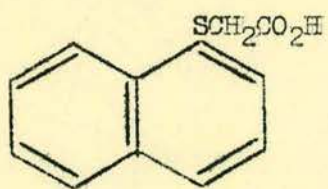
(120)

(119)

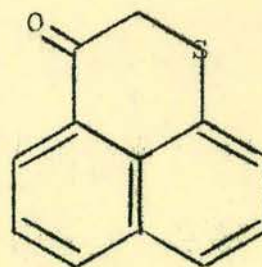
intermolecular ketone formed by acylation of the solvent and (117) arises from acylation of (118). (119) must have arisen from decarbonylation of the acylium ion but since no ortho-benzylthiophenol was found the CH_2 - group must have been lost probably as formaldehyde. The disulphide would be formed by air-oxidation of thiophenol. (120) is an ester formed by reaction of the acid chloride or acylium ion with thiophenol.

The major differences between these reactions and those of the analogous aryloxyacetyl chlorides appear to be that cyclisation occurs less readily and that decarbonylation of the acylium ion is followed by loss of the methylene group rather than attack on a benzene molecule to form an aryl benzyl thioether.

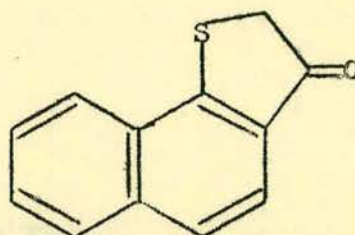
Cyclisation of 1-naphthylthioacetic acid (121) using aluminium chloride in chlorobenzene at temperatures in excess of 100° is claimed to give the peri-ketone (122)⁵² while the use of stannic chloride in the same solvent is said by the Russian workers to give also some of the naphthothiophenone (123)⁵³.



(121)



(122)



(123)

Results and Discussion

2:6 The Preparation of Aryloxyalkanoic Acids

The investigation began with a study of the reactions of the acid chlorides of biphenyl-2-oxyalkanoic acids and related systems with aluminium chloride in benzene. These acid chlorides were readily prepared from the corresponding acids by treatment with thionyl chloride. The acids were prepared from phenols which in most cases were commercially available. Only two phenols had to be prepared as outlined below.

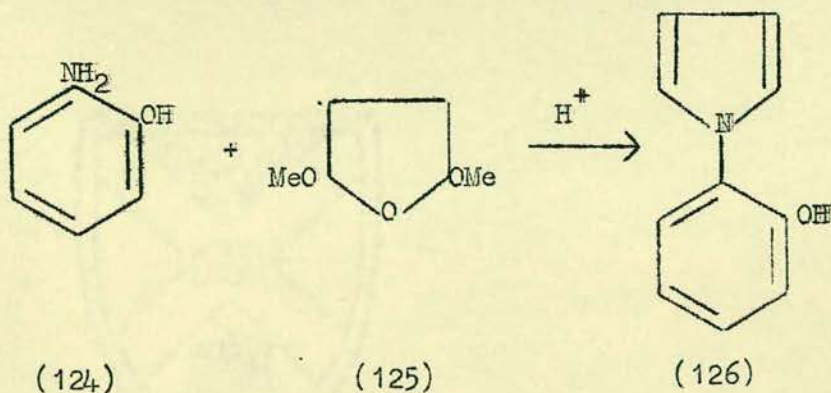
1. Phenols.

(a) 9,9-Dimethylfluoren-4-ol.

Aluminium chloride catalysed rearrangement of 6,6-dimethyldibenzo[b,d]pyran (147) in benzene gives the phenol in quantitative yield. This reaction will be discussed more fully in a later section.

(b) 1-(o-Hydroxyphenyl)pyrrole (126).

This compound was prepared in good yield by refluxing o-hydroxyaniline (124) with 2,5-dimethoxytetrahydrofuran (125) in aqueous acetic acid followed by steam distillation of the product.



2. Aryloxyacetic Acids.

(a) Biphenyl-2-oxyacetic acid and o-(1-pyrrolyl)phenoxyacetic acid.

The general method described by Hayes and Branch⁵⁴ was used to prepare these acids. The phenol was treated with sodium chloroacetate in aqueous sodium hydroxide solution. Acidification of the cooled solution followed by extraction into sodium bicarbonate and acidification of the extract gave the acids in fair yield.

(b) Biphenyl-2,2'-bisoxycetic acid and 2'-hydroxybiphenyl-2-oxyacetic acid.

Both of these acids are formed in the reaction of 2,2'-bishydroxybiphenyl with an excess of sodium chloroacetate in sodium hydroxide as described above. A single recrystallisation of the crude product from benzene affords the pure bis-acid. The liquors contain the hydroxy-acid which was converted to the methoxy-derivative using dimethyl sulphate.

(c) 9,9-Dimethylfluoren-4-oxyacetic acid.

The dry sodium salt of 9,9-dimethylfluoren-4-ol, prepared by treatment of the phenol with ethanolic sodium ethoxide and removal of the solvent, was heated with a small excess of ethyl bromoacetate and a little copper powder to form ethyl 9,9-dimethylfluoren-4-oxyacetate. This gave the acid on alkaline hydrolysis.

(d) 2-(2-Biphenyloxy)propionic acid.

The dry sodium salt of 2-hydroxybiphenyl was heated with ethyl 2-bromopropionate and a little copper powder. Hydrolysis of the ethyl 2-(2-biphenyloxy)propionate formed using aqueous potassium hydroxide followed by acidification gave the acid.

(e) 3-(2-Biphenyloxy)propionic acid.⁵⁵

3-(2-Biphenyloxy)propionitrile was prepared by the base-catalysed reaction of 2-hydroxybiphenyl with acrylonitrile. Hydrolysis of the nitrile gave the acid.

(f) 2-(2-Biphenyloxy)isobutyric acid.

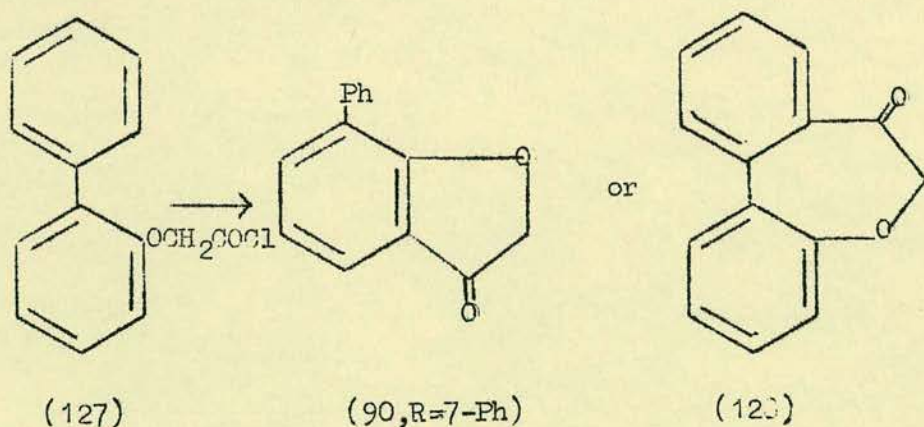
A mixture of 2-hydroxybiphenyl, acetone and sodium hydroxide was treated with chloroform and refluxed⁵⁶. Removal of excess solvent followed by acidification gave the acid.

(g) Biphenyl-2-thioacetic acid.

Two methods were used in this preparation. In the first, 2-aminobiphenyl was diazotised and the diazonium salt added to an aqueous solution of potassium ethyl xanthate⁵⁷. Hydrolysis of the xanthate ester formed gave biphenyl-2-thiol which was converted to the thioacetic acid by treatment with sodium chloroacetate in alkaline solution. The other involved treatment of biphenyl-2-diazonium chloride in neutral solution with aqueous thioglycollic acid to give the azothioglycollic acid which lost nitrogen on heating forming biphenyl-2-thioacetic acid.

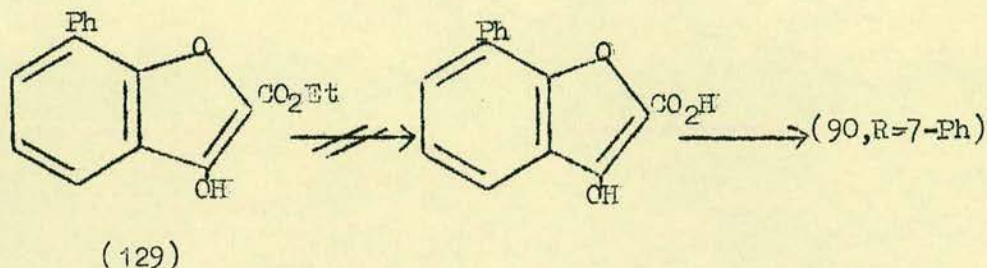
This reaction is fairly typical of an aryloxyacetyl chloride with a weakly electron-withdrawing substituent and can be compared with those of 2- and 4-halogenophenoxyacetyl chlorides.

When biphenyl-2-oxyacetyl chloride (127) was reacted with aluminium chloride in benzene, the result was quite different. Only one product was formed and in good yield (80%). This was shown by P.M.R. spectroscopy and microanalysis to be a cyclic ketone but it was not possible to differentiate between the two possible isomeric products, 7-phenylbenzofuranone (90, R=7-Ph) or dibenz[b, d]oxepin-7(6H)one (128) using I. R. ($\bar{\nu}_{\text{CO}} = 1680 \text{ cm}^{-1}$)

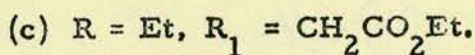
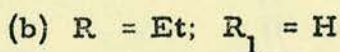
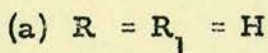
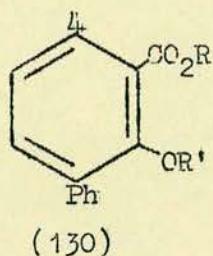


or 60 MHz N.M.R. spectroscopy ($\tau_{\text{CH}_2} = 5.2$). A similar result was obtained when the reaction was performed using carbon disulphide as solvent.

To resolve this problem an unambiguous synthesis of 7-phenylbenzofuran-3-one (90, R=7-Ph) was attempted but it proved impossible to hydrolyse and decarboxylate the ester (129).



In the synthesis of (129) a series of 3-substituted derivatives of 2-hydroxybiphenyl were prepared (130 , a - c)

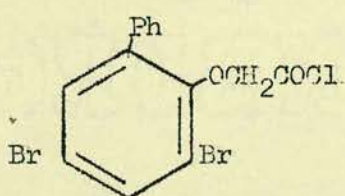


In the 60 MHz N.M.R. spectra of these compounds the deshielding effect of the 3-carboxyl group was sufficient to lower the chemical shift of the 4-proton relative to the remaining aromatic multiplet. In all cases this proton (H_4) was identified as an ortho-meta split quartet centred at around 2.0 τ ($J_{45} = 8$ Hz, $J_{46} = 2$ Hz). A similar effect is found in the spectra of 7-substituted benzofuranones and it may be expected that 7-phenylbenzofuranone would have such a low-field quartet in the aromatic region due to a single proton (H_4).

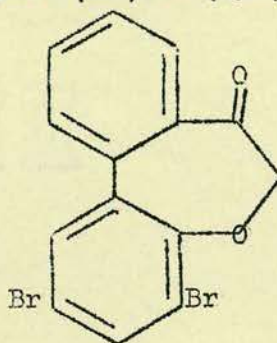
While the 60 MHz N.M.R. spectrum of the cyclisation product derived from biphenyl-2-oxyacetyl chloride gave a low-field multiplet centred on 2.1 τ from a single proton, this did not appear to be a quartet. The 100 MHz spectrum showed this to

be an octet, consistent with the proton being coupled to protons ortho-, meta- and para- to it ($J_{\text{ortho}} = 7 \text{ Hz}$; $J_{\text{meta}} = 1.8 \text{ Hz}$; $J_{\text{para}} = 0.7 \text{ Hz}$). Clearly the observed multiplicity cannot be due to the 4-proton of 7-phenylbenzofuran-3-one. The additional para-coupling allows the multiplet to be assigned to the 8-proton of dibenz[b, d]oxepin-7(6H)one (128).

Cyclisation of 3,5-dibromobiphenyl-2-oxyacetyl chloride (131) also leads to only one product. This was shown by analysis and N.M.R. spectroscopy to be a cyclic ketone and must be 2,4-dibromodibenz[b, d]oxepin-7(6H)one (132).⁵⁸



(131)



(132)

The N.M.R. spectrum of this compound also shows a low-field octet at 2.15 τ , integrating for one proton providing further evidence for the cyclic ketone from (127) being (128).

Comparison of the U.V. spectrum of this cyclic ketone with that of the known oxepinone (132) and with those of a series of 7-substituted benzofuran-3-ones also confirms the structure as (128). The long wavelength absorptions in benzofuran-3-ones ($\lambda_{\text{max}} = 320 - 340 \text{ nm}$) are due to a $\pi-\pi^*$ transition involving the

carbonyl group and are shown to be subject to the normal bathochromic (and presumably hypsochromic) effects of nuclear substituents (Table 1). The introduction of a phenyl group in the 7-position of benzofuran-3-one ($\lambda_{\max} = 325 \text{ nm}$) may be expected to give rise to two competing effects, a resulting increase in conjugation being offset by a steric inhibition of the conjugative effect of the hetero-atom with the benzofuran nucleus. It has been shown⁶⁰ that the non-coplanarity of phenyl groups in the biphenyl series is only of consequence when both the 2- and 2'-positions are substituted by large groups, resulting in the electronic interactions being isolated within each ring. For example 2,2'-dibromobiphenyl ($\lambda_{\max} = 207 \text{ nm}$) has a U.V. spectrum similar to that of bromobenzene ($\lambda_{\max} = 210 \text{ nm}$). However in 2-substituted biphenyls non-coplanarity is not significant and the spectrum is that of a typical biphenyl. That 2-phenylanisole ($\lambda_{\max} = 246 \text{ nm}$) shows a large bathochromic shift relative to anisole ($\lambda_{\max} = 217 \text{ nm}$) and a small hypsochromic shift relative to biphenyl ($\lambda_{\max} = 248 \text{ nm}$) suggests that the steric effects in the former are of secondary importance and it may be expected that the U.V. spectrum of 7-phenylbenzofuran-3-one (90) would show a marked bathochromic shift relative to benzofuran-3-one.

However, since the long-wavelength carbonyl $\pi\text{-}\pi^*$

absorptions in both 2,4-dibromodibenz[b,d]oxepinone (132)

($\lambda_{\text{max}} = 300 \text{ nm}$) and the unknown cyclic ketone ($\lambda_{\text{max}} = 307 \text{ nm}$)

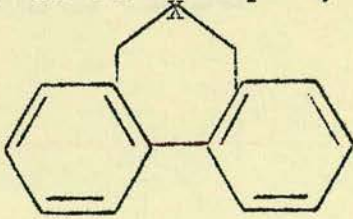
show a large hypsochromic shift relative to the corresponding

absorption in benzofuran-3-one ($\lambda_{\text{max}} = 325 \text{ nm}$), there can be

little doubt that the cyclic ketone formed by the cyclisation of

biphenyl-2-oxyacetyl chloride is dibenz[b,d]oxepin-7(6H)one (128).

It has been shown⁶⁰ that seven-membered ring systems of the type (133), which are readily formed by ring closure of 2,2'-substituted biphenyls, are strain-free when the ring-plane



(133), $X = \text{O}, \text{CHCO}_2\text{R}$

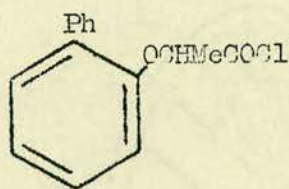
angle of the benzene rings is approximately 50° and it would appear that formation of the oxepinone is a result of the non-coplanarity of the biphenyl system allowing the extreme proximity of the acylium ion and the cyclisation site in the transition state.

2:8 The effects of Side-Chain Substituents.

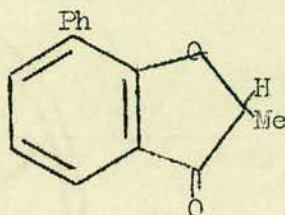
To investigate the effects of alkyl side-chain substituents on the cyclisations of biphenyl-2-oxyacetyl chlorides, the reactions of 2-(2-biphenyloxy)propionyl chloride (134) and 2-(2-biphenyloxy)isobutyryl chloride (135) were studied.

The reaction of 2-(2-biphenyloxy)propionyl chloride (134)

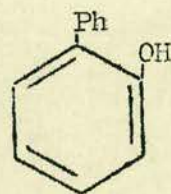
with aluminium chloride in benzene gave four types of product. A



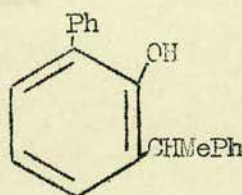
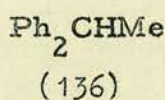
(134)



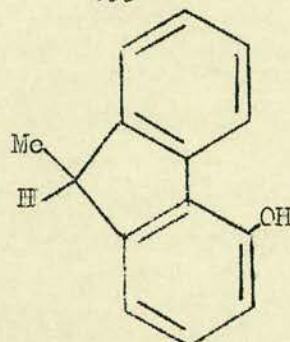
(135)



(93, R = 2-Ph)



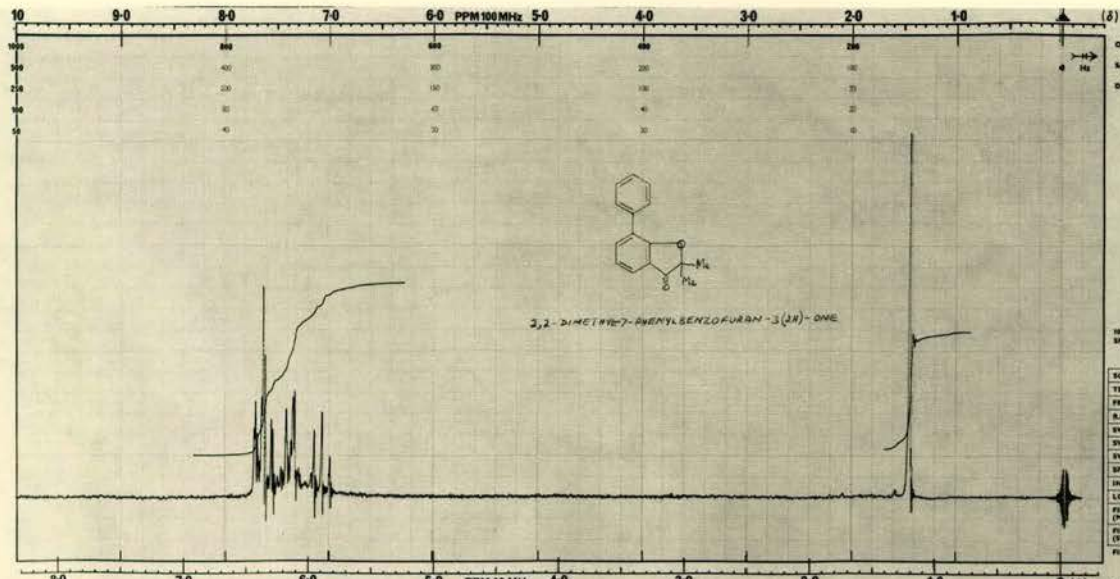
(137)



(138)

cyclic ketone formed in only 5% yield was identified by I.R.

($\bar{\nu} = 1710 \text{ cm}^{-1}$) and N.M.R. spectroscopy ($\tau_{\text{CH}} = 5.3$, quartet, no downfield aromatic octet at 2.0 τ) as 2-methyl-7-phenylbenzofuran-3-one (135). 2-Hydroxybiphenyl (93, R = 2-Ph) and 1,1-diphenylethane (136) were found in 17% and 19% yields respectively. The benzylphenolic fraction contained two components in roughly equal amounts which could not be separated. The n. m. r. spectrum of this mixture suggested the components to be 3-(1-phenylethyl)-2-hydroxybiphenyl (137) and 9-methylfluorene-4-ol (138). These decarbonylation products suggest that the carbonium ion (139) formed by decarbonylation of the acid chloride is reacting in two distinct ways. It can attack a benzene molecule forming the ether (140) which



SPECTRUM NO. 1511

OPERATOR: M.P. DATE: 11-3-72

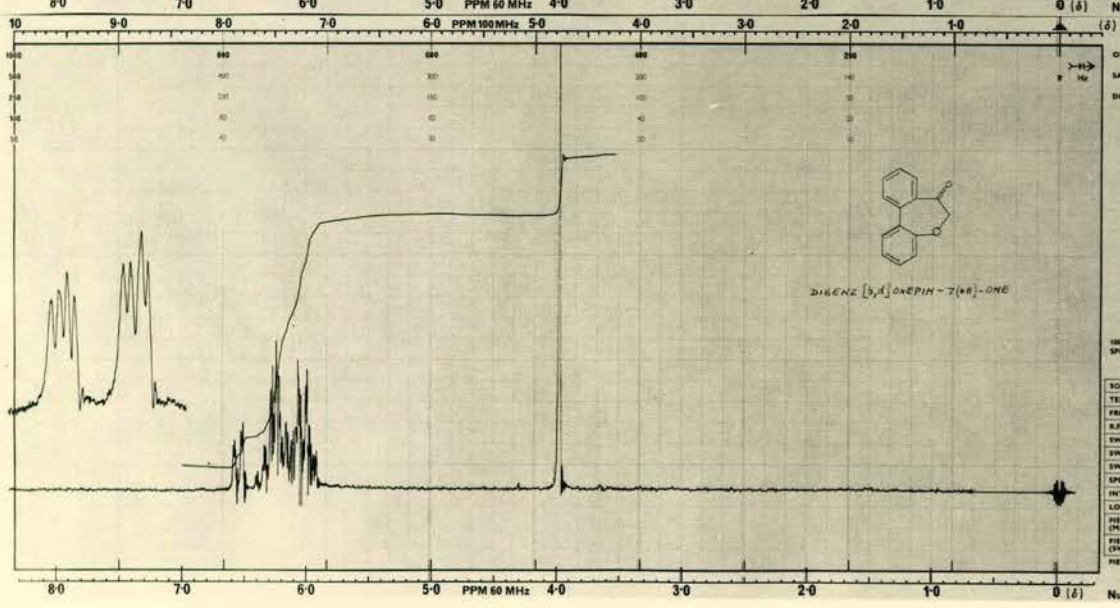
SAMPLE NO. _____

DONOR: _____

c1ccc(cc1)c2c3ccccc3oc2=O

100 MHz NMR SPECTRUM 60 MHz NMR SPECTRUM

NUCLEI	
SOLVENT	CDCl ₃
TEMPERATURE	25 °C
FREQ. RESPONSE	100 Hz
R.F. ATTENUATOR	10 db
SWEEP TIME	1.00 sec
SWEEP WIDTH	1000 Hz
SWEEP OFFSET	0 Hz
SPECTRUM AMP.	10000
INTEGRAL AMP.	10000
LOCK SIGNAL	10000
FIELD MILLIGAUSS (MAN. OSC. FREQ.)	0.0 m. gauss
FIELD MILLIGAUSS (SWEEP FREQ.)	0.1 m. gauss
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SPECTRUM NO. 1512

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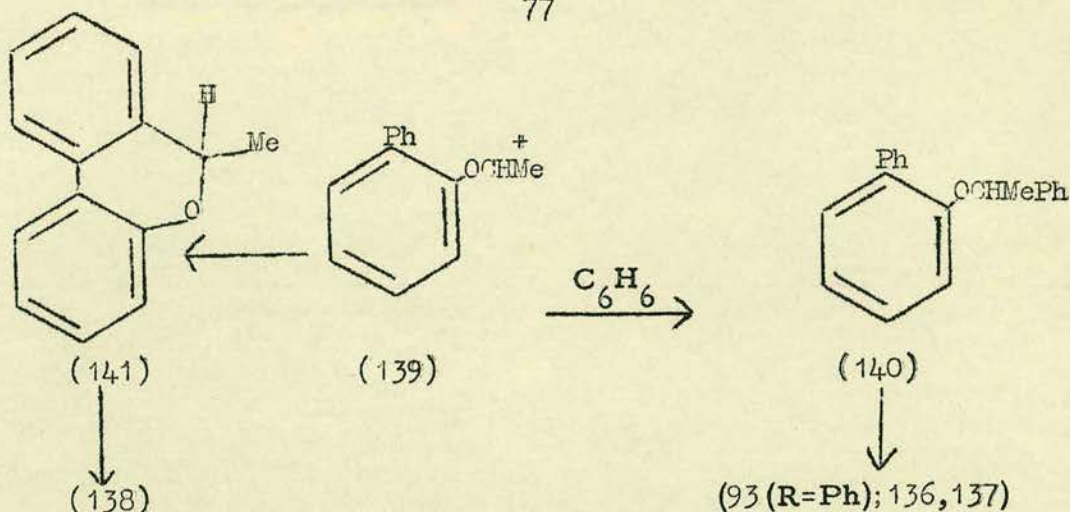
SAMPLE NO. _____

DONOR: _____

O=C1OC2=CC=CC=C2C3=CC=CC=C13

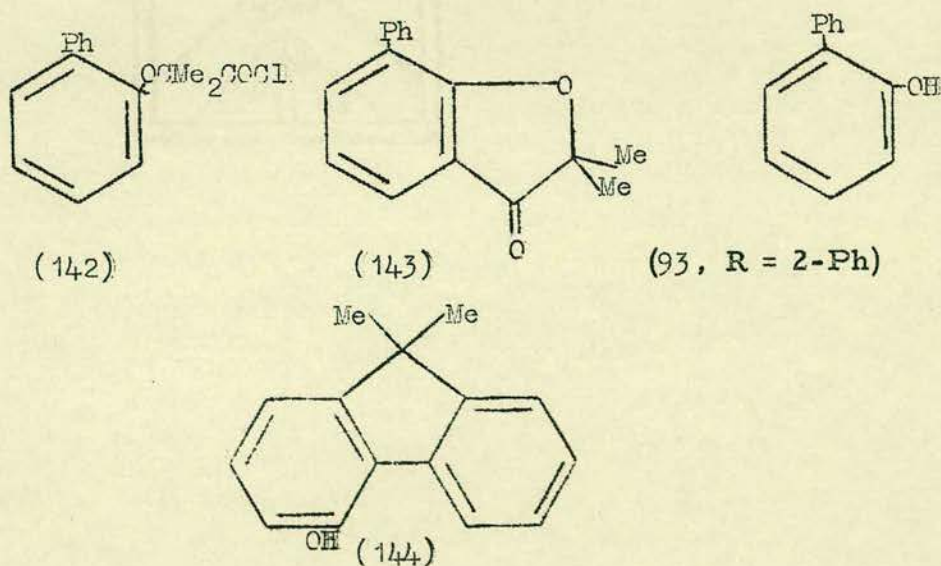
100 MHz NMR SPECTRUM 60 MHz NMR SPECTRUM

NUCLEI	
SOLVENT	CDCl ₃
TEMPERATURE	25 °C
FREQ. RESPONSE	100 Hz
R.F. ATTENUATOR	10 db
SWEEP TIME	1.00 sec
SWEEP WIDTH	1000 Hz
SWEEP OFFSET	0 Hz
SPECTRUM AMP.	10000
INTEGRAL AMP.	10000
LOCK SIGNAL	10000
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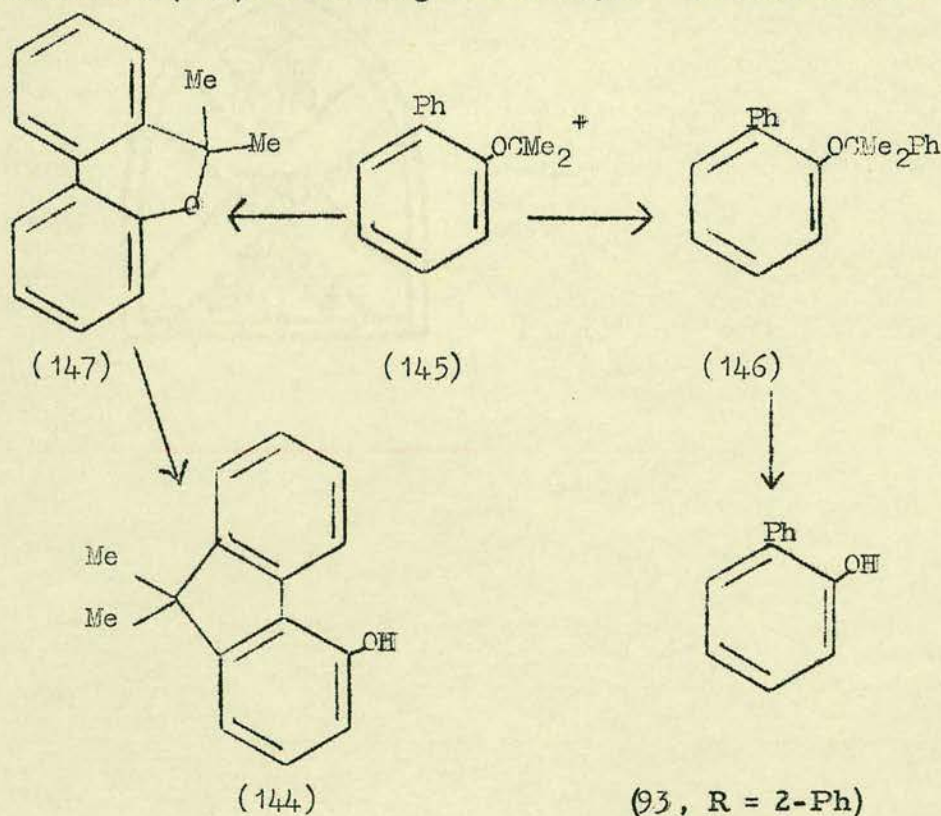
rearranges normally or it can cyclise on the 2'-position giving (141), effectively a cyclic benzyl-type ether, which rearranges to (138).

When 2-(2-biphenyloxy)isobutyryl chloride (142) was reacted with aluminium chloride in benzene, three products were isolated after hydrolysis. These were identified as 2,2-dimethyl-7-phenylbenzofuran-3-one (143) (31%), 2-hydroxybiphenyl (93, R = 2-Ph) (37%) and 9,9-dimethylfluoren-4-ol (144) (21%). Some tarry material was also formed which



proved to be intractable but was probably polymerised α -methylstyrene.

This reaction has followed a similar course to the previous one. The relative rate of cyclisation to the benzofuranone has been increased by the two methyl groups in the side-chain. Decarbonylation is again the major process and again the initial carbonium ion (145) is reacting in two ways. It can attack a



benzene molecule forming the ether (146) which then forms 2-hydroxybiphenyl and a cumyl cation which loses a proton to give α -methylstyrene which is polymerised by the aluminium chloride. Alternatively it can cyclise at the 2'-position to 6, 6-dimethyldibenz[*b, d*]pyran (147), effectively a cyclic benzyl-type ether, which rearranges to (144).

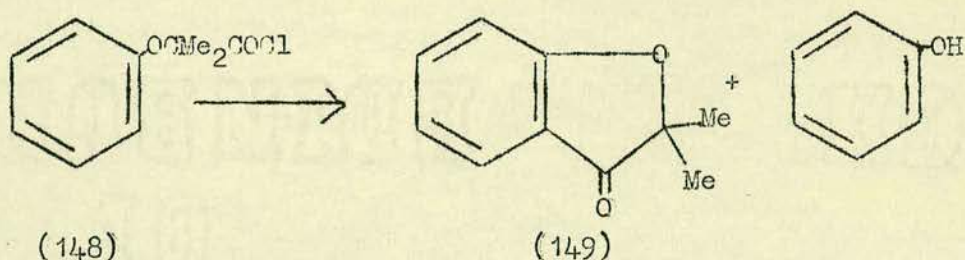
This was substantiated by preparing (147) and reacting it with aluminium chloride under similar conditions to the acid chloride. The fluorenol (144) was formed in quantitative yield.

It is difficult to find an explanation of why the cyclisation of biphenyl-2-oxyacetyl chloride gives the 7-membered ring oxepinone but that introduction of methyl groups in the side-chain of the acid chloride leads to benzofuranone formation. The answer probably lies in the substituted side-chains having a smaller O-C-CO angle than in the unsubstituted case which reduces their effective lengths and increases their curvature. This results from there being a greater steric repulsion between two geminal methyl-groups or a methyl-group and a hydrogen atom than there is between the two hydrogen atoms of a methylene group. In consequence the $\text{CH}_3\text{-C-CH}_3$ and $\text{CH}_3\text{-C-H}$ angles are slightly increased from the normal tetrahedral angle of 109.5° and this has the effect of causing the O-C-CO angle to contract, reducing the effective length of the side-chain.

With the shorter effective length of the side-chain it is possible that the acylium ion may no longer be able to reach the 2'-position of the biphenyl nucleus but, more probably, being more bent it is better able to attack the 3-position.

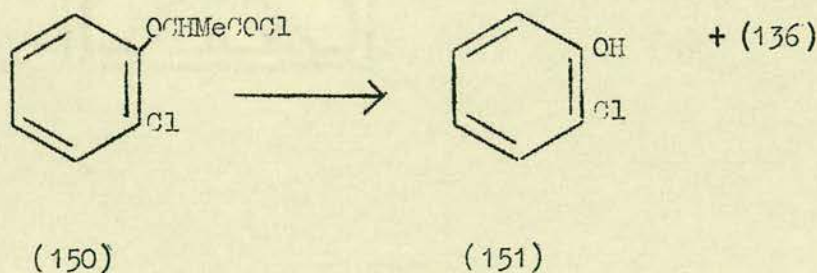
For comparative reasons, 2-phenoxyisobutyryl chloride (148) was reacted with aluminium chloride in benzene. Only two

products were isolated after hydrolysis, the cyclic ketone, 2,2-dimethylbenzofuran-3-one (149) in 36% yield and phenol, also in 36% yield. Again some tarry material was formed, probably



polymerised olefin.

These results fit very well into a pattern. The reaction of (134) can be compared with that of 2-(2-chlorophenoxy)propionyl chloride (150) which, when reacted with aluminium chloride in benzene, gives 2-chlorophenol (151) and 1,1-diphenylethane (136) as the only products⁵⁸. This side-chain appears to have difficulty

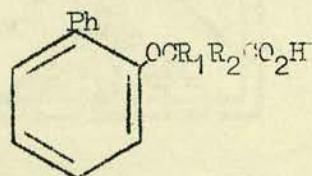


in adopting the conformation required for cyclisation and decarbonylation is enhanced since a secondary carbonium ion is formed.

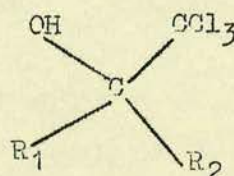
When the side-chain has two methyl substituents the rate of cyclisation is enhanced as has been previously reported⁴⁴

and decarbonylation is also favoured with a tertiary carbonium ion resulting.

In order to investigate further the effects of side-chain substitution on these reactions an attempt was made to prepare compounds of the type (152), where R_1 , R_2 are alkyl groups and $R_1 + R_2 = \text{cyclohexyl}$, by base catalysed reaction of 2-hydroxybiphenyl



(152)

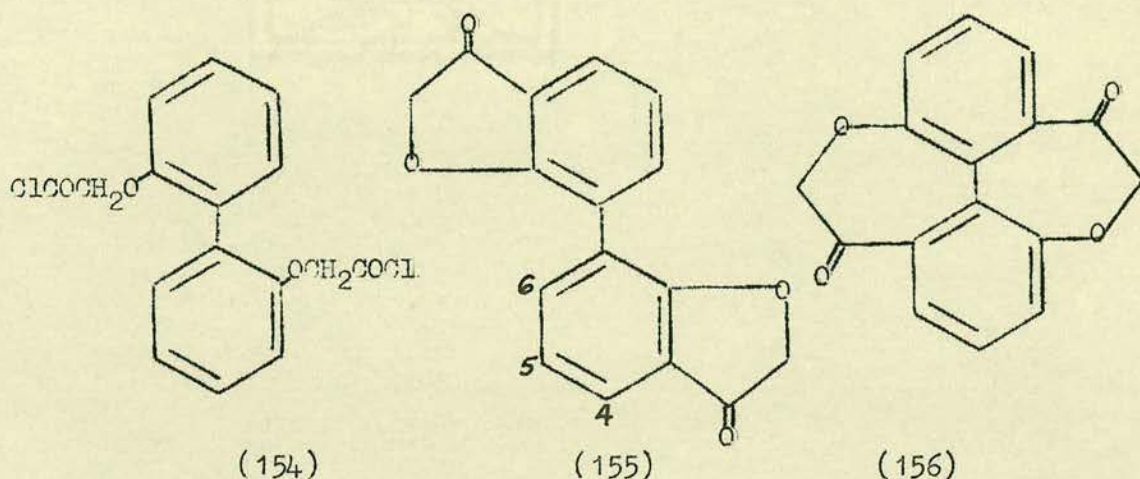


(153)

with chloroform and the appropriate ketone, The only example prepared in very poor yield was $R_1 = \text{Me}$, $R_2 = \text{Et}$ by reaction with butan-2-one. All other examples failed presumably because of steric hindrance to attack by the *o*-phenylphenoxide anion on the trichloromethylcarbinol intermediate (153). The reactions were also attempted using previously prepared (153) with similar negative results. This approach was then abandoned.

2:9 Other cyclisations

When biphenyl-2, 2'-bisoxycetyl chloride (154) was treated with aluminium chloride in benzene a complex reaction took place. Only two products were isolated pure from the mixture, diphenylmethane in 33% yield and a double cyclic ketone in 22% yield. The structure (155) is proposed for this ketone

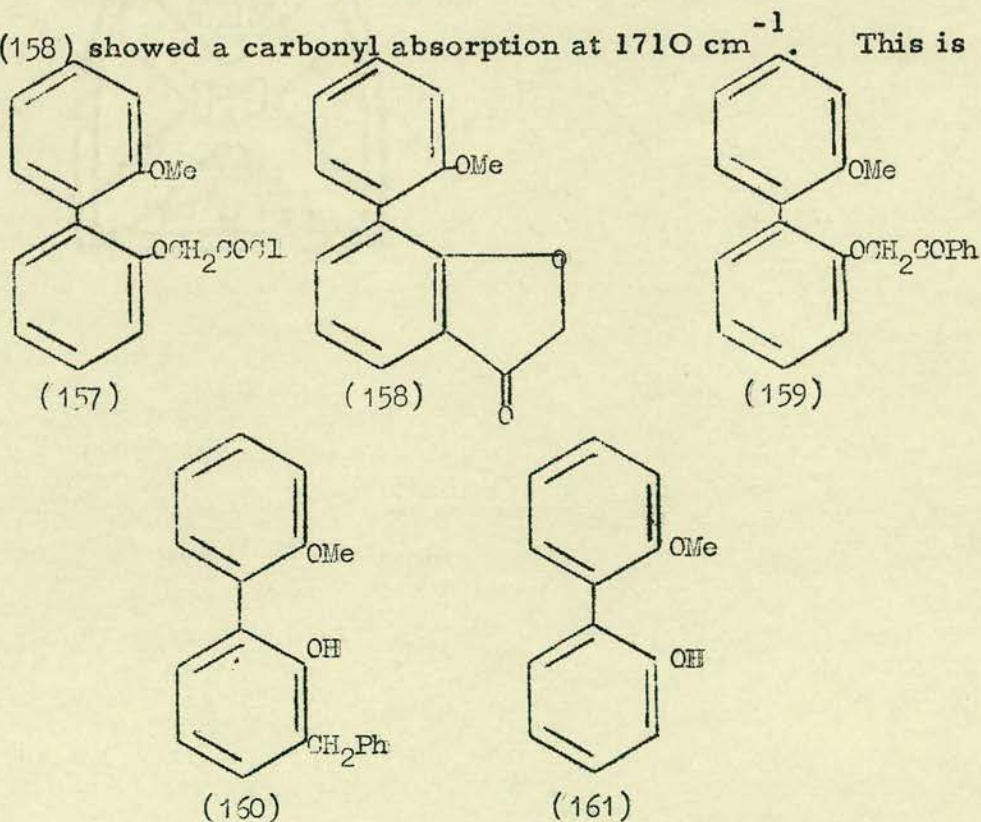


based on the spectral data and its ready reaction with aqueous base forming a red colour. The I.R. spectrum shows a carbonyl absorption at 1710 cm^{-1} which is characteristic of benzofuranones. The N.M.R. spectrum shows that the molecule has a centre of symmetry and shows absorptions at $5.0\text{ }\tau$, singlet (2H); $2.65\text{ }\tau$, triplet ($J = 8\text{ Hz}$); $2.12\text{ }\tau$, quartet ($J = 8\text{ Hz}, 1.5\text{ Hz}$) and $1.82\text{ }\tau$, quartet ($J = 8\text{ Hz}, 1.5\text{ Hz}$). The absorption at $5.0\text{ }\tau$ is assigned to the methylene groups, that at $2.65\text{ }\tau$ to the 5-H, $2.12\text{ }\tau$ to the 6-H and $1.82\text{ }\tau$ to the 4-H. In the case of the possible isomer (156) one would expect the peaks to have the same multiplicities as those observed but the order should be different with the 6-H absorbing at highest field in the aromatic region.

The remaining material was a mixture of compounds containing both phenolic and ketonic groups. None of the components could be identified.

In order to simplify the reaction but preserve similar,

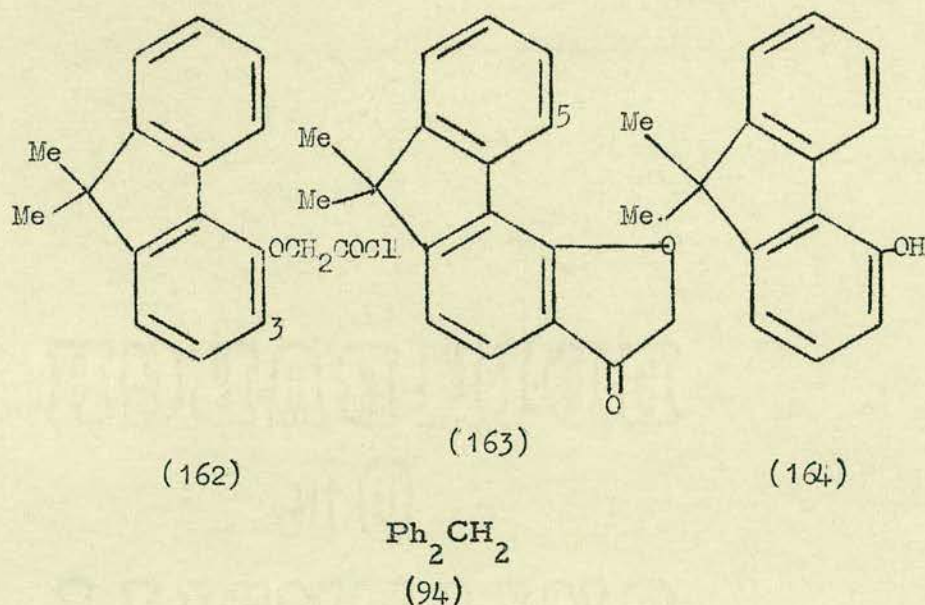
overall characteristics, 2'-methoxybiphenyl-2-oxyacetyl chloride (157) was reacted with aluminium chloride in benzene. This also proved to be a complex reaction and not all the products could be isolated. They could, however, be identified spectroscopically and the proportions estimated from the integrated N.M.R. spectrum. The reaction products were 7-(2-methoxyphenyl)benzofuran-3-one (158) (33%), 2-(2-methoxyphenyl)phenoxyacetophenone (159) (20%), the benzyl phenol (160) (7%), 2'-hydroxy-2-methoxybiphenyl (161) (19%) and diphenylmethane (11%). The I.R. spectrum of the cyclic ketone (158) showed a carbonyl absorption at 1710 cm^{-1} . This is



corroborative evidence that the cyclic ketone formed by double cyclisation of (154) is, in fact, (155).

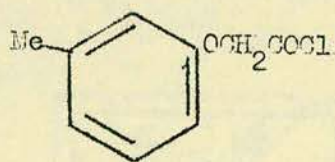
In the cyclisations of biphenyl-2-oxyacetic acids described

so far the two aromatic rings have been free to rotate with respect to each other. To investigate the effect of having the rings constrained to coplanarity, the reaction of 9,9-dimethylfluoren-4-oxyacetyl chloride (162) with aluminium chloride in benzene was studied. The 9,9-dimethyl-derivative of 4-fluorenol was used only because it is more simply prepared than the parent compound. An attempt was made to synthesise 4-fluorenol by a lengthy route starting from diphenic acid but this was unsuccessful. The methyl groups are sufficiently remote that their effect should be

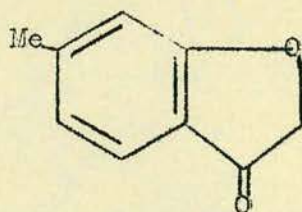


negligible. The major reaction in this case is cyclisation to a 5-membered ring with the product (163) accounting for 87% of the product. That (163) and not the isomeric seven-membered ring system is the correct structure is shown by a low-field multiplet at 2.15 τ in the N.M.R. spectrum from the 5-H which characteristically shows a low-field resonance in 4-substituted fluorenes. The other

products were 9,9-dimethylfluoren-4-ol (164) and diphenylmethane, each formed in 3% yield from decarbonylation. In this case the ortho-position of the second ring is not in a suitable position for acylation and the oxepinone is not formed. However the 3-position of (162) is activated by the isopropylidene-group of the fluorene nucleus and cyclisation readily occurs there. An analogy can be drawn with the reaction of 3-methylphenoxyacetyl chloride (165) which cyclises to (166) in 83% yield⁴² where the methyl group activates the position para-to itself to electrophilic



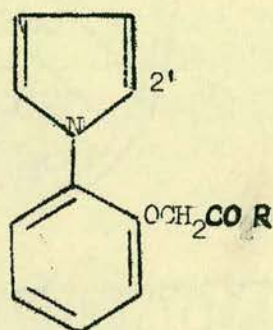
(165)



(166)

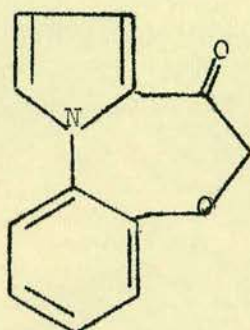
attack.

At a later date, during a study of the cyclisation reactions of substituted pyrrole alkanolic acids, 2(1-pyrrolyl)phenoxyacetic acid (167a) was prepared. This acid had previously been cyclised, using polyphosphoric acid as a condensing agent, by Cheeseman and Roy⁶¹, who found that 4-oxopyrrolo [2,1-d]-1,5-benzoxazepin (168) was formed in only 8% yield along with 6% of benzo-2H, -1,4-oxazin-3(4H)one (169). The latter product has presumably arisen from attack of the acyl group on the nitrogen atom of the pyrrole ring followed by

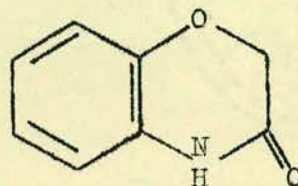


(167)

(a) R = OH

(b) R = NMe₂

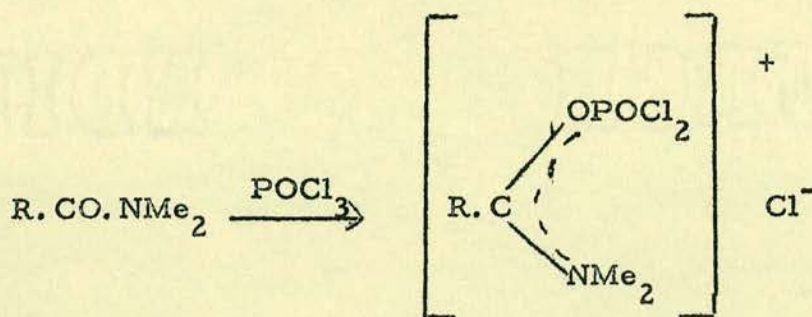
(168)



(169)

elimination of the rest of the ring. The formation of (168) as the primary acylation product is analogous to (128) resulting from cyclisation of biphenyl-2-oxyacetyl chloride when the 2'-position is easily attacked by the acylium ion. In this case, the 2'-site is also an α -position of a pyrrole ring and highly activated to electrophilic attack. The low yield of (168) is presumably due to acid-catalysed decomposition of the pyrrole ring during the cyclisation.

It is well-known that the Vilsmeier⁶² reaction, involving treatment of a five-membered-ring heterocycle with a tertiary amide and phosphorus oxychloride is a better method of introducing acyl substituents than normal Lewis-acid-catalysed acylation. The reaction is thought to proceed via the intermediate (170) formed by interaction of the amide and phosphorus oxychloride.



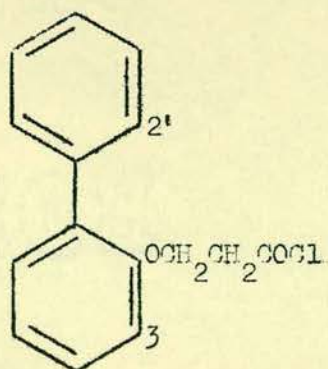
(170)

With this in mind the dimethylamide of the acid (157b) was

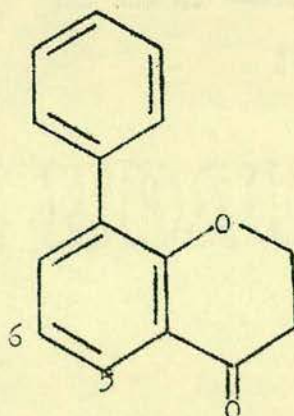
prepared and treated with phosphorus oxychloride in ethylene dichloride as solvent. Cyclisation to (168) occurred in 53% yield and no other products were observed.

2:10 Cyclisation of 3-(2-biphenyloxy)propionyl chloride

One example of the reaction of a 3-aryloxypropionyl chloride with aluminium chloride in benzene was examined, that of 3-(2-biphenyloxy)propionyl chloride (171). In this case, cyclisation at the 2'-position would give an 8-membered ring and at the 3-position a 6-membered ring. A previous report⁵⁵ states that (171) cyclises to 8-phenylchromanone (172). Only one product is formed in the reaction. Its I. R. spectrum shows a



(171)



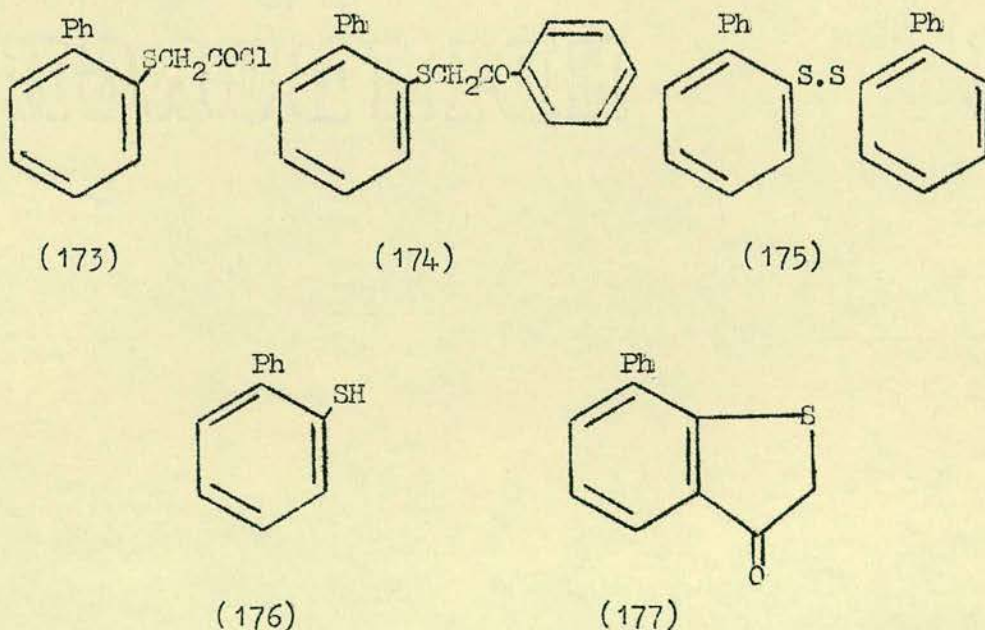
(172)

carbonyl absorption at 1690 cm^{-1} and the N.M.R. spectrum has absorptions at $7.4\ \tau$, triplet ($J = 7\text{ Hz}$), 2H ; $5.68\ \tau$, triplet ($J = 7\text{ Hz}$), 2H ; $2.66\ \tau$, multiplet, 8H . The fine structure of the aromatic region reveals a triplet at $3.07\ \tau$ ($J = 8\text{ Hz}$) assigned to H-6 and a quartet centred on $2.04\ \tau$ ($J = 8\text{ Hz}$, 2Hz) assigned to H-5, showing that (172) is indeed the product formed.

2.11: Reaction of Biphenyl-2-thioacetyl chloride

a) In Benzene

When biphenyl-2-thioacetyl chloride (173) was reacted with aluminium chloride in benzene, the only acylation product formed was 2-(2-biphenylthio)acetophenone (174). A trace amount of a



second component was isolated which did not contain a carbonyl group. Although not fully identified this was thought to be 2-biphenyl disulphide (175) formed by air oxidation of biphenyl-2-thiol (176).

The I.R. spectrum of the crude reaction product did show a small

absorption at 2250 cm^{-1} which could be a thiol S-H stretch. No other decarbonylation products were found, however.

b) In an Inert Solvent

The reaction was repeated using sym-tetrachloroethane as solvent to prevent intermolecular ketone formation. The sole product under these conditions was a cyclic ketone to which the structure 7-phenylbenzothiophenone (177) has been assigned from its I. R. ($\bar{\nu}_{\text{C=O}} = 1700\text{ cm}^{-1}$) and N. M. R. (absence of low-field octet in aromatic region) spectral characteristics. This compound was air-sensitive and oxidized readily on exposure to the atmosphere and could only be isolated as the oxime derivative.

Chapter Three

Rearrangements of Aryl Benzyl Ethers.

Section One .

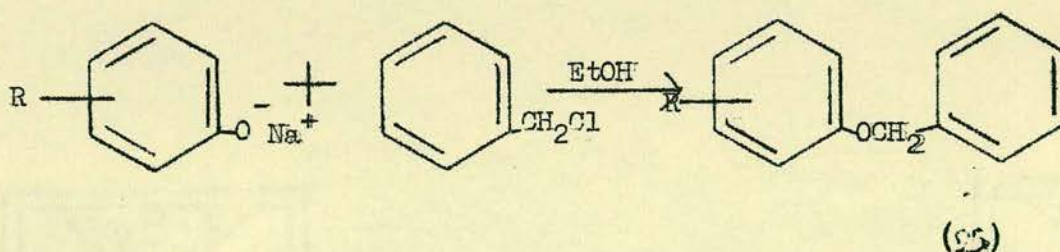
Introduction

3:1 Scope of the Investigation.

The rearrangement reactions of a number of aryl benzyl ethers when treated with aluminium chloride in benzene have been investigated with particular reference to cases where the aryl group is biphenyl. It was found that in most cases the distribution of products was consistent with the reaction proceeding via a π -complex intermediate which either rearranged to an ortho-benzylphenol or was attacked by a solvent molecule.

3:2 Historical Background.

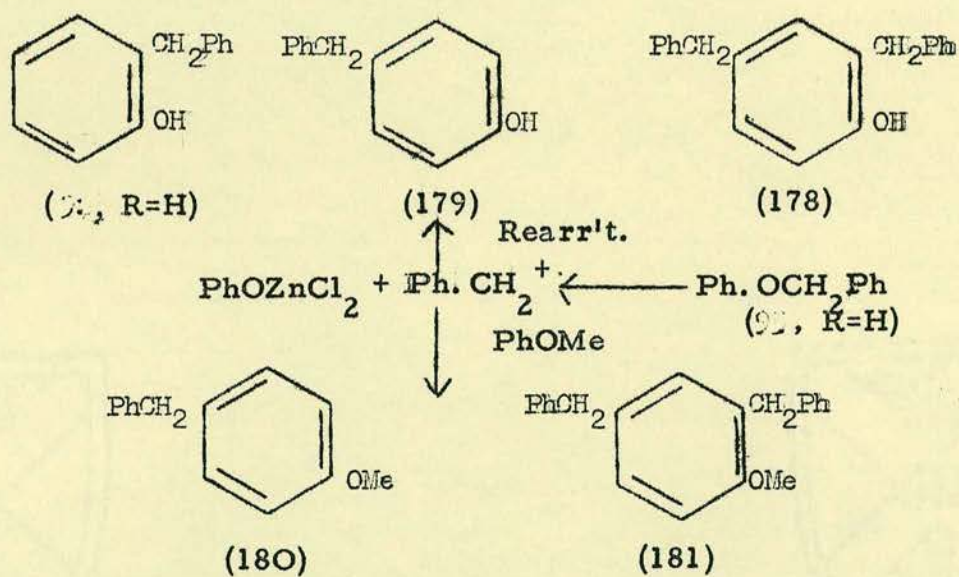
The general method of synthesis of the aryl benzyl ethers used in this study has been by the reaction of the sodium salt of a phenol with an equimolar proportion of benzyl chloride in ethanol solution. Conversion to the ether is high and alcoholysis of the halide of little importance. These reactions are reported extensively in the literature and take place under a variety of basic conditions^{63, 64.}



Aryl benzyl ethers (95) have long been known to rearrange when treated with Lewis Acids but only comparatively recently has it become apparent that two distinct mechanisms operate

depending on the conditions of the reaction.

Benzyl phenyl ether (92, R=H) undergoes zinc-chloride catalysed rearrangement at 160° in the absence of a solvent to give a mixture of 2- and 4- benzylphenols (92, R=H, 179) in a molar ratio of 1:2⁶³ with some 2,4-dibenzylphenol (174) also produced. In anisole at 100°C these same products are also formed in similar molar ratios together with large amounts of 4-benzylanisole (180) and 2,4-dibenzylanisole (181).

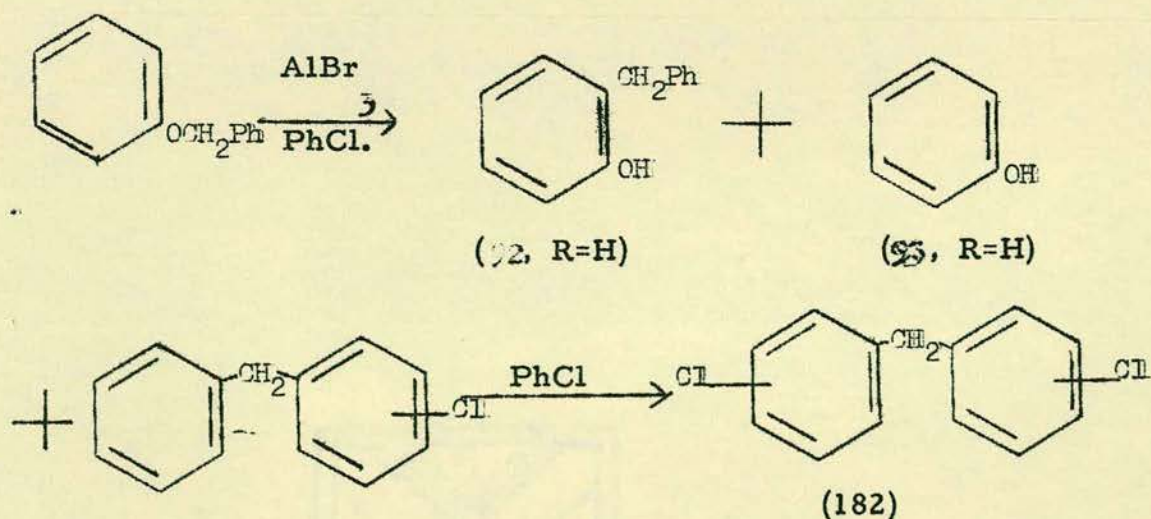


The nature and proportions of the products are consistent with the formation of a free benzyl carbonium ion which attacks the phenol or anisole in a competitive intermolecular reaction. The intermolecular nature of such rearrangements has been substantiated by the zinc chloride-catalysed rearrangement of benzyl 2-methylphenyl ether (92, R = 2-Me) where the ratio of 4- and 6-benzyl- and 4,6-dibenzyl-2-methyl phenols obtained was

similar to that found in the direct benzylation of 2-methylphenol (95, R = 2-Me) using benzyl alcohol and zinc chloride⁶⁵.

Hickinbottom has shown⁶⁶ that aryl benzyl ethers will also undergo thermal rearrangement. The product ratio again suggests the reaction is intermolecular. When benzyl phenyl ether (95, R=H) is refluxed for several days the phenolic fraction of the products contains 2-benzylphenol (92, R=H), 4-benzylphenol (179) and 2,4-dibenzylphenol (178). Similar results were obtained using substituted aryl benzyl ethers.

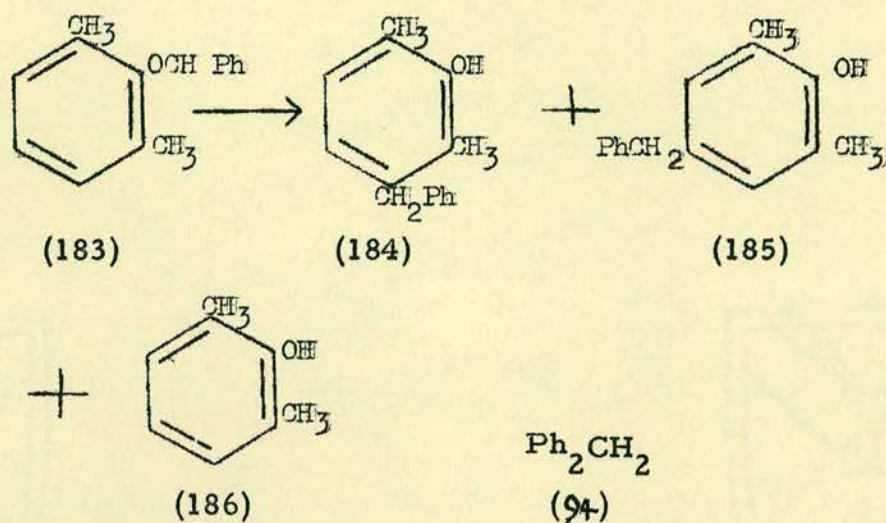
A striking contrast is shown in the aluminium bromide-catalysed rearrangement of benzyl phenyl ether at low temperature in chlorobenzene as solvent⁶⁷. Kinetic studies showed that the ether was rapidly converted to a mixture of 2-benzylphenol (92, R=H) (55%), phenol (93, R=H) (40%) and a mixture of isomeric di-(chlorophenyl) methanes (182). This was followed by a



slow unimolecular conversion of 2-benzylphenol to phenol and (182). The notable feature of this reaction is the formation of 2-benzylphenol as the sole rearrangement product. The absence of 4-benzylphenol and 2,4-dibenzylphenol suggests an intramolecular process.

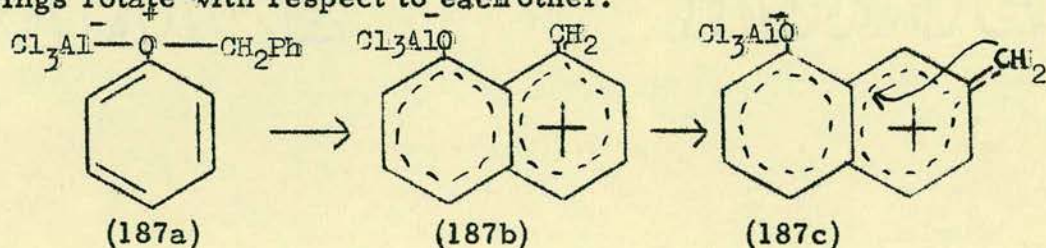
Palmer and McVie⁶⁸ studied the reactions of a series of aryl benzyl ethers with aluminium chloride in benzene and found that when there was a vacant ortho-position in the aryl nucleus, the rearrangement product was always the 2-benzylphenol with no more than a trace of other isomers. The other products in these rearrangements are always the parent phenol (5) and diphenylmethane (24) formed in equimolar proportions by intermolecular attack of solvent on the intermediate.

Only when both ortho-positions were blocked were meta- and para-benzylphenols formed with the meta-isomer predominating. In the reaction of 2,6-dimethylphenyl benzyl ether (183), the rearrangement products were 3-benzyl-2,6-dimethylphenol (184), the meta isomer, and 4-benzyl-2,6-dimethylphenol (185), the para isomer, in the ratio 3:1. The same compounds were formed

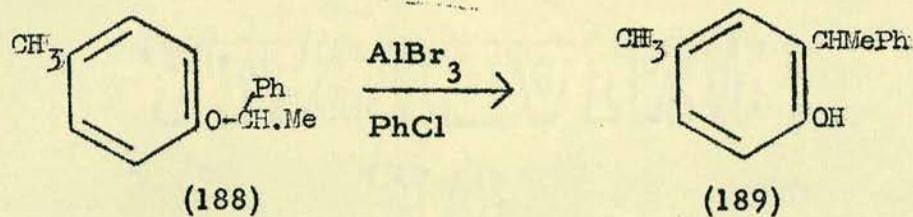


in opposite proportions by direct benzylation of 2,6-xyleneol (186) using benzyl chloride and aluminium chloride. Thus intermolecular electrophilic attack gave largely para-substitution while intramolecular rearrangement gave mainly meta-substitution.

These results are consistent with the formation of a π -complex intermediate (187b), as suggested by Dewar⁶⁹, in which the two rings rotate with respect to each other.



Further evidence for a π -complex intermediate is found in the work of Hart and Elia⁷⁰ who showed that the aluminium bromide-catalysed rearrangement of optically active α -methylbenzyl 4-methylphenyl ether (188) gave 2-(α -methylbenzyl)-4-methylphenol (189) with 75% retention of optical activity.



These results and others to be presented later lead to the conclusion that the Lewis-Acid catalysed rearrangements of aryl benzyl ethers in aromatic solvents at low temperatures proceed via a π -complex intermediate. At higher temperatures a free carbonium ion mechanism operates.

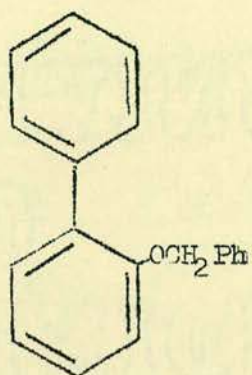
Section Two.

Results and Discussion.

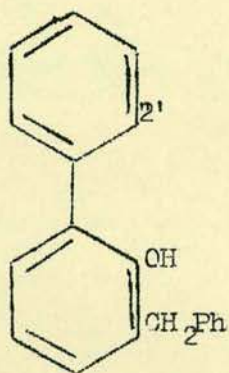
3:3 Rearrangements of Aryl Benzyl Ethers.

The reactions of a series of benzyl biphenyl ethers with aluminium chloride were investigated. These were all carried out at low temperatures ($5-10^{\circ}$) by adding a solution of the ether in benzene to a stirred suspension of aluminium chloride in benzene. After a reaction time of around two hours the mixture was hydrolysed by pouring into ice-cooled dilute hydrochloric acid. The reaction products were extracted into benzene from the hydrolysis mixture. From the integrated n.m.r. spectrum of the crude product it was possible to obtain a good indication of the relative amounts of each product formed. Separation of these products was generally achieved by extraction of the parent hydroxybiphenyl into aqueous 2M sodium hydroxide followed by chromatography of the residue on alumina to isolate diphenylmethane and the benzyl phenol.

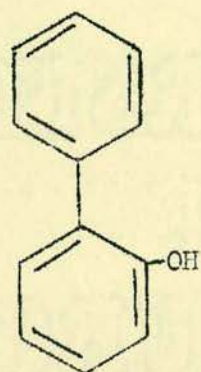
The product distributions from the rearrangements of benzyl 2-biphenyl (190) and benzyl 4-biphenyl (191) ethers were very similar. In the latter case 3-benzyl-4-hydroxybiphenyl (192), the ortho-benzyl phenol accounted for 33% of the product. Also isolated were 4-hydroxybiphenyl (193) (43%) and diphenylmethane (67%). The molar amounts of these two components should be equal. However (193) is only moderately soluble in dilute sodium hydroxide and not all can have been extracted. The remainder



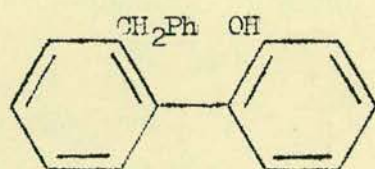
(190)



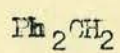
(194)



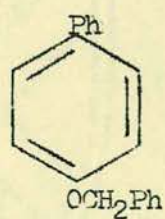
(195)



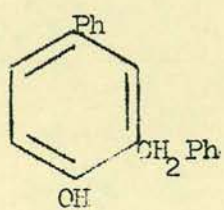
(196)



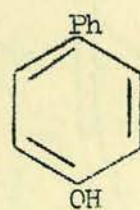
(94)



(191)



(192)

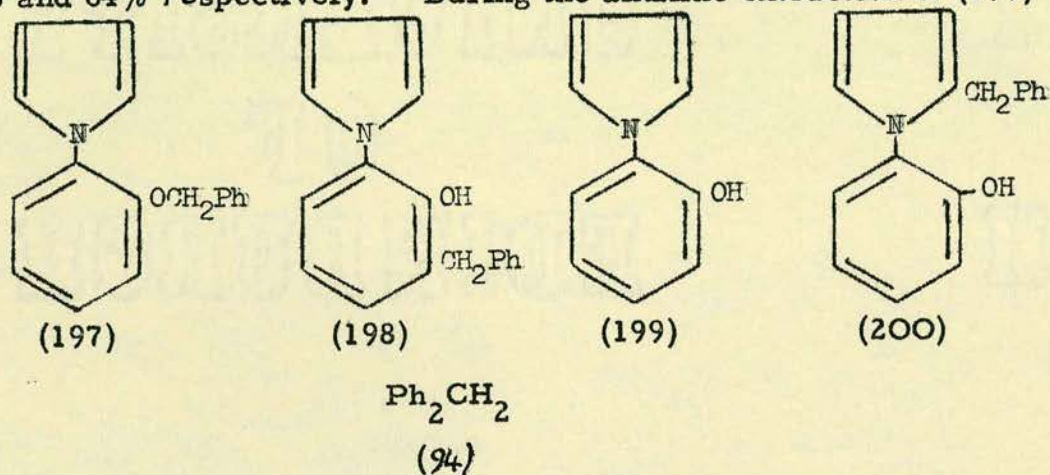


(193)

would remain on the column during the chromatographic separation of (192) and (94). The proportion of rearrangement is quite low probably because the ortho-position in this case while being activated by the oxygen atom is also the 3-position of the biphenyl nucleus and meta- to the other phenyl group. It is therefore not particularly favoured in electrophilic attack. In the case of benzyl 2-biphenyl ether (190), 3-benzyl-2-hydroxy biphenyl (194), the product of ortho-rearrangement, comprised 31% of the total along with 67% and 69% of 2-hydroxybiphenyl (195) and diphenylmethane respectively. It is interesting to note that none of the isomeric 2'-benzyl-2-hydroxy biphenyl (196) was detected in the benzyl phenolic fraction. This is further confirmation that such rearrangements proceed through a π -complex intermediate (187b) in which rotation of one ring leads to substitution at a vacant ortho-position (187c) since the 2' position, although quite sterically hindered, is very susceptible to electrophilic attack and if a free benzyl cation had been formed it would probably, in part, have attacked that position.

A more striking example of the intramolecular nature of this rearrangement is found in the reaction of benzyl 2-(1-pyrrolyl) phenyl ether (197) with aluminium chloride. The benzyl group again rearranges to the 3-position although only 11% of 2-benzyl-6-(1-pyrrolyl)-phenol (198) is formed. Also isolated were

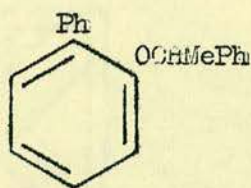
2-(1-pyrrolyl) phenol (199) and diphenyl methane (94) in yields of 35% and 64% respectively. During the alkaline extraction of (199)



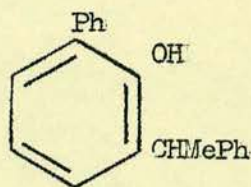
some dark insoluble material was encountered. This was thought to be the salts of the polymeric phenols formed by the action of the Lewis acid on (199) and probably accounts for the small amount of (199) actually isolated.

There was no evidence at all of benzyl substitution of the pyrrole ring which would be inevitable if a free carbonium ion was involved in the rearrangement. The α -positions especially are so highly activated to electrophilic attack that a benzyl carbonium ion would certainly substitute there forming (200). The total absence of this is further strong evidence in support of the intermediate being a species of the type (187b).

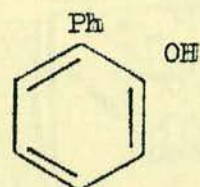
2-Biphenyl 1-phenyl ethyl ether (201) rearranges in a very similar fashion to (190). The ortho-(1-phenylethyl) phenol (202) forms 35% of the product and 2-hydroxybiphenyl (195) and



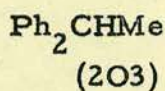
(201)



(202)



(195)



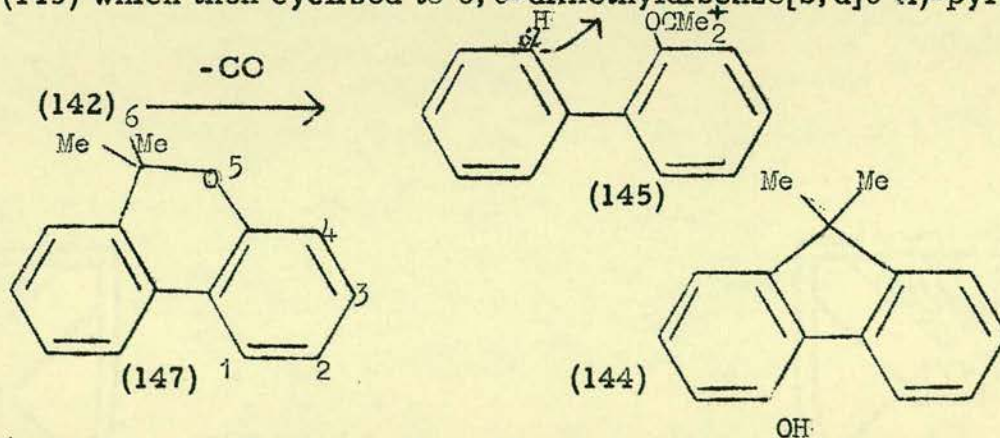
(203)

1,1-diphenylethane (203) account for 48% and 55% respectively.

Methyl substitution of the benzyl group appears to have negligible effect on the reaction.

3:4 Rearrangements of Cyclic Ethers.

One of the products formed when 2-(2-biphenyloxy) isobutyryl chloride (142) was treated with aluminium chloride in benzene was shown to be 9,9-dimethylfluoren-4-ol (144). This was thought to occur by decarbonylation of the acid chloride giving the carbonium ion (145) which then cyclised to 6,6-dimethyldibenzo[b,d]6'H)-pyran

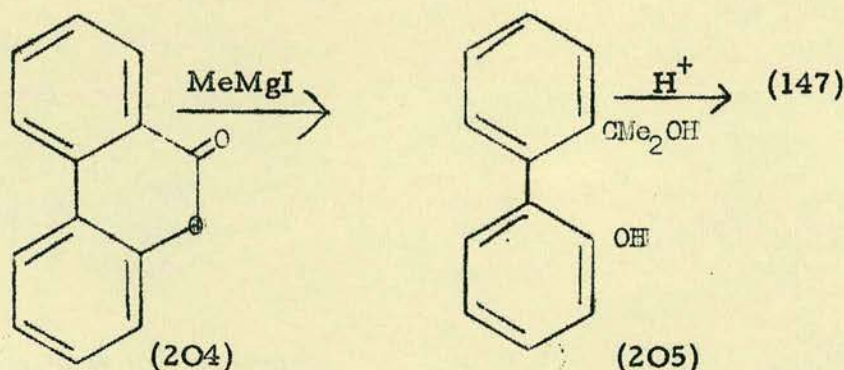


(147) which is in effect a cyclic, side-chain substituted benzyl

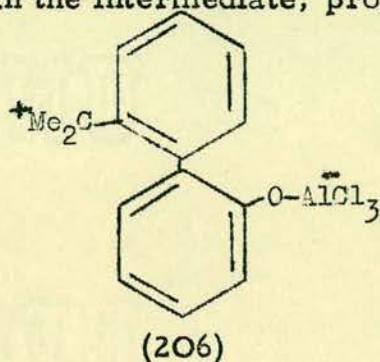
ether. This then rearranged in the presence of aluminium

chloride by cleavage of the 5-6 bond, rotation about the bond joining the two aromatic rings and cyclisation at the 1- position to give (144).

To investigate this hypothesis, (147) was synthesised using the method described by Cahn⁷¹ wherein the diazonium sulphate of anthranilic acid was reacted with phenol to give 3,4-benzocoumarin (204). Treatment of this with methylmagnesium iodide formed the diol (205) which cyclodehydrated, under acid catalysis to (147).

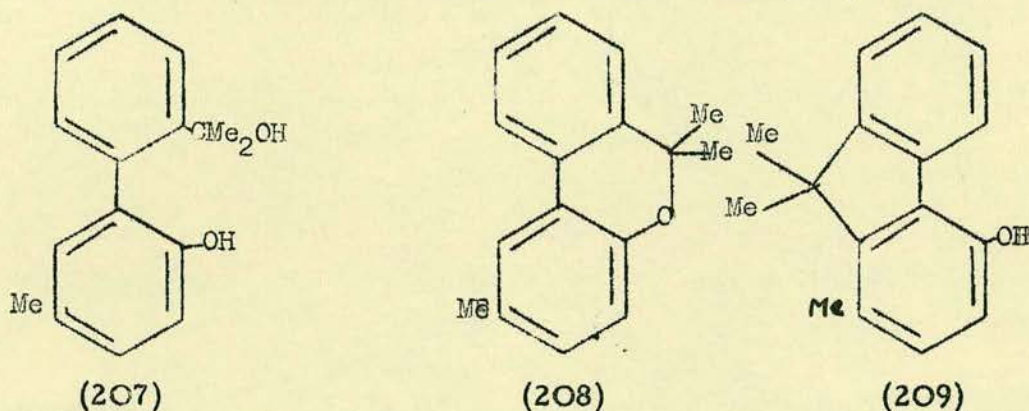


When (147) was reacted with aluminium chloride under identical conditions to the acid chloride it underwent quantitative conversion to the fluorenyl cation (206). Although this reaction was carried out at low temperature using a strong Lewis acid a free carbonium ion must be involved in the intermediate, probably of the form (206)



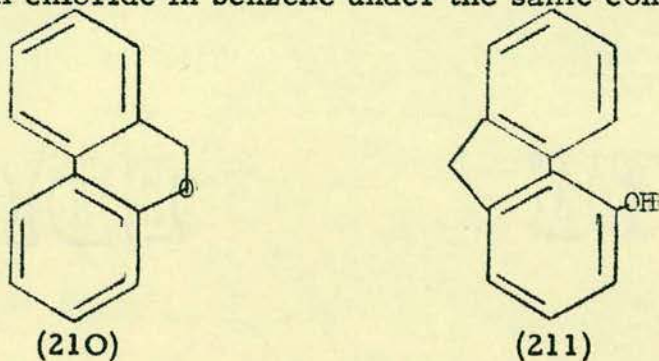
since it is impossible for this molecule to adopt a sandwich-complex structure.

A very similar observation has been reported by Anchell and Blatt⁷². They found that when the diol (207) was heated in a sealed tube at 200° for twenty-four hours with a mixture of hydrochloric and acetic acids the product was 1,9,9-trimethylfluoren-4-ol (209). It seems reasonable to assume that (207) initially



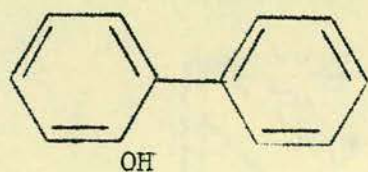
underwent acid-catalysed cyclo-dehydration to the pyran derivative (208) which was rearranged by the acid to (209).

In these two cases, cleavage of the pyran ring leads to the formation of a stabilised tertiary carbonium ion. To assess the effect of the side-chain methyl substituents on the reaction, the unsubstituted dibenzo [b, d]-6(H)pyran (210) was treated with aluminium chloride in benzene under the same conditions. This

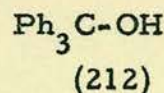
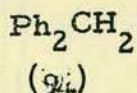


time the rearrangement product, fluoren-4-ol (211) was formed in only 15% yield with the remaining material being recovered as unchanged (210). Cleavage of the ether ring in this example leads to a primary, benzyl-type carbonium ion and obviously does not readily occur. This reaction was performed by adding a solution of (210) in benzene to a stirred suspension of aluminium chloride in benzene at 5 - 10°C over 15 minutes followed by stirring the mixture at this temperature over a further 1.5 hours.

In an attempt to promote the rearrangement reaction, the experiment was repeated initially as above. At the end of the first 1.5 hours stirring at 5 - 10°C, the mixture was warmed to 50 - 60°C and stirred at this temperature for a further 1.5 hours. After hydrolysis the product was shown by thin-layer chromatography to have three components. These were separated by chromatography on silica-gel and found to be 2-hydroxybiphenyl

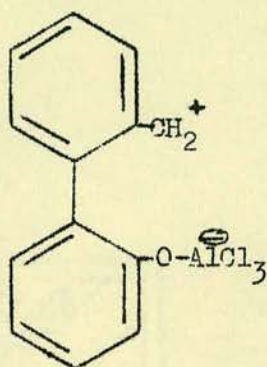


(195)

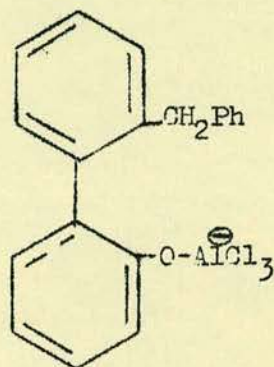


(195) (87%), diphenylmethane (94) (80%) and triphenylcarbinol (212) (20%). At first sight this is a rather odd result but the explanation almost certainly lies in the reactivity of the primary

carbonium ion (213) formed by the initial ether cleavage. This ion attacks a benzene molecule forming a benzyl group in (214). It can



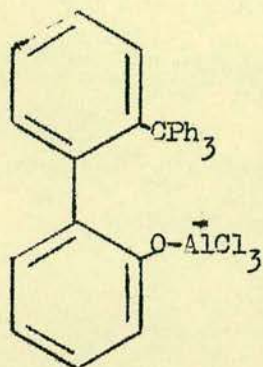
(213)



(214)

now be envisaged that (214) will react in one of two ways. The benzyl group can be cleaved off by aluminium chloride as a benzyl carbonium ion complex which will then alkylate a benzene molecule forming diphenylmethane (9.). The other fragment from (214) is 2-hydroxybiphenyl probably co-ordinated with aluminium chloride. Alternatively the $\text{-O}-\overset{\ominus}{\text{AlCl}}_3$ substituent can act as a neighbouring group promoting innisation of the benzyl substituent to a carbonium ion which alkylates a benzene molecule.

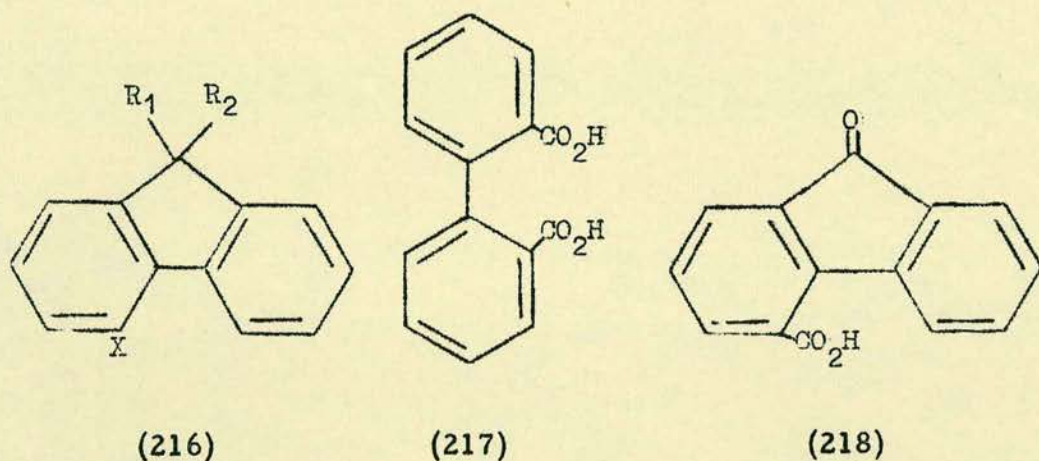
Introduction of a second phenyl group by the same means would lead to the triphenylmethyl-substituted species (215). The bond between the triphenylmethyl group and the aromatic ring will be considerably weakened by steric overcrowding and will break easily forming 2-hydroxybiphenyl and a triphenylmethyl cation. During hydrolysis this cation is converted to triphenylcarbinol (212).



(215)

The above mechanism seems preferable to the alternative one wherein (214) loses the benzyl group exclusively to form diphenylmethane and 2-hydroxybiphenyl since the aluminium chloride present will almost certainly remain co-ordinated to an oxygen atom throughout the series of reactions and would not be available to promote progressive substitution of the methylene group of the diphenylmethane formed in the reaction which could also lead to triphenylcarbinol and probably some other species. Indeed when diphenylmethane was treated with aluminium chloride in benzene for 1 hour at 55° no triphenylmethanol was detected in the complex mixture of products formed.

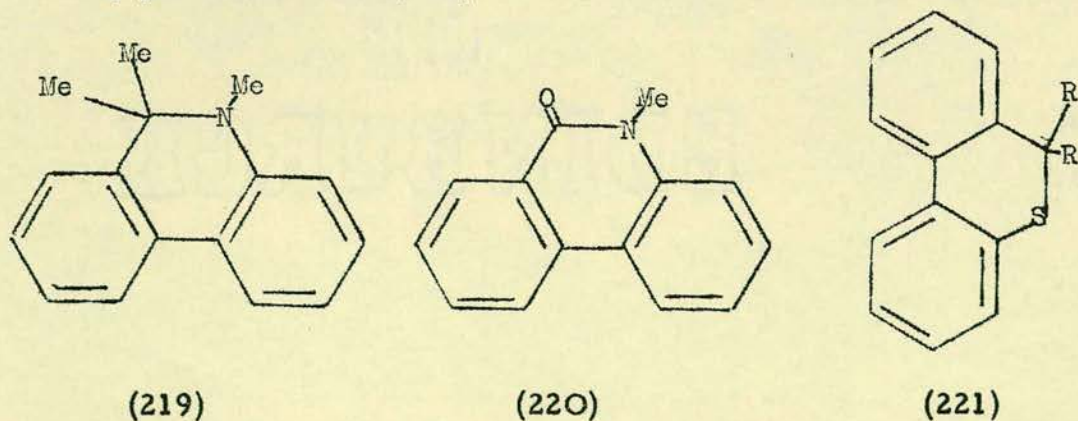
The rearrangements of (147) and (210) provide a convenient route to 4-substituted fluorene derivatives (216, X = OH) which are not otherwise readily accessible. The preparation of fluorene derivatives with a carbon-containing substituent in the 4-position is quite straightforward with the first step generally being the



cyclisation of diphenic acid (217) to 4-carboxyfluorenone (218).

However, conversion of the carboxyl group to groups such as hydroxyl- or amino- is difficult.

Accordingly, in an attempt to extend this rearrangement reaction to compounds containing hetero-atoms other than oxygen, 5,6-dihydro-5,6,6-trimethylphenanthridine (219) was prepared by the Grignard reaction of methylmagnesium iodide on 5-methylphenanthridone (220) and treated with aluminium chloride in



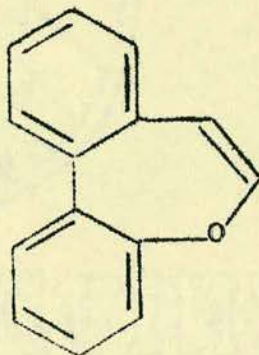
benzene at $5 - 10^{\circ}$ for two hours. No reaction occurred and (219) was recovered unchanged. The reaction of the sulphur analogue (221) was not investigated owing to non-availability of starting materials.

Chapter Four

The Dibenz[b, d]oxepin Ring System

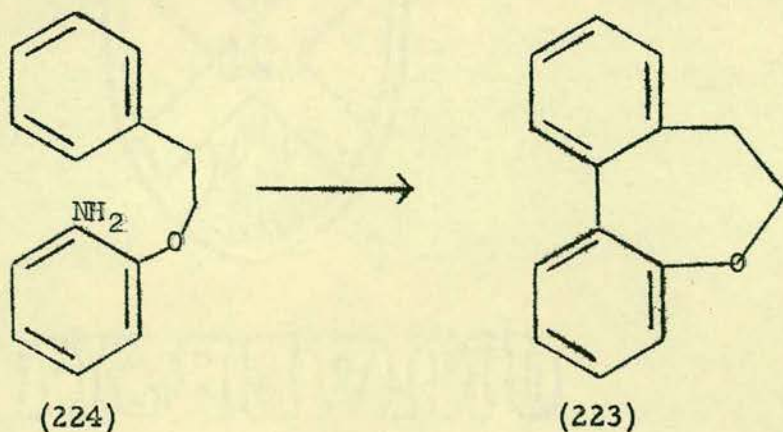
Section One

Introduction

4:1 Dibenz[b, d]oxepin.

(222)

Although the other, isomeric dibenzoxepins are fairly well-described in the chemical literature, little is known of this ring system. Its derivatives have been reported only four times and the parent compound was unknown at the start of this investigation. Three of the examples ^{73,74,75} are intermediates in terpene syntheses and are substituted polyhydro-lactones of 2'-hydroxybiphenyl-2-acetic or -glyoxylic acids. The fourth example ⁷⁶, 6,7-dihydrodibenz[b, d]oxepin (223) was prepared by the Pischorr cyclisation of *o*-aminophenyl β -phenethylether (224) during a study of pyran and homopyran derivatives. Sieglitz and Koch then



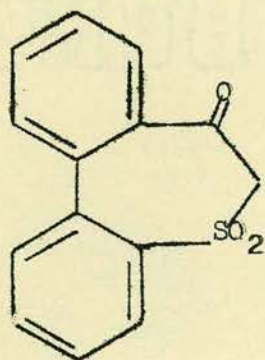
(224)

(223)

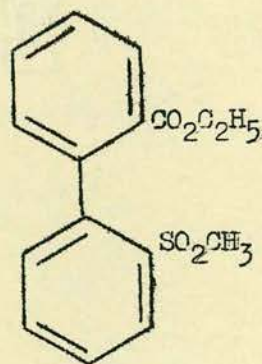
converted (223) to a mixture of phenanthrene and hydrophenanthrenes by treatment with hydriodic acid.

4:2 Dibenzo[b, d]thiepin and Dibenz[b, d]azepin

Little also is known of the sulphur and nitrogen analogues of (222), dibenzo[b, d]thiepin and dibenz[b, d]azepin. In neither case is the parent compound known. The simplest derivative of the former which has been described is dibenzo[b, d]thiepin-7(6H)-one-1,1-dioxide (225) which was prepared by Dieckmann cyclisation of (226).⁷⁷ An analogous cyclic ketone, 5-p-toluenesulphonyl-5(H)dibenz[b, d]azepin-7(6H)-one (227) has been prepared by

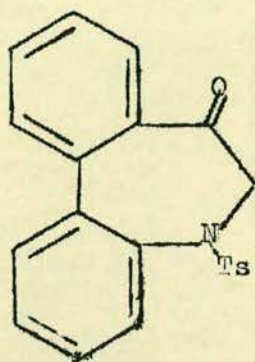


(225)

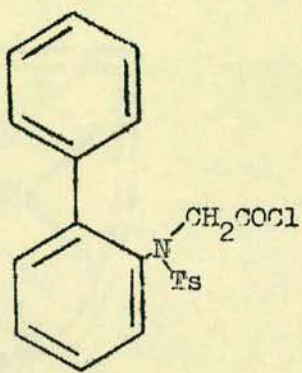


(226)

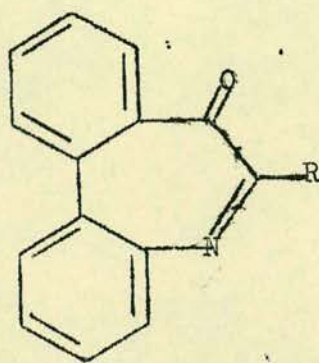
cyclisation of the acid chloride (228) at low temperature using aluminium chloride as catalyst in chloroform as solvent. The ketone has been reduced to the corresponding alcohol with lithium aluminium hydride and derivatives of the type (229), where R is an alkoxy group, have been prepared by the action of base on (227). Several dimeric species have also been reported.⁷⁸



(227)



(228)



(229)

Section Two

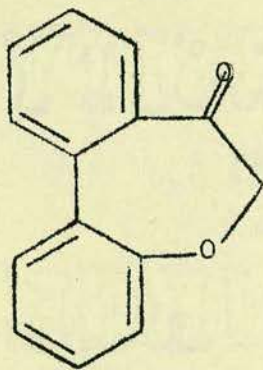
Results and Discussion

Results and Discussion

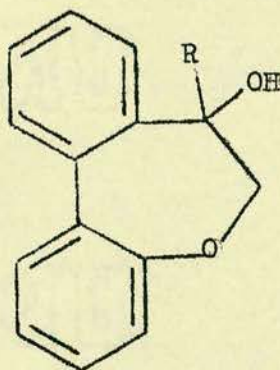
The cyclic ketone dibenz[b, d]oxepin-7(6H)-one(128) was the starting material used in the preparation of all other derivatives of the ring system. It is therefore appropriate to consider first the chemistry of this compound.

4:3 Reactions of Dibenz[b, d]oxepin-7(6H)-one

In most of its reactions dibenz[b, d]oxepin-7(6H)-one behaves as a fairly typical, if rather unreactive ketone. The carbonyl group is readily reduced by lithium aluminium hydride in ether or more slowly by sodium borohydride in ethanol to the secondary alcohol (230, R=H). It reacts readily with Grignard reagents



(128)



(230)

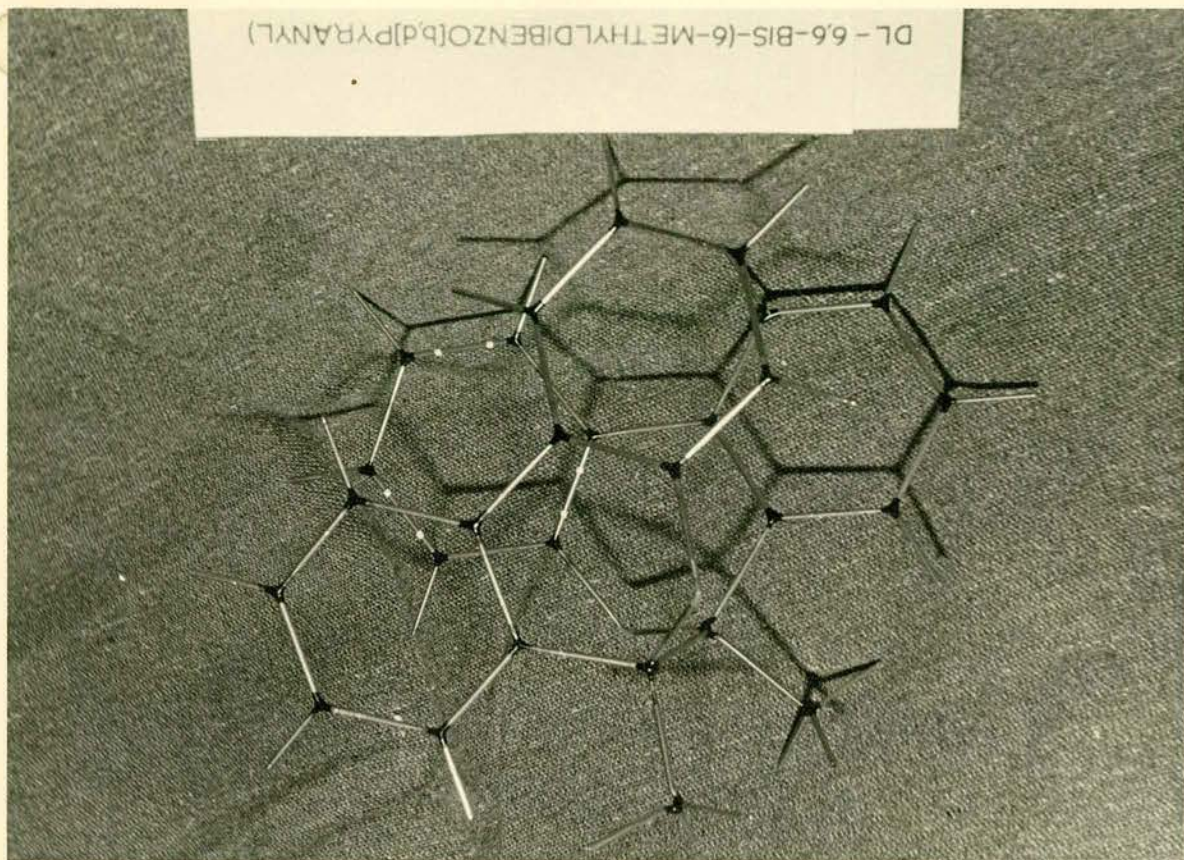
methylmagnesium iodide and phenylmagnesium bromide to form the tertiary alcohols (230, R = Me, Ph). These alcohols are all very viscous, almost colourless oils which have shown no tendency to crystallise.

The ketone forms a crystalline oxime when treated with hydroxylamine hydrochloride in basic alcoholic solution. When Beckmann rearrangement of this oxime was attempted the product

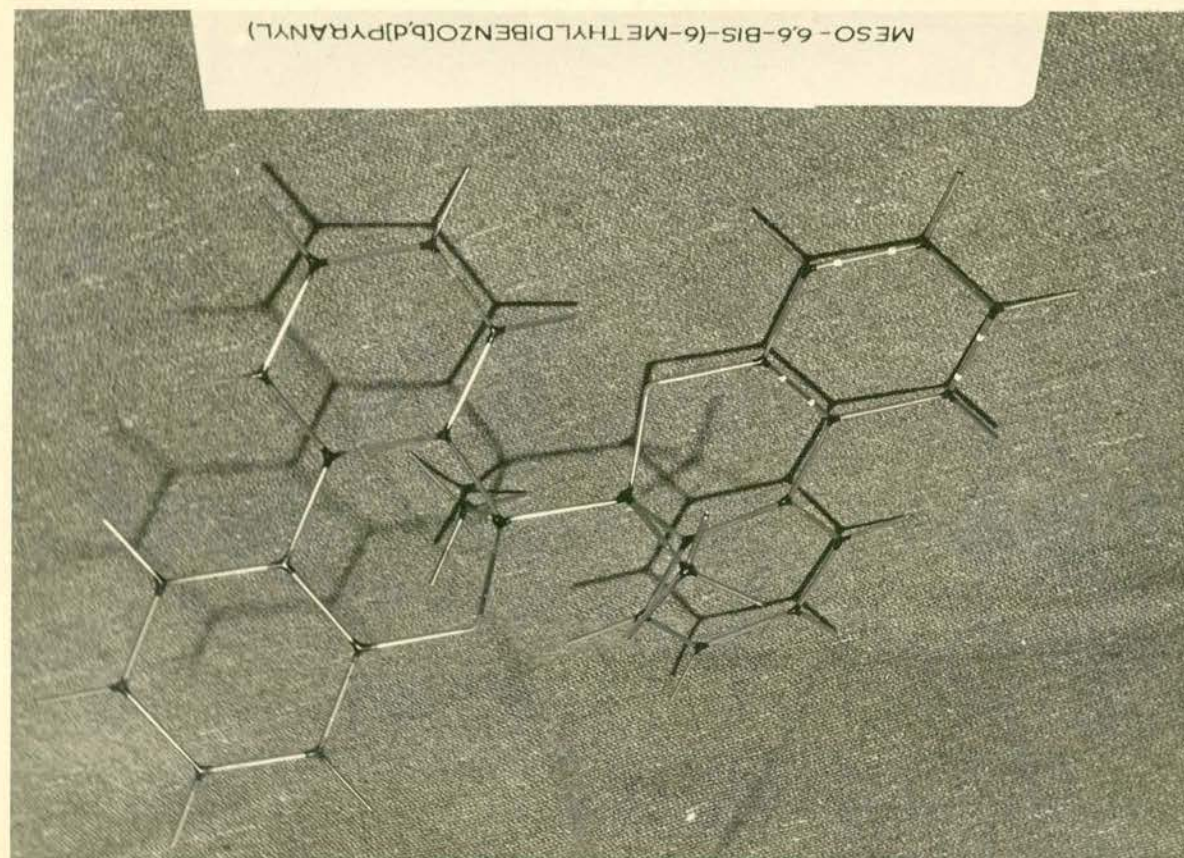
was a pale brown, amorphous solid which was quite insoluble in organic solvents and did not appear to be the desired eight-membered ring lactam. The I.R. spectrum of this substance was very indistinct but a broad, rounded peak at 1640 cm^{-1} may have been due to an amide C=O stretch. In general the N-methyl derivatives of amides are much more soluble than the unsubstituted compounds and an attempt was made to methylate this substance using dimethylsulphate and aqueous potassium hydroxide but this met with no success.

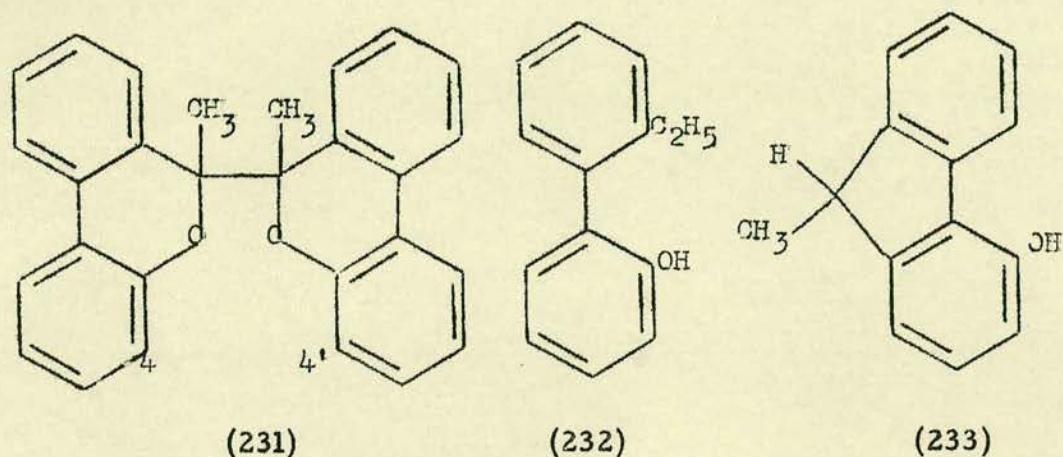
Three different methods were used in attempts to reduce the carbonyl-group to a methylene-group. Hydrogenation over palladium-charcoal at one hundred atmospheres did not reduce the compound at all. Clemmensen reduction using the Martin⁷⁹ modification gave a complex mixture of products several of which were identified. The crude product partially crystallised and crystallisation from ethanol gave a colourless compound, M.P. $216 - 8^{\circ}$. The n.m.r. spectrum of this compound showed only aromatic protons as a complex multiplet (8H) and a singlet methyl group. The mass spectrum showed a small parent ion peak at m/e 390 with a large half-mass peak at m/e 195 and strong peaks at m/e 165 (9-fluorenyl cation) and m/e 152 (biphenylene radical cation). From these observations the compound was identified as 6,6-bis-(6-methyldibenzo[b,d]pyranyl) and subsequently found to be the meso-isomer.

DL - 6,6-BIS-(6-METHYLDIBENZO[b,d]PYRANYL)



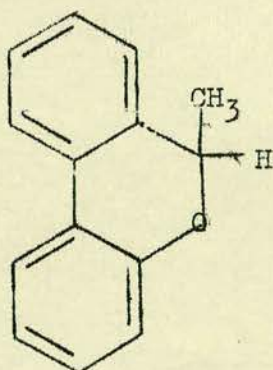
MESO - 6,6-BIS-(6-METHYLDIBENZO[b,d]PYRANYL)





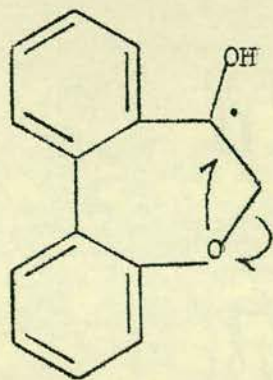
The I. R. spectrum of the material remaining after the crystallisation showed a phenolic -OH stretch and extraction with 2M sodium hydroxide gave a small amount of phenolic material whose n. m. r. spectrum showed -C₂H₅ and -CHMe- groups, suggesting a mixture of 2'-ethyl-2-hydroxybiphenyl (232) and 9-methylfluoren-4-ol (233). Low temperature crystallisation of the remain from light petroleum gave a colourless compound, M. P. 146 - 8°C. The n. m. r. spectrum was similar to that of the meso-isomer of (231) but the aromatic region showed a distinct upfield ortho-, meta- quartet ($J_{\text{ortho}} = 8\text{Hz}$, $J_{\text{meta}} = 1.4\text{ Hz}$) integrating for one proton when compared with the singlet for the methyl group (3H). The mass spectra of the two compounds were identical. On this basis, the structure was assigned as the dl-form of (231). From the photographs of the Dreiding models of these isomers it can be seen that the 4- and 4'- protons of the dl-form in what is most probably the preferred conformation lie directly above a benzene ring in the other half of the molecule

and are shielded by the effect of the ring current in that ring, appearing as the upfield aromatic signal in the n.m.r. spectrum. The n.m.r. spectrum of the liquors from this crystallisation showed the presence of a small amount of a compound containing a -CHMe- group with the methine proton absorbing at 4.85 τ (quartet, $J = 7$ Hz). This is probably 6-methyldibenzo[b,d]-6H-pyran (234).

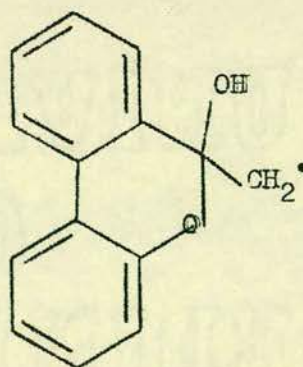


(234)

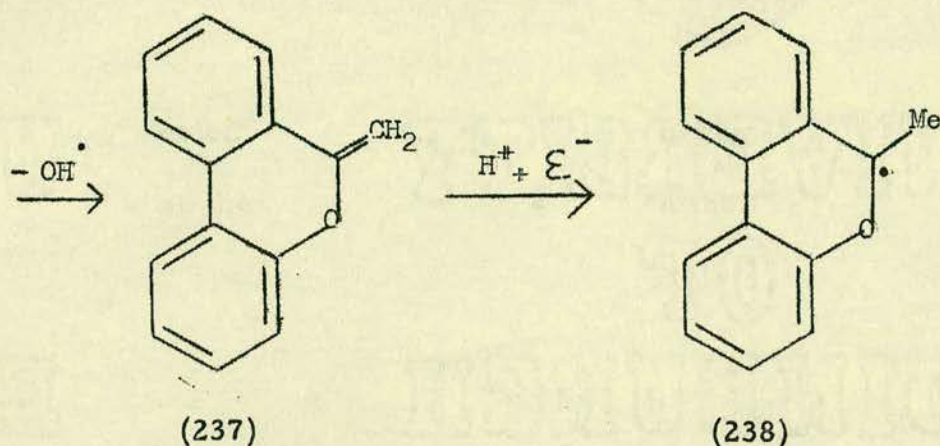
The Clemmensen reduction is thought to proceed by a radical mechanism and, in this case, the initial intermediate is probably the hydroxy-radical (235) which rearranges to (236).



(235)

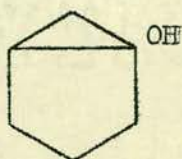


(236)



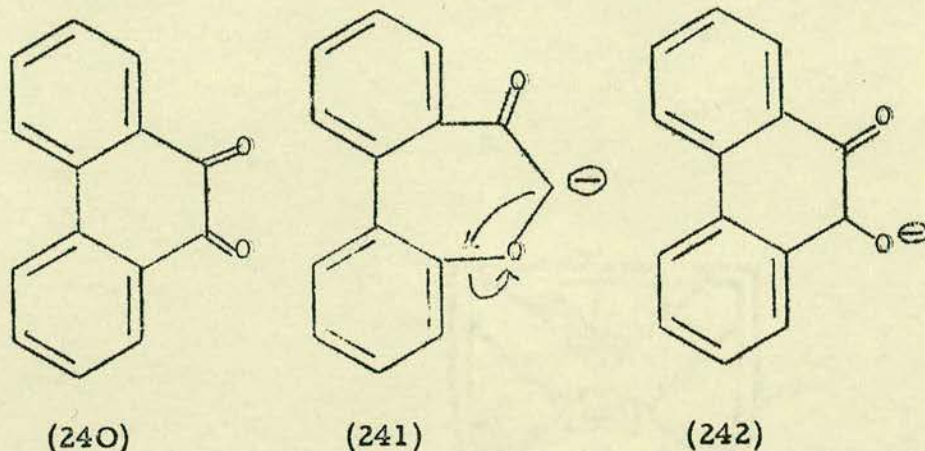
Loss of a hydroxyl radical leads to (237) which adds a proton and an electron to form the 6-methyldibenz[b,d]pyran radical (238). Coupling of two of these radicals leads to the meso- and dl- forms of (231) dependent on the orientations of the two halves at the time of reaction. Addition of a hydrogen atom leads to the pyran (234) which can undergo acid-catalysed rearrangement to the fluorenol (233). 2'-Ethyl-2-hydroxybiphenyl (232) can arise by cleavage of the 5, 6-bond of (236) followed by reduction of the acetyl group formed.

This proposed scheme finds a close analogy in the Clemmensen reductions of cyclonexenone and related systems when ring contraction occurs which has been shown to proceed through a cyclopropanol intermediate of the type (239).



(239)

Wolff-Kishner reduction (using the Huang-Minlon modification) also failed to give the dihydrooxepin (223). Two major products were formed in this reaction which were identified as phenanthrenequinone (240) and 2'-ethyl-2-hydroxybiphenyl (232).



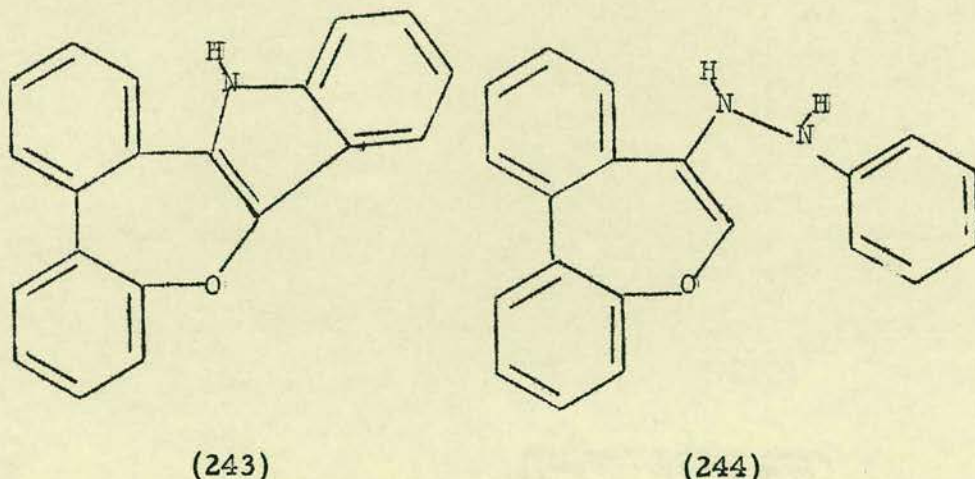
The n. m. r. spectrum of the crude product also showed a third component, present in small amount, which contained a $-CHMe-$ group with the methine proton absorbing at 6.03 τ (quartet, $J = 7\text{Hz}$). This was thought to be 9-methylfluoren-4-ol (233), although not isolated.

The formation of phenanthrenequinone must have occurred by Wittig rearrangement of the cyclic ketone. Abstraction of a proton by the base would lead to the anion (241) which rearranged to the alcoholate anion (242). Subsequent oxidation, presumably by atmospheric oxygen gives the quinone. This was confirmed by heating the oxepinone with potassium hydroxide in digol, omitting the hydrazine, when phenanthrenequinone was formed in high yield.

Although dibenz[b, d]oxepin-7(6H) one undergoes the Wittig

rearrangement when strongly heated with potassium hydroxide, the methylene group is generally unreactive. No reaction was observed when the ketone was treated with Claisen alkali (35 g. potassium hydroxide, 75 ml. methanol, 25 ml. water) in the cold and (128) was recovered unchanged. No methylation of the 6-position occurred when the pyrrolidine enamine was treated with methyl iodide and reaction of the ketone with sodium nitrite in glacial acetic acid failed to give the 6- isonitroso derivative.

When the ketone (128) was heated with phenylhydrazine the phenylhydrazone readily formed. Addition of glacial acetic acid followed by further heating resulted in the formation of indolo [3,2-g]dibenz[b,d]oxepin (243) by the Fischer Indole reaction. In this reaction the initially formed phenylhydrazone is known to

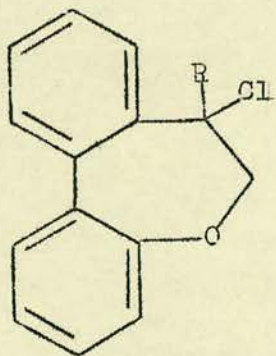


rearrange to an ene-hydrazine⁸⁴ which subsequently cyclises under acid catalysis with the elimination of ammonia. In this case the ene-hydrazine intermediate will be (244).

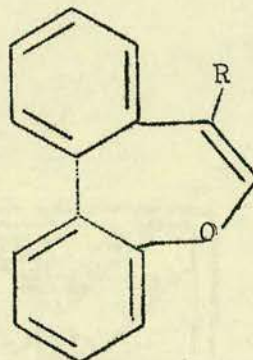
The formation of the pyrrolidine enamine and the ene-hydrazine (244) show that enolisation does occur in species of these types.

4:4. Preparation of the Dibenz[b, d]oxepin System

When the secondary alcohol (23O, R=H) formed by reduction of dibenz[b, d]oxepin-7(6H)-one with sodium borohydride or lithium aluminium hydride was heated with a suspension of phosphorus pentoxide in benzene, the n.m.r. spectrum of the product showed, along with an aromatic multiplet centred on 2.8 τ , two small doublets (J = 6Hz) centred on 3.45 τ and 4.05 τ . These were assigned to the 6-H and 7-H of dibenz[b, d]oxepin (222). Numerous peaks in the upfield region of the spectrum



(245)



(246)

suggested the presence of large amounts of polymeric material and when this product, dissolved in a little benzene, was poured into methanol the polymer separated as a white, amorphous solid. This obviously, was not a satisfactory preparative method.

When the alcohol (23O, R=H) was heated with thionyl chloride in benzene solution it was converted to 7-chloro-6,7-dihydrodibenz[b, d]oxepin (245, R=H) which distilled as a colourless liquid, B.P. 116 - 20^o (0.01 m.m) but rapidly darkened on standing.

After several trial attempts it was found that when this

chloro- compound was refluxed with a 25% solution of potassium hydroxide in ethanol for four hours it was converted to dibenz[b, d]oxepin without polymeric impurities in good yield. Chromatography of the product on alumina followed by distillation under nitrogen gave dibenz[b, d]oxepin as a colourless liquid B.P. 102 - 4°/0.2 mm.

Similar results were obtained with the 7- methyl- and 7- phenyl- substituted alcohols (23C, R= Me, Ph). When these were heated with phosphorus pentoxide in benzene some oxepin was formed but much polymeric material resulted. Reaction with thionyl chloride gave the 7- chloro- derivatives (245, R = Me, Ph) along with some of the oxepins. Heating these mixtures with ethanolic potassium hydroxide solution gave the oxepins (246, R = Me, Ph) in good yields.

The acid-catalysed polymerisation of these oxepins probably occurs by protonation of the 6- position. This will create a carbonium ion at the 7- position which can then attack another oxepin molecule and so on forming a chain.

4: 5 Reactions of Dibenz[b, d]oxepin

From the n. m. r. spectrum of this compound, which shows the 6-H as a doublet centred on 3.45 τ and the 7-H as a doublet (with the peaks slightly broadened by long-range coupling) centred on 4.05 τ , it appears that the 6-7 bond is olefinic in character.

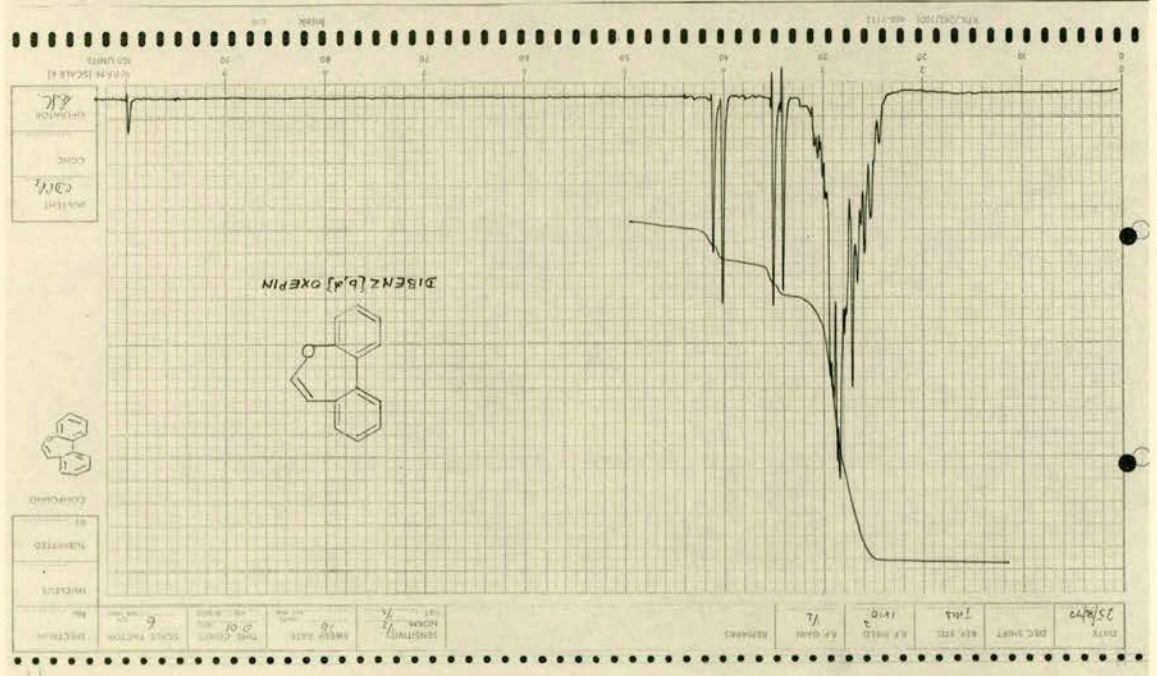
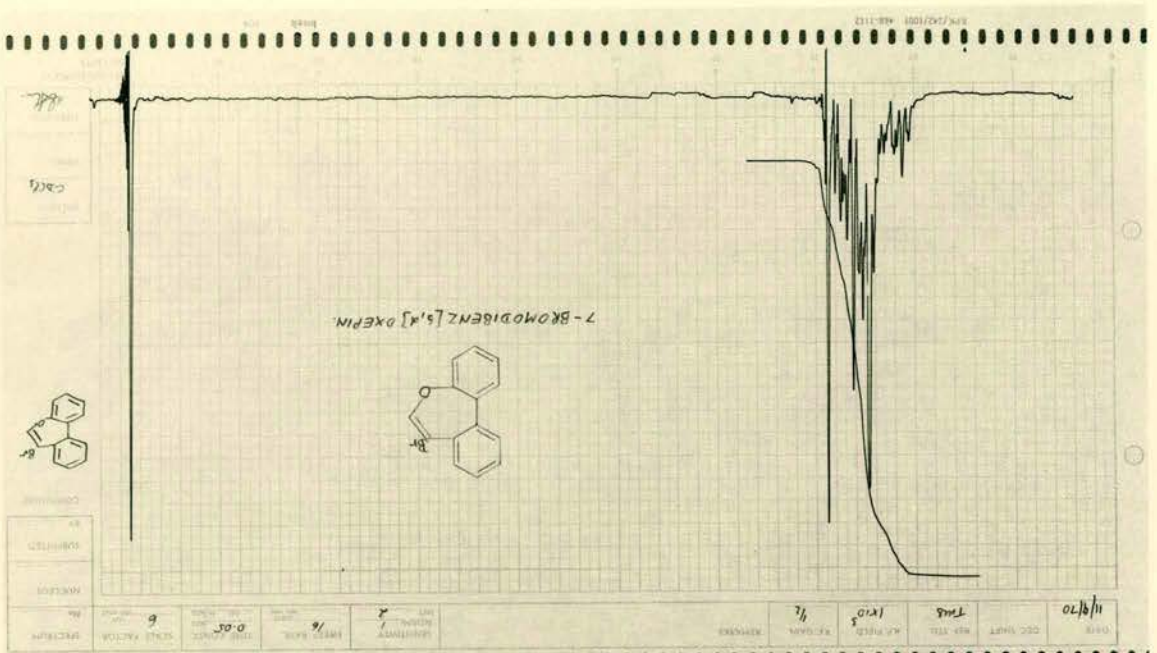
This is also supported by an absorption at 1647 cm^{-1} in the I.R. spectrum. One would not expect the system to be aromatic since there are sixteen π -electrons in the periphery and eight π -electrons in the oxepin ring and in its reactions it behaves as a cyclic vinyl ether.

The molecule is non-planar with the 7-membered ring held in a boat-type conformation. From models of the molecule, the angle between the two benzene rings is found to be around 40° and the molecule is fairly rigid.

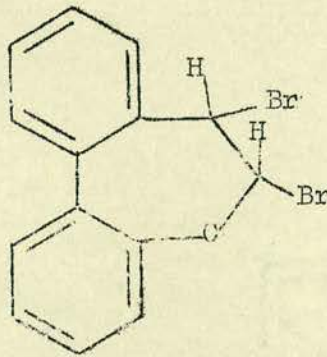
Dibenz[b, d] oxepin reacts readily with acid and is polymerised by it. This was shown by adding one drop of trifluoroacetic acid to a solution of the oxepin in deuteriochloroform in an n. m. r. tube and recording the spectrum at intervals. The doublets from the 6-H and 7-H diminished in intensity to be replaced by multiplets centred on 7.0 τ and 8.7 τ . After twenty-two hours this process was complete.

Attempts to nitrate the ring system were unsuccessful, both with fuming nitric acid in acetic anhydride and with cupric nitrate in acetic anhydride, when complex mixtures of products were formed. No nitro-derivatives were detected from either reaction.

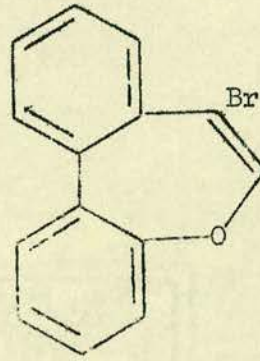
The most characteristic reaction of the system is addition to the 6,7- double bond. Dibenz[b, d] oxepin was slowly hydrogenated at atmospheric pressure over Raney nickel to form 6,7- dihydrodibenz[b, d]oxepin (223).



Bromine readily adds to the double bond to give the crystalline but unstable 6,7- dibromo-6,7-dihydrodibenz[b,d]oxepin (247). The n.m.r. spectrum of this product was interesting



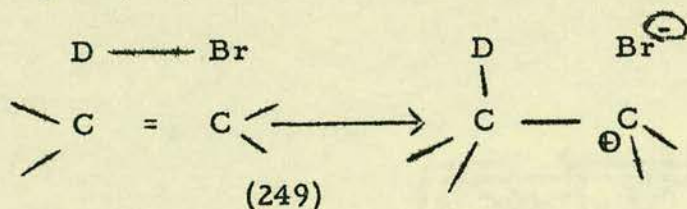
(247)



(248)

in that, instead of showing the 6- and 7- hydrogen atoms as two doublets, they appeared as two pairs of doublets with coupling constants of 3.5 Hz and 9.5 Hz respectively. From Dreiding models it was seen that these resonances could arise from either a mixture of cis- and trans- isomers or from two conformers of the trans- isomer. This ambiguity could be resolved by recording the n.m.r. spectrum at several different temperatures. If the product was a mixture of conformers, the ratio of the two should change with changing temperature and a mixture of cis- and trans- isomers should give the same spectrum at different temperatures. When the spectrum was recorded at -60° , 0° and $+20^{\circ}$ C, the intensities of the peaks remained constant showing that it was, indeed, a mixture of cis- and trans- isomers. The two crystallised together from light petroleum as colourless needles M.P. $101 - 9^{\circ}$ C.

Such *cis*- additions have been reported and rationalised by Dewar and Fahey⁸⁵ in the reactions of deuterium bromide and chloride with acenaphthylene,⁸⁶ indene⁸⁷ and *cis*- and *trans*- 1-phenylpropene.⁸⁸ They showed that the reactions were polar and not free radical in nature and rejected the idea of a π - complex intermediate which would lead exclusively to the *trans*- isomer or of a free carbonium ion intermediate which should give an equimolar mixture of *cis*- and *trans*-. Their suggested intermediate is a classical carbonium ion which does not exist free but as an ion pair (249) with the bromide ion on the same side of the



olefin. Quick collapse of this ion pair leads to a high proportion of the *cis*- isomer and the *trans*- isomer is formed only if the ion pair survives long enough for the bromide ion to migrate to the opposite side of the planar carbonium ion. This should be enhanced in polar solvents which can stabilise the ion pair and, indeed, these workers found that a greater proportion of the *cis*- isomer was formed in less polar solvents.

It is possible that a similar process is operative in this bromination although the ion-pair effect will be weaker owing to the larger size of the bromine atom when compared with deuterium or hydrogen. Similar *cis*- additions have been observed in the chlorination of phenanthrene and acenaphthylene and in the

bromination of styrene derivatives where a non-symmetrical bromonium ion has been proposed as intermediate.^{91,92}

The product ratios from this reaction were not found to be consistent. On one occasion equimolar amounts of the two isomers were formed but in all other cases the trans- isomer formed around 80% of the total.

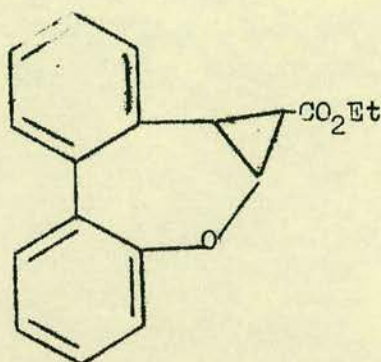
The reactivity of the α -bromine atom of α, β -dibromoethers is well-known to be many thousands of times greater than that of the β -bromine in both acyclic and cyclic systems⁹³ and dehydrobromination to β -bromovinylethers readily occurs.

This dibromide (247) is very readily dehydrobrominated by ethanolic potassium hydroxide to 7- bromodibenz[b, d]oxepin (248), a viscous, colourless liquid which showed no tendency to crystallise. The n. m. r. spectrum of this compound shows H-6 as a very sharp singlet at 2.98 τ . None of the 6- isomer, which would be expected to show H-7 as a singlet, broadened by long-range coupling and absorbing at higher field was detected.

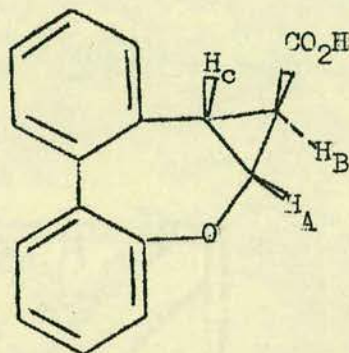
Attempted nucleophilic displacement of bromine by cyanide was attempted with (248) by heating with cuprous cyanide in dimethylformamide. A complex reaction which appeared to involve opening of the oxepin ring occurred and there was no evidence that the 7- cyano- derivative had formed.

Dibenz[b, d]oxepin reacted sluggishly with ethyl diazoacetate both when warmed in the presence of copper powder and when the mixture was strongly heated alone. A small amount of the

cyclopropane derivative (250) formed by addition of ethoxycarbonyl carbene to the 6,7- double bond was formed along with large



(250)



(251)

amounts of diethyl fumarate. After hydrolysis of the ester it was possible to isolate the acid (251) in a fairly pure state but in very low yield. The high-field region of the n. m. r. spectrum of this compound was of considerable interest. The resonances occurred at 5.43 τ (quartet, $J_{AB} = 6.0$ Hz; $J_{AC} = 2.5$ Hz; 1H; H_A), 7.15 τ (triplet, $J_{AB} = J_{BC} = 6.0$ Hz; 1H; H_B) and at 7.72 τ (quartet, $J_{BC} = 6.0$ Hz, $J_{AC} = 2.5$ Hz; 1H; H_C), showing that the hydrogen atom of the $=CH \cdot CO_2H$ group is trans- to the other two hydrogens of the cyclopropane ring which originate from the oxepin ring and that those two are cis- with respect to each other. The structure of the acid must therefore be (247) or its enantiomer formed by cis- addition of the carbene to the double bond. This is in accord with previous observations that alkoxy-carbonyl-carbenes undergo stereospecific cis- additions with olefins,^{94,95} and is also an indication that there is no intermediate formation of a pyrazoline.

EXPERIMENTAL SECTION

GENERAL NOTES

1. Melting points were recorded using a Koffler hot-stage melting point apparatus.
2. Microanalyses were carried out in this department using a Perkin Elmer Elemental Analyser, Model 240.
3. Nuclear Magnetic Resonance spectra were recorded using a Perkin Elmer R.10 (60 MHz) or a Varian Associates HA 100 (100 MHz) spectrometer with tetramethylsilane as internal standard. Data are given for 60 MHz spectra unless otherwise stated.
4. Infra-red spectra were recorded on a Unicam SP 200 Spectrophotometer.
5. Mass spectra were recorded using an AEL-GEC MS 902 double-focussing mass spectrometer.
6. Solutions were dried over magnesium sulphate monohydrate.
7. Boiling points are uncorrected.

CHAPTER 11.1. Preparation of 3-Arylpropionic Acids.(a) 3-(Biphenyl-2) propionic acid.²⁹

A solution of diethyl malonate (4.5g., 0.028 mole) in ethanol (10 ml.) was added to a stirred solution of sodium ethoxide prepared by adding sodium (0.625g., 0.027 mole) to ethanol (40 ml.). After 0.5 hours, a solution of 2-chloromethylbiphenyl (5.5g., 0.027 mole) in ethanol (30 ml.) was added slowly. After the addition was completed, stirring at room temperature was continued for a further two hours and then the mixture was refluxed for 0.5 hours. After cooling it was poured into cold water (500 ml.) and extracted with benzene. After drying the extract, the benzene was removed under vacuum leaving the crude diethyl o-phenylbenzylmalonate as an oil. This was hydrolysed by refluxing with aqueous potassium hydroxide for 3 hours. The hydrolysis mixture was poured into water and washed with benzene to remove any non-acidic material present. O-phenylbenzylmalonic acid was precipitated on acidification of the basic solution. It was filtered, dried and recrystallised from benzene to give colourless clusters M.P. 126-7° (lit. 125.5° - 127.5°). Yield 67%. When this acid was heated at 130-140° for 2.5 hours, it decarboxylated smoothly to give 3-(biphenyl-2) propionic acid purified by recrystallisation from benzene/light petroleum (60/80°).

M.P. 111-12° (lit. 110-113°).

(b) 3-(4-Fluorenyl) propionic acid.

Using the method described by Quelet and Barge,⁹⁶ 4-chloromethylfluorene was prepared in several stages from diphenic acid.

The chloromethyl compound (5.0g., 0.023 mole) was reacted with sodio-diethyl malonate (0.023 mole) as above. Hydrolysis of the diester followed by decarboxylation gave 3-(4-fluorenyl) propionic acid which was recrystallised from benzene.

M.P. 175-7° (lit. 177°) Yield 67%.

1.2. Cyclisations of 3-arylpropionyl chlorides with aluminium chloride.

(a) 3-(Biphenyl-2) propionyl chloride

(i) In benzene.

To a suspension of 2.22g. (0.0167 moles) aluminium chloride in 14 ml. dry benzene at 5-10°C. was added a solution of 3-(biphenyl-2) propionyl chloride (prepared from 2.70g., 0.0134 moles of the acid) in 14 ml. benzene over 15 minutes and with vigorous stirring. The reaction mixture was stirred for a further 1.5 hours at this temperature and then poured into iced, diluted hydrochloric acid and the mixture hydrolysed over 0.5 hours. The product was extracted into benzene and the organic layer washed with saturated sodium bicarbonate solution from which no unreacted starting material was recovered after acidification.

The benzene solution was dried and the benzene was distilled out under vacuum leaving the product as a yellow oil, 2.61g. The t.l.c. of this product on silica gel, eluting with benzene showed three components, a strong band at R_F 0.3, a weak one at R_F 0.4 and a trace at R_F 0.6. The n.m.r. spectrum showed a complex aromatic multiplet centred on 2.5 τ (8H), two triplets ($J=7\text{Hz}$) centred on 6.82 τ and 7.27 τ and a singlet at 7.05 τ . The I.R. spectrum showed $\bar{\nu}_{C=O}$ at 1705 cm^{-1} with a shoulder at 1680 cm^{-1} .

The product was chromatographed on 250g. silica-gel when three fractions were obtained:

Fraction 1. (eluent 20% $\text{CHCl}_3/\text{C}_6\text{H}_6$). This contained 0.11g. and the I.R. spectrum showed no carbonyl absorption. It was thought to contain a hydrocarbon, possibly 9, 10-dihydrophenanthrene which could have resulted from decarbonylation of the acylium ion followed by cyclisation, but was not fully identified.

Fraction 2. (eluent 50% $\text{CHCl}_3/\text{C}_6\text{H}_6$). Yield 1.77g. This was a mixture of two cyclic ketones.

Fraction 3. (eluent 50% $\text{CHCl}_3/\text{C}_6\text{H}_6$). Yield 0.49g. 4-Phenylindanone. The I.R. spectrum showed $\nu_{\text{C=O}}$ at 1705 cm^{-1} and the n.m.r. spectrum showed a multiplet at 2.35 τ (8H, aromatic protons), a triplet ($J=7\text{Hz}$, 2H, 2-methylene group) at 6.82 τ and a triplet which also showed some fine structure at 7.3 τ ($J=7\text{Hz}$, 2H, 3-methylene group).

Further chromatography of fraction 2 and recrystallisation failed to isolate the second cyclic ketone, dibenzocycloheptadienone, in a pure state. From the n.m.r. spectrum of the crude product, it was estimated to account for 20% of the total.

The total amount of 4-phenylindanone isolated was 1.2g. (58%), M.P. 84-6°C.

Oxime: Buff-coloured needles, M.P. 166-8°.

$\text{C}_{15}\text{H}_{13}\text{NO}$ requires: C, 80.69; H 5.87; N 6.27%

found: C, 80.38; H 5.60; N 6.00%

(ii) In sym-tetrachloroethane.

A solution of 3-(biphenyl-2) propionyl chloride (from 2.0g., 0.0089 mole of the acid) in sym-tetrachloroethane (10 ml.) was added to a suspension of aluminium chloride (1.47g., 0.011 mole) in the same solvent (10 ml.) and the reaction carried out as above. The reaction complex became dark red in colour and homogeneous.

After hydrolysis the solvent and products were extracted into chloroform. The chloroform solution was washed with sodium bicarbonate solution which, on acidification yielded 0.04g., 2%, recovered 3-(biphenyl-2) propionic acid. After drying, the chloroform was distilled out under vacuum and the residue steam-distilled to remove tetrachloroethane. This left the product as a yellow oil (1.82g.). T.L.C. again showed three bands and the n.m.r. spectrum showed the two cyclic ketones present in the same ratio as before.

The product was chromatographed on silica-gel and also on alumina but again only 4-phenylinone could be isolated pure (1.1g., 53%).

(b) 3-(4-fluorenyl) propionyl chloride.

A solution of the acid chloride (from 1.06g., 0.0045 mole acid) in dry benzene (5 ml.) was added over 10 minutes to a stirred suspension of aluminium chloride (0.74g., 0.0056 mole) in dry benzene (5 ml.) at 5-10°C. Stirring was continued at this temperature for a further 1.5 hours. The reaction mixture became dark green and was not homogeneous. It was hydrolysed by pouring into iced dilute hydrochloric acid and stirring for 30 minutes. The products were extracted into benzene and the organic layer washed with sodium bicarbonate solution. No starting material was recovered on acidification. The benzene solution was dried and the benzene distilled out under vacuum leaving the product as a yellow oil, 0.95g. T.L.C. showed only one component at R_f 0.4 along with some impurity on the baseline. The product was purified by chromatography on alumina followed by crystallisation from light petroleum (B.P. 80-100°C.) which gave white clusters M.P. 87-9°C.

Yield 0.7g. The I.R. spectrum showed $\nu_{\text{C=O}}$ at 1675cm^{-1} and the n.m.r. spectrum showed a quartet at 2.1δ ($J=7.5, 1.0\text{Hz}$; 1H; H-7), a multiplet centred on 2.6δ (5H; remaining aromatic protons), a singlet at 6.2δ (2H, CH_2) and a broad singlet at 6.95δ (4H, 9- CH_2 and 10- CH_2). This enabled the product to be identified as 9,10-dihydrocyclohepta [def] fluoren-8(4H)one.

$\text{C}_{16}\text{H}_{12}\text{O}$ requires: C, 87.25; H 5.49%

found: C, 87.4; H 5.57%

1.3. Preparation of Pyrrole-2-propionic Acids.

I. Without a 5-methyl substituent.

N-substituted pyrrole-2-propionic acids without a 5-methyl substituent were prepared by reaction of the appropriate pyrrole with β -propiolactone. N-methylpyrrole was available commercially and was purified by distillation. N-phenylpyrrole was prepared as described below:

N-phenylpyrrole.

A solution of aniline (20.0g., 0.215 mole) in glacial acetic acid (100 ml.) was cooled in a cold water bath while 2,5-diethoxytetrahydrofuran (34.4g., 0.215 mole) was added slowly. The mixture was refluxed for 1 hour during which time it became dark in colour. It was poured into 500 ml. water and steam-distilled. N-phenylpyrrole crystallised in the distillate as white plates, M.P. $57-58^\circ\text{C}$. Yield = 25.4g., 82%.

(a) N-phenylpyrrole-2-propionic acid.

A mixture of N-phenylpyrrole (2.5g.) and β -propiolactone (5.0g.) was refluxed for two hours. A further 5g. of propiolactone were added and refluxing was continued for a further two hours.

On cooling, the mixture solidified. 100 ml. of 15% aqueous potassium hydroxide were added and the mixture refluxed for 30 minutes. The cooled solution was extracted twice with benzene. After washing with water, drying and removing the benzene under reduced pressure, this extract yielded 2.0g. of unreacted N-phenylpyrrole. After acidifying the alkaline solution to pH 4 and stirring for 30 minutes, N-phenylpyrrole-2-propionic acid precipitated as a brown solid. This was filtered off, washed with water and dried. Recrystallisation from light petroleum (80-100°) gave the product as white needles M.P. 87-9°C. Yield 0.5g., 13%.

The n.m.r. spectrum showed peaks at -0.2 τ (singlet; 1H; -OH), 2.66 τ (singlet; 5H; phenyl), 3.1 τ (multiplet; 1H; H-5), 3.8 τ (multiplet; 2H; H-4 and H-5), 7.2 τ (multiplet; 4H; methylene groups).

$C_{13}H_{13}NO_2$ requires: C, 72.54; H, 6.09; N, 6.51

found: C, 72.35; H 5.94; N 6.4

(b) N-methylpyrrole-2-propionic acid.

A mixture of N-methylpyrrole (10.0g.) and β -propiolactone (20.0g.) was refluxed (146°C) for three hours. The work-up was as above. The acid did not precipitate when the alkaline solution was acidified and was extracted into ether. The ether extract was washed with water, dried and distilled under reduced pressure to remove the ether, leaving the product as a brown oil which was crystallised from light petroleum (80-100°C) to give N-methylpyrrole-2-propionic acid as white needles M.P. 80-82°. Yield 0.8g., 4.2%.

The n.m.r. spectrum of this acid showed peaks at -2.0 τ (singlet; 1H; -OH), 3.5 τ (multiplet; 1H; H-5), 4.05 τ (multiplet;

2H; H-3 and H-4), 6.47 τ (singlet; 3H; -Me), 7.25 τ (multiplet; 4H; methylene groups).

$C_8H_{11}NO_2$ requires: C, 62.73; H, 7.24; N, 9.14%

found: C, 62.80; H, 7.31; N, 9.08%

II. 5-methylpyrrole-2-propionic acids.

These were prepared by reaction of the appropriate amine with 4, 7- dioxooctanoic acid. This, in turn, was formed by acid hydrolysis of furylidene acetone

Furylidene acetone.

A mixture of furfural (50g.), acetone (64g.), water (400 ml.) and 5% aqueous sodium hydroxide (20 ml.) was stirred at room temperature for four hours. After neutralising with acetic acid, it was extracted thoroughly with methylene chloride. This extract was dried and the solvent removed under reduced pressure. The residue was distilled and two fractions were collected. The first which distilled at 124-6°C/19 mm. was furylideneacetone. Yield 43.6g. The second, distilling at 224-6°/17 mm. and subsequently solidifying was difurylideneacetone. Yield 20.2g.

4, 7- Dioxooctanoic acid.

Furylideneacetone (42.8g.) was refluxed with a mixture of ethanol (1l.) and concentrated hydrochloric acid (400 ml.) for 16 hours. The resulting solution was evaporated to dryness under reduced pressure. A mixture of concentrated hydrochloric acid (400 ml.), glacial acetic acid (200 ml.) and water (600 ml.) was added to the residue and the mixture heated under reflux for 5 hours. After cooling the solution was filtered and the filtrate evaporated to dryness leaving 4, 7-dioxooctanoic acid as a brownish solid which was used without further purification. Yield 37.3g.

(a) 5-Methyl-1-phenylpyrrole-2-propionic acid.

A solution of 4, 7-dioxooctanoic acid (5.0g., 0.029 mole) in glacial acetic acid (25 ml.) was added to a cooled solution of aniline (2.7g., 0.029 mole) in 25 ml. acetic acid. The mixture was heated under reflux for one hour and poured into cold water (300 ml.) containing 5 ml. concentrated hydrochloric acid. The product was extracted into chloroform. The extract was washed with water, dried and distilled under reduced pressure to remove the solvent, leaving the product as a brown gum. This was crystallised from light petroleum (B.P. 80-100°C) to give pale yellow needles M.P. 109-11°C. Yield 4.2g., 63%.

The n.m.r. spectrum showed absorptions at -1.3τ (broad singlet; 1H; -OH), 2.5 - 3.0 τ (complex multiplet; 5H; phenyl), 4.13 τ (singlet; 2H; H-3 and H-4), 7.15 - 7.75 τ (complex multiplet; 4H; methylene groups), 8.05 τ (singlet; 3H; Me).

$C_{14}H_{15}NO_2$ requires: C, 73.34; H, 6.59; N, 6.11%

found: C, 73.5; H, 6.7; N, 6.02%

(b) 1, 5-Dimethylpyrrole-2-propionic acid.

The reaction was carried out as above using 5.0g. of 4, 7-dioxooctanoic acid and 5.5 ml. of a 25% aqueous solution of methylamine. Crystallisation of the product from light petroleum (B.P. 80-100°C) gave pale pink leaflets M.P. 103.5 - 106.5° Yield 2.5g., 43%.

Some decomposition occurred on standing.

The n.m.r. spectrum showed absorptions at -1.2τ (broad singlet; 1H; -OH), 4.24 τ (singlet; 2H; H-3 and H-4), 6.65 τ (singlet; 3H; N-Me), 7.0 - 7.45 τ (complex multiplet; 4H; methylene groups), 7.83 τ (broad singlet; 3H; 5-Me).

$C_9H_{13}NO_2$ requires: C, 64.65%; H, 7.84%; N, 8.38%.

found: C, 64.84%; H, 7.81%; N, 8.5%.

(c) Attempted preparation of 5-methylpyrrole-2-propionic acid.

Reaction of 5.0g. (0.029 mole) of 4,7-dioxooctanoic acid and 2.5g. (0.032 mole) of ammonium acetate in 50 ml. glacial acetic acid gave 3.59g. of a dark oil which subsequently solidified. The n.m.r. spectrum showed it to be a complex mixture and no absorption from a $-CO_2H$ group could be detected. None of the desired acid could be isolated by recrystallisation.

(d) 5-Methyl-1-(1-pyrrolyl) pyrrole-2-propionic acid.

1-Aminopyrrole was prepared in low (7%) yield from phthalimide as described by Flitsch, Krämer and Zimmermann.³⁶

A solution of 1-aminopyrrole (0.9g., 0.011 mole) and 4, 7-dioxooctanoic acid (1.56g., 0.011 mole) in 10 ml. glacial acetic acid was heated at $100^{\circ}C$ for 30 minutes. The normal work-up procedure gave 0.52g. of a red oil which subsequently partially crystallised. The n.m.r. spectrum of this product showed that it contained around 35% of the desired compound. The other component was also a pyrrole and was probably 5-methylpyrrole-2-propionic acid. Recrystallisation from light petroleum (B.P. $80-100^{\circ}C$) using a little decolourising charcoal gave 5-methyl-1-(1-pyrrolyl) pyrrole-2-propionic acid as colourless needles M.P. $95-96^{\circ}C$. Yield 0.12g., 5%.

The n.m.r. spectrum showed absorptions at 0.3 τ (broad singlet; 1H; -OH), 3.26 τ (triplet, $J=2.3$ Hz; 2H; H-2' and H-5'), 3.75 τ (triplet, $J=2.3$ Hz; 2H; H-3' and H-4'), 4.16 τ (singlet; 2H; H-3 and H-4), 7.42 τ (broad singlet; 4H; methylenes), 8.04 τ (singlet; 3H; $-CH_3$).

$C_{12}H_{14}N_2O_2$ requires: C, 66.04; H, 6.47; N, 12.84%
 found: C, 66.4; H, 6.81; N, 12.62%

1.4. Other propionic acids.

(a) 5-Methylthiophene-2-propionic acid.

A mixture of 4,7-dioxooctanoic acid (5.8g., 0.0336 mole), phosphorus pentasulphide (7.5g., 0.0336 mole) and dry toluene (50 ml.) was refluxed with stirring for four hours. After cooling, water (200 ml.) was added and the mixture allowed to stand for twelve hours with occasional shaking. It was filtered and the organic layer separated, dried and distilled under reduced pressure to remove the toluene. This left the product as a dark oil (3.0g.) which slowly solidified. It was crystallised from light petroleum (B.P. 60-80°C.), using decolourising charcoal, at -78°C. to give pale yellow needles M.P. 37-38°C.

The n.m.r. spectrum showed absorptions at τ 0.4 (singlet; 1H; -OH), τ 3.45 (singlet showing some fine structure; 2H; H-3 and H-4), τ 6.75 - 7.5 (complex multiplet; 4H; methylenes), τ 7.62 (singlet; 3H; -Me).

$C_8H_{10}O_2S$ requires: C, 56.47; H, 5.92%
 found: C, 55.9; H, 5.69%

(b) 5-Methylfuran-2-propionic acid.

Phosphorus pentoxide (10.0g.) was added to a solution of 4, 7-dioxooctanoic acid (5.0g., 0.029 mole) in dry benzene (100 ml.) and the mixture heated under reflux for two hours. After cooling it was poured into water (200 ml.) and the benzene layer separated. The benzene solution was washed with water,

dried and distilled under reduced pressure to remove solvent, leaving the product as a red oil (2.6g.) which subsequently solidified. It was recrystallised from light petroleum (B.P. 80-100°C.) at -78°C. to give white needles M.P. 54-56°.

The n.m.r. spectrum showed absorptions at -1.1 τ (broad singlet; 1H; -OH), 4.13 τ (singlet showing some fine structure; 2H; H-3 and H-4), 6.85 - 7.55 τ (two A₂B₂ triplets, J = 6-7Hz; 4H; methylenes), 7.78 τ (singlet; 3H; -Me).

C₈H₁₀O₃ requires: C, 62.3; H, 6.54%

found: C, 61.9; H, 6.28%

1.5. 5-Methyl-1-phenyl-pyrrole-2-acetic acid.

(i) Ethyl 2-ethoxycarbonyl-3, 6-dioxohexanoate.

Levulinic acid (23.2g., 0.20 mole) was converted to its acid chloride by refluxing with thionyl chloride for 15 minutes. Excess thionyl chloride was distilled out under vacuum; 50 ml. dry benzene were added and distilled out to remove the last traces of thionyl chloride. This was dissolved in ether (100 ml.) and added to a suspension of diethyl ethoxymagnesiummalonate (0.25 mole) in dry ether. After the normal work-up, the product was found, from its n.m.r. spectrum, to contain around 55% of the desired compound with diethyl malonate accounting for the remainder. T.L.C. showed two components. This mixture was distilled and the fraction which came over at 190-210°/11 mm. was collected. Yield 20.1g. The n.m.r. spectrum showed this to be almost entirely the product, contaminated by a little diethyl malonate. It was used without further purification in the following reaction.

(ii) A solution of the above product (5.0g., 0.0194 mole) and aniline (1.80g., 0.0194 mole) in acetic acid (100 ml.) was heated under reflux for one hour. After cooling, it was poured into water (300 ml.) containing 5 ml. concentrated sulphuric acid and the product was extracted into ether. The ether extract was washed with sodium bicarbonate solution, dried and distilled under vacuum leaving the crude diester as a red oil. This was hydrolysed by boiling with 30 ml. of 10% aqueous/methanolic potassium hydroxide. After cooling, the solution was poured into water and washed with ether to remove any non-acidic material. Acidification, followed by extraction into benzene, washing with water, drying and removal of solvent under reduced pressure gave the product as a yellow crystalline solid. Yield 3.7g. It was recrystallised from light petroleum (B.P. 80-100°C.) to give pale yellow needles M.P. 109-110°.

The n.m.r. spectrum showed absorptions at -0.63τ (broad singlet; 1H; -OH), 2.45 - 2.95 τ (complex multiplet; 5H; phenyl), 3.89 τ (doublet, $J = 3.5\text{Hz}$; H-3), 4.04 τ (octet, $J = 3.5, 0.8 \text{ Hz}$; 1H; H-4), 6.58 τ (singlet; 2H; CH_2), 8.01 τ (singlet; 3H; Me).

$\text{C}_{13}\text{H}_{13}\text{NO}_2$ requires: C, 72.5; H, 6.09; N, 6.51%

found: C, 72.2; H, 5.88; N, 6.3%

1.6. Pyrrole-2-butyric Acids.

I. Unambiguous preparations of 5-methylpyrrole-2-butyric acids could theoretically be achieved by reaction of a suitable primary amine with 5, 8-dioxononanoic acid in reactions analogous to the preparations of the 5-methyl-2-propionic acids from 4, 7-dioxooctanoic acid. With this in view, several attempts were made to prepare derivatives of 5, 8-dioxononanoic acid.

(i) Attempted preparation of 4,4-bisethoxycarbonyl-5,8-dioxononanitrile.

(a) A solution of diethyl malonate (0.2 mole), acrylonitrile (0.2 mole) and triethylamine (20 ml.) in isopropanol (60 ml.) and water (60 ml.) was allowed to stand for three days at room temperature. It was then heated under reflux for twelve hours, cooled, diluted with water (400 ml.) and extracted with ether. The ether extract was washed with dilute hydrochloric acid and water, dried and distilled under reduced pressure leaving the product as a colourless oil which then solidified. The product was still slightly contaminated with diethyl malonate which was removed by trituration with light petroleum (B.P. 60-80°C.), 3 x 100 ml., which left the product, 4,4-bisethoxycarbonyl-butyronitrile, as colourless needles. Recrystallisation from benzene gave M.P. 69°. Yield 19.7g.

Magnesium (2.14g., 0.089 mole), ethanol (2 ml.) and carbon tetrachloride (0.2 ml.) were warmed to start reaction. After several minutes dry ether (50 ml.) was added cautiously with stirring. A solution of the above compound (19.0g., 0.089 mole) in 6 ml. ethanol and 10 ml. dry ether was added to the stirred mixture at such a rate that gentle boiling was maintained. The mixture was then refluxed on the steam bath for three hours.

A solution of levulinyl chloride (prepared by reaction of 10.32g., 0.089 mole the acid with thionyl chloride) in 30 ml. dry ether was added over 15 minutes. A dark red, insoluble complex was formed. The mixture was refluxed and stirred for five hours, cooled and hydrolysed by pouring into dilute sulphuric acid. The products were extracted into ether and the ether extract washed with sodium bicarbonate which gave a very dark aqueous solution

with some suspended material. The ether solution was dried and evaporated under reduced pressure leaving a red oil (25.0g.) which was found to be almost entirely starting material and soon crystallised.

(b) A solution of ethyl 2-ethoxycarbonyl-3, 6-dioxohexanoate (10.0g.), acrylonitrile (2.1g.) and 20% methanolic potassium hydroxide (1.0g.) in 40 ml. tert-butanol was kept at 30°C. for four hours. No reaction occurred and there was a quantitative recovery of starting material.

(c) A solution of ethyl 2-ethoxycarbonyl-3, 6-dioxohexanoate (5.0g.), acrylonitrile (5.0g.) and potassium tert-butoxide (2.17g.) in tert-butanol (35 ml.) was refluxed for three hours, cooled and poured into water (200 ml.). Extraction with ether gave a yellow oil (6.1g.) which crystallised. The mass spectrum showed a parent ion at m/e 213 and the product was thought to be a cyclopentenone derivative. This reaction was not pursued further.

(ii) Attempted preparation of $CH_3.CO.CH_2.CH_2.CO.CH_2.CH_2.CH_2.CN$.

Solid potassium tert-butoxide (2.8g., 0.05 mole) was added to a solution of hexan-2, 5-dione (5.7g., 0.05 mole) and acrylonitrile (2.65g., 0.05 mole) in 50 ml. tert-butanol. The mixture was refluxed for one hour. The usual work-up gave a dark oil (5.3g.) which was found to be a complex mixture and no identifiable products could be isolated.

II. At this point it was decided to attempt direct substitution of the pyrrole nucleus which would lead to pyrrole-2-butyric acids with a free 5-position.

(a) 3-(1-Phenyl-2-pyrroloyl) propionic acid and 1-phenylpyrrole-2-butyric acid.

(i) Reaction of N-phenylpyrrole (5.0g., 0.035 mole) with succinic anhydride (3.5g., 0.035 mole) and aluminium chloride (5.60g., 0.042 mole) in symtetrachloroethane (50 ml.) at 5-10°C. gave no readily identifiable products.

(ii) A similar reaction using γ -butyrolactone and stannic chloride in an attempt to alkylate the ring led to recovery of starting materials.

(iii) 3-Methoxycarbonylpropionic acid was prepared by refluxing succinic anhydride with an excess of methanol for twelve hours.

A solution of 3-methoxycarbonylpropionyl chloride (from 4.62g., 0.035 mole the acid by reaction with thionyl chloride) in tetrachloroethane (20 ml.) was added slowly to a stirred solution of N-phenylpyrrole in tetrachloroethane simultaneously with a solution of stannic chloride (10.95g., 0.042 mole) in 20 ml. of the same solvent. The reaction was carried out at 5-10°C. Hydrolysis followed by steam distillation of the solvent left the product as a red oil, 6.03g. The n.m.r. spectrum was rather complex and suggested the product was a mixture of keto esters.

This product was reduced using the Huang Minlon modification of the Wolff-Kishner method by heating with potassium hydroxide (4.7g., 0.084 mole) and 85% hydrazine hydrate (4 ml.) in 35 ml. digol. This also hydrolysed the ester group. The product after the usual work-up was again an oil, 5.0g. The n.m.r. spectrum showed that this was a mixture of 1-phenylpyrrole-2-butyric acid and 1-phenylpyrrole-3-butyric acid in the ratio 1:2. It was found impossible to separate this mixture even by chromatography of the

(b) 3-(1-Methyl-2-pyrroloyl) propionic acid and 1-methylpyrrole-2-butyric acid.

N-methylpyrrole (6.60g., 0.0814 mole) was reacted with 3-methoxycarbonylpropionyl chloride (from 10.74g., 0.0814 mole of the acid) and stannic chloride (22.0g., 0.084 mole) in tetrachloroethane as above. The usual work-up gave the crude product as a red oil, 14.1g., which the n.m.r. spectrum and t.l.c. showed to be a complex mixture. After lengthy chromatography on silica gel, 1.15g. of methyl 3-(1-methyl-2-pyrroloyl) propionate was isolated as a yellow oil which did not crystallise.

Without further purification this was reduced by the Wolff-Kishner method, the ester being hydrolysed during the reaction. This acid could not be crystallised even from petroleum at -78° and was obtained as an oil, 0.6g.

1.7. Cyclisations of Heterocyclic Alkanoic Acids.

These were performed by heating the acid (1 part) with polyphosphoric acid (approximately 100 parts) at 100°C . with vigorous stirring. Heating was stopped when the reaction mixture darkened noticeably or after three hours if no colour change occurred. The reaction mixture was hydrolysed by pouring into cold water (300-400 ml.) and stirring for 30 minutes. The products were extracted into chloroform and any unreacted acid removed by washing the chloroform extract with saturated sodium bicarbonate solution. It was recovered by acidification of the washings. The chloroform solution was dried and a t.l.c. was run on silica gel eluting with chloroform. Removal of the chloroform left the crude product whose n.m.r. spectrum was recorded.

Mixtures of cyclic ketones were separated by column chromatography generally on alumina and the ketones were

recrystallised from light petroleum (B.P. 80-100°C.) unless otherwise stated.

(a) Cyclisation of 1-Phenylpyrrole-2-propionic Acid.

(i) From the reaction of 1-phenylpyrrole-2-propionic acid (0.14g.) and polyphosphoric acid (15g.) for 3 hours, 0.13g. of non-acidic product was recovered. The t.l.c. showed two major bands at R_F values of 0.3 and 0.6 with a minor one at R_F 0.4. The n.m.r. spectrum also showed the presence of three components. Chromatography of the product on alumina led to isolation of the two major components which were found to be 5,6-dihydro-1-phenyl-4H-cyclopenta[b] pyrrol-6-one (61), eluted first and 5,6-dihydro-1-phenyl-4H-cyclopenta[b] pyrrol-4-one (62). The third component was not isolated.

(ii) The cyclisation was repeated using 0.95g. of the acid and 100g. polyphosphoric acid for 3 hours. The product was a brownish oil, 0.80g., whose t.l.c. again showed three bands. After chromatography on 30g. alumina lasting two days the three components were isolated:

Fraction 1. Eluent toluene 5, 6-dihydro-1-phenyl-4H-cyclopenta[b] pyrrol-6-one, 0.30g. It was recrystallised from petroleum ether giving colourless rods, M.P. 88.5°-89.5°.

The n.m.r. spectrum showed absorptions at 2.32-2.87 τ (complex multiplet; 6H; phenyl and H-5), 3.86 τ (doublet, $J = 2.9$ Hz; 1H; H-4), 7.24 τ (singlet; 4H; methylenes) and the I.R. shows ν_{CO} at 1660 cm^{-1}

$C_{13}H_{11}NO$ requires: C, 79.17; H, 5.62; N, 7.10%

found: C, 79.25; H, 5.74; N, 7.04%

Fraction 2. Eluent 20% chloroform/toluene. 5, 6-Dihydro-2-phenyl-4H-cyclopenta[c]pyrrol-4-one, 0.05g. Recrystallisation gave colourless needles, M.P. 126-8°.

The n.m.r. spectrum showed absorptions at 2.61 τ (multiplet; 5H; phenyl), 2.68 τ (doublet, $J=1.6\text{Hz}$; 1H; H-3), 3.16 τ (multiplet; 1H; H-1), 7.10 τ (multiplet; 4H; methylenes). Irradiation at 7.10 τ caused the multiplet at 3.16 τ to collapse to a doublet, $J = 1.6 \text{ Hz}$. The I.R. spectrum showed ν_{CO} at 1670 cm^{-1} .

$\text{C}_{13}\text{H}_{11}\text{NO}$ requires: C, 79.17; H, 5.62; N, 7.10%
found: C, 78.9; H, 5.4; N, 6.9%

Fraction 3. Eluent 20% chloroform/toluene. 5, 6-Dihydro-1-phenyl-4H-cyclopenta [b] pyrrol-4-one, 0.14g. Recrystallisation gave white needles, M.P. 87-88.5°.

The n.m.r. spectrum showed absorptions at 2.57 τ (singlet; 5H; phenyl), 2.90 τ (doublet, $J = 3.2 \text{ Hz}$; 1H; H-2), 3.52 τ (doublet, $J = 3.2 \text{ Hz}$; 1H; H-3), 7.02 τ (singlet; 4H; methylenes). The I.R. spectrum showed ν_{CO} at 1680 cm^{-1} .

$\text{C}_{13}\text{H}_{11}\text{NO}$ requires: C, 79.17; H, 5.62; N, 7.10%
found: C, 79.22; H, 5.76; N, 7.03%

The n.m.r. spectrum of the crude product from the first cyclisation showed that the ratios of the products in the above order were 45%, 20% and 35% while in the second cyclisation they were 50%, 25% and 25%.

(b) 1-Methylpyrrole-2-propionic acid.

(i) Cyclisation of the acid (0.5g.) with polyphosphoric acid for 1 hour gave 0.39g. of crude product. The t.l.c. showed two

bands at R_F values of 0.3 and 0.5 and the n.m.r. spectrum showed two products in the ratio 7:2. The ring protons of the major component showed absorption at 3.06 τ and 4.02 τ (doublets, $J = 3\text{Hz}$) and of the minor component at 3.29 τ and 3.80 τ (doublets $J = 4\text{Hz}$). Attempts to separate them by chromatography on alumina failed as did attempted fractional crystallisation of the oximes.

(ii) The cyclisation was repeated using 0.50g. acid and 50g. polyphosphoric acid for 1.5 hours giving 0.38g. crude product. The t.l.c. again showed two bands and the n.m.r. spectrum showed the same two compounds but this time present in equal amounts. Surprisingly, this crude product crystallised. Chromatography on alumina again gave no separation but this was achieved using silica-gel:

Fraction 1. Eluent 60% chloroform/40% toluene. 5, 6-Dihydro-1-methyl-4H-cyclopenta[b]pyrrol-6-one, 0.12g. Recrystallisation gave off-white needles, M.P. 57-8°.

The n.m.r. spectrum showed absorptions at 3.08 τ (doublet, $J = 3.0\text{Hz}$; IH; H-2), 4.02 τ (doublet, $J = 3.0\text{Hz}$; IH; H-3), 6.25 τ (singlet; 3H; -CH₃), 7.23 τ (singlet; 4H; methylenes) and the I.R. spectrum showed $\nu_{\text{C=O}}$ at 1665 cm^{-1}

$\text{C}_8\text{H}_9\text{NO}$ requires: C, 71.69; H, 6.71; N, 10.36%

found: C, 71.17; H, 6.78; N, 10.31%

Fraction 2. Eluent chloroform then methanol. 5, 6-Dihydro-1-methyl-4H-cyclopenta[b]pyrrol-4-one, 0.12g. Recrystallisation from petroleum ether gave white needles, M.P. 140-1°.

The n.m.r. spectrum showed absorptions at 3.36 τ (doublet, $J = 2.8\text{ Hz}$; IH; H-2), 3.79 τ (doublet, $J = 2.8\text{ Hz}$; IH;

H-3), 6.45 τ (singlet; 3H; $-\text{CH}_3$), 7.19 τ (singlet; 4H; methylenes) and the I.R. showed ν_{CO} at 1675 cm^{-1}

$\text{C}_8\text{H}_9\text{NO}$ requires: C, 71.09; H, 6.71; N, 10.36%

found: C, 71.14; H, 6.82; N, 10.29%

(c) 5-Methyl-1-phenylpyrrole-2-propionic acid.

Cyclisation of the acid (1.40g.) with 100g. polyphosphoric acid for three hours gave the product as a dark oil, 1.30g. The t.l.c. showed only one band as did the n.m.r. spectrum. Recrystallisation gave 5, 6-dihydro-2-methyl-1-phenyl-4H-cyclopenta[b]pyrrol-6-one as pale yellow needles M.P. $103-5-105.5^\circ\text{C}$.

The n.m.r. spectrum showed absorptions at 2.35 - 2.80 τ (complex multiplet; 5H; $-\text{phenyl}$), 3.87 τ (quartet, $J = 1.0 \text{ Hz}$; 1H; H-3), 7.23 τ (singlet; 4H; methylenes), 7.80 τ (doublet, $J = 1.0 \text{ Hz}$; 3H; $-\text{Me}$) and the I.R. showed ν_{CO} at 1675 cm^{-1}

$\text{C}_{14}\text{H}_{13}\text{NO}$ requires: C, 79.59; H, 6.20; N, 6.63%

found: C, 79.81; H, 6.17; N, 6.92%

(d) 1, 5-Dimethylpyrrole-2-propionic acid.

Reaction of the acid (0.5g.) with polyphosphoric acid (50g.) for 2.5 hours gave the product as yellow crystals, 0.22g., along with 0.16g. recovered acid. The t.l.c. of the product showed only one component. Recrystallisation gave very pale yellow needles, M.P. $145-7^\circ$, shown to be 5, 6-dihydro-1, 2-dimethyl-4H-cyclopenta[b]pyrrol-6-one.

The n.m.r. spectrum showed absorptions at 4.0 τ (quartet, $J = 0.9 \text{ Hz}$; 1H; H-3), 6.53 τ (singlet, 3H; N-CH_3), 7.21 τ (singlet; 4H; methylenes), 7.78 τ (doublet, $J = 0.9 \text{ Hz}$; 3H; $-\text{CH}_3$) and the I.R. spectrum showed ν_{CO} at 1672 cm^{-1}

$C_9H_{11}NO$ requires: C, 72.46; H, 7.43; N, 9.39%

found: C, 72.58; H, 7.61; N, 9.18%

(e) 5-Methyl-1-(1-pyrrolyl) pyrrole-2-propionic acid.

Reaction of the acid (0.042g.) with polyphosphoric acid (20g.) for twenty minutes gave the crude neutral product as a brown oil (0.034g.). The t.l.c. showed a strong band at R_f 0.7 and trace bands at 0.2 and 0.3. The n.m.r. spectrum suggested that the major product was the bis-pyrrolodiazepinone, formed by attack at the 2' position of the second ring, accounting for around 50% of the total. The downfield region showed a quartet ($J = 4.2, 2.7$ Hz) at 3.73 τ of the same intensity as a singlet at 4.13 τ (H-3 and H-4). Attempts to separate the mixture or recrystallise the major product were unsuccessful.

(f) 5-Methylthiophene-2-propionic acid.

Reaction of the acid (0.54g.) with polyphosphoric acid (30g.) for 45 minutes gave 0.41g. neutral product along with 0.10g. recovered acid. The t.l.c. of the neutral product showed only one band. It was crystallised from petroleum ether to give very pale yellow needles, M.P. 65.5 - 66.5°C. The n.m.r. spectrum at 60 MHz showed absorptions at 3.30 τ (broad singlet, 1H), 6.75-8.30 τ (multiplet, 4H) and 7.57 τ (singlet, 3H). At 100 MHz, the downfield singlet was found to be a quartet ($J = 1.2$ Hz), the four-proton multiplet separated into a triplet ($J = 6$ Hz) centred on 6.92 τ and a triplet ($J = 6$ Hz) showing further fine structure centred on 7.17 τ . On expansion, the 3-proton singlet at 7.57 τ was found to be a 1:2:2:2:1 quintet ($J = 1.2, 0.6$ Hz). Irradiation

at 3.3 τ caused this to collapse to a triplet ($J = 0.6$ Hz) and irradiation at 7.57 τ caused the quartet at 3.3 τ to collapse to a singlet. The I.R. spectrum showed ν_{CO} at 1708 cm^{-1} . These data allow the product to be identified as 5, 6-dihydro-2-methyl-4H-cyclopenta[b]thiophen-4-one.

C_8H_8OS requires: C, 63.15; H, 5.30; %

found: C, 62.7; H, 5.1%

(g) 5-Methylfuran-2-propionic acid.

Reaction of the acid (0.5g.) with polyphosphoric acid (50g.) for 0.5 hour gave 0.40g. neutral product along with 0.65g. recovered acidic material. The t.l.c. of the neutral product showed two bands, a major one at R_f 0.4 and a minor at 0.3. The n.m.r. spectrum showed singlets in the downfield region at 4.4 τ and 3.74 τ in the ratio 3:1 indicative of the rearranged and normal cyclic ketones. However, the upfield region was very complex suggesting that considerable hydrolysis of the furans had occurred. No separation was achieved by chromatography on neutral alumina. Recrystallisation from petroleum ether gave a white microcrystalline solid which melted, with decomposition, in the range $140-170^\circ$. The analysis was correct for a cyclic ketone but this was thought to be polymeric material.

$C_8H_8O_2$ requires: C, 70.58; H, 5.92%

found: C, 69.9; H, 5.6%

(h) Attempted cyclisation of 5-methyl-1-phenylpyrrole-2-acetic acid.

(i) When the acid (0.5g.) was reacted with polyphosphoric acid (50g.) for three hours, the product was a brown gum. The n.m.r. spectrum showed the absence of all pyrrole protons. No

identifiable products could be isolated by chromatography.

(ii) Similarly when the acid (0.5g.) was heated under reflux with acetic anhydride (30 ml.) and anhydrous sodium acetate (1.0g.), no identifiable products were formed and no pyrrole protons could be seen in the n.m.r. spectrum of the product.

(i) Cyclisation of a mixture of 1-phenylpyrrole-2- and -3-butyrac acids.

The mixture of acids (41% 2- acid) (1.23g.) was reacted with polyphosphoric acid (100g.) for two hours giving the product as a yellow oil, 0.84g. The t.l.c. showed three bands and the n.m.r. spectrum showed three components. The product was chromatographed on alumina giving three fractions all eluted with t luene:

Fraction 1. 6, 7-Dihydro-1-phenylindol-7(6H)-one (86). Yield 0.19g. Recrystallisation from petroleum ether gave white needles, M.P. 100 - 100.5°C. The n.m.r. spectrum showed absorptions at 2.68 τ (singlet; 5H; -phenyl), 3.08 τ (doublet, J = 2.8 Hz; IH; H-2), 3.85 τ (doublet, J = 2.8 Hz; IH; H-3), 7.1 - 8.1 τ (multiplet; 6H; methylenes). The I.R. spectrum showed ν_{CO} at 1655 cm^{-1}

$C_{14}H_{13}NO$ requires: C, 79.59; H, 6.20; N, 6.63%

found: C, 79.51; H, 6.13; N, 6.66%

Fraction 2. 4, 5, 6, 7-Tetrahydro-2-phenylbenzo[c]pyrrol-4-one (87). Yield 0.24g. but slightly contaminated by (86).

The n.m.r. spectrum showed absorptions at 2.36 τ (doublet, J = 2.1 Hz; IH; H-3), 2.61 τ (singlet; 5H; -phenyl), 3.14 τ

(two overlapping triplets, $J = 2.1, 1.1$ Hz; IH; H-1), 7.1 - 8.1 τ (multiplet; 6H; methylenes) and the I.R. showed ν_{CO} at 1665 cm^{-1}

Fraction 3. 6, 7-Dihydro-1-phenylindol-4(5H)-one (85). Yield 0.22g. Recrystallisation from petroleum ether gave white needles, M.P. $65-66^{\circ}\text{C}$. The n.m.r. spectrum showed absorptions at 2.38-2.88 τ (multiplet; 5H; -phenyl), 3.23 τ (doublet, $J = 3.2$ Hz; IH; H-2), 3.35 τ (doublet, $J = 3.2$ Hz; IH; H-2), 7.1 - 8.05 τ (multiplet; 6H; methylenes) and the I.R. showed ν_{CO} at 1665 cm^{-1}

$\text{C}_{14}\text{H}_{13}\text{NO}$ requires: C, 79.59; H, 6.20; N, 6.63%

found: C, 79.76; H, 6.34; N, 6.32%

(j) 1-Methylpyrrole-2-butyric acid.

Reaction of the acid (0.28g.) with polyphosphoric acid (50g.) at 100° for 1.5 hours gave 0.18g. neutral product. The t.l.c. showed only one band and the product was crystallised from petroleum ether giving white needles, M.P. $83-5^{\circ}\text{C}$. The n.m.r. spectrum showed absorptions at 5.49 τ (singlet; 2H; H-2 and H-3), 6.47 τ (singlet; 3H; $-\text{CH}_3$), 7.15 - 8.05 τ (multiplet; 6H; methylenes) and the I.R. showed ν_{CO} at 1665 cm^{-1} . This enables the product to be identified as 6, 7-dihydro-1-methylindol-4(5H)-one (82).

$\text{C}_9\text{H}_{11}\text{NO}$ requires: C, 72.46; H, 7.43; N, 9.39%

found: C, 72.28; H, 7.31; N, 9.17%

CHAPTER 22.1. Preparation of Phenols.(a) 9, 9-Dimethylfluoren-4-ol.

(i) 6, 6-Dimethyldibenzo[b, d] -6H-pyran was prepared from anthranilic acid and phenol, as described by Cahn, in 12% overall yield.

(ii) A solution of the above compound (5.35g., 0.0254 mole) in dry benzene (25 ml.) was added over 20 minutes to a stirred suspension of aluminium chloride (4.2g., 0.0318 mole) in dry benzene (25 ml.) at 5-10°C. Stirring was continued at this temperature for a further 1.5 hours. The mixture was hydrolysed by pouring into iced dilute hydrochloric acid and stirring for 30 minutes. The benzene layer was separated and the aqueous extracted with benzene (2 x 50 ml.). The combined benzene solutions were washed with sodium bicarbonate solution, dried and distilled under reduced pressure leaving the product as a pale oil which crystallised to small white cubes. Yield, 5.34g., 100%. Recrystallisation from light petroleum (B.P. 80-100°C.) gave M.P. 90-1°.

(b) 1-(o-Hydroxyphenyl) pyrrole.

A solution of 2-aminophenol (25g.) and 2, 5-dimethoxy-tetrahydrofuran (30.3g.) in 150 ml. acetic acid and 150 ml. water was heated under reflux for 1.5 hours. It was then added to 1l. hot water and steam distilled. 1-(o-Hydroxyphenyl) pyrrole partially separated in the distillate as a colourless oil. It was extracted into chloroform; the chloroform solution was dried

and distilled under reduced pressure leaving the product as a colourless oil which slowly turned pink on standing. Yield 28.9g., 79%.

2.2. Preparation of Aryloxyacetic Acids.

I. From the phenol and sodium chloroacetate.

(a) Biphenyl-2-oxyacetic acid.

A solution of 2-hydroxybiphenyl (71g., 0.418 mole), chloroacetic acid (39g., 0.418 mole) and sodium hydroxide (33.6g., 0.84 mole) in 300 ml. water was refluxed for four hours. The cooled mixture was poured into 1 l. water and acidified with 50% hydrochloric acid. The crude acid separated as a pink oil and was extracted into chloroform. Extraction into sodium bicarbonate followed by acidification gave the product as a pale pink solid which was filtered, dried and recrystallised from benzene, M.P. 99-100°C. Yield 80g., 84%.

(b) 2-(1-Pyrrolyl) phenoxyacetic acid.

A solution of 1-(o-hydroxyphenyl) pyrrole (11.37g., 0.0714 mole), chloroacetic acid (10.00g., 0.107 mole) and sodium hydroxide (7.15g., 0.179 mole) in water (100 ml.) was refluxed for four hours. The cooled mixture was poured into water and acidified to pH 4 when the product separated as a pink oil. This was extracted into benzene and the acid back-extracted into sodium bicarbonate. Acidification gave a precipitate of pinkish crystals which was filtered off and dried. Recrystallisation from light petroleum (B.P. 60-100°C.) gave colourless crystals, M.P. 109-10°. Yield 8.6g., 57%. Unreacted phenol (3.2g., 40%) was recovered when the dried benzene extract was evaporated.

$C_{12}H_{11}NO_3$ requires: C, 66.35; H, 5.1; N, 6.45%

found: C, 66.58; H, 5.23; N, 6.29%

(c) Biphenyl-2, 2'-bisoxyacetic acid.

A solution of 2, 2'-dihydroxybiphenyl (20.0g., 0.107 mole), chloroacetic acid (40.0g., 0.43 mole) and sodium hydroxide (25.6g., 0.64 mole) in water (100 ml.) was refluxed for five hours. The cooled solution was acidified with dilute hydrochloric acid and extracted with chloroform. Back-extraction into sodium bicarbonate followed by acidification gave an orange oil which was extracted into chloroform. The dried chloroform solution was distilled to remove solvent leaving the product as a pink, oily solid. Recrystallisation from benzene gave the product as fine, white needles, M.P. 148-9°. Yield 7.2g., 22%.

$C_{16}H_{14}O_6$ requires: C, 63.57; H, 4.67%

found: C, 63.7, H, 4.8%

The liquor from the crystallisation contained 2'-hydroxybiphenyl-2-oxyacetic acid which was recovered as an orange oil after distillation of the benzene. This was used without further purification in the preparation of the methoxy-acid below.

(d) 2'-Methoxybiphenyl-2-oxyacetic acid.

The crude hydroxy-acid, above, 9.6g., was dissolved in an excess of aqueous sodium hydroxide solution. This stirred solution was treated dropwise with dimethyl sulphate (25 ml.) sodium hydroxide pellets being added to keep the pH above 7. The mixture was poured into water, acidified and extracted with benzene. Back-extraction of the benzene solution with sodium bicarbonate

followed by acidification gave the methoxy-acid as a pale-pink solid. This was filtered, dried and recrystallised from benzene/light petroleum (B.P. 80°-100°C.) using a little decolourising charcoal to give colourless needles, M.P. 109-110°. Yield 7.8g.

$C_{15}H_{14}O_4$ requires: C, 69.76; H, 5.46%

found: C, 69.81; H, 5.38%

II. From the sodium salt of the phenol and ethyl bromoacetate.

(e) Biphenyl-4-oxyacetic acid.

4-Hydroxybiphenyl (17.0g., 0.1 mole) was dissolved in a solution of sodium ethoxide (from 2.3g., 0.1 mole sodium) in 150 ml. ethanol. Ethyl bromoacetate (17.0g., 0.11 mole) was added and the solution refluxed for 4.5 hours. On cooling, ethyl biphenyl-4-oxyacetate precipitated as a colourless solid. Yield 8.0g., 33%.

This ester (8.0g., 0.03 mole) was refluxed with 100 ml. 10% sodium hydroxide containing 30 ml. ethanol for three hours. The insoluble solid formed on cooling was collected, washed with water and refluxed with 50% hydrochloric acid for two hours. The solid product was filtered from the cooled mixture, washed with water, dried and recrystallised from ethanol to give pure biphenyl-4-oxyacetic acid, M.P. 188°. Yield 7.0g., 96%.

(f) 9, 9-Dimethylfluoren-4-oxyacetic acid.

A solution of sodium ethoxide (from 0.73g., 0.032 mole sodium) in 20 ml. ethanol was added to 9, 9-dimethylfluoren-4-ol (6.7g., 0.032 mole). Evaporation to dryness, under reduced pressure, of the resulting solution gave the sodium salt of the phenol as a yellow solid. Ethyl bromoacetate (20 ml.) and a small

amount of copper powder were added and the mixture refluxed for four hours. After cooling, 50 ml. of 15% alcoholic potassium hydroxide were added and the mixture was refluxed for one hour. The resulting solution was filtered, added to water (500 ml.) and acidified with 50% hydrochloric acid. The product was filtered and recrystallised from benzene/light petroleum (B.P. 60-80°C.) giving pale yellow crystals, M.P. 193-5°C. Yield 6.9g., 80%.

$C_{17}H_{16}O_3$ requires: C, 76.10; H, 6.01%

found: C, 76.32; H, 6.17%

2.3. 2-(Biphenyl-2)oxypropionic acid.

2-Hydroxybiphenyl (15.0g., 0.088 mole) was added to a solution of sodium ethoxide (from 2.07g., 0.088 mole sodium) in 50 ml. ethanol. The resulting solution was evaporated to dryness under reduced pressure. Ethyl 2-bromopropionate (20 ml.) and a small amount of copper powder were added and the mixture refluxed for three hours. After cooling, 100 ml. of 15% aqueous potassium hydroxide were added and the mixture was refluxed for one hour. The cooled solution was filtered and diluted with water (200 ml.). Acidification with 50% hydrochloric acid gave a pinkish oil which was extracted into benzene. Back-extraction into sodium bicarbonate followed by acidification gave the product as a pale pink solid. This was filtered, washed with water, dried and recrystallised from benzene giving colourless needles, M.P. 137-5 - 139°C. Yield 12.1g.

$C_{15}H_{14}O_3$ requires: C, 74.36; H, 5.82%

found: C, 74.29; H, 5.91%

2.4. 3-(Biphenyl-2) oxypropionic acid.

(i) 3-(Biphenyl-2)oxypropionitrile. A mixture of 2-hydroxybiphenyl (25g., 0.147 mole), acrylonitrile (39 ml., 31.2g., 0.59 mole) and Tricon-B (1.5 ml., 40% aqueous benzyltrimethylammonium hydroxide) was refluxed for 72 hours. After cooling the solution was neutralised with dilute hydrochloric acid and the excess acrylonitrile removed under vacuum. After pouring into water and stirring for 10 minutes the product solidified. It was filtered, washed with water and dried. Yield 20.1g.

(ii) The nitrile (20.0g., 0.09 mole) was heated at 100° for five hours with a mixture of glacial acetic acid (60 ml.) and concentrated hydrochloric acid (45 ml.). The cooled solution was poured into iced water and the product precipitated as a pinkish solid, 14.3g. Recrystallisation from benzene gave 3-(biphenyl-2) oxypropionic acid as colourless crystals, M.P. 95°C.

2.5. Biphenyl-2-oxyisobutyric acid.

Sodium hydroxide pellets (70g.) were added to a solution of 2-hydroxybiphenyl (54g.) in 300 ml. acetone. The mixture was refluxed and 50g. chloroform were added dropwise during one hour to the refluxing mixture. A red colour developed and refluxing was continued for a further six hours. Excess acetone was distilled out and water (500 ml.) was added to the dry residue. Acidification of the resulting solution gave the product as an oily solid. This was taken up in chloroform and the product extracted into sodium bicarbonate solution. Acidification gave the product as a pale pink solid which was filtered and dried. Recrystallisation from water gave colourless needles, M.P. 102-4°C. Yield 56.1g., 69%.

$C_{16}H_{16}O_3$ requires: C, 74.98; H, 6.29%

found: C, 75.03; H, 6.37%

2.6. Phenoxyisobutyric acid.

By the same method, using 30g. phenol, phenoxyisobutyric acid was prepared in 73% yield. Recrystallisation from water gave colourless crystals, M.P. 96.5 - 97.5°C. (lit. 97-98°).

2.7. Attempted preparation of 1-(biphenyl-2)oxycyclohexanecarboxylic acid.

(i) A mixture of 2-hydroxybiphenyl (20.0g.), powdered potassium hydroxide (70g.) and cyclohexanone (200 ml.) was stirred at 60°C. Chloroform (50 ml.) was added slowly and the mixture became very hot requiring external cooling in an ice-bath. The addition of chloroform was completed very slowly with cooling. The mixture was stirred at 60°C. for twelve hours, cooled, poured into water and the organic layer discarded. After the usual work-up, 1-hydroxycyclohexanecarboxylic acid was found to be the only acidic product.

The reaction was repeated several times using different temperatures, concentrations, bases and states of division of bases but none of the desired product was formed.

(ii) 1-Trichloromethylcyclohexanol was prepared by reaction of cyclohexanone with chloroform and potassium hydroxide. B.P. 110-116°/9 mm. Yield 84%.

A mixture of 2-hydroxybiphenyl (17.0g., 0.1 mole) and potassium hydroxide (23.0g., 0.41 mole) in tert-butanol (25 ml.) was stirred and treated dropwise with a solution of 1-trichloromethylcyclohexanol (21.7g., 0.1 mole) in 24 ml. tert-butanol. Stirring was continued for a further hour after the addition was

completed. The mixture was poured into water and the usual work-up again gave only the hydroxy-acid.

(iii) The reaction (i) was repeated using other ketones but only in the case of butan-2-one was a small amount of substituted biphenyloxyacetic acid formed.

2.8. Biphenyl-2-thioacetic acid.

(i) 2-Aminobiphenyl (42.0g., 0.25 mole) was added slowly to a stirred mixture of 50 ml. concentrated hydrochloric acid and 50g. ice. A precipitate of the hydrochloride separated. This was diazotised at 0°C. using a solution of sodium nitrite (18.3g.) in 40 ml. water. The solution of the diazonium salt was filtered and kept at 0°C. It was added slowly and in small portions to a stirred solution of potassium ethyl xanthate (46.7g.) in 60 ml. water kept at 45°C. After stirring for a further 30 minutes the xanthate ester was extracted into chloroform. The chloroform solution was washed with 2M sodium hydroxide till neutral, dried and the chloroform distilled out under reduced pressure leaving the xanthate as a deep red oil, 45.1g.

The crude xanthate was dissolved in 150 ml. ethanol and the solution boiled. Potassium hydroxide pellets (60g.) were added and the mixture refluxed a further six hours. Most of the ethanol was distilled out under vacuum and the residue was dissolved in 200 ml. water. The aqueous solution was washed with ether (3 x 100 ml.) and the washings discarded before being vigorously stirred and acidified with sulphuric acid. Carbon oxysulphide was liberated and the product thiol was extracted into chloroform. The chloroform solution was dried and the solvent removed under

reduced pressure leaving the crude thiol as an oil, 19.6g.,
0.105 mole.

To this was added a solution of chloroacetic acid (10.0g.) and sodium hydroxide (8.4g.) in 100 ml. water. The resulting solution was refluxed for four hours. After cooling it was acidified and extracted with chloroform. The product was extracted into sodium bicarbonate solution and liberated, on acidification, as a white solid which was filtered, dried, and recrystallised from benzene giving M.P. 172-3.5°C. Yield 6.0g.

The chloroform solution contained biphenyl-2-disulphide which crystallised on removal of the solvent.

(ii) 2-Aminobiphenyl (30.0g., 0.177 mole) was diazotised in 100 ml. of 50% hydrochloric acid at 0°C. by the addition of a solution of sodium nitrite (14.7g., 0.2 mole) in 30 ml. water. The diazonium salt solution was almost neutralised with sodium bicarbonate and added to a solution of thioglycollic acid (12.5 ml., 16.5g., 0.18 mole) in 100 ml. water. An oily solid precipitated and was extracted into chloroform. This was biphenyl-2-azothioacetic acid. It was extracted into 2M sodium hydroxide and the alkaline solution stirred at 100°C. till evolution of nitrogen ended. The cooled solution was acidified and the orange-coloured product filtered. Recrystallisation from benzene (charcoal) gave biphenyl-2-thioacetic acid as pale yellow needles, M.P. 172-173.5°C. Yield 12.3g.

2.9. The Preparation of Aryloxyalkanoyl Chlorides.

The aryloxyalkanoic acid and a twofold excess of thionyl chloride were refluxed in dry benzene (30-60 ml.) for 45-60 minutes.

The benzene and excess thionyl chloride were removed under reduced pressure. 50 ml. dry benzene were added and distilled out under reduced pressure to remove the last traces of thionyl chloride.

The acid chlorides were not further purified before use but their purity was always checked spectroscopically; the requirement being a single CH_2 or other resonance in the n.m.r. spectrum and ν_{CO} $1800 \pm 15 \text{ cm}^{-1}$ in the I.R. spectrum.

2.10. Reactions of Aryloxyacetyl Chlorides with Aluminium Chloride in Benzene.

All reactions with benzene as solvent were performed in the following general manner.

The acid chloride, previously prepared from the acid (one molar equivalent), in dry benzene (15 molar equivalents) was added dropwise over 20-30 minutes to a vigorously stirred suspension of freshly powdered anhydrous aluminium chloride (1.25 molar equivalents) in dry benzene (15 molar equivalents) at $5-10^\circ\text{C}$. Stirring at this temperature was continued for a further two hours. Moisture was carefully excluded throughout the reaction.

The reaction mixture was hydrolysed by pouring into crushed ice and dilute hydrochloric acid and stirring vigorously for 30-60 minutes. The benzene layer was separated from the acidic aqueous solution which was extracted twice with further quantities of benzene. The combined benzene extracts were washed several times with saturated sodium bicarbonate solution, washed with water, dried and the solvent removed under reduced pressure. Acidification of the bicarbonate wash gave recovered acid (i.e. unreacted acid chloride which had been hydrolysed during

the decomposition) which was identified in the usual manner. The crude product of the reaction (after removal of carboxylic acid) was examined by I.R. and n.m.r. spectroscopy to determine the nature and range of products obtained. The n.m.r. spectrum also provided a quantitative measure of these products.

The general method used to separate the products was as follows:

The crude product was divided into two portions, treated separately.

(i) Chromatography on silica gel gave diphenylmethane and in some cases the o-benzylphenol and the ketonic products.

(ii) The second portion was dissolved in benzene or ether and was washed thoroughly with 2M. sodium hydroxide and alcoholic potassium hydroxide (35g. KOH, 25 ml. H₂O, 75 ml. MeOH). The neutral fraction obtained from the organic layer gave the aryloxyacetophenone and diphenylmethane, separated by chromatography and the potassium hydroxide extract gave, on acidification, the benzylphenol. The 2M sodium hydroxide extract generally gave the parent phenol along with self-condensation products of the benzofuranone.

(a) Biphenyl-4-oxyacetyl chloride (4-phenylphenoxyacetyl chloride).

Reaction of the acid chloride (from 4.63g., 0.204 mole the acid) with aluminium chloride (3.65g., 0.0275 mole) in 45 ml. benzene gave 4.2g. neutral product and no recovered acid. This was divided into two equal portions. The first was chromatographed on 200g. silica gel:

Fraction 1. Diphenylmethane, 0.23g. Eluent 50% benzene/light petroleum.

Fraction 2. Eluent benzene. 2-Benzyl-4-phenylphenol, 0.45g. M.P. 181-2°C, $\bar{\nu}_{OH} = 3600 \text{ cm}^{-1}$.

Fraction 3. Eluent 50% ether/benzene. A mixture of the benzylphenol and two ketonic components.

The second portion was dissolved in ether and extracted in turn with 1M NaOH and alcoholic KOH. Acidification of the NaOH extract gave 4-hydroxybiphenyl, 0.39g. and acidification of the alcoholic KOH extract gave, after chromatographic separation on a silica-gel column, 2-benzyl-4-phenylphenol, 0.42g. and products of self-condensation of 5-phenylbenzofuranone, 0.34g.

The material remaining in the ether solution was chromatographed on silica gel giving diphenylmethane, 0.25g., and 4-phenylphenoxyacetophenone, 0.25g., $\bar{\nu}_{CO} = 1690 \text{ cm}^{-1}$.

The products of the reaction are:

5-phenylbenzofuran-3(2H)-one	16% (I)
4-phenylphenoxyacetophenone	9% (II)
2-benzyl-4-phenylphenol	16%
4-hydroxybiphenyl	23%
diphenylmethane	15%

Notes: (I) Estimated from the integrated n.m.r. spectrum of the crude product. Only products of self-condensation were isolated.

(II) M.P. 94-6°C. when recrystallised from ethanol/light petroleum (B.P. 60-80°C.).

$C_{20}H_{16}O_2$ requires: C, 83.3; H, 5.59%

found: C, 83.1; H, 5.55%

2-methyl-7-phenylbenzofuran-3 (2H) one, 0.42g., 5% The I.R. spectrum showed $\bar{\nu}_{\text{CO}}$ at 1710 cm^{-1} and the n.m.r. showed absorptions at 2.2 - 2.7 τ (aromatic multiplet; 7H), 2.90 τ (triplet, $J = 7\text{Hz}$, 1H; H-5), 5.33 τ (quartet, $J = 8\text{Hz}$; 1H; H-2), 8.46 τ (doublet, $J = 8\text{Hz}$; 3H; 2 - CH_3).

2-hydroxybiphenyl, 1.00g., 17%

1, 1-diphenylethane, 1.25g., 19%

A benzylphenolic fraction, 3.01g., $\sim 36\%$ containing two components which could not be separated. The n.m.r. spectrum showed τ_{OH} at 4.6 and two -CHMe- groups. These were thought to be 2-phenyl-6-(1-phenylethyl) phenol and 9-methylfluoren-4-ol.

(d) Biphenyl-2-oxyisobutyryl chloride.

From the reaction of the acid chloride (prepared from 10.7g., 0.042 mole the acid) with aluminium chloride (6.9g., 0.052 mole) in dry benzene (total 84 ml.) 11.9g. of non-acidic product were recovered. This was dissolved in benzene and extracted with 2M sodium hydroxide (4 x 25 ml.) Acidification of this gave 2-hydroxybiphenyl, 2.64g., 37%.

The residue was chromatographed on an alumina column when two fractions were obtained:

Fraction 1. Eluent benzene. 2, 2-Dimethyl-7-phenylbenzofuran-3 (2H) - one. Yield 3.08g., 31%. Recrystallisation from light petroleum (B.P. 80-100°C.) gave M.P. 112-114°C. The I.R. spectrum showed $\bar{\nu}_{\text{CO}}$ at 1710 cm^{-1} and the n.m.r. spectrum at 100 MHz showed 2.22 - 2.68 τ (aromatic multiplet; 7H), 2.89 τ (triplet, $J = 7.8\text{Hz}$; 1H; H-5), 8.52 τ (singlet; 3H; - CMe_2 -).

$\text{C}_{16}\text{H}_{14}\text{O}_2$ requires: C, 80.65; H, 5.92%

found: C, 80.45; H, 5.72%

Fraction 2. Eluent chloroform. 9, 9-Dimethylfluoren-4-ol. Yield 1.83g., 21%. Recrystallisation from light petroleum (B.P. 80-100°C.) gave M.P. 90 - 1°C.

The product was contaminated with some tarry material, probably polymerised α -methyl styrene, which could form by loss of a proton from a cumyl cation which would be produced along with 2-hydroxybiphenyl.

(e) Phenoxyisobutyryl chloride.

Reaction of the acid chloride (from 5.0g., 0.028 mole the acid) with aluminium chloride (4.6g., 0.035 mole) in benzene (56 ml. total) gave 4.6g. non-acidic product contaminated with some tarry material. Extraction with 2M NaOH gave phenol, 0.95g., 36%. The remainder was chromatographed on an alumina column. Elution with benzene gave 2, 2-dimethylbenzofuranone, 1.81g., 36%. The I.R. spectrum showed $\bar{\nu}_{\text{CO}}$ at 1715 cm^{-1} .

(f) Biphenyl-2, 2'-bisoxycetyl chloride.

Reaction of the bis-acid chloride (from 5.2g., 0.0172 mole the diacid) with aluminium chloride (5.65g., 0.0425 mole - 1.25 molar equivalents per chlorocarbonyl group) in benzene (68 ml. total) gave the crude product, 7.0g., as a red oil which partially crystallised. Crystallisation from benzene gave 1.0g., (22%) of very pale yellow needles, M.P. 253° (dec.). This was found to be a double cyclic ketone. The I.R. spectrum showed $\bar{\nu}_{\text{CO}}$ at 1712 cm^{-1} and the parent ion in the mass spectrum had m/e 256. The n.m.r. spectrum was very simple, showing a high degree of symmetry in the molecule, showing absorptions at 1.80 τ (o-, m-quartet, J = 7.2, 1.5 Hz; 2H; H-4 and H-4'), 2.04 τ

(o-, m-quartet, $J = 7.6, 1.5$ Hz; 2H; H-6 and H-6'), 2.64 τ
 (triplet, $J = 7.5$ Hz; 2H; H-5 and H-5'), 5.00 τ (singlet;
 4H; methylenes). This allows the product to be identified as
 7, 7'-bisbenzofuranane.

$C_{16}H_{10}O_4$ requires: C, 72.18; H, 3.79%

found: C, 72.11; H, 3.92%

Chromatography of the remainder on silica gel gave
 diphenylmethane, 0.96g. (33%) and several other fractions found
 to be complex mixtures of ketonic and phenolic products which
 were not identified.

(g) 2'-Methoxybiphenyl-2-oxyacetyl chloride.

The acid chloride (from 2.71g., 0.0105 mole the acid) was
 reacted with aluminium chloride (1.54g., 0.0116 mole) in benzene
 (22 ml. total) giving 2.90g. crude neutral product which was
 chromatographed on silica gel:

Fraction 1. Eluent benzene. Diphenylmethane. Yield 0.16g., 9%

Fraction 2. Eluent 10% chloroform/benzene. 2-Benzyl-6-(2-
 methoxyphenyl)phenol. Yield 0.22g., 7%. Recrystallisation from
 petroleum ether (B.P. 80-100°C.) gave white crystals, M.P.
 109.5 - 110.5°C.

$C_{20}H_{18}O_2$ requires: C, 82.7; H, 6.25%

found: C, 82.5; H, 6.22%

Fraction 3. Eluent chloroform. 7-(2-Methoxyphenyl)
 benzofuran-3 (2H) - one. Yield 1.06g., 42%. The I.R. spectrum
 shows ν_{CO} at 1702 cm^{-1} and the n.m.r. spectrum shows τ_{CH_2}
 at 5.47 τ

Fraction 4. Eluent methanol. 2'-Methoxy-2-hydroxybiphenyl.
 Yield 0.19g., 9%.

(h) 9, 9-Dimethylfluoren-4-oxyacetyl chloride.

The acid chloride (from 1.02g., 0.0038 mole the acid) was reacted with aluminium chloride (0.63g., 0.0043 mole) in benzene (8 ml. total) giving 0.96g. crude product. The t.l.c. showed three bands and the product was chromatographed on alumina:

Fraction 1. Eluent benzene. Diphenylmethane. Yield 0.02g., 3%

Fraction 2. Eluent benzene. 9, 9-Dimethylfluoreno[4,3-b]furanone.

Yield 0.83., 87%. The I.R. spectrum showed $\nu_{\text{C=O}}$ at 1710 cm^{-1} and the n.m.r. spectrum showed absorptions at 2.20 τ (multiplet; 1H; H-5), 2.55 τ (doublet, $J = 8\text{Hz}$; 1H; H-2), 2.65-2.90 τ (multiplet; 3H; H-6, H-7, H-8), 3.00 τ (doublet, $J = 8\text{Hz}$; 1H; H-1), 5.44 τ (singlet; 2H; CH_2), 8.60 τ (singlet; 6H; CMe_2).

This material decomposed very rapidly and was not fully characterised.

The I.R. spectrum of the crude product showed a weak absorption at 3400 cm^{-1} indicating that some phenolic material was present. 9, 9-dimethylfluoren-4-ol must have been formed along with the diphenylmethane but it was not isolated from the chromatography.

(i) 2-(1-Pyrrolyl)phenoxyacet-dimethylamide.

(i) 2-(1-Pyrrolyl)phenoxyacetic acid (2.0g.) was converted to the ethyl ester by refluxing with a solution of ethanol (1 ml.) and a crystal of p-toluenesulphonic acid in 10 ml. ethylene dichloride for 15 hours. After cooling, the solution was poured into water and extracted with chloroform (30 ml.). The chloroform extract was washed with sodium bicarbonate solution (2 x 25 ml.), dried and the solvent removed under reduced pressure. Yield 1.8g.

(ii) The ester, above, was dissolved in methanol (10 ml.) and treated with an excess of a 30% solution of dimethylamine in methanol. The mixture was refluxed for 1 hour, cooled, poured into water and extracted with chloroform. The chloroform extract was washed with dilute (0.5M) hydrochloric acid then with water, dried and the solvent removed under reduced pressure leaving the dimethylamide which was used in the cyclisation without further purification. The n.m.r. spectrum showed absorptions at 2.60-2.96 τ (multiplet; 4H; benzene ring protons), 3.01 τ (triplet, $J = 2.0$ Hz; pyrrole α - protons), 3.72 τ (triplet, $J = 2.0$ Hz; 2H; pyrrole β - protons), 5.39 τ (singlet; 2H; CH₂), 7.10 τ and 7.12 τ (two signals; 6H; NMe₂). Yield 1.69g.

(iii) The dimethylamide (1.69g.) was dissolved in ethylene dichloride (9 ml.). This solution was cooled in an ice-bath while phosphorus oxychloride (1.07g.) dissolved in ethylene dichloride (5 ml.) was added and then for a further 15 minutes with occasional shaking. The solution was refluxed for 1.5 hours, cooled and a solution of sodium acetate (0.6g.) in 15 ml. water was added and the mixture boiled for 15 minutes. After pouring into water, the product was extracted into chloroform. Removal of solvent gave the product as a yellow waxy solid which was purified by chromatography on alumina and identified as 4-oxopyrrolo [2, 1-d] - 1, 5 benzoxazepin. Yield 0.73g., 53%. Recrystallisation from light petroleum (B.P. 80-100°C.) gave M.P. 78-79°C.

The I.R. spectrum showed $\bar{\nu}_{\text{C=O}}$ at 1680 cm^{-1} and the n.m.r. spectrum showed absorptions at 2.72 τ (broad singlet; 6H; H-1,

H-3, H-7, H-8, H-9, H-10), 3.53 τ (quartet, $J = 3.9, 3.0$ Hz; 1H; H-2), 5.33 τ (singlet; 2H; CH₂).

C₁₂H₉NO₂ requires: C, 72.35; H, 4.55; N, 7.0%

found: C, 72.4; H, 4.6; N, 6.9%

(j) 3-(Biphenyl-2) oxypropionyl chloride.

Reaction of the acid chloride (from 1.5g., 0.0062 mole the acid) with aluminium chloride (1.03g., 0.0075 mole) in benzene (14 ml. total) gave 8-phenylchromanone, 1.4g., as the only product. Recrystallisation from methanol gave pale yellow needles, M.P. 64-6° (lit. 65-7°). The I.R. spectrum showed $\nu_{\text{C=O}}$ at 1700 cm⁻¹ and the n.m.r. spectrum showed absorptions at 2.15 τ (quartet, $J_{56}=7.6$ Hz, $J_{57} = 2.0$ Hz; 1H; H-5), 2.5 - 2.8 τ (multiplet; 6H; H-7 and 8-Ph), 3.07 τ (quartet, $J_{67} = 8.7$ Hz, $J_{56} = 7.6$ Hz; 1H; H-6), 5.68 τ (triplet, $J = 7$ Hz; 2H; 2 - CH₂), 7.37 τ (triplet, $J = 7$ Hz; 2H; 3-CH₂).

(k) Biphenyl-2-thioacetyl chloride.

(i) In benzene.

The acid chloride (from 1.16g., 0.0048 mole the acid) was reacted with aluminium chloride (0.79g., 0.006 mole) in benzene (10 ml. total) to give the product as a red oil, 1.25g., which was chromatographed on alumina. Elution with benzene gave trace amounts of what appeared to be biphenyl-2, 2'-disulphide from the I.R. spectrum (by comparison with the spectrum of an authentic sample). Using 50% chloroform/benzene, 0.93g. of 2-biphenylthioacetophenone was eluted as the only other product. The I.R. spectrum showed $\nu_{\text{C=O}}$ at 1675 cm⁻¹ and the n.m.r. spectrum showed

absorptions at 2.21 - 2.42 τ (multiplet; 2H; ortho protons of benzoyl group), 2.45 - 3.02 τ (aromatic multiplet; 12H; remaining aromatic protons), 6.22 τ (singlet; 2H; methylene group). This compound was rather unstable and was isolated as the yellow, crystalline oxime, M.P. 161-4°C.

$C_{20}H_{17}NOS$ requires: C, 75.22; H, 5.37; N, 4.39%

found: C, 75.5; H, 5.47; N, 4.26%

(ii) In sym-tetrachloroethane.

The acid chloride (from 0.6g., 0.0025 mole the acid) was reacted with aluminium chloride (0.41g., 0.0031 mole) in tetrachloroethane (10 ml. total). A dark green homogeneous mixture was formed which, after hydrolysis and the usual work-up gave the product as a very dark red oil, 0.45g., which rapidly darkened further. The t.l.c. showed one band and the product was purified by chromatography on silica gel, proving to be 7-phenylbenzo[b]thiophen-3(2H)-one. The I.R. spectrum showed $\bar{\nu}_{CO}$ at 1700 cm^{-1} and the n.m.r. spectrum showed absorptions at 2.15 - 2.89 τ (aromatic multiplet; 8H), 6.20 τ (singlet; 2H; CH_2). The compound was characterised as the oxime which crystallized from ethanol/light petroleum (B.P. 60-80° as colourless plates, M.P. 182-4°C.

$C_{14}H_{11}NOS$ requires: C, 69.7; H, 4.6; N, 5.8%

found: C, 69.81; H, 4.6; N, 5.84%

CHAPTER THREE3.1. Preparation of Acyclic Aryl Benzyl Ethers.

The preparation of biphenyl-4 benzyl ether outlined below illustrates the general method of preparation.

A solution of 4-hydroxybiphenyl (18.7g., 0.11 mole) in ethanol (50 ml.) was added to a solution of sodium ethoxide (prepared from 2.53g., 0.11 mole sodium metal) in ethanol (50 ml.) A solution of benzyl chloride (12.6g., 0.10 mole) in 50 ml. ethanol was added to this and the mixture refluxed for three hours during which time sodium chloride separated out. After cooling, this mixture was poured into 1M sodium hydroxide (300 ml.). The product was extracted into ether (2 x 100 ml.) and the ether solution washed with water, dried and evaporated under reduced pressure leaving the product as a pinkish solid which was recrystallised from ethanol to give colourless needles, M.P. 133 - 133.5°C. Yield 11.4g., 44%.

Table IIPhysical Constants of Aryl Benzyl Ethers.

<u>Aryl Benzyl Ether</u>	<u>M.P. or B.P.</u> <u>°C</u>	<u>Yield</u> <u>%</u>	<u>τCH₂(a)</u>	<u>Notes</u>
Biphenyl-4	133	44	5.45	
Biphenyl-2	273/11 mm.	85	5.2	
2-(1-Pyrrolyl)phenyl	53	47	5.2	(b), (c)
Biphenyl-2 1-phenylethyl	-	38	4.75	(d), (e)

Notes (a) τ CH₂ denotes the chemical shift of the methylene group relative to T.M.S. Spectra were recorded in CDCl₃ solution.

(b) Recrystallised from light petroleum (B.P. 80 - 100°C).

(c) C₁₇H₁₅NO requires: C, 81.90; H, 6.06; N, 5.62%

found: C, 82.2; H, 6.06; N, 5.93%.

(d) τ CH (quartet, J = 7Hz), CH₃ = 8.52 (doublet, J = 7Hz)

(e) Did not distil below 250°/7 mm.

3.2. Preparation of Cyclic Ethers.

(a) 6, 6-Dimethyldibenzo[b, d]-6H-pyran.

(i) 3, 4-Benzocoumarin was prepared in 12% yield from phenol and the diazonium sulphate of anthranilic acid using the method described by Cahn.⁷¹

(ii) Again following Cahn's method, 3, 4-benzocoumarin (14.7g., 0.075 mole) was reacted with methylmagnesium iodide (from 7.0g. magnesium) in ether/benzene solution. The usual work up gave dimethyl-2-(2'-hydroxyphenyl)phenyl carbinol as the initial product. This was taken up in benzene (100 ml.) and the solution refluxed with 10 ml. dilute sulphuric acid for 30 minutes. The benzene layer was separated, washed with sodium bicarbonate solution, dried and the solvent removed under reduced pressure. The product distilled as a colourless liquid, B.P. 180°/20 mm. Yield 14.1g., 89%.

(b) Dibenzo[b, d]-6H-pyran.

(i) A solution of 3, 4-benzocoumarin (2.0g.) in ethanol (50 ml.) was added to a stirred suspension of sodium borohydride (1.0g.) in ethanol (20 ml.) at 0°C. The mixture was stirred for two hours at room temperature then hydrolysed by pouring into iced dilute hydrochloric acid (200 ml., 0.5 M.) and stirring for 30 minutes. The product was extracted into methylene chloride. The extract was washed with sodium bicarbonate solution, dried and evaporated leaving the product, 2'-hydroxybiphenyl-2-methanol, as a white solid, 1.9g. Recrystallisation from benzene gave white prisms, M.P. 131-2°C.

(ii) 2'-hydroxybiphenyl-2-methanol (1.9g.) dissolved in dry benzene (50ml.) was treated with phosphorus pentoxide (4g.). The mixture was refluxed for four hours, cooled and decomposed using aqueous ammonia. After acidification, the product was extracted into benzene. The benzene solution was washed with sodium bicarbonate solution, dried, and distilled, giving, after removal of benzene, dibenzo[b, d]-6H-pyran as a colourless oil, B.P. 109°/0.2 mm. Yield 1.3g.

3.3 The Reactions of Acyclic Aryl Benzyl Ethers with Aluminium Chloride in Benzene.

The method outlined below for the reaction of biphenyl-2 benzyl ether with aluminium chloride in benzene illustrates the general scheme used. The results obtained are given in table III.

(a) Biphenyl-2 benzyl ether.

A solution of biphenyl-2 benzyl ether (5.0g., 0.0192 mole) in dry benzene (20 ml.) was added dropwise over 20 minutes to a stirred suspension of finely powdered aluminium chloride (3.2g., 0.024 mole) in dry benzene (20 ml.) at 5-10°C. Stirring was continued for a further 1.5 hours at this temperature. The reaction mixture was hydrolysed by pouring into iced dilute hydrochloric acid and stirring for 30 minutes. The benzene layer was separated and the aqueous solution extracted with further portions (2 x 50 ml.) of benzene. The combined benzene solutions were washed with sodium bicarbonate solution, dried and evaporated under reduced pressure leaving the product as a yellow oil, 6.18g. The n.m.r. and I.R. spectra of this product were recorded.

This crude product was dissolved in benzene (100 ml.) and extracted with 2M sodium hydroxide (3 x 50 ml.). Acidification of this extract gave, after extraction into chloroform, washing with water, drying and removal of solvent, 2-hydroxybiphenyl, 2.20g., 67%.

The remaining material was chromatographed on 150g. alumina giving:

Fraction 1. Eluent benzene. Diphenylmethane, 2.28g., 70%.

Fraction 2. Eluent 75% chloroform, 25% benzene. 2-Benzyl-6-phenylphenol, 1.6g., 30%.

(b) The Reactions of Aryl Benzyl Ethers with $AlCl_3$ in Benzene at 5-10°C.

Table III.

Aryl Benzyl Ether	Diphenylmethane %	Phenol %	2-Benzyl-phenol %
Biphenyl-2	70	67	30
Biphenyl-4	67	43	33
2-(1-Pyrrolyl)phenyl	64	11	35
Biphenyl-2 1-phenylethyl	55(a)	48	35(b)

Notes: (a) 1, 1-Diphenylethane

(b) 2-(1-Phenylethyl)-6-phenylphenol.

3.4. Reactions of Cyclic Ethers with Aluminium Chloride in Benzene.

(a) 6, 6-Dimethyldibenzo[b, d]-6H-pyran.

A solution of 6, 6-dimethyldibenzo[b, d]-6H-pyran (5.35g., 0.025 mole) in dry benzene (25 ml.) was added over 20 minutes to a stirred suspension of finely powdered aluminium chloride (4.2g.,

0.032 mole) in dry benzene (25 ml.) at 5-10°. After the addition was complete, stirring was continued at this temperature for a further 1.5 hours before the reaction mixture was hydrolysed by pouring into iced dilute hydrochloric acid. After the usual work-up, the product was obtained as a white solid, identified as 9, 9-dimethylfluoren-4-ol, 5.3g., 99%. Recrystallisation from light petroleum (B.P. 80-100°) gave white cubes, M.P. 90-91°C.

(b) Dibenzo[b, d]-6H-pyran.

(i) This compound (1.25g., 0.0069 mole) was reacted with aluminium chloride (1.14g., 0.0086 mole) in dry benzene (14 ml. total) as above. The crude product was obtained as an almost colourless oil, 1.22g., after the usual work up. The n.m.r. spectrum of this product showed it to comprise 85% unreacted starting material and 15% fluoren-4-ol which was isolated by chromatography on 100g. silica gel in a yield of 0.11g., 9%. M.P. 106-8°C.

(ii) The reaction was repeated as above using 1.14g., 0.0063 mole of the ether and 1.04g., 0.0078 mole of aluminium chloride in dry benzene (20 ml. total). After being stirred for 1.5 hours at 5-10°C., the mixture was warmed to 55° and stirred for a further 1.5 hours at this temperature before being hydrolysed by pouring into iced dilute hydrochloric acid and stirring for 30 minutes. After the usual work up the product was obtained as a dark red oil, 2.02g. The t.l.c. showed three bands; the n.m.r. spectrum showed a complex aromatic multiplet and a single-CH₂-resonance at 6.05 and the I.R. spectrum

showed ν_{OH} at 3600 and 3400 cm^{-1} . This product was chromatographed on 200g. silica gel:

Fraction 1. Eluent benzene. Diphenylmethane, 0.86g., 80%.

Fraction 2. Eluent 50% chloroform, 50% benzene. 2-Hydroxybiphenyl, 0.93g., 87%.

Fraction 3. Eluent chloroform. Triphenylmethanol, 0.35g., 20%.

The mass spectrum of this material also showed traces of the methyl and ethyl ethers which would be formed by acid-catalysed reaction on the column with methanol and ethanol present in the chloroform.

CHAPTER FOUR.4.1. Preparation of Dibenz[b, d]oxepin-7(6H)-one.

This was prepared by cyclisation of biphenyl-2-oxyacetyl chloride with aluminium chloride in benzene as described in 2.10(b). The yield was typically around 90%. Recrystallisation from benzene gave very pale yellow needles, M.P. 79-80°C.

$C_{14}H_{10}O_2$ requires: C, 80.0; H, 4.8%

found: C, 79.8; H, 4.9%

Oxime: Straw-coloured needles from aqueous ethanol, M.P. 188-9°C.

$C_{14}H_{11}NO_2$ requires: C, 74.65; H, 4.92; N, 6.22%

found: C, 74.59; H, 5.01; N, 6.15%

4.2. 7-Hydroxy Derivatives.(a) 6, 7-Dihydro-7-hydroxydibenz[b, d]oxepin.

(i) Lithium aluminium hydride (1.9g., 0.05 mole) was placed in a dry 500 ml. three-necked flask fitted with a double-surface reflux condenser, a sealed stirrer and a dropping funnel. Dry ether (150 ml.) was added cautiously and the mixture stirred for 10 minutes.

A solution of dibenz[b, d]oxepin-7(6H)-one (18.5g.) in dry benzene (100 ml.) was added dropwise at such a rate that the solution refluxed gently. After the addition was complete, the mixture was refluxed for 30 minutes. After cooling, excess LAH was decomposed by the cautious addition of 5 ml. ethyl acetate followed by stirring for 15 minutes. The mixture was hydrolysed by pouring into iced dilute hydrochloric acid (400 ml.) and stirring for 30 minutes. The organic layer was separated and the aqueous phase extracted with ether (2 x 100 ml.). The combined

organic solutions were washed with sodium bicarbonate solution, dried and evaporated under reduced pressure leaving the product as a viscous, pale yellow oil, 18.4g. This was purified by chromatography on alumina which gave the alcohol as a colourless very viscous oil which did not crystallise and did not distil without decomposition.

The n.m.r. spectrum showed absorptions at 2.5 - 3.2 τ (aromatic multiplet; 8H), 5.5 - 6.0 τ (ABC multiplet; 3H; CH₂ and H-7), 7.0 τ (broad singlet; 1H; OH).

(ii) A solution of dibenz[b, d]oxepin-7(6H)-one (5.0g.) in ethanol (15 ml.) was treated with a solution of sodium borohydride (0.6g.) in 15 ml. ethanol and the mixture stirred for one hour before being poured into iced dilute hydrochloric acid (50 ml.). The product was extracted into chloroform and the extract was washed with sodium bicarbonate solution, dried and distilled under reduced pressure leaving the product as a pale yellow oil which was purified by chromatography on alumina. Yield 4.8g.

(b) 6, 7-Dihydro-7-hydroxy-7-methyldibenz[b, d]oxepin.

A solution of dibenz[b, d]oxepin-7(6H)-one (15.0g.) in dry benzene (75 ml.) was added to a stirred solution of methylmagnesium iodide (prepared from 5.1g. magnesium and 30.0g. methyl iodide) in dry ether (150 ml.) at such a rate that gentle refluxing was maintained. When the addition was complete, the mixture was refluxed for 30 minutes, cooled and hydrolysed by pouring into iced dilute hydrochloric acid and stirring for 30 minutes. The organic layer was separated and the aqueous extracted with

benzene (2 x 100 ml.) The combined organic solutions were washed with sodium bicarbonate solution, dried and distilled under reduced pressure to remove solvent leaving the product as a brownish oil, 16.0g., which was purified by chromatography on alumina. Elution with 75% chloroform/25% benzene gave the alcohol as a very viscous, orange oil, 15.5g. The n.m.r. spectrum showed absorptions at 2.35 - 3.05 τ (multiplet; 8H; aromatic protons), 5.63 and 5.82 τ (two AB doublets, $J = 12\text{Hz}$; 2H; CH_2), 7.78 τ (broad singlet; 1H; OH), 8.70 τ (singlet; 3H; CH_3).

(c) 6, 7-Dihydro-7-hydroxy-7-phenyldibenz[b, d]oxepin.

In a similar fashion, a solution of dibenz[b, d]oxepin-7(6H)-one (10.5g., 0.05 mole) in dry benzene (50 ml.) was added to a solution of phenylmagnesium bromide (prepared from 7.9g. bromobenzene and 1.2g. magnesium) in 50 ml. dry ether. After the addition, the mixture was refluxed for three hours, cooled and hydrolysed using ammoniacal ammonium chloride solution. After the usual work up the product was obtained as a very viscous, yellow oil which was purified by chromatography on alumina. Yield 7.6g., 53%.

4.3. Other Reduction Reactions of Dibenz[b, d]oxepin-7(6H)-one.

(a) Catalytic Hydrogenation.

A solution of dibenz[b, d]oxepin-7(6H)-one (10.0g.) in ethanol (100 ml.) was treated with 10% palladium charcoal (0.5g.) and subjected to hydrogen at 100 ats. pressure for 8 hours at 50°C. No reduction occurred and the starting material was recovered unchanged.

(b) Clemmensen Reduction.

Following the method described by Martin, 9.1g. of dibenz[b, d]oxepin-7(6H)-one was reduced, in toluene solution, using zinc amalgam and hydrochloric acid. The crude product, 8.3g., was a reddish oil which partially crystallised. The crystalline component was isolated in 1.7g. yield by crystallisation from ethanol as colourless plates, M.P. 216-8°C. The n.m.r. spectrum showed only two absorptions, at 2.4 τ - 3.3 τ (complex multiplet; 8H; aromatic protons) and 8.1 τ (singlet; 3H; CH₃). The mass spectrum showed the parent ion at m/e 390 with a large half-mass peak at m/e 195 along with its doubly charged ion at m/e 97.5. From the cracking pattern (see text) and the very simple n.m.r. spectrum, this product was identified as 6, 6-bis-(6-methyldibenzo[b, d]pyranyl) and subsequently found to be the meso- form.

The I.R. spectrum of the liquors showed a phenolic -OH group. This material was dissolved in benzene (100 ml.) and extracted with 8 x 25 ml. portions of 2M sodium hydroxide. Acidification of this extract gave an inseparable mixture of two phenols, 0.4g., which was found from the n.m.r. spectrum to comprise around 70% of 2'-ethyl-2-hydroxybiphenyl and 30% of 9-methylfluoren-4-ol. The residue was chromatographed on 200g. alumina. Elution with benzene gave 4.7g. of a golden oil whose n.m.r. spectrum showed it to be a mixture of two components. The minor component (30% of the mixture) showed absorptions at 4.85 τ (quartet, J = 7Hz; 2H; CHMe) and 8.45 τ (doublet, J = 7Hz; 3H; CH₃) with the aromatic region obscured by the major component which showed a methyl group as a singlet at 8.31 τ . The first compound was thought to be 6-methyldibenzo[b, d]-6H-pyran although it could not be isolated in a pure state.

The major component was isolated by crystallisation from light petroleum (B.P. 60-80°) at -78°C. in 1.3g. yield, M.P. 146-8°C. The mass spectrum of this material was identical with that of meso-6, 6-bis-(6-methyldibenzo[b, d]pyranyl) and the n.m.r. spectrum at 100 MHz showed absorptions at 2.62 - 3.40 τ (complex multiplet; 7H; aromatic protons except H-4), 3.61 τ (quartet, $J_{ortho} = 8.0\text{H}$, $J_{meta} = 1.4\text{Hz}$; 1H; H-4) and 8.31 τ (singlet, 3H; CH_3). This allowed the compound to be identified as the dl-form of 6, 6-bis(6-methyldibenzo[b, d]pyranyl).

Meso- 6, 6-bis-(6-methyldibenzo[b, d]pyranyl):

$\text{C}_{28}\text{H}_{22}\text{O}_2$ requires: C, 86.13; H, 5.68%

found: C, 86.2; H, 5.53%

DL - 6, 6-bis-(6-methyldibenzo[b, d]pyranyl):

$\text{C}_{28}\text{H}_{22}\text{O}_2$ requires: C, 86.13; H, 5.68%

found: C, **85.8** ; H, **5.76%**

(c) Wolff-Kishner Reduction.

A mixture of dibenz[b, d]oxepin-7(6H)-one (9.5g.), potassium hydroxide (5.0g.) and 85% hydrazine hydrate (5 ml.) in 40 ml. digol was refluxed for one hour. The condenser was removed and replaced when the internal temperature reached 200°C. Refluxing was continued for a further three hours. After cooling, the mixture was poured into dilute hydrochloric acid (100 ml.) and extracted with benzene (2 x 50 ml.). The benzene solution was washed with sodium bicarbonate solution, dried and the solvent was removed under reduced pressure leaving the product as a brown, semi-solid mass. Crystallisation of this from ethanol gave phenanthrenequinone, 4.9g., as orange needles, M.P. 202-3°. The melting point was not depressed in a mixture with an authentic

sample. The mass spectrum showed the parent ion at m/e 188 with two consecutive losses of 28 mass units, and the I.R. spectrum showed ν_{CO} at 1680 cm.^{-1}

The I.R. spectrum of the remaining material showed a phenolic $-\text{OH}$ at $\nu_{\text{OH}} = 3400 \text{ cm.}^{-1}$. Extraction with 2M sodium hydroxide followed by acidification and extraction of the product into chloroform gave, after removal of the solvent, 1.5g. of phenolic material which the n.m.r. spectrum showed to be a mixture of 2'-ethyl-2-hydroxybiphenyl (86%) and 9-methylfluoren-4-ol (14%). Crystallisation from light petroleum (B.P. 40-60°C) gave the former in 0.9g. yield, M.P. 103-10°C.

A further 1.9g. of phenanthrenequinone was isolated from the liquors after alkaline extraction.

4.4. Other reactions of Dibenz[b, d]oxepin-7(6H)-one.

(a) Wittig Rearrangement.

A solution of dibenz[b, d]oxepin-7(6H)-one (1.5g.) and potassium hydroxide pellets (3.0g.) in digol (50 ml.) was refluxed for four hours. After cooling, the mixture was poured into dilute hydrochloric acid (250 ml.). The product was extracted into ether (2 x 50 ml.) and benzene (2 x 50 ml.). The combined extracts were washed with sodium bicarbonate solution, dried and distilled under reduced pressure, leaving the product as a brownish solid which was recrystallised from ethanol giving phenanthrenequinone as fine, orange needles, M.P. 202-3°C., in 0.95g. yield.

(b) Attempted preparation of the 6-isonicroso-derivative.

Sodium nitrite (5.0g.) was added in portions to a stirred solution of the oxepinone (4.0g.) in glacial acetic acid (50 ml.)

at 5-10°C. After 4 hours a further 5.0g. of sodium nitrite were added and the mixture was stirred at room temperature overnight before being poured into cold water. A pale yellow solid precipitated which was filtered, dried and recrystallised from aqueous methanol giving almost colourless needles, M.P. 79-80°. It was found to be unchanged starting material.

(c) Attempted Methylation of 6-position.

(i) A solution of the oxepinone (17.0g., 0.081 mole), pyrrolidine (11.5g., 13.0 ml., 0.16 mole) and a few crystals of p-toluenesulphonic acid in dry toluene (50 ml.) was refluxed with removal of water for 5 hours. Removal of the toluene under reduced pressure left the pyrrolidine enamine as a dark viscous oil which was used without further purification. The I.R. spectrum showed $\nu_{C=C}$ at 1640 cm.^{-1}

(ii) Methyl iodide (25 ml.) and dioxan (75 ml.) were added to the enamine and the solution was refluxed for 16 hours. A solution of acetic acid (2 ml.) in water (30 ml.) was added and this solution was refluxed for 4 hours before being poured into water (300 ml.). After acidification, the product was extracted into chloroform and obtained after drying the solution and removal of solvent as a dark oil, 15.9g. This was found to be almost entirely starting material and none of the 6-methyl derivative was detected.

(d) With Phenylhydrazine.

A mixture of the oxepinone (21g.) and phenylhydrazine (17.8g.) was warmed on the water bath and the phenylhydrazone separated.

Glacial acetic acid was added with stirring, at 100°C., till the solid all dissolved. After heating for a further one hour, the mixture was cooled and a solid separated which was filtered off and recrystallised twice from ethanol giving 14.7g. of pale yellow needles, M.P. 200-2°C. The mass spectrum showed the parent ion at m/e 283, the n.m.r. showed absorptions at τ 0.3 (broad singlet; 1H; NH) and 2.15 - 3.05 (complex multiplet; 12H; aromatic protons) and the I.R. spectrum showed ν_{H} at 3300 cm.^{-1} showing the product to be indole[3,2-g]dibenz[b,d]oxepin.

$\text{C}_{20}\text{H}_{13}\text{NO}$ requires: C, 84.8; H, 4.62; N, 4.94%
 found: C, 85.0; H, 4.7; N, 4.8%

4.5 Preparation of Dibenz[b, d]oxepin.

(i) Phosphorus pentoxide (10g.) was added to a solution of 6, 7-dihydro-7-hydroxydibenz[b, d]oxepin (13.6g.) in dry benzene (200 ml.) and the mixture was refluxed with stirring for three hours. After hydrolysis with aqueous ammonia the benzene layer was separated, dried and the solvent was removed under reduced pressure leaving the product as a brown oil, 13.0g. The t.l.c. showed two components. Chromatography on alumina gave a red oil, 12.0g., eluted with benzene. When this was treated with methanol, a white solid was precipitated. This softened at around 105°C. with some decomposition. The n.m.r. spectrum showed aromatic protons and some broad peaks in the region τ 7-8 and the material was found to be polymeric.

(ii) A solution of the alcohol, 6,7-dihydro-7-hydroxydibenz[b,d]oxepin, (4.8g.) and thionyl chloride (2.5 ml.) in dry benzene (50 ml.)

was refluxed with the exclusion of moisture for 30 minutes. The solvent and any excess thionyl chloride were removed under reduced pressure leaving the chloro-compound as a pale red oil (4.9g.) 7-Chloro-6,7-dihydrodibenz[b,d]oxepin distilled under nitrogen as a colourless oil, B.P. 116-20°/0.01 mm. which rapidly darkened on standing. Yield 4.2g.

After several trials, the most satisfactory conditions for the preparation of dibenz[b, d]oxepin were found to be those given below. A solution of 7-chloro-6,7-dihydrodibenz[b,d]oxepin (3.8g.) and potassium hydroxide pellets (10g.) in ethanol (40 ml.) was refluxed for four hours during which a precipitate of potassium chloride formed. The mixture was poured into water (150 ml.) and the product extracted into ether. The ether extract was washed with water, dried and the solvent removed under reduced pressure leaving the product as pale yellow oil (2.5g.). This was purified by chromatography on alumina followed by distillation under nitrogen to give dibenz[b,d]oxepin as a colourless oil, B.P. 102-4°/0.2 mm., which slowly reddened on standing. The I.R. spectrum showed $\nu_{C=C}$ at 1647 cm.^{-1} and the n.m.r. spectrum showed absorptions at 2.4 - 3.05 τ (multiplet; 8H; aromatic protons), 3.75 τ (doublet, $J = 6.0 \text{ H}$; 1H; H-6), 4.05 τ (doublet slightly broadened by l.r. coupling, $J = 6.0 \text{ H}$; 1H; H-7).

$\text{C}_{14}\text{H}_{10}\text{O}$ requires: C, 86.6; H, 5.19%
found: C, 86.8; H, 5.3%.

4.6. 7-Substituted Dibenz[b,d]oxepins.

(a) 7-Methyldibenz[b,d]oxepin.

(i) 6, 7-Dihydro-7-hydroxy-7-methyl dibenz[b,d]oxepin (7.5g.,

0.032 mole) dissolved in dry benzene (100 ml.) was treated with thionyl chloride (3.0 ml., 4.8g.) and the solution refluxed for 1 hour. The solvent and any excess thionyl chloride were distilled out under reduced pressure; 100 ml. dry benzene were added and distilled out to remove the last traces of thionyl chloride leaving the product as a pale yellow oil, 7.4g., which was found, from the n.m.r. spectrum, to be a mixture of the 7-chloro-derivative and the 7-methyl-oxepin.

(ii) The product, above, was dissolved in 20% ethanolic potassium hydroxide (70 ml.) and the solution refluxed for 3 hours before being poured into water (200 ml.). The product was extracted into methylene chloride and the extract was washed with water, dried and the solvent removed under reduced pressure leaving the product as a dark yellow oil which was purified by chromatography on alumina to give a pale yellow oil, 6.0g. Crystallisation from light petroleum (B.P. 60-80°C.) gave white clusters, M.P. 72-4°C.

The I.R. spectrum showed $\nu_{C=C}$ at 1640 cm.^{-1} and the n.m.r. spectrum showed absorptions at 2.4 - 3.6 τ (multiplet; 8H; aromatic protons), 3.45 τ (quartet, $J = 1.6 \text{ H}$; 1H; H-6) and 8.13 τ (doublet, $J = 1.6 \text{ H}$; 3H; CH_3).

$\text{C}_{15}\text{H}_{12}\text{O}$ requires: C, 86.5; H, 5.81%

found: C, 86.8; H, 5.97%

(b) 7-Phenyldibenz[b,d]oxepin.

In a similar fashion, 7-phenyldibenz[b,d]oxepin was prepared from the alcohol by reaction with thionyl chloride followed by dehydrochlorination with ethanolic potassium hydroxide.

Crystallisation from light petroleum (B.P. 60-80°C.) gave small

white clusters, M.P. 97-9°C. Yield 59%.

The I.R. spectrum showed $\nu_{C=C}$ at 1630 cm.^{-1} and the n.m.r. spectrum showed absorptions at 2.20 - 2.94 τ (multiplet; 13H; aromatic protons including 7-Ph) and 3.12 τ (singlet; 1H; H-6).

$C_{20}H_{14}O$ requires: C, 88.9; H, 5.22%

found: C, 89.1; H, 5.41%

4.7. Reactions of Dibenz[b,d]oxepin.

(a) Hydrogenation.

A solution of dibenz[b,d]oxepin (1.0g.) in ethanol, containing 0.2g. Raney nickel was hydrogenated at atmospheric pressure. After five hours, approximately half of the theoretical volume of hydrogen had been absorbed. The catalyst was filtered off and the solvent removed leaving the product as a pale yellow oil, 1.02g. The t.l.c. showed two bands and the n.m.r. spectrum showed approximately equimolar amounts of 6,7-dihydrodibenz[b,d]oxepin and unreduced starting material. These were separated by chromatography on silica gel with the starting material being eluted with light petroleum and the dihydro-derivative with benzene. 6, 7-Dihydrodibenz[b,d]oxepin crystallised from light petroleum as small, white needles, M.P. 112-13°C. (Sieglitz and Koch report 116°C.).

The n.m.r. spectrum shows absorptions at 2.5 - 3.05 τ (multiplet; 8H; aromatic protons), 5.63 τ (triplet, $J = 7\text{ H}$; 2H; 6- CH_2) and 7.33 τ (triplet, $J = 7\text{ H}$; 2H; 7- CH_2).

(b) Bromination.

A stirred solution of dibenz[b,d]oxepin (1.0g.) in chloroform (20 ml.) was treated dropwise at room temperature with a solution

of bromine (0.8g.) in chloroform (10 ml.). The bromine colour disappeared quickly and no HBr was liberated. After the addition was completed, the solvent was removed under reduced pressure; 30 ml. of carbon tetrachloride were added and distilled out under reduced pressure leaving the product as a pink oil (1.9g.). The I.R. spectrum showed the absence of a double bond and the n.m.r. spectrum showed two pairs of doublets centred on 3.15 τ and 4.70 τ ($J = 3.8$ H) and on 3.45 τ and 4.95 τ ($J = 9.5$ H) respectively of approximately equal intensity. The intensities of the peaks did not change when the spectrum was recorded at -60°C ., 0°C and $+28^{\circ}\text{C}$. showing that the two components were the cis- and trans-dibromides.

When the reaction was repeated, the product contained 80% trans- and 20% cis- isomers. This product crystallised from light petroleum (B.P. $60-80^{\circ}\text{C}$.) as colourless needles, M.P. $101-9^{\circ}\text{C}$.

$\text{C}_{14}\text{H}_{10}\text{Br}_2\text{O}$ requires: C, 47.5; H, 3.39%

found: C, 47.24; H, 3.18%

(c) Attempted Nitration.

(i) A solution of fuming nitric acid (0.6 ml.) and acetic anhydride (2.0 ml.) in methylene chloride (10 ml.) was added over 30 minutes to a stirred solution of dibenz[b,d]oxepin (1.0g.) in methylene chloride (5 ml.) containing 1 drop of glacial acetic acid at 0°C . Stirring was continued for a further hour at this temperature. The mixture was poured into crushed ice and the products extracted into methylene chloride when the ice had melted. The extract was washed with sodium bicarbonate solution, dried and the solvent removed leaving the product as an orange gum,

(ii) A suspension of cupric nitrate (1.4g.) in acetic anhydride (70 ml.) was added slowly to a stirred solution of dibenz[b,d]oxepin (1.0g.) in acetic anhydride (30 ml.) at -78°C . After the addition was complete, stirring was continued for a further 15 minutes at this temperature. The external cooling was removed and the mixture was allowed to come to room temperature. 100 ml. water were added and the mixture was shaken with a further 300 ml. of water before the products were extracted into methylene chloride. This extract was washed with dilute ammonia and water, dried and the solvent was removed under reduced pressure leaving the product as a brown oil, 1.5g.

In neither case were any nitro-derivatives isolated and both products were found to be complex mixtures. Both polymerisation and hydrolysis of the oxepin ring seemed to have taken place.

4.8 7-Bromodibenz[b,d]oxepin.

A solution of 6,7-dibromo-6,7-dihydrodibenz[b,d]oxepin (0.95g.) and potassium hydroxide (1.0g.) in ethanol (10 ml.) was refluxed for 15 minutes. Potassium bromide precipitated quickly. The mixture was poured into water (100 ml.) and the product extracted into methylene chloride. The extract was washed with water, dried and the solvent removed under reduced pressure leaving the product as a pale yellow oil, 0.6g. 7-Bromodibenz[b,d]oxepin crystallised from light petroleum (B.P. $40-60^{\circ}\text{C}$.) at -78°C . as fine, white needles which melted below 0°C .

The I.R. spectrum showed $\nu_{\text{C}=\text{C}}$ at 1630 cm^{-1} and the n.m.r. spectrum at 100 MH showed absorptions at 2.18τ (octet, $J_{\text{ortho}} = 7.0\text{ H}$, $J_{\text{meta}} = 1.6\text{ H}$, $J_{\text{para}} = 0.6\text{ H}$; 1H; H-8), $2.26 - 2.96\tau$ (multiplet; 7H; remaining aromatic protons), 3.05τ (singlet;

1H; H-6). The mass spectrum showed parent ions of equal intensities at m/e 274 and m/e 272 with the fragmentation pattern consistent with the proposed structure.

4.9. Attempted preparation of 7-cyanodibenz[b,d]oxepin.

A mixture of 7-bromodibenz[b,d]oxepin (1.0g.), cuprous cyanide (0.7g.) pyridine (1 drop) and dimethylformamide (5 ml.) was refluxed for 1 hour during which it became homogeneous. After cooling it was poured into aqueous ammonia and the product extracted into methylene chloride. The extract was washed with dilute hydrochloric acid then three times with water, dried and the solvent removed under reduced pressure leaving the product as a brown tar. The I.R. spectrum showed $C=O$, $C\equiv N$ and OH groups. Chromatography on alumina isolated 0.4g. of unreacted starting material. The remainder was a complex mixture and no identifiable products were isolated.

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ABSTRACT OF THESIS

Name of Candidate DAVID S. LEITCH
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Title of Thesis ACYLATION AND ALKYLATION REACTIONS OF BIPHENYL- AND
..... N-PHENYLPYRROLE- ALKANOID ACID DERIVATIVES.

This thesis is presented in four distinct parts , necessary because of the apparent independence of the subjects studied.

The initial object was an investigation of the interaction of a series of biphenyl-2-oxalkanoyl chlorides with aluminium chloride in benzene as solvent. Ring closure can occur at two distinct sites leading, in general, to the formation of five- or seven- membered- ring cyclic ketones and an attempt has been made to assess the steric and electronic factors affecting these cyclisations.

In some of these reactions decarboxylation of the acid chloride was found to occur and some alkylated products were isolated. Such reactions had previously been shown to involve an aryl benzyl ether as intermediate and the interactions of several biphenyl benzyl ethers with aluminium chloride in benzene were studied. These, generally, led to the same alkylated products formed in similar proportions to those in the cyclisations.

In the course of the initial study the cyclic ketone, dibenz b,d oxepin-7(6H)-one, was prepared by cyclisation of biphenyl-2-oxoacetyl chloride. From this several other derivatives, including the previously unknown parent compound, of the dibenz b,d oxepin ring system were prepared. Some reactions of dibenz b,d oxepin were investigated.

The study of cyclisation reactions was extended initially to ring closure of N-phenylpyrrole-propionic acids and subsequently to some other heterocyclic alkanoid acids, using polyphosphoric acid as condensing agent. In the course of this work, a rearrangement, leading to inversion of the cyclic ketone ring was discovered, which is thought to involve a four-membered-ring spirocyclic intermediate. Some S.C.F. molecular orbital calculations using the CNDO approximation and the computer program CNINDO were performed on the starting materials, products and proposed intermediates involved in these reactions.