STUDIES IN CYCLISATION REACTIONS:

ACYLATION AND DECARBONYLATION REACTIONS

OF 2-ARYLOXYALKANOIC ACID CHLORIDES

by

GRAHAM JAMES McVIE B.Sc.

Thesis presented for the Degree of

Doctor of Philosophy

University of Edinburgh

August 1967

EX BIBL. UNIV. EDINBURGEN

TO LINDA AND OUR PARENTS

ACKNOWLEDGEMENTS

I wish to express my sincere appreciation to Dr. M. H. Palmer for his advice and encouragement throughout the period of this study.

I also wish to thank the University of Edinburgh for the provision of laboratory facilities and a maintenance grant.

The contributions made to this study by Messrs. P. S. McIntyre B.Sc. and D. S. Leitch B.Sc. are gratefully acknowledged.

G. J. McVIE

INDEX

Page

INTRODUCTION

1. Scope of the Present Investigation 1

2. Competitive Inter- and Intra-Molecular Acylation of Acid Chlorides 2

3. Competitive Acylation and Decarbonylation of Acid Chlorides 10

4. Lewis Acid-Catalysed Rearrangements of Aryl Benzyl Ethers 20

DISCUSSION

1. Mechanism of the Friedel-Crafts Acylation Reaction 24

2. Preparation of 2-Aryloxyacetic Acids 31

3. Preparation of 2-Aryloxypropionic-, 2-Aryloxyisobutyric-, and 2-Arylthio-Acetic Acids 34

4. Reactions of 2-Aryloxyacetyl Chlorides with Aluminium Chloride in Non-Aromatic Solvents 38

5. Reactions of 2-Aryloxyacetyl Chlorides with Aluminium Chloride in Aromatic Solvents 54

6. Mechanism of the Decarbonylation Stage 84

EXPERIMENTAL

1. Preparation of Phenols 106

2. Preparation of 2-Aryloxyacetic Acids 111

3. Preparation of 2-Aryloxypropionic Acids and 2-Aryloxyisobutyric Acids 117

4. Preparation of 2-Arylthioacetic Acids 119

5. Reactions of 2-Aryloxyacetyl Chlorides with Aluminium Chloride in Non-Aromatic Solvents: Preparation of Aryloxymethyl Chlorides 121

6. Reactions of 2-Arylthioacetyl Chlorides with Aluminium Chloride in Non-Aromatic Solvents 139

7. Nuclear Magnetic Resonance Spectra of 2-Aryloxyacetyl Chlorides and 2-Arylthioacetyl Chlorides 141

Page

EXPERIMENTAL (cont'd.)

8. Reactions of 2-Aryloxyacetyl Chlorides with Aluminium Chloride in Aromatic Solvents 143

9. Unambiguous Syntheses of 2-Aryloxyacetophenones 168

10. Synthesis of Aryl Benzyl Ethers 171

11. Reactions of Aryl Benzyl Ethers with Aluminium Chloride in Benzene 173

12. Reactions of 2-Aryloxypropionyl Chlorides with Aluminium Chloride in Aromatic Solvents 178

13. Preparation of 4-Chlorophenyl α-Phenylethyl Ether and its Reactions with Aluminium Chloride in Aromatic Solvents 181

14. Reaction of 2-(4-Chlorophenoxy)isobutyryl Chloride with Aluminium Chloride in Benzene 183

REFERENCES 184

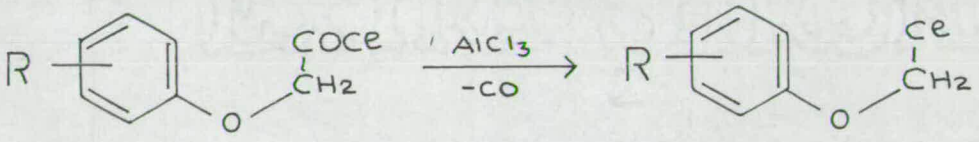
INTRODUCTION

1. Scope of the Present Investigation

The major reaction scheme studied has been the Friedel-Crafts reactions of 2-aryloxyacetyl chlorides (1). In view of the diversity of the products obtained it is suitable at this early stage to give a brief outline of the present work. This has comprised two separate studies and may be classified as follows.

(a) Reactions in Inert Solvents

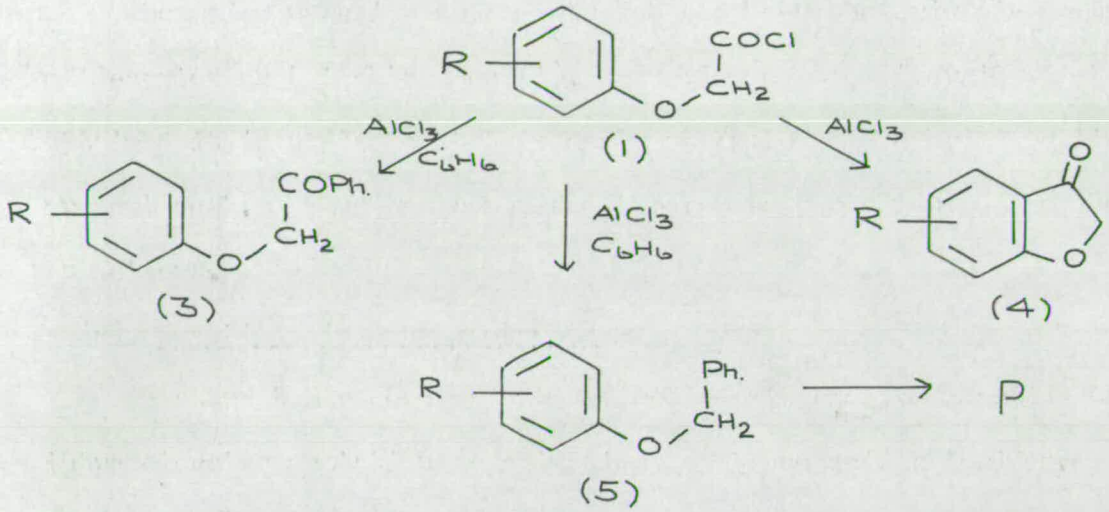
An attempt has been made to effect an alternative reaction to the intramolecular acylation (cyclisation) of these acid chlorides. This was found to be successful only when the nucleus contained strong -E-M groups, a carbon monoxide elimination (decarbonylation) resulting in the formation of the corresponding aryloxymethyl chloride (2)[1].



(1) (2)

(b) Reactions in Aromatic Solvents

Competitive inter- and intra-molecular acylation of 2-aryloxyacetyl chlorides (1) in benzene was shown to result in the formation of 2-aryloxyacetophenones (3) and benzofuran-3(2H)ones (4). In many cases a competing decarbonylation reaction occurred in which the initial product formed was the corresponding aryl benzyl ether (5), shown to be a precursor to the final reaction products (P).



Before discussing the results of these studies a summary of other relevent investigations will be given.

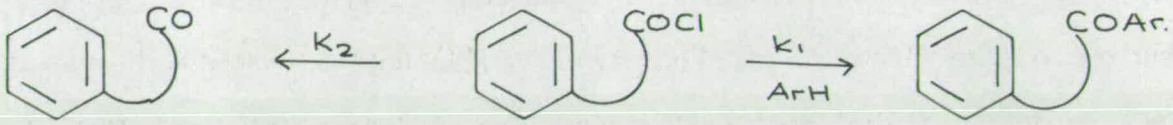
2. Competitive Inter- and Intra-Molecular Acylation of Acid Chlorides

The intermolecular acylation of aromatic compounds with acid chlorides under Friedel-Crafts conditions is an important synthetic route to aromatic ketones.

$$RCOCl + ArH \longrightarrow RCOAr + HCl$$

The reaction is first order with respect to the aromatic component and in consequence the rate (R_1) is susceptible to variation in both the concentration and nucleophilic character of this component.

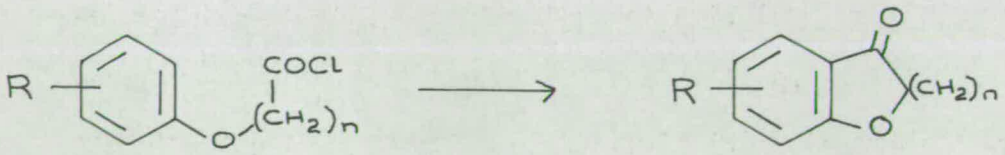
When the acid chloride contains an aromatic substituent competitive intramolecular acylation is theoretically possible and since this is a unimolecular process the dependence of the rate of cyclisation (R_2) on the aromatic substrate, normally the solvent, is essentially a reflection of the rate of competitive intermolecular acylation. That is, the product distribution is a function of the relative rate ratio (R_1/R_2).



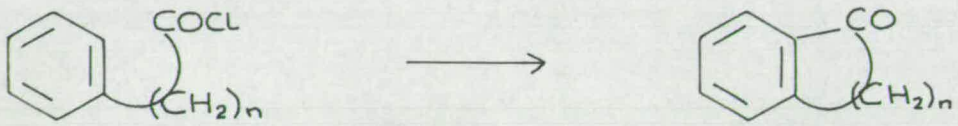
Relative rate ratio $\frac{R_1}{R_2} = \frac{K_1[ArH]}{K_2}$

The failure of acid chlorides of this type to cyclise under these conditions is therefore not a consequence of the absolute rate of cyclisation (R_2). Before assessing the significance of the product distribution it is necessary to determine that the acid chloride has an inherent tendency to cyclise in the absence of competitive intermolecular reaction. Studies in inert solvents have therefore provided much information on the factors influencing cyclisation.

The effect of ring size is of major importance. In the absence of comparable data it is difficult to assess this effect in the cyclisations of aryloxyaliphatic acid chlorides (6). There is however much evidence to show that both the 5-membered benzofuran-3-ones (4) and the 6-membered chroman-4-ones (7) are readily formed.[2.3.4.] No information is available for the higher homologues (6) (n> 2).

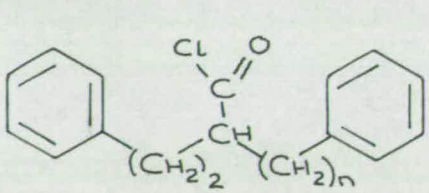


However an extensive study on the effects of ring size on the cyclisations of arylaliphatic acid chlorides (8) to hydroaromatic ketones (benzocyclanones) (9) has been carried out.[5.6.7.] The failure of benzoyl and phenylacetyl chlorides to cyclise is primarily due to the high ring strain developed in the formation of 3- and 4-membered rings.

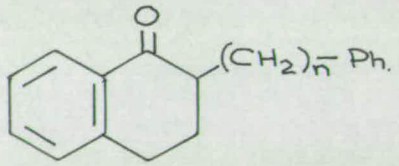


(8) (9)

In general it was shown that only 5-, 6-, or 7-membered cyclic ketones (9) are formed readily, a result consistent with their strainless configurations. By the cyclisations of acid chlorides of the form (10) which can formally lead to two isomeric ketones, differing only in their ring size, it has been shown that the 6-membered ketone, the tetralone (11), is preferrentially formed.

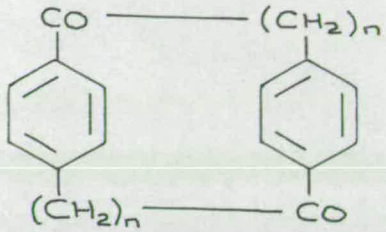


(10; n=1,3)

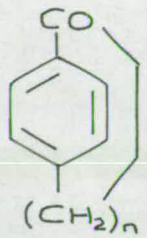


(11; n=1,3)

The synthesis of large ring benzocyclanones and naphthocyclanones has shown that ring strain is not the sole factor determining cyclisation.[8.9.] The formation of the dimers (12) and the 1, 4-benzocyclanone (13) from the acid chlorides (8) of a specific chain length only cannot be rationalised in terms of ring strain.

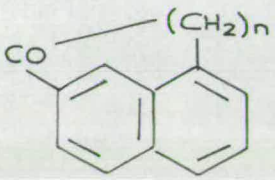


(12; n=6,9)

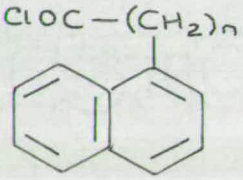


(13; n= 9)

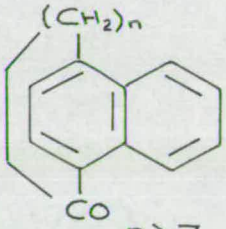
The cyclisations of ω -(1-naphthyl) alkanoyl chlorides (14) followed a similar pattern, competing 1,4 and 1,7 ring closures occurring only with the higher homologues of (14).



n > 7



(14)

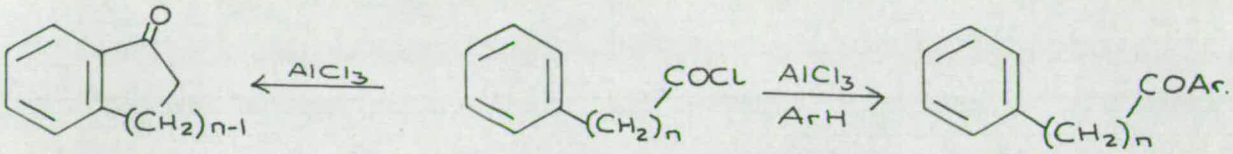


n > 7

Thus in large ring systems, where the variation in ring strain with ring size is not significant, the proximity of the carbonyl group to the cyclisation site is of importance. A similar effect is no doubt responsible for the formation of the 1,2-benzocyclanones (9) in smaller ring systems. In consequence variations in the proximity effect, together with ring strain effects, must be considered when comparing the cyclisations to 5-, 6-, and 7-membered 1,2-benzocyclanones.

The following discussion is predominantly limited to the competing acylations of 2-aryloxyacetyl chlorides and their corresponding 3-arylpropionyl chlorides. It will be shown that the variations in product distribution for each series are similar.

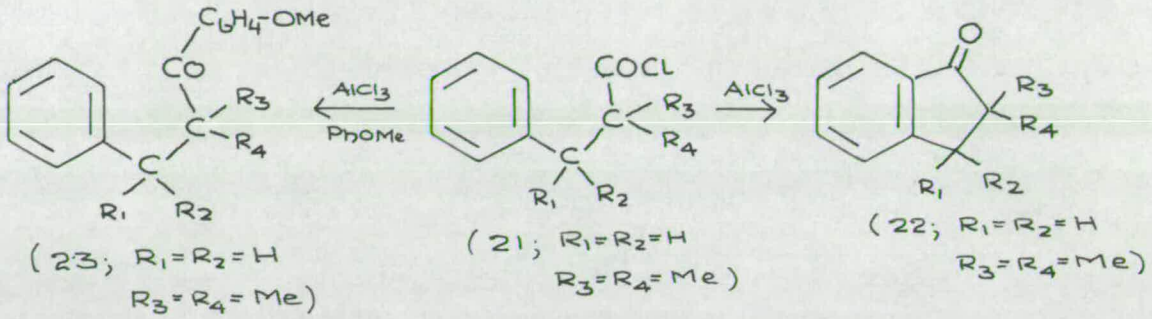
Studies of the competing acylation reactions of 3-phenylpropionyl chloride (15) and 4-phenylbutyryl chloride (16) in a variety of aromatic solvents have illustrated again the inherent tendency to 5- and 6-membered ketone formation and the greater ease of formation of the latter.[10]



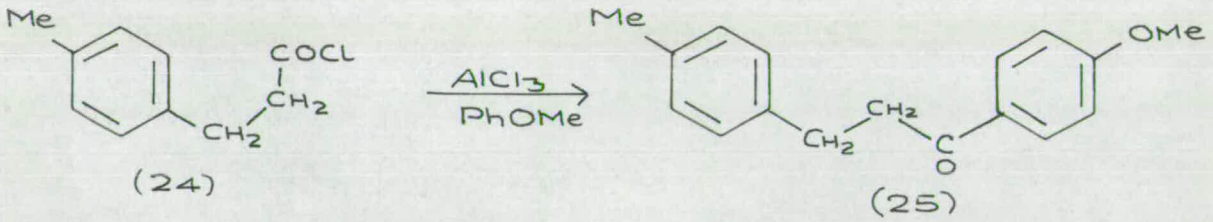
(17; n=2) (15; n=2) (19; n=2)
(18; n=3) (16; n=3) (20; n=3)

In benzene only the cyclic ketones (17) and (18) were formed and in high yield (90%) while in anisole the intermolecular ketones (19) and (20) were formed exclusively. In ethylbenzene both cyclic ketones and intermolecular ketones were formed, the major product in each case being the tetralone (18) (70%) and the indanone (17) (50%). Thus in each series the relative rate of cyclisation is decreased when the reactivity of the solvent to electrophilic substitution is increased. The relative yields of the tetralone and indanone under identical conditions reflect the greater rate of formation of 6-membered ketones.

The presence of alkyl side chain substituents has a marked influence on the rate of cyclisation.[11] Thus 2,2-dimethyl-3-phenylpropionyl chloride (21) cyclises in anisole to give a mixture of the indanone (22) and the propiophenone (23) while progressive substitution in the 3-position leads exclusively to the cyclic indanones.



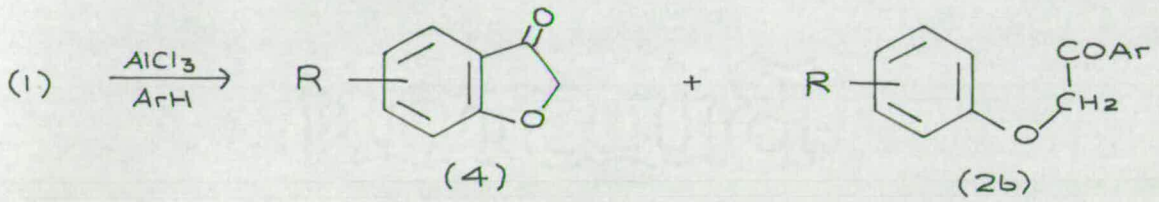
It is unlikely that this is solely an electronic effect in which the side chain substituents donate electrons to the ring, thus increasing the relative rate of cyclisation. That 3-(p-tolyl)propionyl chloride (24) gives exclusively the intermolecular ketone (25) in anisole also indicates this.



It is possible that the above results are more consistent with an increase in the proximity effect with increasing side chain substitution whereby an increase in restricted rotation about the C_2-C_3 bond 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.

As expected, the presence of substituents in the nucleus of the acid chloride markedly affect their relative rates of cyclisation. Thus 3-(p-tolyl)propionyl chloride (24) gives exclusively the cyclic indanone in benzene as solvent when, under identical conditions only the intermolecular ketone was formed from 3-(p-chloro)propionyl chloride.[10]

A detailed study of the competitive intra- and inter-molecular acylation of 2-aryloxyacetyl chlorides (1) has not been carried out. In the absence of truly comparable data it is therefore difficult to assess the significance of the independent studies reported in the literature.

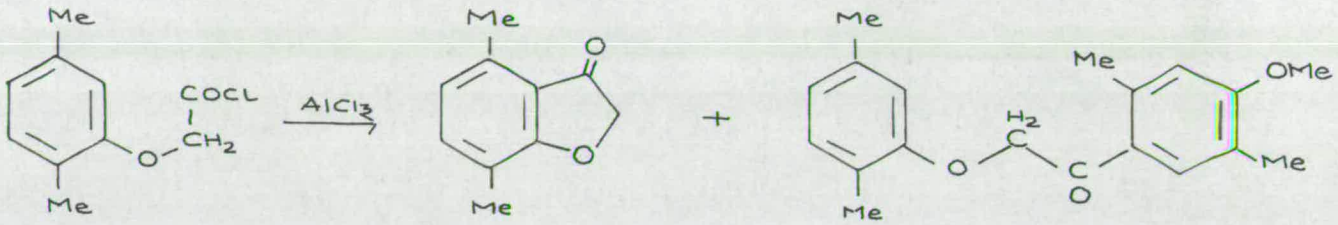


Stoermer and Atenstadt[13] have claimed that the reaction of phenoxyacetyl chloride (1; R=H) with aluminium chloride in benzene as solvent gave, in addition to the major product, benzofuran-3-one (4; R=H), a trace amount of 2-phenoxyacetophenone (26; R=H, Ar=Ph) while Higginbotham and Stephen[14] reported the cyclic ketone as the sole product of the reaction. This acid chloride has been shown to give only the corresponding phenoxyacetophenones (26; R=H) when reacted in m-xylene or anisole.[13]

In general aryloxyacetyl chlorides containing electron donating nuclear substituents readily cyclise in benzene and without the formation of the corresponding intermolecular ketones[12] while 2,4-dichlorophenoxyacetyl chloride (1; R=2,4-Cl_2) gives exclusively 2,4-dichlorophenoxyacetophenone (26; R=2,4-Cl_2; Ar=Ph) in the same solvent.[15]

Although the variations in product distributions are those expected the above evidence also suggests that the "ether" oxygen of aryloxyacetyl chlorides does not have a substantial effect in promoting the cyclisation of these relative to their 3-arylpropionyl chloride analogues. This was also indicated

from a study of the reaction of 2,5-dimethylphenoxyacetyl chloride (27) in 2,5-dimethylanisole.[12]



(27) (28) (29)

In a molar excess of this solvent the major product was the intermolecular ketone (29), the cyclic ketone (28) being obtained in 44% yield, while a ten-fold molar excess of the solvent reduced the yield of the latter to 15%. Since 3-phenylpropionyl chloride (15) is known to cyclise in 50% yield in the presence of five molar equivalents of ethylbenzene yet afford only the intermolecular ketone with a similar amount of anisole[10] it would appear that, while the overall effect of the "ether" oxygen is to activate the ring to cyclisation, the inherent tendency of aryloxyacetyl chlorides to cyclise is less than for the corresponding 3-arylpropionyl chlorides.

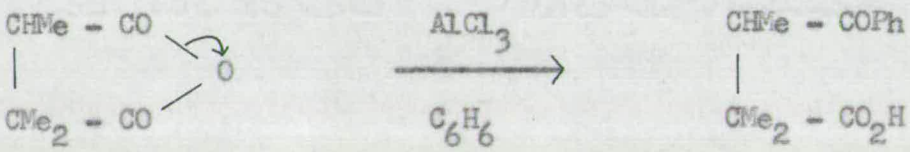
A suggestion has been made that this may be due in part to the greater electron withdrawing effect of the positively-charged acylium ion on the nucleus of aryloxyacetyl chlorides than on the corresponding 3-arylpropionyl chlorides. Differences in the simple proximity effect are thought to be small since this is essentially a function of chain length and shape.

3. Competitive Acylation and Decarbonylation of Acid Chlorides

The Friedel-Crafts decarbonylation of acid chlorides in aromatic solvents has been the subject of a comprehensive study by Rothstein and his co-workers.

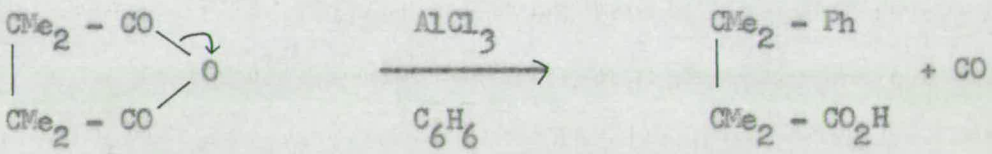
An initial study[16] investigated the aluminium chloride-catalysed acylation of benzene with alkylated succinic anhydrides and showed their reactions to fall into two classes.

It was found that both primary and secondary anhydrides acylated benzene and gave a single ketonic acid, establishing that in all cases the phenyl nucleus attacked the carbonyl group attached to the least substituted centre. Thus trimethylsuccinic anhydride (30) gave only 3-benzoyl-2,2,3-trimethylpropionic acid (31) on reaction with aluminium chloride in benzene.



(30) (31)

Tertiary anhydrides, under identical conditions, readily eliminated carbon monoxide however and gave 3-phenylpropionic acids, illustrated by the conversion of tetramethylsuccinic anhydride (32) to 3-phenyl-2,2,3,3-tetramethylpropionic acid (33).

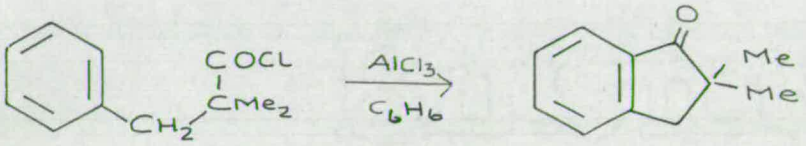


(32) (33)

It was originally claimed that the presence of an ionisable hydrogen atom was necessary to give a ketonic product, unsaturated intermediates being proposed to rationalise the above observations and concluded that the failure

of tertiary acid chlorides to afford ketonic products was also a consequence of a similar mechanism.

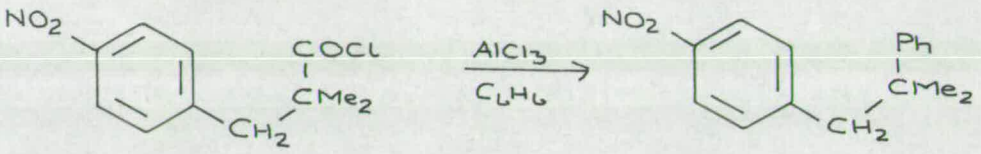
This was subsequently shown to be incorrect[17] by the synthesis of 2,2-dimethylindan-1-one (34) from 2,2-dimethyl-3-phenylpropionyl chloride (35) with aluminium chloride in benzene as solvent.



(35) (34)

The failure of tertiary aliphatic acid chlorides and anhydrides to acylate benzene may be more readily rationalised by their greater relative rates of decarbonylation and not through a mechanistic difference between these and their primary and secondary analogues.

It was readily demonstrated that the apparently anomalous behaviour of (35) was solely due to its inherent tendency to cyclise and not due to any stabilisation of the carbonyl group by the presence of the aromatic nucleus. Therefore precluding cyclisation by the influence of strongly electron withdrawing nuclear substituents results only in the formation of decarbonylation products; this is illustrated by the formation of 2-phenyl-1-(p-nitrophenyl)-isobutane (36) as the sole product in the reaction of 2,2-dimethyl-3-(p-nitrophenyl)propionyl chloride (37) with aluminium chloride in benzene.



(37) (36)

The formation of ketonic products from tertiary aliphatic acid chlorides and anhydrides in strongly nucleophilic aromatic solvents finally confirmed the conclusions previously stated.[18] The reactions of pivaloyl chloride (38) with aluminium chloride in a variety of aromatic solvents were of particular interest since in many cases both intermolecular ketones (39) and decarbonylation products (40) were formed concurrently.

$$Me_3C - COCl \xrightarrow[ArH]{AlCl_3} Me_3C - COAr + Me_3C - Ar + CO$$

(38) (39) (40)

In benzene only the decarbonylation product, tert-butylbenzene (40; Ar=Ph), was formed while in anisole the sole product was the intermolecular ketone, p-methoxyphenyl tert-butyl ketone (39; Ar=p-MeO-C_6H_4). Approximately equimolar quantities of ketone (39) and hydrocarbon (40) were formed using toluene or ethylbenzene as solvent and in tert-butylbenzene the decarbonylation product was predominant. The variation in product distributions obtained with solvents of differing nucleophilic character was perhaps an initial indication that a unimolecular decarbonylation of these acid chlorides was in competition with bimolecular ketone formation.

Kinetic studies on the decarbonylation of pivaloyl chloride (38) in benzene[19] have shown the reaction rate to be independent of the solvent concentration. While this has shown the rate determining stage to be either the rate of formation or unimolecular decomposition of the acylium ion complex it is impossible to differentiate between these. In extending this study to other solvents[20] in which both acylation and decarbonylation occur simultaneously it has been tentatively suggested, in view of the complexity of the kinetic expression, that the observed independence of the overall rate on the solvent was consistent with the rate determining stage being the rate of formation of the acylium ion complex.

Kinetic evidence,[19.20.] together with the marked dependence of the product distributions on the aromatic solvent[18] is therefore consistent with the following competitive scheme.

(i) The slow rate-determining formation of the acylium ion complex (41).

(ii) The irreversible slow unimolecular decarbonylation of the complex (41) to give a carbonium ion complex (42) which undergoes rapid nucleophilic attack by the solvent (ArH).

(iii) The slow bimolecular attack by the solvent on the complex (41) to give the ketonic product complex (43).

$$RCOCl + AlCl_3 \rightleftharpoons \underset{(41)}{RCO^+\ AlCl_4^-} \qquad (i)$$

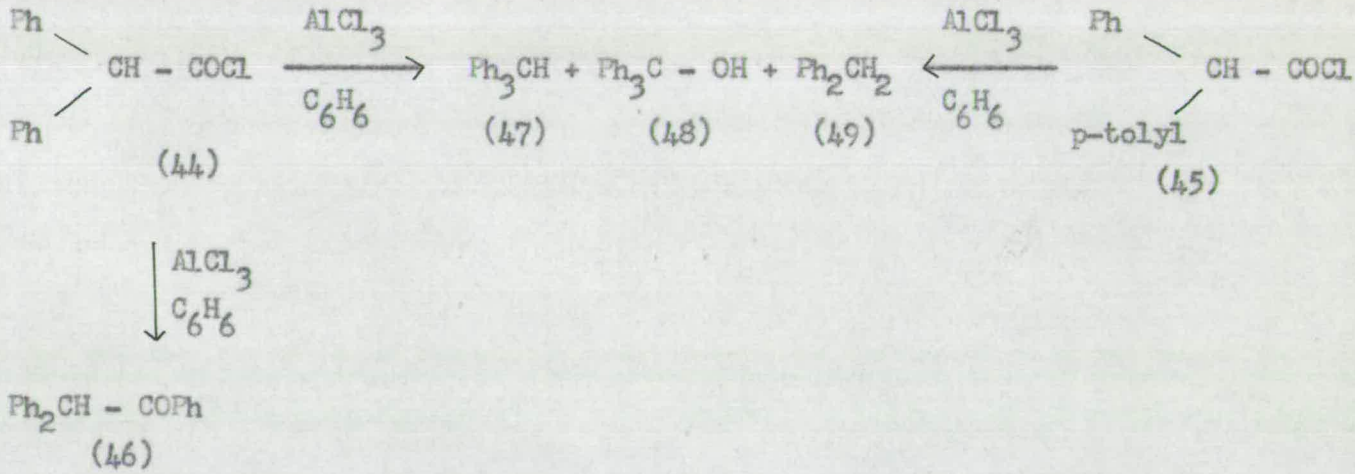
$$RCO^+\ AlCl_4^- \ (41) \xrightarrow{-CO} \underset{(42)}{R^+\ AlCl_4^-} \xrightarrow{ArH} R - Ar + AlCl_3 \qquad (ii)$$

$$RCO^+\ AlCl_4^- \ (41) + ArH \longrightarrow \underset{(43)}{RCOAr\ AlCl_3} \qquad (iii)$$

The general factor determining the product ratio is the stability of the acylium ion complex to unimolecular decomposition. Thus the simple rule that

primary or secondary acid chlorides do not decarbonylate is rationalised by the above scheme, for the ability of the complex to decarbonylate is possibly determined by structural and electronic effects similar to those facilitating the unimolecular solvolyses of alkyl halides. However providing the necessary electronic requirements are satisfied the decarbonylation of primary and secondary acid chlorides is not precluded.

It has been shown[21] that the secondary acid chlorides, diphenylacetyl chloride (44) and phenyl-p-tolylacetyl chloride (45), readily decarbonylate in benzene, the latter (45) exclusively, while a small amount of the intermolecular ketone (46) was obtained from the former. The electron donating effect of the aromatic methyl group in (45) promoting decarbonylation is expected from the previous discussion.



The nature of the decarbonylation products derived from (44) and (45) have been established;[21.22.23] in each case a mixture of triphenylmethane (47), diphenylmethane (49) and triphenylcarbinol (48) was obtained although previous studies[22.23] incorrectly postulated a mechanism in which decarbonylation was not considered. While it is difficult to formulate a mechanism which involves

the formation of the diphenylmethyl carbonium ion (Ph_2CH^+), the loss of the p-tolyl group occurring by exchange with the solvent, it is reasonable to assume that such an ion is initially formed for in both reactions carbon monoxide was liberated in large quantities (70%). Their anomalous behaviour may be a consequence of their resonance stabilisation allowing an alternative to solvent attack; thus the formation of a stabilised carbonium ion, together with the relief from steric strain involved in its formation, may be a significant factor in assisting these secondary acid chlorides to readily eliminate carbon monoxide.

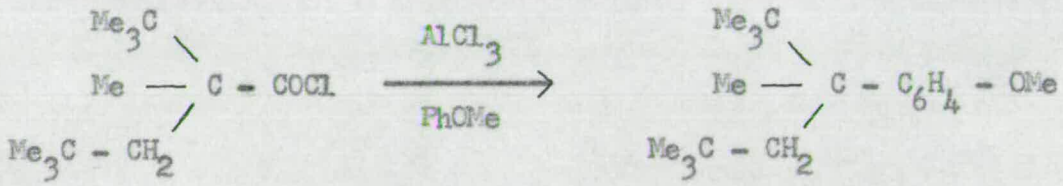
The diarylacetyl chlorides parallel the behaviour of their tertiary aliphatic analogues in that only intermolecular ketone formation occurs in anisole as solvent.

A re-investigation of the kinetics of the aluminium chloride catalysed decarbonylation and acylation of pivaloyl chloride (38) in a series of aromatic solvents,[24] where both the rates of carbon monoxide elimination and the overall rates were measured, confirmed the results obtained from a previous study.[19,20]

The reactions in the mixed anisole/benzene solvent showed the rate of carbon monoxide elimination to decrease with an increase in the molar proportion of anisole but without a significant increase in the overall rate of removal of the acid chloride. These results, together with the fact that the overall rate expression did not involve the aromatic component, can again be rationalised on the basis of a rate-determining formation of the acylium ion complex followed by competitive unimolecular decarbonylation and bimolecular ketone formation.

A kinetic study on the rates of decarbonylation of a series of tertiary alkylated acid chlorides[25] in benzene indicated that progressive substitution of the methyl groups of pivaloyl chloride (38) by ethyl-, tert-butyl, or neopentyl-substituents markedly increased the overall rates relative to (38).

No intermolecular ketones were formed in this solvent. Kinetic evidence showed the rate determining stage to be the formation of the acylium ion complex and it is therefore most likely that the inductive effects of these substituents are responsible for the increased rates, this being the major factor in influencing charge separation in the carbon-chlorine bond of the acid chloride. Since increasing electron donating power of these substituents is also parallelled by an increase in their steric size, and since both effects favour unimolecular decarbonylation and inhibit bimolecular ketone formation, the stability of the carbonyl group may be expected to be significantly decreased in the above hindered acid chlorides relative to pivaloyl chloride. The above discussion therefore rationalises the quantitative decarbonylation of methyl-tert-butyl-neopentyl acetyl chloride (50) with aluminium chloride in anisole when under identical conditions both triethylacetyl chloride and pivaloyl chloride give almost exclusively the intermolecular ketones.



(50)

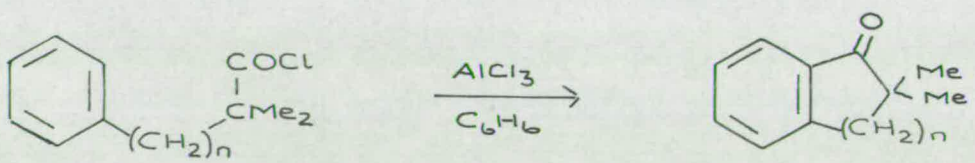
The rates of decarbonylation and the overall reaction rates have been measured for a series of para-substituted diarylacetyl chlorides and afford a study of substituent effects on the decarbonylation stage in which steric effects are of little importance.[26]

As expected electron donating groups accelerate the rate of decarbonylation while the converse applies for electron withdrawing groups. Since the effects of these substituents on the overall rate, that is, the rate of removal of the acid chloride, are less marked changes in the relative rate of decarbonylation to ketone formation occur and are evident in the variations

of the product distributions obtained. This is illustrated in the following discussion.

Nuclear substituent effects are expected to be greater at the α-carbon atom than at the carbonyl group, for in the former there is one less bond to reduce such influences. Thus, when an electron withdrawing group is introduced, the retarding influence on complex formation (and therefore on the overall rate) is parallelled by an even greater inhibition to carbon monoxide elimination. Moreover, because electron withdrawal at the acylium ion accelerates ketone formation the overall influence of the substituent is to decrease the relative rate of decarbonylation in addition to the overall rate. The converse applies for electron donating groups. Therefore phenyl-p-tolylacetyl chloride (45), in addition to reacting more rapidly than diphenylacetyl chloride (44), decarbonylates exclusively while the latter gives approximately 30% ketone formation.

It has previously been established that the failure of 3-phenyl-2,2-dimethylpropionyl- (35) and 4-phenyl-2,2-dimethylbutyryl- chlorides (51) to decarbonylate in benzene was a consequence of the ease with which 5- and 6-membered ring ketones are formed,[17] and was also indicated by the exclusive decarbonylation



(35; n=1.)
(51; n=2.)

n= 1,2.

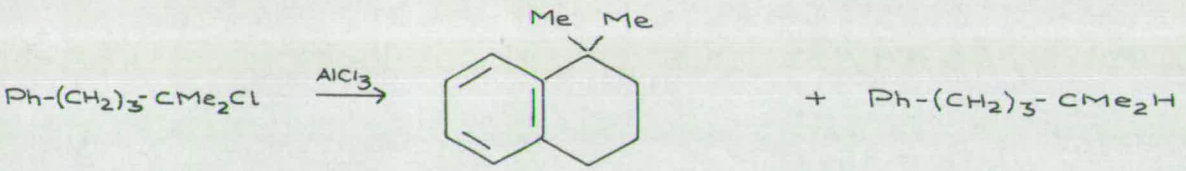
of 2-phenyl-2,2-dimethylacetyl chloride (52) to a mixture of (53) and (54),

cyclisation to the 4-membered cyclic ketone being inhibited by both proximity and ring strain effects.

$$PhCMe_2 - COCl \xrightarrow[C_6H_6]{AlCl_3} Ph_2CMe_2 + PhCHMe_2$$

(52) (53) (54)

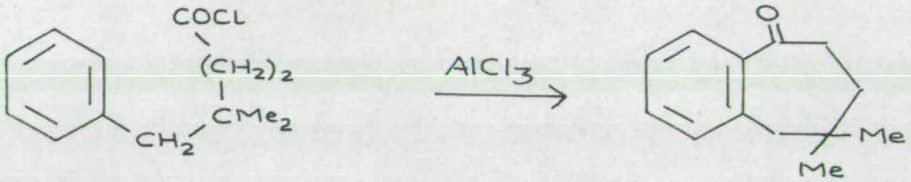
It is of interest to note that the decarbonylation product (54), assuming it to be derived from the expected carbonium ion, must have been formed by a hydride ion transfer mechanism. The generality of such processes has been recently reported,[27] and a typical example is the formation of isohexylbenzene (55) (in 55% yield) and 1,1-dimethyltetralin (57) in the reaction of 5-phenyl-2-chloro-2-methylpentane (56) with aluminium chloride.



(56) (57) (55)

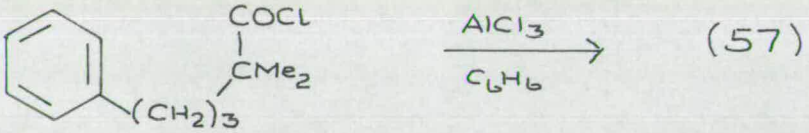
The effect of ring size on the competitive cyclisation and decarbonylation of a series of 5-phenylvaleryl chlorides[28] has been studied as an extension to the above scheme.[17]

While 5-phenyl-4,4-dimethylvaleryl chloride (58) with aluminium chloride in benzene gave the cycloheptanone (59) as the sole reaction product,



(58) (59)

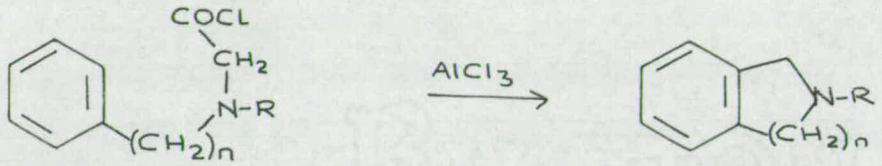
5-phenyl-2,2-dimethylvaleryl chloride (60) did not give the corresponding 7-membered cyclic ketone; carbon monoxide was readily evolved and the product formed was 1,1-dimethyltetralin (57) in 57% yield.



(60)

An uncharacterised product isomeric with (57) was also present. The study of Khalaf and Roberts[27] has shown that this may be isohexylbenzene (55), derived from (57), or the carbonium ion from (56), by hydride ion transfer. However, irrespective of the subsequent alternative reactions exhibited by the alkyl carbonium ion, this series of reactions has demonstrated the ability of tertiary acid chlorides to decarbonylate even under conditions in which cyclic ketone formation is a distinct possibility. In addition it affords a measure of the relative ease of formation of 5-, 6-, and 7-membered ring ketones.

The decarbonylation of (60) finds an analogy in the cyclisations of the phenylalkylglycines (61) to the corresponding derivatives of tetrahydroisoquinoline (62) and tetrahydro-2-benzazepine[29.30] (63). This is also the only reference available to the decarbonylation of



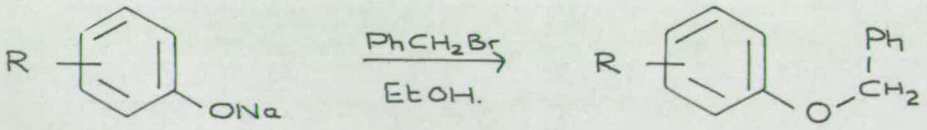
(61; n=2,3)
(R= CH_3- or $PhSO_2$-)

(62; n=2)
(63; n=3)

primary acid chlorides under Friedel-Crafts conditions.

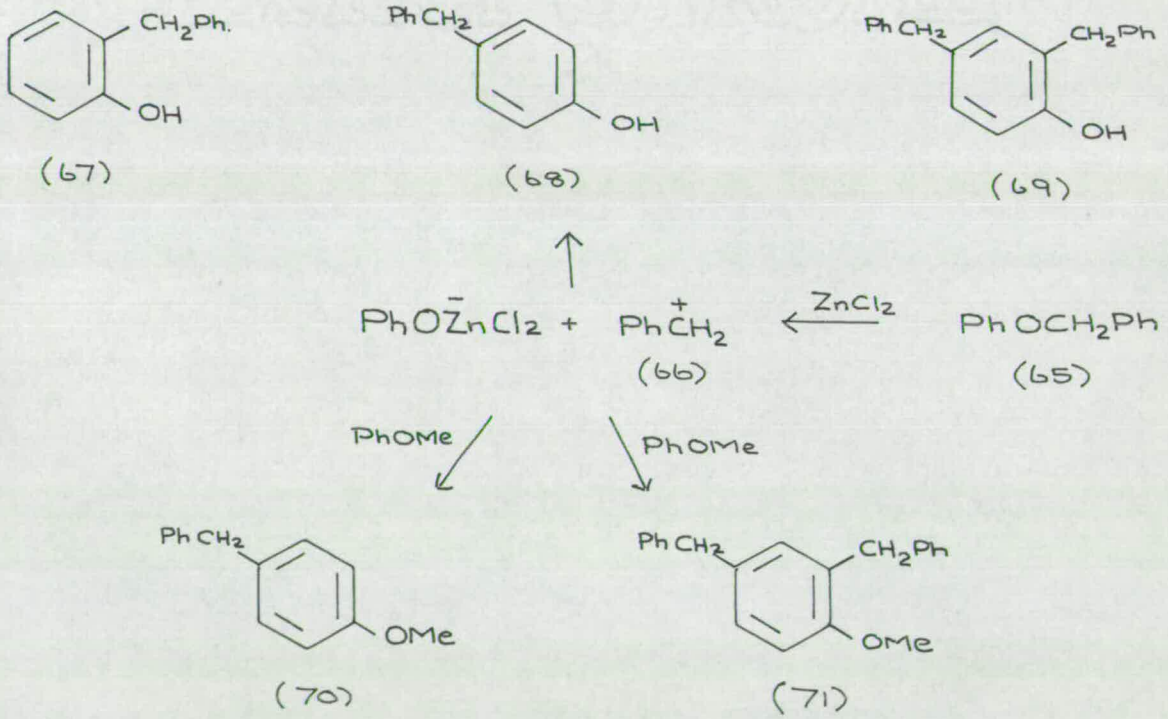
4. Lewis Acid-Catalysed Rearrangements of Aryl Benzyl Ethers

The general method of synthesis of the aryl benzyl ethers (64) used in this study has comprised the reaction of the sodium salt of a phenol with an equimolar proportion of benzyl bromide (or chloride) in ethanolic solution. Conversion to the ether is generally high and concurrent alcoholysis of the benzyl halide is therefore of little importance. These reactions have been reported extensively in the literature and proceed under a variety of basic conditions.[31.32]



(64)

Phenyl benzyl ether (65) undergoes zinc chloride-catalysed rearrangement at 160°C. in the absence of a solvent[31] to give a mixture 2- and 4-benzylphenols, (67) and (68) respectively, in a molar ratio of 1:2; 2,4-dibenzylphenol (69) is also formed. In anisole at 100°C. the above products were also formed and in a similar molar ratio together with considerable amounts of 4-benzylanisole (70) and 2,4-dibenzylanisole (71). The product range and distribution is consistent with the formation of a benzyl carbonium ion (66) which attacks the phenol or anisole in a competitive intermolecular mechanism.



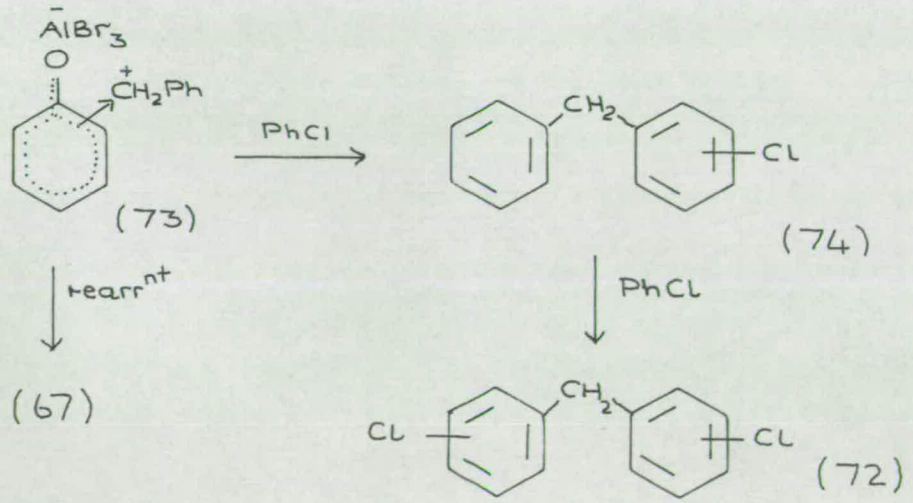
The intermolecular nature of such rearrangements has been substantiated by the zinc chloride-catalysed rearrangement of 2-methylphenyl benzyl ether (64; R = 2-Me), where the molar ratio of the 4- and 6-benzyl- and 4,6-dibenzyl-2-methylphenols obtained was similar to that formed in the direct

benzylation of 2-methylphenol with benzyl alcohol and zinc chloride.[33]

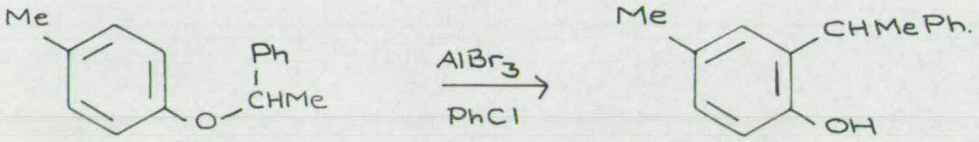
The aluminium bromide-catalysed rearrangement of phenyl benzyl ether[34] (65) in chlorobenzene at low temperatures shows a striking contrast in mechanism to the above scheme.[31,33] Kinetic studies have shown the ether to be rapidly converted to a mixture of 2-benzylphenol (67) (55%), phenol (40%) and an isomeric mixture of di-(chlorophenyl)methanes (72); this is followed by a slow unimolecular conversion of (67) to phenol and (72).

The significant feature of this reaction is the exclusive formation of 2-benzylphenol (67) as the rearrangement product, the absence of (68) and (69) being indicative of an intramolecular process.

While the available information on rearrangements of aryl benzyl ethers under these conditions is limited it would appear that cleavage of the ether does not result in the formation of a simple benzyl carbonium ion. The reaction is more suitably represented by the initial formation of a type of π complex (73) which undergoes intramolecular rearrangement to (67) in competition with solvent attack; this has been postulated by Dewar[35] and finds a formal analogy in the intramolecular rearrangements of aryl alkyl ethers under these conditions. The initial product derived by attack on the solvent (74) is not isolated as it undergoes rapid aluminium bromide-catalysed exchange with chlorobenzene to give the isomeric mixture (72).



Hart and Elia[36] have shown the aluminium bromide-catalysed rearrangement of optically active α-methylbenzyl 4-methylphenyl ether (75) in chlorobenzene gives 2-(α-methylbenzyl)-4-methylphenol (76) with 75% retention in optical activity; this is a further indication that a free carbonium ion is not involved and again is more consistent with a π complex intermediate.



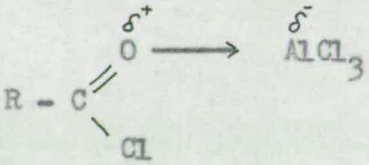
(75) (76)

DISCUSSION

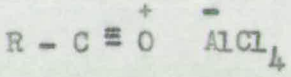
1. Mechanism of the Friedel-Crafts Acylation Reaction

It is necessary in any Friedel-Crafts study to appreciate the complexity of the mechanisms involved. Although the present work has in no way investigated the nature of the acylating complexes a brief discussion of the possible mechanisms will be given.

The Friedel-Crafts acylation reaction constitutes the introduction of an acyl group into the aromatic nucleus by the action of an acylating agent, usually an acid chloride or anhydride, in the presence of a Lewis acid. Since the reaction is acid-catalysed and because of directive influences there is little doubt that electrophilic aromatic substitution is involved. The role of the Lewis acid is therefore to act on the chlorocarbonyl group (of acid chlorides) rendering the acyl carbon atom electrophilic. There is however doubt as to the exact nature of the acylating complex. For an acid chloride two major structural possibilities have been proposed; both are substantiated by experimental evidence and are the polarised donor-acceptor complex (A) and the acylium ion (B).



(A)



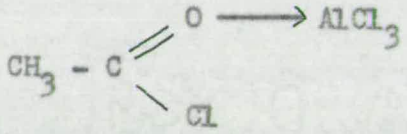
(B)

Acyl halides are known to form stable 1:1 addition complexes with Lewis acids at low temperatures and yield the expected ketonic products on treatment with aromatic compounds. The Perrier ketone synthesis,[37] where the complex is pre-formed and treated with an appropriate aromatic hydrocarbon to give the expected ketonic complex, illustrates this. Structural determinations of these acylating complexes have therefore made an important contribution to mechanistic studies although it must be emphasised that only

the primary complexes are being investigated. While these are inevitably precursors to the reactive intermediate complexes it does not follow that the most stable primary complex formed is necessarily the complex undergoing reaction.

Spectroscopic studies have become increasingly important in recent years in the structural determination of acyl halide-Lewis acid primary complexes.

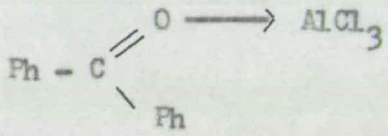
Cook[38] examined the infra-red spectrum of the acetyl chloride-$AlCl_3$ complex as a pure liquid sample. A strong absorption at 1637 $cm.^{-1}$, not present in the spectrum of acetyl chloride, was assigned to the carbonyl stretching vibration of the donor-acceptor complex (C).



ν_{co} 1637 $cm.^{-1}$

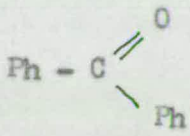
(C)

This conclusion was based on the assumption that complex formation through the oxygen atom has lowered the frequency of the carbonyl absorption relative to acetyl chloride (ν_{co} 1807 $cm.^{-1}$) by lowering the π bond order of the carbonyl group. A similar shift was observed in the benzophenone-$AlCl_3$ complex (D) relative to the free ketone (E) and apparently justifies the assignment of (C).



ν_{co} 1525 $cm.^{-1}$

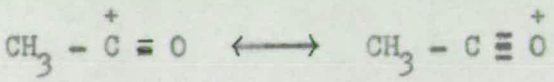
(D)



ν_{co} 1650 $cm.^{-1}$

(E)

Two weaker bands in the triple bond region, at 2307 $cm.^{-1}$ and 2203 $cm.^{-1}$ suggest the formation of acylium ion type complexes, assuming the positive charge on the carbon atom to result in a C-O bond order approaching three.



(F)

However the exact nature of these species is unknown. In addition to the free acylium ion (F) the alternative structures, the complex acylium ion (G) and the acylium ion pair (H) were postulated but a clear differentiation is not possible.

$$\left[\overline{CH_3} - C \equiv \overset{+}{O}\right] \cdots AlCl_3 \qquad \left[\overline{CH_3} - C \equiv \overset{+}{O}\right]\left[\overline{AlCl_4}\right]$$

(G) (H)

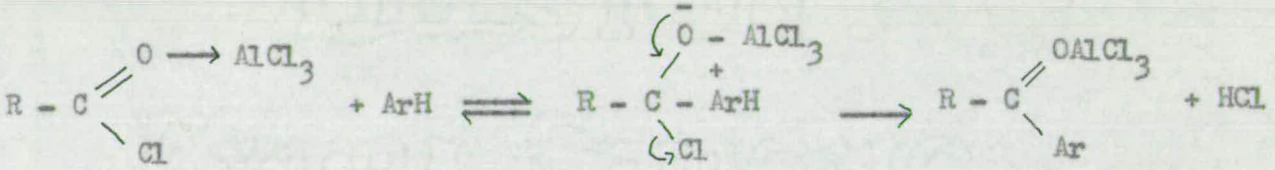
Susz and Wuhrmann[39] studied this system in the solid state and the infra-red spectrum showed differences only in the relative intensities of the absorptions in the carbonyl region. The main differences were ascribed to the physical states of the complexes, the solid sample allowing a greater contribution from the ionic acylium type complexes than in the liquid phase. This system was also studied in solution; in solvents of low dielectric constant the donor-acceptor complex (C) was favoured, while in the highly polar solvent nitrobenzene the predominant species were of the acylium ion type (F), (G) or (H). It has been shown by infra red and high resolution proton and fluorine magnetic resonance spectroscopy that the addition complexes of acetyl, propionyl and benzoyl fluorides with SbF_5, PF_5, AsF_5 and BF_5 exist as the acylium ion complexes in the solid state and as donor acceptor complexes in solution.[40]

Spectroscopic evidence is therefore conclusive in demonstrating that two different types of complex may be formed. The donor-acceptor complex (A) has been justified in particular while acylium type complexes, although no doubt present, are unable to be characterised with any certainty. Since Friedel-Crafts acylations with acyl halides are known to proceed readily in solvents of high and low dielectric constant it is likely that both types act as acylating species.

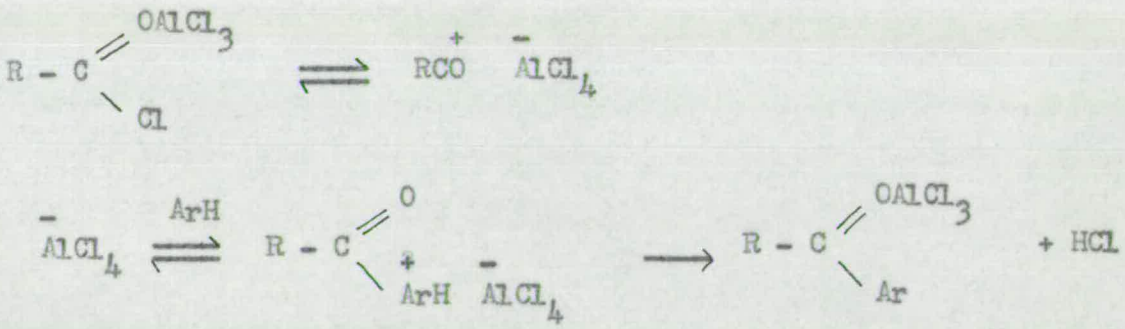
The reactive acylating intermediate is also influenced by the steric and electronic requirements of the transition states leading to the final products and it is therefore possible that the predominant primary complex formed may not be the reacting complex in certain cases.

The most likely mechanisms (i) and (ii), based on the concept that both types of complexes are potential acylating intermediates, are given and the following discussion will attempt to rationalise the factors influencing each from the available experimental evidence.

(i) Carbonyl Addition mechanism.



(ii) Acylium Ion mechanism.



In a study of the $AlCl_3$-catalysed benzoylation of toluene in nitrobenzene, Brown and co-workers[41] found the isomer distribution to be 92% para-, 1% meta-, and 7% ortho-benzoyl toluenes; the rate of benzoylation of toluene relative to benzene was found to be 151:1. The low ortho/para ratio indicated the acylating species to have a high steric requirement while the high toluene/benzene rate ratio and high para/meta ratio shows it to possess a high selectivity and therefore a relatively low reactivity. The carbonyl addition mechanism was stated to be more consistent with the observed results.

Similar results have been obtained in 1,2-dichloroethane and benzoyl chloride as solvents; it is probable that a single mechanism is operative in each case even though it is likely that the predominant primary complex formed is not the donor-acceptor complex in all cases, especially in the highly polar nitrobenzene.

Studies of the $AlCl_3$-catalysed acetylation of toluene and benzene showed the relative overall rate of acetylation of toluene to be 128:1 and the isomer distribution was 98% para-, 1% meta-, and 1% ortho-acetyl toluenes.[45] Again the acetylating species has a large steric requirement and is highly selective. The higher steric requirement in acetylation than in benzoylation was attributed to the change in the transition state from the fully coplanar phenyl group of Van der Waals radius 1.7A° to the tetrahedral methyl group of Van der Waals radius 2.0A°. Again the observed results are more consistent with a carbonyl addition mechanism.

Jensen[42] studied the kinetics and isomer distributions obtained from the benzoylation of toluene with a series of Lewis acid catalysts. The constancy of the isomer ratios (89% para-, 2% meta-, and 9% ortho-) for all catalysts furnishes strong evidence for the acylium ion mechanism for it was thought that a carbonyl addition mechanism, where the Lewis acid is an integral part of the complex, would exhibit differences in both steric requirements and possibly selectivity. Assuming an acylium ion mechanism to predominate the observed isomer distribution is consistent with a highly selective reagent having a large steric requirement and therefore a clear distinction between the possible mechanisms is difficult on this basis alone.

Studies on the relative reactivities of acyl halides have also afforded useful information on the diversity of the mechanisms involved. The reactivity of acetyl halides in the $AlCl_3$-catalysed acetylation of benzene

in carbon disulphide was shown to increase with decreasing electronegativity of the halogen.[43] The relative reactivities, measured by determining the incipient reaction temperature, were in good agreement with the yields of ketones obtained and the order $CH_3COI > CH_3COBr > CH_3COCl > CH_3COF$ was obtained. A more comprehensive study by Yamase[44] showed that the relative reactivities were dependent on the nature of the acyl group. For the general reaction the following results were obtained.

$$RCOX + ArH \xrightarrow[CS_2]{AlCl_3} ArCOR + HX$$

For a given aromatic compound it was found that with acyl halides having small groups, R, (R = Me) the order X = I > Br > Cl > F was obtained; steric factors are thought to be of little importance and the reactivity to be due to the lability of the carbon-halogen bond. With increasing steric hindrance in the acyl halide ($R = PhCH_2$ or Me_2CH) the order of reactivity was found to be X = I < Br ≃ Cl > F and indicates that in these cases the steric requirements of the complexes are more important. However with highly hindered acyl halides ($R = Me_3C$, $246Me_3C_6H_2$) the order X = I > Br > Cl > F suggests the steric effects of the halogen to be unimportant.

The observed changes in order of reactivity with increasing steric hindrance in the acyl group can only be explained in terms of an increasing contribution from the acylium ion mechanism for clearly a single mechanism is not operative in all of the above examples.

In conclusion, it is difficult to rationalise the Friedel-Crafts acylation in terms of a single mechanism. There is evidence to suggest that both carbonyl addition and acylium ion mechanisms are operative although a clear differentiation between these is not possible, and it would therefore appear

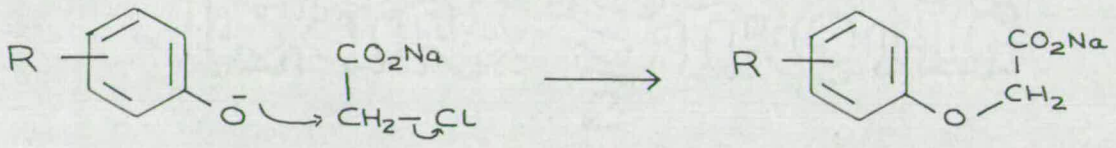
that many Friedel-Crafts acylations are most suitably represented as a competitive scheme involving both types of reactive complexes.

In the following discussion while any complex will be denoted as in (B), the acylium ion complex, this is only meant to convey that a complex is involved in the mechanism and is therefore only a general representation.

2. Preparation of 2-Aryloxyacetic Acids

This study has necessitated the preparation of a large number of 2-aryloxyacetyl chlorides and in all cases were prepared by the action of thionyl chloride on the corresponding 2-aryloxyacetic acids (77). These will be referred to throughout the text simply as aryloxyacetic acids.

In the majority of cases these acids were synthesised by the general method of Hayes and Branch;[46] this constitutes the reaction of a phenol with sodium chloroacetate in aqueous sodium hydroxide solution and is presumably a typical bimolecular nucleophilic substitution reaction.



(77)

While these reactions were not carried out under standard conditions and maximum yields were not sought, conversion to the acid was generally high, indicating that competing hydrolysis of sodium chloroacetate was of secondary significance. However, it was apparent that phenols containing strongly electron withdrawing groups did not readily react with sodium chloroacetate, by virtue of their reduced basicity. The failure of 2,4-dinitrophenol and 2- and 4-nitro-1-napthols to form their corresponding acids, even in the presence of an excess of sodium chloroacetate, illustrates this. Since in these reactions the mixture was refluxed until neutral hydrolysis of the chloroacetate must have been predominant. In examples where the yield of acid was low, for example with 4-nitrophenol, a significant increase in yield was

obtained by the use of an excess (normally 2-4 molar) of sodium chloroacetate. The yields of aryloxyacetic acids obtained by this method are given in Table I , page 111 , in the experimental section.

The alternative synthetic methods to aryloxyacetic acids used are given below.

(a) 4-Phenylphenoxyacetic Acid (77; R = 4-Ph)

Although 2-phenylphenoxyacetic acid (77; R = 2-Ph) was readily prepared by the general method,[46] 4-phenylphenol did not react with sodium chloroacetate, it was noted that the sodium salt of the phenol was largely insoluble in the reaction mixture. However 4-phenylphenol readily dissolved in ethanolic sodium ethoxide and on treatment with ethyl bromoacetate gave ethyl 4-phenylphenoxyacetate in 33% yield. Alkaline hydrolysis of this product gave a quantitative conversion to sodium 4-phenylphenoxyacetate, the free acid only being liberated by treatment with hot 50% hydrochloric acid over several hours.

(b) 4-(p-Toluenesulphonyl)phenoxyacetic Acid (77; R = 4-p-toluenesulphonyl)

The synthesis of the required phenol and its reaction with sodium chloroacetate was not attempted; the acid was instead prepared by the alkaline hydrolysis of methyl 4-(p-toluenesulphonyl)phenoxyacetate. This ester was prepared by the aluminium chloride-catalysed reaction of methyl phenoxyacetate with p-toluenesulphonyl chloride in 1,2-dichloroethane as solvent in 81% yield, using 2 molar equivalents of the Lewis acid. With an equimolar amount of Lewis acid only the starting materials were recovered, suggesting the ester to preferrentially co-ordinate with the Lewis acid.

No ortho-substituted product was detected in the N.M.R. spectrum of the crude product, the aromatic region of which showed only a pair of A_2B_2 spectra which approximated to 2 pairs of ortho-coupled doublets centred at 2.1τ (3-H) and

3.0τ(2-H), and at 2.15τ(3'-H) and 2.7τ(2'-H). From these were calculated $J_{23} = 9_{c/s}$ and $J_{2'3'} = 8_{c/s}$ (assuming the para coupling constants J_{25} and $J_{2'3'}$ to be negligible).

Studies on the benzene sulphonylation of anisole have shown that only para substitution occurred.[47] The above result is consistent with this although it is generally accepted that arylsulphonyl chlorides are Friedel-Crafts reagents of low selectivity.[48]

(c) The Nitration of Aryloxyacetic Acids

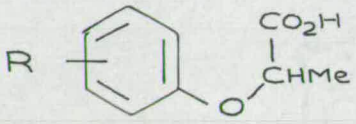
Dinitration of phenoxyacetic acid (77; R = H) with nitric acid (S.G. 1.5) gave a single product whose N.M.R. spectrum showed a 1,2,4-trisubstituted aromatic ring and was therefore 2,4-dinitrophenoxyacetic acid (77; R = 2,4-$(NO_2)_2$). Similarly the reaction of 4-chlorophenoxyacetic acid with nitric acid gave a dinitro derivative whose N.M.R. spectrum showed the presence of 2 equivalent aromatic protons and therefore, on first principles, was 4-chloro-2,6-dinitrophenoxyacetic acid (77; R = 4-Cl-2,6-$(NO_2)_2$).

The mononitration of 1-naphthoxyacetic acid also afforded a single product, the orientation of the nitro group being established by N.M.R. spectroscopy in the following way.

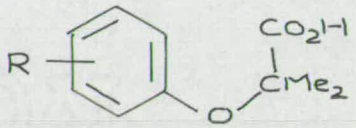
From the complex aromatic multiplet two ortho-coupled doublets ($J = 8.8_{c/s}$) centred at 2.9τ and 1.6τ were noted; these correlated more closely to the 2- and 3-protons of 4-nitro-1-napthol (2-H, 3.1τ; 3-H, 1.7τ; $J_{23} = 8.8_{c/s}$) than to the 3- and 4-protons of 2-nitro-1-napthol (4-H, 2.8τ; 3-H, 2.1τ; $J_{34} = 9.5_{c/s}$). Also since the 4-proton of 2-nitro-1-napthol shows an observable inter-ring coupling ($J_{48} = 0.5_{c/s}$) not evident in the spectrum of 4-nitro-1-napthol or the prepared nitro-1-napthoxyacetic acid the product was characterised as 4-nitro-1-napthoxyacetic acid.

3. Preparation of 2-Aryloxypropionic-, 2-Aryloxyisobutyric- and 2-Arylthio-Acetic Acids

(a) The reaction of a phenol with sodium 2-chloropropionate, in the few cases attempted gave reasonable yields of the 2-aryloxypropionic acid (78) although the phenol never contain strong electron withdrawing groups.



(78)

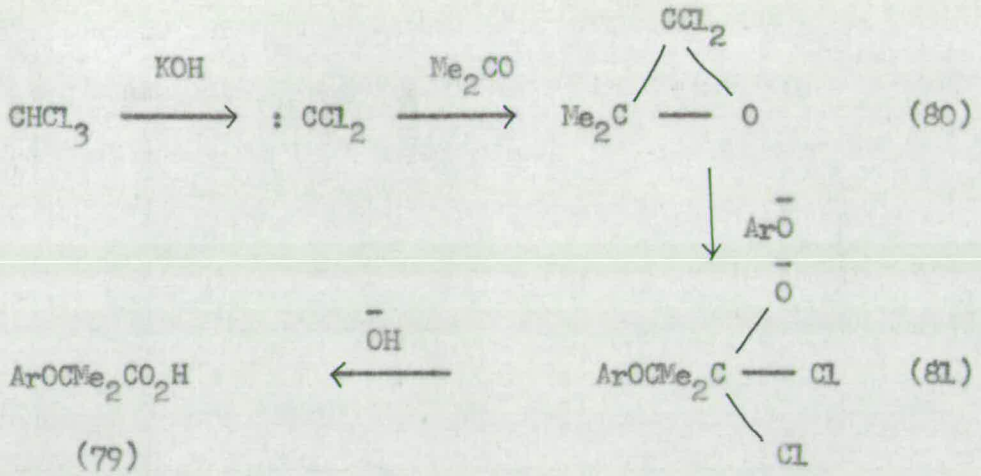


(79)

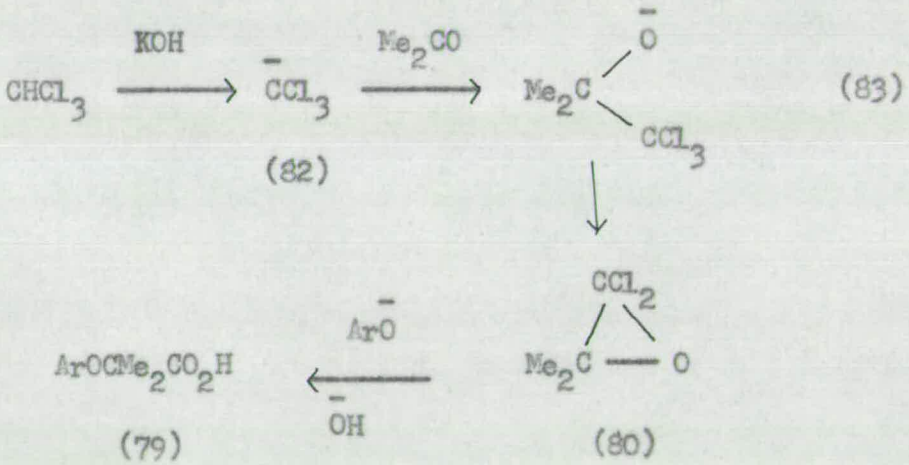
This method was not extended to the synthesis of 2-aryloxyisobutyric acids (79); the method of Bargellini,[49] in which a phenol (1 mole), dry potassium hydroxide (2 moles) and chloroform (2 moles) was refluxed in an excess of acetone, was attempted and gave the requisite acids from phenol and 4-chlorophenol in yields of 31% and 17% respectively.

Two mechanisms are possible and differ only in the nature of the formation of the epoxide intermediate (80).

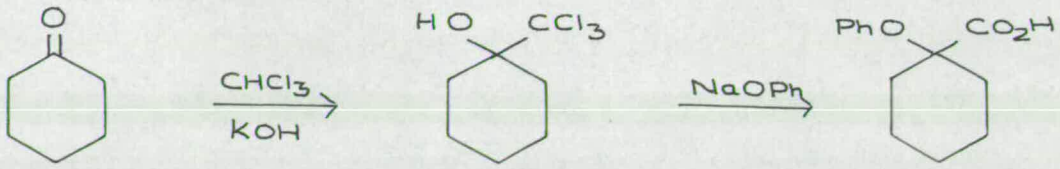
(i) Dehydrohalogenation of chloroform gives dichlorocarbene which undergoes a carbonyl addition with acetone to give the epoxide (80). Bimolecular nucleophilic attack by the phenoxide ion cleaves the ring and the dichlorocarbinol (81) formed is hydrolysed to the acid (79).



(ii) In this case the trichloromethyl carbanion (82) is initially formed and attacks the ketone to give 2-trichloromethylpropan-2-ol (83) and in turn the epoxide (80).

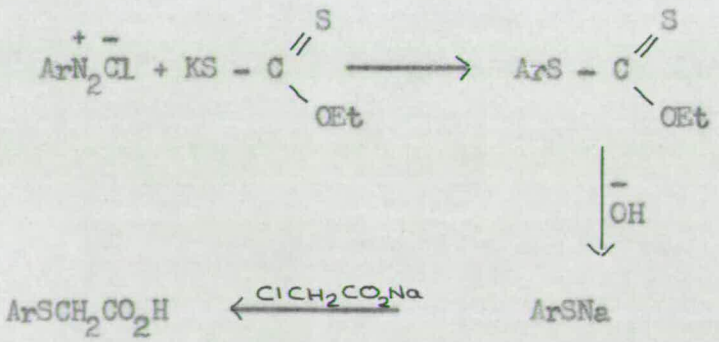


The formation of the isolable 1-trichloromethylcyclohexanol (84) from cyclohexanone on treatment with potassium hydroxide in chloroform and the synthesis of the expected acid (85) from this product (84) and sodium phenoxide may be evidence that mechanism (ii) is operative. It is possible however that compounds of the form (84) may arise from an epoxide by nucleophilic attack by halide ion, although this seems less likely.



(84) (85)

(b) The syntheses of phenylthioacetic acid and 2-chlorophenylthioacetic acid from aniline and 2-chloroaniline respectively by the method of Dalgleish and Mann[50] was found to be an excellent synthetic route to these compounds, the final products being obtained in overall yields greater than 60% theoretical and in a high state of purity although the scheme does not require the isolation of any intermediate. The mechanism is well established and requires only brief description; the diazonium chloride, on treatment with potassium xanthate in alkaline solution gives the xanthate ester, alkaline hydrolysis of which yields the thiophenol. This was converted to the arylthioacetic acid with sodium chloroacetate.



The lability of the chlorine atom in 2-and 4-nitro-chlorobenzenes to nucleophilic substitution facilitated the syntheses of the corresponding arylthioacetic acids by the reaction of disodium thioglycollate in aqueous ethanol.[51] The yields of acids obtained were initially extremely low (5-10%) although subsequent attempts gave yields of 30-40%. It was noted that the thioglycollate was insoluble in the reaction mixture and it is reasonable to assume that this is the major factor responsible for the competing alkaline reduction of the chloronitrobenzene to the corresponding dichloro-azoxybenzene predominating. On repeating the reaction in ethanolic sodium ethoxide the disodium thioglycollate again precipitated from the reaction mixture and the yields of the 2- and 4-nitrophenylthioacetic acids obtained were 31% and 33% respectively.

In contrast, 2,4-dinitrochlorobenzene gave 2,4-dinitrophenylthioacetic acid with di-sodium thioglycollate in ethanolic sodium acetate in 88% yield.

4. The Reactions of 2-Aryloxyacetyl Chlorides with Aluminium Chloride in non-aromatic solvents

(a) Initial Study

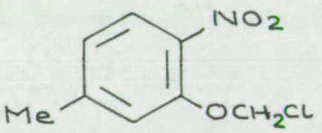
In a study of the Friedel-Crafts intramolecular acylations of substituted aryloxyacetyl chlorides in aromatic solvents it was established that the presence of electron-donating nuclear substituents resulted in the exclusive formation of the intramolecular acylation product, the benzofuran-3-one, except in cases where the aromatic solvent was itself more reactive to electrophilic attack than the acylating species. When cyclisation was precluded in this way the major product formed was the intermolecular ketone.[12] Conversely, it is clear that the presence of electron-withdrawing substituents in the nucleus of the aryloxyacetyl chloride will favour the formation of the intermolecular ketone by inhibiting the cyclisation reaction. While a detailed investigation of the factors responsible for the product distributions obtained in the above scheme are given elsewhere in the text a brief summary has been given at this point, since the reactions of aryloxyacetyl chlorides containing electron-withdrawing nuclear substituents in inert solvents may be considered to be an extension of the above system; in this case however the most effective nucleophile is no longer an aromatic nucleus.

The reaction of 3-methyl-6-nitrophenoxyacetyl chloride (86) with $AlCl_3$ in CS_2 was attempted initially to determine whether an alternative reaction to cyclisation could be effected under these conditions.

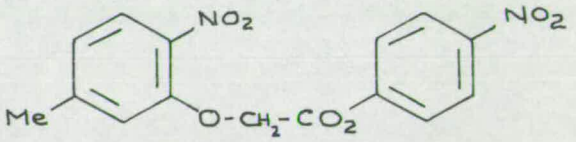
At room temperature over 1 hour complex formation was observed, indicated by the formation of a dark insoluble viscous oil, but no acidic gas was evolved. On hydrolysis the acid was recovered in almost quantitative yield. On repeating this reaction in refluxing CS_2 (46° C.) over 3 hours, the acid was recovered by sodium bicarbonate extraction in 61% yield, and a non-acidic

fraction obtained as a red low-melting solid. The I.R. spectrum showed no hydroxyl or carbonyl absorption, indicating the absence of the parent phenol, unhydrolysed acid chloride or cyclic ketone. The N.M.R. spectrum (in $CDCl_3$) was consistent with a 1,2,4-trisubstituted aromatic nucleus (carrying the same substituents as in the phenoxy acid) and well-resolved singlets at 4.15τ and 7.55τ were noted, the integrated spectrum giving a ratio 3:2:3.

The product contained chlorine and vapour pressure osmomentry gave a molecular weight of 195 ± 10. Microanalysis gave an empirical formula of $C_8H_8ClNO_3$ and therefore an empirical weight of 202, consistent with the product being 3-methyl-6-nitrophenoxymethyl chloride (87). The characterisation was completed by conversion to the ester (88) on treatment with a methanolic solution of sodium 4-nitrobenzoate, confirming the presence of chloride to be exclusively in the side chain.

(86) $\xrightarrow[CS_2]{AlCl_3}$ 

(87)



(88)

Under identical reaction conditions 3-methyl-2-nitrophenoxymethyl chloride as a clear yellow oil which solidified on standing at -10°C. and which appeared to decompose on standing at room temperature. Its N.M.R. spectrum again showed a characteristic singlet at 4τ (OCH_2Cl). While microanalysis data was not within the required limits, the stable 4-nitrobenzoate ester gave a satisfactory analysis.

To complete the initial study of this method as a synthetic route to

aryloxymethyl chlorides, 2- and 4-nitrophenoxyacetyl chlorides were reacted with $AlCl_3$ in refluxing CS_2 as before and gave good yields (70%) of the corresponding 2- and 4-nitrophenoxymethyl chlorides. The physical properties of these compounds and their 4-nitrobenzoate esters were consistent with those reported by Barber and co-workers[52] who synthesised these aryloxymethyl chlorides by the interaction of the sodium aryloxymethane sulphonate with phosphorous pentachloride.

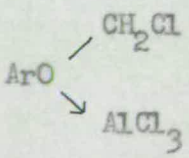
Before investigating the scope of this reaction an attempt was made to determine the optimum reaction conditions. 4-Nitrophenoxyacetyl chloride was chosen for this purpose since the reaction in CS_2 was known to give the aryloxymethyl chloride in good yield and in a reasonable state of purity. The absolute yields of chloromethyl ether formed and acid recovered were determined by quantitative N.M.R. spectroscopy on a weighed sample of the crude reaction product containing a known quantity of 1,2-dibromoethane as the calibrating compound (τ_{CH_2} = 6.4). From the integrated spectrum the molar proportions of 4-nitrophenoxymethyl chloride (τ_{CH_2} = 4.0) and 4-nitrophenoxyacetic acid (τ_{CH_2} = 5.2) were calculated. The method requires that side products do not give rise to absorption at, or sufficiently near, 4.0, 5.2, or 6.4τ to make an accurate determination of the integral ratio impossible. By recording the spectrum under highly expanded conditions it was shown that the above absorptions were each due to a single component. In cases where significant side product formation did occur, generally indicated by the presence of additional peaks in the region 3.8 to 4.2τ and extra multiplicity in the aromatic region, the yield recorded was that of the product isolated.

The effect of the solvent, the reaction time and temperature, and the molar ratio of acid chloride to Lewis acid were studied; the results obtained are given in Table II in the experimental section (page 124).

(i) Reactions with Aluminium Chloride in Carbon Disulphide

With 0.5 molar equivalents $AlCl_3$ in CS_2 at 46°C. over 3 hours the aryloxymethyl chloride was formed in 37% yield (based on the acid chloride) and no significant increase was observed after 16 hours. In both cases the yields of acid recovered were high. With one molar equivalent of $AlCl_3$ the maximum yield (68%) was obtained after 3 hours at 46°C., again with a high recovery of the acid. After 6 hours at 46°C. slightly lower yields of both the chloride and the acid were obtained, with obvious deterioration of product quality. Using 2 molar equivalents of $AlCl_3$ at 46°C. over 3 hours the aryloxymethyl chloride was isolated in 32% yield and no acid was recovered. The N.M.R. spectrum of the crude product showed a minimum of three peaks in the 3.9 to 4.1τ region and in consequence no quantitative analysis of the spectrum was possible.

While no definite conclusions may be reached with the limited information available, it is tentatively suggested that the reaction bears an analogy to Friedel-Crafts acylation in that stoichiometric quantities of the Lewis acid are required for maximum conversion to the aryloxymethyl chloride. This suggests that the final product is itself a complex, possibly of the donor-acceptor type. Consequently, the catalytic activity of the Lewis acid, and hence the reaction rate, is reduced in the later stages of the reaction when less than 1 molar equivalent of catalyst is used. The nature of the complex can again only be postulated, the most probable form being shown below.



It would also appear that the aryloxymethyl chloride, or its associated complex, is not completely stable under the reaction conditions since an

increase in time does not necessarily lead to an increase in the yield of aryloxymethyl chloride formed. That decomposition of the product is considerable in the presence of a molar excess of the Lewis acid is consistent with the ease by which aryl alkyl ethers in general, and aryloxymethyl chlorides in particular, undergo acid-catalysed dealkylation.

(ii) With Aluminium Chloride in Nitromethane

With 1 molar equivalent of $AlCl_3$ and at 0°C. for 3 hours no aryloxymethyl chloride was formed and the acid was recovered in almost quantitative yield. The reaction was shown to be markedly temperature dependent since at 25°C. the product was formed in 35% yield and without the formation of side-products; while at 50°C. no acid was recovered, extensive side-product formation occurred, the N.M.R. spectrum showing several peaks around the 4 τ region, and the aryloxymethyl chloride was isolated in only 23% yield.

With 1 molar equivalent of $AlCl_3$ and at 25°C. for 16 hours the amount of aryloxymethyl chloride formed was not significantly greater than that obtained after a 3 hour reaction period and side-products were more in evidence. Under identical reaction conditions, but with 0.5 molar equivalents, an almost identical yield of the chloride was formed and side-product formation was minimal.

It would appear that the (qualitative) rate of formation of aryloxymethyl chloride is slower in $MeNO_2$ at 25°C. than in CS_2 at 46°C. and that side-product formation is favoured by an increase in reaction time or temperature. In contrast to the reactions in CS_2 however a 0.5 molar deficit of Lewis acid does not appear to significantly reduce the conversion to the aryloxymethyl chloride and the results indicate that this is primarily due to the inhibition of side products.

(iii) Other solvents and catalysts

The reaction, with 1 molar equivalent of $AlCl_3$ in dichloromethane at 40°C. over 3 hours gave only a high recovery of acid. In 1,2-dichloroethane at 50°C., or with the mixed solvent, CS_2/CH_2Cl_2 (3:1 v/v), at 45°C. the aryloxymethyl chloride was formed in 43% and 47% respectively without significant side-product formation.

It was thought that, by using a solvent of low dielectric constant which is known to be an effective Friedel-Crafts solvent and in which both the Lewis acid and the acid chloride had relatively high solubilities, an increase in reaction rate would be observed without side-products being formed. While the reaction in dichloroethane gave a good quality product the (qualitative) rate was slower than in CS_2. The failure of dichloromethane as a solvent under similar conditions is unexpected and it is not clear why the reaction is obviously favoured by the presence of a solvent (CS_2) in which solvation of the reactants, the intermediate complex, and the final product is minimal.

Stannic chloride was not an effective catalyst in CS_2 at 46°C. or in $MeNO_2$ at 50°C.; in both cases the acid was recovered in almost quantitative yields. In refluxing $MeNO_2$ (82°C.) over 3 hours, no acid was recovered and the N.M.R. spectrum was extremely complex. A preparative scale reaction gave the aryloxymethyl chloride in trace amounts only.

In conclusion, it is evident that the most suitable reaction conditions established comprised the reaction of the acid chloride with 1 molar equivalent of $AlCl_3$ in CS_2 at 46°C. over 3 hours.

(iv) Carbon Monoxide Determination

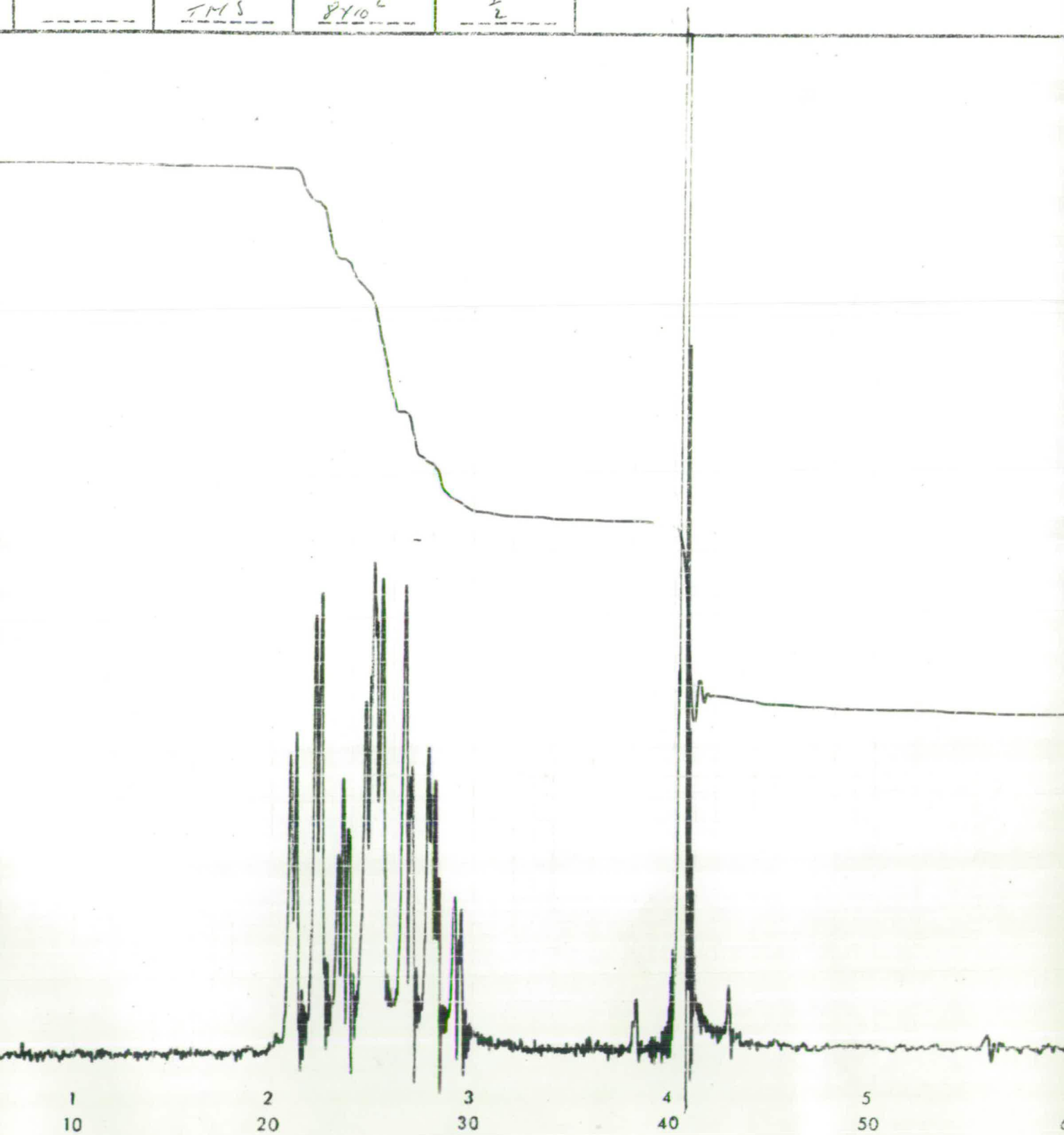
Although it is impossible at this point to formulate a detailed mechanism it is reasonable to assume that it involves a Friedel-Crafts decarbonylation of the acid chloride and therefore it is highly probable that carbon monoxide

is evolved during the course of the reaction. To conclusively establish its presence and to correlate the amounts of carbon monoxide evolved and aryloxymethyl chloride formed the reaction of 4-nitrophenoxyacetyl chloride with $AlCl_3$ (1 molar equivalent) in CS_2 at 46°C. over 2 hours was again studied. These conditions were chosen since a high conversion to the aryloxymethyl chloride was obtained without a significant quantity of side-products. The yield of aryloxymethyl chloride was determined, as before, by quantitative N.M.R. spectroscopy. The volume of carbon monoxide was determined by selective absorption of this product from the collected gas mixture with cuprous sulphate/2-naphthol/sulphuric acid reagent and was expressed as a percentage of the theoretical volume (based on the acid chloride). Under the above conditions the theoretical yields of carbon monoxide and aryloxymethyl chloride were 59% and 56% respectively, indicating that the decarbonylation stage results in the exclusive formation of free carbon monoxide.

(b) Scope and Mechanism of the Reaction

A series of aryloxyacetyl chlorides containing electron withdrawing substituents were reacted with aluminium chloride in refluxing CS_2 over 3-6 hours and the non-acidic residue obtained after hydrolysis of the reaction mixture was examined for the presence of cyclic ketones and phenols in addition to aryloxmethyl chlorides. Maximum yields of the latter were not sought. In cases where the aryloxymethyl chloride was formed a small scale reaction was carried out under the standard conditions given in section 5L, page 132 in the experimental part. The yields of aryloxymethyl chloride formed and acid recovered were determined by quantitative N.M.R. spectroscopy in the usual manner; it was hoped that, in the absence of kinetic data, the yields of aryloxymethyl chlorides would reflect the electronic and/or steric effects of nuclear substituents on the rate of decarbonylation of the acid chloride.

DEC. SHIFT	REF. STD.	R.F. FIELD	R.F. GAIN	REMARKS
------	TMS	8×10^2	½	



2-Nitrophenoxymethyl Chloride.

The preparative aspects of these reactions require only brief comment.

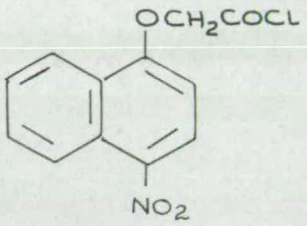
On hydrolysis of the reaction mixture over one hour the crude non-acidic residue in many cases contained both the acid chloride and the corresponding ethyl ester, the latter a consequence of the use of chloroform (which contains a small amount of ethanol as a stabiliser) in the extraction procedure. The apparent resistance of these acid chlorides to hydrolysis is probably a solubility effect rather than evidence of a unimolecular solvolysis mechanism. By increasing the hydrolysis period to approximately four hours and using ethanol-free solvent both complications were minimised.

The N.M.R. spectra of the aryloxymethyl chlorides prepared showed in every case a characteristic singlet at approximately 4τ, associated with the $-OCH_2Cl$ group; table IIA, page 132, in the experimental section illustrates this. In general, these compounds were not sufficiently stable to give satisfactory analyses and were characterised by conversion to their stable 4-nitrobenzoate esters. Exceptions were the 2,4-dinitro- and 4-chloro-2,6-dinitro-phenoxymethyl chlorides (2; R = 2,4-$(NO_2)_2$ and 4-Cl-2,6-$(NO_2)_2$ respectively), which analysed satisfactorily but which gave mainly the parent phenol in the attempted esterification reaction.

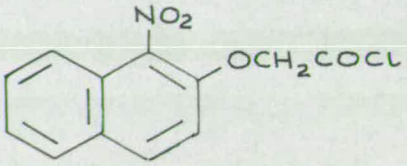
When aryloxymethyl chloride formation was not favoured the high recovery of acid obtained showed alternative reactions to be unimportant. Normally a small amount of phenol was formed and may have been a result of dealkylation of either the acid chloride or the aryloxymethyl chloride; however the only definative side reaction observed was the cyclisation of 2- and 4-chloro-phenoxyacetyl chlorides to their corresponding 7- and 5-chloro-benzofuran-3-ones (4; R = 7-Cl and 5-Cl).

An attempt was made to extend the scope of the reaction to naphthoxyacetyl chlorides; it was expected that the relatively highπ bond order between the α-

and β- positions of the naphthalene nucleus would lead to the ready decarbonylation of 4-nitro-1-naphthoxyacetyl chloride (89).



(89)

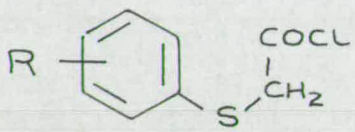


(90)

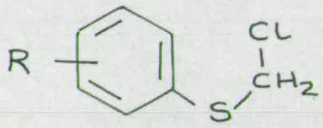
With aluminium chloride in refluxing carbon disolphide over 3 hours the acid was recovered in 56% yield and, although a carbon monoxide determination gave 40% of the theoretical volume, no aryloxymethyl chloride was detected or isolated in the uncharacterisable viscous oil obtained as the neutral component. On repeating the reaction in nitromethane at 40-50°C. only 11% of the acid was recovered; no decarbonylation products were characterised although carbon monoxide was once more evolved. 1-Nitro-2-naphthoxyacetyl chloride (90) behaved in a similar way. In view of the fact that these compounds apparently eliminated carbon monoxide yet failed to give characterisable decarbonylation (or decarboxymethylation) products it was decided to abandon this aspect of the study. At present, a comprehensive study of the Friedel-Crafts reactions of naphthoxyacetyl chlorides is being carried out;[53] once the electronic and steric effects of substituents are well established it may be possible to rationalise the behaviour of (89) and (90) and successfully extend the scope of the method to this series.

The reactions of 2- and 4-nitro- and 2,4-dinitro-phenylthioacetyl chlorides (91) with aluminium chloride were studied in an attempt to prepare the corresponding arylthiomethyl chlorides (92). Under a wide range of conditions (given in Table III, page 140, in the experimental section) these acid chlorides were found to be more stable than their corresponding aryloxyacetyl

chlorides. When reaction did occur neither carbon monoxide nor the arylthiomethyl chloride was detected. The following discussion will attempt to formulate a mechanism for the decarbonylation of aryloxyacetyl chlorides and the failure of arylthioacetyl chlorides to behave similarly will also be mentioned.



(91)



(92)

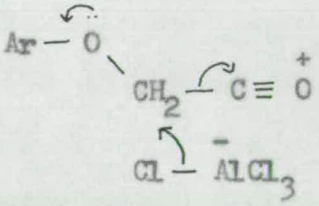
The failure of 3-nitrophenoxyacetyl chloride and the 2- and 4-halogeno-phenoxyacetyl chlorides to decarbonylate under conditions in which both the 2- and 4-nitro-compounds gave high yields of aryloxymethyl chloride indicates that the decarbonylation stage requires the nucleus to contain strong electron withdrawing substituents orientated such that their effects are readily transmitted to the "ether" oxygen. The substantial decrease in yield on the introduction of a methyl group even in the 3- and 5-(meta) positions of 2-nitrophenoxyacetyl chloride further typifies the extreme electronic requirements necessary for decarbonylation to occur. Each of the aryloxymethyl chlorides prepared in this scheme contained strong -E-M groups in the 2- or 4-positions; unfortunately no information is available on the effects of strong -I substituents (e.g. $-CF_3$) for the required phenol was not prepared.

The experimental evidence suggests that the aryloxy group acts as an electron acceptor; it is therefore unlikely that a unimolecular decarbonylation

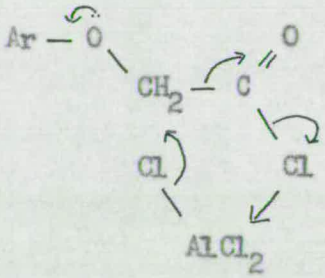
of the intermediate complex occurs. This mechanism would be expected to be similar to the unimolecular decarbonylation of diarylacetyl chlorides in which it has been well established that the reaction is assisted by electron donating nuclear substituents.[26] Clearly it is impossible to explain the behaviour of these acid chlorides in terms of such a mechanism and the failure of 2,4-dinitrophenoxyisobutyryl chloride to decarbonylate under conditions where the corresponding aryloxyacetyl chloride readily gives the aryloxymethyl chloride is further evidence against a unimolecular decarbonylation.[54]

Bimolecular decarbonylation of the complex, influenced by the degree of positive charge at the methylene group, correlates more closely with the results obtained; here the electron withdrawing effect of the aryloxy group renders the methylene group sufficiently electrophilic to allow bimolecular attack by chloride or tetrachloroaluminate anions. Carbon monoxide is subsequently eliminated and the aryloxymethyl chloride (or its associated complex) formed. Two closely related mechanisms are possible,

(i) Acylium ion mechanism



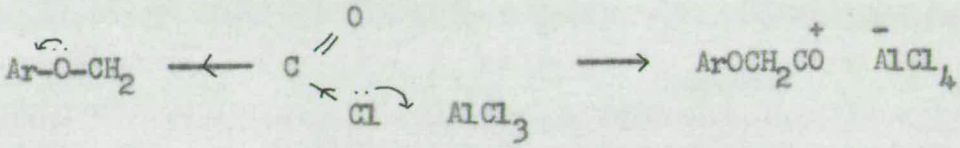
(ii) "SN^i" mechanism



Measured from the yields of aryloxymethyl chlorides formed under standard conditions, the decarbonylation of these acid chlorides appeared to be more rapid as the electron withdrawing ability of the nuclear substituent increased. However, the (qualitative) rates of decarbonylation of 2,4-dinitro- and 4-chloro-2,6-dinitro-phenoxyacetyl chlorides were slower than those of the 2- and 4-nitro-phenoxyacetyl chlorides; since there is no reason to suppose that the rates of <u>decomposition</u> of the complexes in the former examples should

be inhibited it is necessary to consider the effects of electron withdrawing substituents on the rate of formation of the complex.

By reducing the dipole in the C-Cl bond of the chlorocarbonyl group, electron withdrawing substituents retard the rate of formation of the complex intermediate; the acylium ion complex is illustrated only.



It is possible in these extreme cases that the rate of decarbonylation is governed by the rate of formation of the complex although in the absence of kinetic data it is impossible to justify this conclusion. Moreover both these acid chlorides gave yields of aryloxymethyl chlorides which varied markedly on repeating the reaction under the same conditions; therefore it is equally possible that solubility and surface effects are responsible for the slow rates of reaction. The failure of a mixture of 2,4,5- and 2,3,4-trinitro-phenoxyacetyl chlorides to decarbonylate under identical conditions[54] may also be due to similar effects.

All attempts to prepare the arylthiomethyl chlorides failed and it was therefore necessary to determine the role of the hetero-atom in both arylthio- and aryloxy-acetyl chlorides before explaining the behaviour of the former. The reactions of aryloxyacetyl chlorides have shown that the ability of the electron-deficient aromatic nucleus to enhance the electronegativity of the "ether" oxygen is the significant factor promoting bimolecular decarbonylation. It follows that two factors could be responsible for the failure of arylthioacetyl chlorides to react similarly; that is, the low electro-negativity of the sulphur atom or its inability to donate electrons to the aromatic nucleus.

An N.M.R. study of the variation in chemical shift of the methylene

group (τ CH_2) in aryloxy- and arylthio-acetyl chlorides was carried out in an attempt to solve this problem. By measuring the absolute values of the chemical shifts at infinite dilution, intermolecular association effects were minimised and it was assumed that for each series of acid chlorides any change in the chemical shift on the introduction of a nuclear substituent reflected a change in electron density at the methylene group. Therefore the chemical shift for any substituted acid relative to the parent acid ($\Delta\tau$ CH_2) gives a measure of the electronic interaction between the substituent and the methylene group. The results obtained, given in Table IV, page 142, in the experimental section, show that for a given substituent the values of $\Delta\tau$ CH_2 are greater in the arylthioacetyl chloride series; therefore, although a comprehensive study has not been carried out, it would appear that the failure of arylthioacetyl chlorides to decarbonylate is not due to the inability of the sulphur atom to interact with the nucleus; indeed the effect of the nuclear substituent appears to be greater in the arylthioacetyl chloride series. It follows that the lower electronegativity of sulphur relative to oxygen is probably the dominant effect and this is, in part, responsible for the large differences in chemical shift between corresponding pairs of aryloxy- and arylthio-acetyl chlorides.

It has been shown[46] that the theoretical dissociation constants of aryloxyacetic and arylthioacetic acids, calculated by the Hammet equation, correlated with the experimental constants[46,55] when their ρ valves were 0.3 and 0.4 respectively; this is once more consistent with the greater ability of the sulphur atom to interact with the ring. As expected, the greater electronegativity of the oxygen atom results in the aryloxyacetic acids having significantly greater dissociation constants than their sulphur analogues. These studies, together with the chemical shift data, suggest

that the differences in reactivity of these acid chlorides can only be attributed to the relative electronegativities of the hetero atom.

It is of interest to note that the dissociation constant of 3-nitrophenoxyacetic acid, although less than those of the 2- and 4-isomers is of the same order as those of 2- and 4-cyanophenoxyacetic acids.[46] On this basis alone it may have been expected that 3-nitrophenoxyacetyl chloride would readily decarbonylate. A similar effect was noted from the chemical shift data where there was no significant differences between the 3-, or 4-nitrophenoxyacetyl chlorides. In the absence of further information it is tentatively suggested that the apparently anomalous behaviour of 3-nitrophenoxyacetyl chloride may be explained by assuming these ground state properties to be mainly influenced by the inductive effect of such substituents; in the transition states leading to decarbonylation the conjugative effects of 2- and 4-substituents may therefore be a significant factor in assisting the reaction.

There is little doubt that the bimolecular decarbonylation of these aryloxyacetyl chlorides requires the aryloxy group to act as an electron acceptor. This contrasts with the desulphonylation reactions of aryloxymethanesulphonate salts (93) with phosphorous pentachloride, the most widely applicable method known for the syntheses of aryloxymethyl chlorides.[52]

$$ArOCH_2SO_3Na \xrightarrow{PCl_5} ArOCH_2Cl + SO_2$$

(93)

The obvious intermediate, the aryloxymethanesulphonyl chloride, was never isolated, for all attempts to prepare it led to the formation of the corresponding aryloxymethyl chloride. Since the reactivities of the isolable sulphonyl chlorides RSO_2Cl, to desulphonylation with phosphorous pentachloride, increased

EX BIBL. UNIV. EDINBURGEN

along the series R = $PhO(CH_2)_2-$ > $Ph(CH_2)_2-$ > Ph-, it was claimed that the extreme reactivity of aryloxymethanesulphonyl chlorides was due to the electron donating properties of the aryloxy group. Moreover the electronic effects of nuclear substituents are apparently of secondary importance for this method gives excellent yields of aryloxymethyl chlorides when the nucleus contains both strong electron donating and electron withdrawing groups. The results suggest that the electron withdrawing properties of the sulphonyl group are sufficient to enable the aryloxy group to act as an electron donor at all times.

A unimolecular mechanism, basically similar to the unimolecular decarbonylation of secondary and tertiary acid chlorides, is therefore most likely and appears to be operative even when the nucleus is extremely electron deficient.

$$ArOCH_2SO_3Na \xrightarrow{PCl_5} [ArOCH_2\text{-}SO_2\text{-}OPCl_4] \xrightarrow{-SO_2} [ArO\overset{+}{C}H_2][\overset{-}{P}OCl_4] \longrightarrow ArOCH_2Cl$$

It is clear that the chlorocarbonyl group in aryloxyacetyl chlorides does not have a similar influence in promoting the unimolecular decarbonylation of these compounds; for this reason it has been possible to prepare a number of aryloxymethyl chlorides by a bimolecular route when the nucleus of the acid chloride is sufficiently electron deficient. In view of the extreme electronic requirements necessary for bimolecular decarbonylation to occur it would appear that the aryloxy group has an inherent tendency to act as an electron donor; this will be evident in a later discussion for it will be shown that aryloxyacetyl chlorides more readily undergo unimolecular

decarbonylation. It is therefore not surprising that this method has only limited value as a synthetic route to aryloxymethyl chlorides. However, this is a useful complement to the more general methods of Barber[52.56] for these are not suited to the preparation of aryloxymethyl chlorides containing strong electron withdrawing substituents. For example, the sodium salts of 2,4-dinitro- or 4-chloro-2,6-dinitro-phenoxymethanesulphonic acids could not be prepared by dinitration of the parent compounds and the only products formed were the corresponding dinitrophenols. The attempted side-chain chlorination of 2,4-dinitroanisole in the presence of PCl_5 as catalyst also failed to give the aryloxymethyl chloride.

5. The Reactions of Aryloxyacetyl Chlorides with Aluminium Chloride in Aromatic Solvents

In view of the difficulty with which aryloxyacetyl chlorides undergo bimolecular decarbonylation it appeared that the aryloxy group could more readily act as an electron donor. The possibility therefore remained that decarbonylation could take place by a unimolecular mechanism and clearly this would be most likely when the nucleus does not carry electron withdrawing groups. While Rothstein and his co-workers have shown that primary acid chlorides are in general resistant to Friedel-Crafts unimolecular decarbonylation in aromatic solvents, due to their high relative rates of acylation, the carbonium ion mechanism does not eliminate the possibility of carbon monoxide elimination at a primary centre when the α substituent is potentially a powerful electron donor. Moreover, in a study of the intramolecular acylation reactions of meta-substituted aryloxyacetyl chlorides in benzene as solvent, Scollick[12] has reported the formation of non-characterisable side products (in trace amounts) in which the carbonyl group was absent. While it was equally possible that these products could have arisen by Lewis acid-catalysed decarboxymethylation of these acid chlorides the evidence suggested that an initial study of the Friedel-Crafts decarbonylation of aryloxyacetyl chlorides was warranted. These reactions were carried out in aromatic solvents in an attempt to determine whether decarbonylation was of any consequence when both intra- and inter-molecular acylation of these acid chlorides was possible.

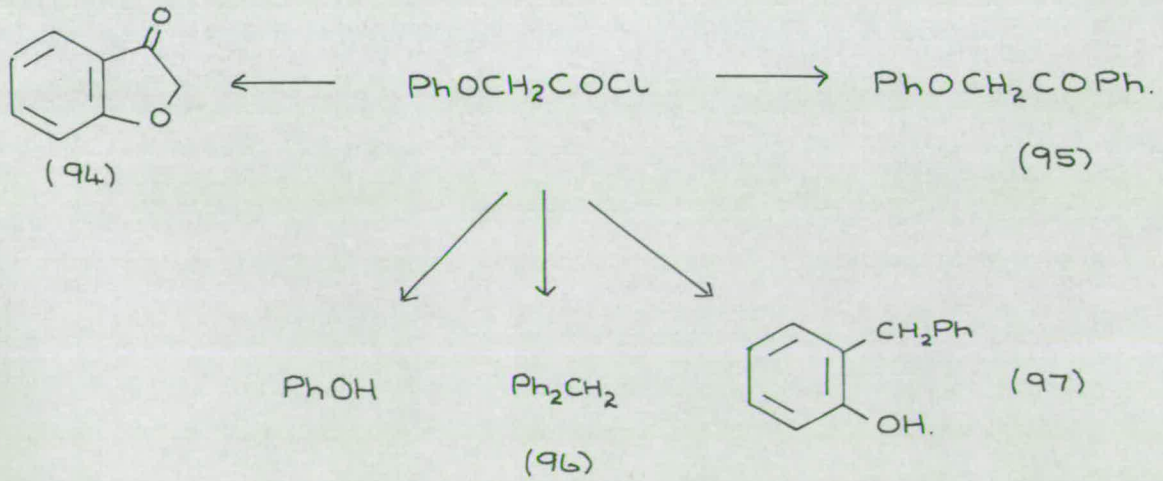
(a) Initial Study - The Reactions of Phenoxyacetyl Chloride with Aluminium Chloride in Aromatic Solvents

(i) In Benzene

It has been well established[12,13,14] that this reaction provides a convenient synthesis of benzofuran-3-one (94), generally obtained in 40-50% yield by

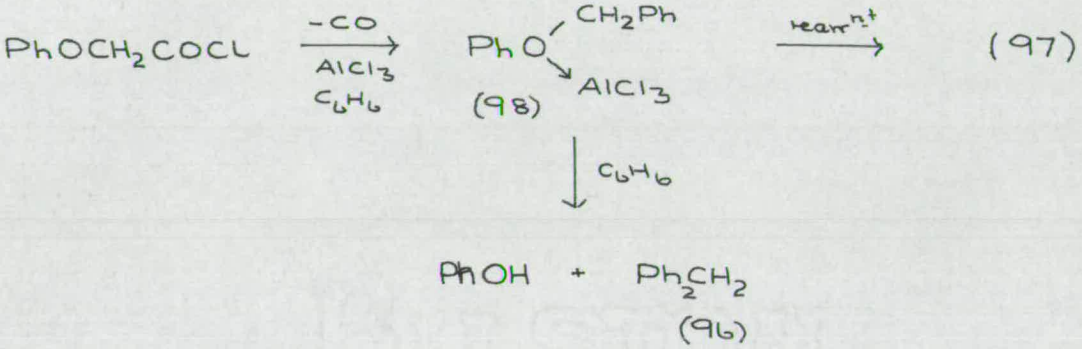
steam distillation of the crude non-acidic product. It appeared, however, that the nature of the residual reaction product was never investigated, although it has been claimed[13] that a trace amount of 2-phenoxyacetophenone (95) was present. This reaction was therefore a suitable starting point in this investigation.

The reaction of phenoxyacetyl chloride with $AlCl_3$ (1 molar equivalent) in benzene (20 molar equivalents) at 5-10°C. over 1½ hours gave a red oil (after acid hydrolysis of the reaction mixture) from which a small amount (2%) of unreacted acid was obtained by sodium bicarbonate extraction. A single recrystallisation of the crude non-acidic product gave a pure sample of benzofuran-3-one (94) (33%) and the residue from the filtrate was steam distilled. Silica Gel chromatography on the steam volatile component gave, in addition to a further quantity (11%) of benzofuran-3-one (94), small amounts of 2-phenoxyacetophenone (95) (2%), diphenylmethane (96) (5%), 2-benzylphenol (97) (6%) and phenol (1%). The steam non-volatile component was a viscous red oil from which a trace amount of (97) (1%) was the only characterisable product isolated by silica gel chromatography. Each product was characterised by comparison with known samples or by derivative formation.



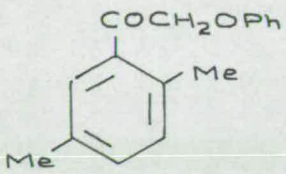
The expected decarbonylation product, phenyl benzyl ether (98), was prepared from phenol and benzyl bromide in ethanolic sodium ethoxide. Its N.M.R. spectrum was recorded and compared with that of the crude reaction product from which it was shown that phenyl benzyl ether was not a final product derived from the decarbonylation of phenoxyacetyl chloride. However, the reaction of phenyl benzyl ether with $AlCl_3$ in benzene at 5-10°C. over 1½ hours gave a mixture of phenol (45%), diphenyl methane (96) (45%) and 2-benzylphenol (97) (54%) and no unreacted ether was detected in the N.M.R. spectrum of the crude product. There is therefore little doubt that decarbonylation of phenoxyacetyl chloride has occurred and has led to the initial formation of phenyl benzyl ether for a similar product range and distribution has been obtained from both reactions. It is significant to note that neither reaction gave 4-benzylphenol (68) and this is consistent with a Lewis acid-catalysed intramolecular rearrangement of the ether (98) in both cases, similar to the aluminium bromide-catalysed rearrangement of phenyl benzyl ether in chlorobenzene.[34] This contrasts with the thermal[57] and zinc chloride catalysed[31,33] rearrangements of aryl benzyl ethers in which an intermolecular reaction occurs and always leads to the formation of the corresponding 4-benzylphenol.

In conclusion, it would appear that the decarbonylation of phenoxyacetyl chloride in benzene has led to the initial formation of phenyl benzyl ether; this has undergone an $AlCl_3$-catalysed intramolecular rearrangement to give 2-benzylphenol in competition with an intermolecular reaction with the solvent, leading to equimolar amounts of phenol and diphenylmethane.

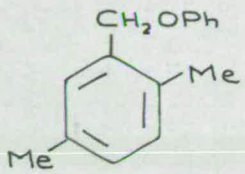


(ii) In p-Xylene

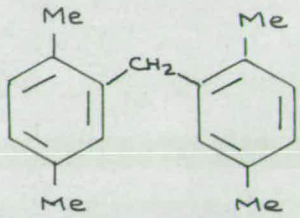
From the reaction of phenoxyacetyl chloride with $AlCl_3$ (1 molar equivalent) in p-xylene (20 molar equivalents) at 10-15°C. over 1½ hours the major product formed was 2',5'-dimethyl-2-phenoxyacetophenone (99) (65%); this was characterised by its unambiguous synthesis from phenol and 2',5'-dimethyl-2-bromoacetophenone, using the general method of Mohlau.[58] A single recrystallisation removed the bulk of this product from the crude non-acidic product and silica gel chromatography on the residue obtained from the filtrate gave a further quantity of (99), together with small amounts of benzofuran-3-one (5%) and di-(2,5-xylyl)methane (100) (1%). The latter (100) was characterised by its unambiguous synthesis from p-xylene and paraformaldehyde[59] and its presence is again evidence that decarbonylation has occurred for this is the product expected by cleavage of the benzyl ether (101). No phenolic products were isolated.



(99)



(101)



(100)

An increase in the nucleophilic character of the solvent has led to a marked increase in the ratio of intermolecular to intramolecular ketonic products and is no doubt a consequence of the bimolecular formation of the former. Since the increase in yield of the intermolecular ketone (the acetophenone) is not paralleled by a similar increase in the formation of decarbonylation products, this may be an indication that the acid chloride undergoes a slow unimolecular elimination of carbon monoxide followed by a rapid attack by the solvent on the phenoxymethylene carbonium ion. Thus the concentration and nucleophilic character of the solvent can influence the relative rate of decarbonylation to acetophenone formation through its effect on bimolecular reactions. The unimolecular nature of the decarbonylation stage is also indicated by comparing the relative rates of cyclisation and decarbonylation in benzene and p-xylene. Since both rate-determining stages are independent of the solvent, it may be expected that their relative rates should not be substantially different in different solvents. In benzene and p-xylene the approximate relative rates of cyclisation to decarbonylation (based only on the relative yields) were 4:1 and 5:1 respectively; this contrasts with the relative rates of intermolecular ketone formation to decarbonylation which were 1:6 in benzene and 65:1 in p-xylene, although again these are merely based on the relative yields. However since the differences in the product distributions obtained

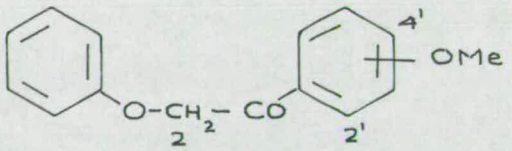
in benzene and p-xylene are large the results are clearly more consistent with a unimolecular decarbonylation scheme.

(iii) In Anisole

The reaction of phenoxyacetyl chloride with $AlCl_3$ (1 molar equivalent) in anisole (15 molar equivalents) at 5-10°C. over 1½ hours gave a crude non-acidic product whose N.M.R. spectrum was consistent with the exclusive formation of two isomeric methoxy-2-phenoxyacetophenones of the form

$$PhOCH_2CO\text{-}C_6H_4\text{-}OMe.$$

Fractional recrystallisation led to the isolation of the major component, 4'-methoxy-2-phenoxyacetophenone (102) which was a known compound. Attempts to obtain the minor isomer by silica gel chromatography failed, both products being eluted as a single band. There is however little doubt that this isomer was 2'-methoxy-2-phenoxyacetophenone (103).



(102; 4'-OMe) (103; 2'-OMe)

τ_{CH_2} 4·85 τ_{CH_2} 4·9.

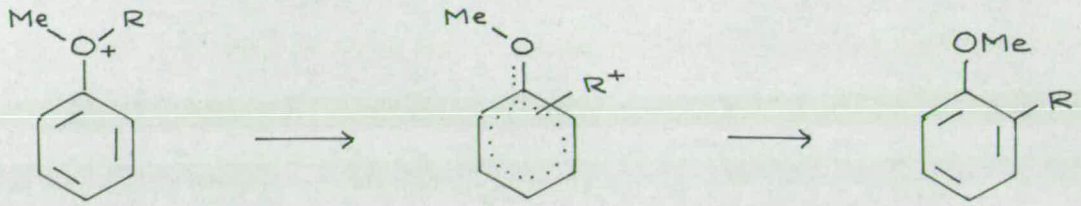
The overall yield of these ketonic products was extremely low (25%) and the acid recovered accounted for the remainder of the material. Measured from the integrated N.M.R. spectrum of the crude non-acidic product, the para-ortho ratio for the phenoxyacetylation of anisole was found to be 2:1. This reaction was repeated under identical conditions but varying the molar ratio of acid chloride:$AlCl_3$:anisole; with ratios of 1:1:14, 1:1:7, and 1:2:14 the overall yields of the ketones were 24%, 46%, and 52% (in each case

to the exclusion of the cyclic ketone or the decarbonylation products) and the para-ortho ratio was always 2:1, confirming that the ketonic products were indeed isomeric.

While the exclusive formation of the intermolecular ketones reflect the high nucleophilic character of anisole the rate of formation of these products appears to be much slower than expected. While initial experiments showed that the reaction rate increased with a decrease in the molar concentration of anisole, in contrast to the normal kinetic expression for bimolecular reactions, it was confirmed that the molar ratio of $AlCl_3$ to anisole was the significant factor. The increase in reaction rate with increasing molar ratios of $AlCl_3$:anisole is consistent with the slow rate of ketone formation being a result of catalyst deactivation by the solvent, probably due to the equilibrium

$$PhOMe + ArOCH_2COCl \longrightarrow AlCl_3 \rightleftharpoons ArOCH_2COCl + PhO\overset{Me}{\underset{AlCl_3}{}}.$$

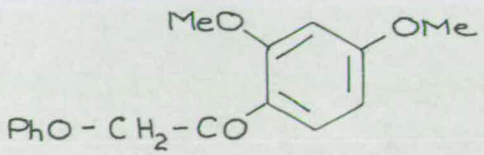
Since the ketonic product distribution is independent of the molar ratio of reactants and catalyst the para-ortho ratio obtained is only a consequence of the directive influence of anisole. The high proportion of ortho-substituted anisole is unexpected for there is much evidence to suggest that anisole is essentially para-directing in Friedel-Crafts acylations.[60] In this case the large steric effect would be expected to inhibit ortho-substitution even moreso and the only logical explanation would appear to be due to the contribution from a co-ordination effect involving a π complex intermediate. This has successfully rationalised the large ortho-para ratios obtained in the alkylation of anisole.[61]



This effect has obvious similarities to the intramolecular rearrangements of aryl benzyl ethers and aryl alkyl ethers.[62]

(iv) In m-Dimethoxybenzene

From phenoxyacetyl chloride, $AlCl_3$ (1 molar equivalent), and m-dimethoxybenzene (20 molar equivalents) at 5-10°C. over 2 hours, again a large quantity of unreacted acid was recovered (48%). A single recrystallisation of the crude non-acidic product gave a pure sample of 2',4'-dimethoxy-2-phenoxyacetophenone (104) in 17% yield. The residue from the filtrate appeared to be a mixture of (104) and products derived from an $AlCl_3$-catalysed demethylation of either the solvent or the ketone (104), the N.M.R. spectrum showing a singlet at 7.8τ (which is probably due to an aromatic methyl group), and several peaks in the 4.8τ($O-CH_2-CO$) and 6.2τ($O-CH_3$) regions. However the I.R. spectrum showed no hydroxyl absorption and no phenolic products could be isolated by alkaline extraction of this product. Silica gel chromatography gave a single fraction and fractional recrystallisation also failed to give a separation.

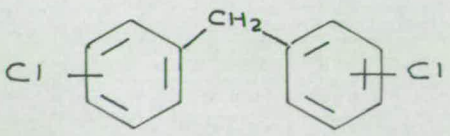


(104)

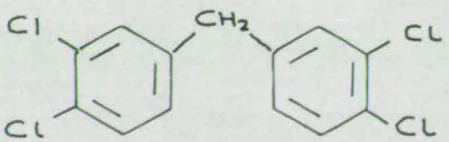
(v) In Chlorinated Aromatic Hydrocarbons

The crude non-acidic fraction obtained from the reaction of phenoxyacetyl chloride with $AlCl_3$ (1 molar equivalent) in chlorobenzene (15 molar equivalents) at 5-10°C. over 1½ hours was a viscous oil. The I.R. and N.M.R. spectra of this fraction were extremely complex and the distinct lack of resolution suggested the majority of this to be polymeric. Steam distillation over several hours gave a small amount of a yellow oil which was separated by silica gel chromatography into benzofuran-3-one (10%), phenol (1%) and an isomeric mixture of three di-(chlorophenyl)methanes (105) (10%). The latter product, which was eluted rapidly with benzene (and therefore behaved similarly to diphenyl- and di-(2,5-xylyl)-methanes) was characterised only by I.R. and N.M.R. spectroscopy. On repeating the reaction at 60°C. the only products isolated (by steam distillation and silica gel chromatography) were again benzofuran-3-one and the isomeric di-(chlorophenyl)methanes (105), both in yields of 3-4%.

The crude non-acidic fraction obtained from the reaction of phenoxyacetyl chloride with $AlCl_3$ in ortho-dichlorobenzene at 5-10°C. over 1½ hours was again complex. Steam distillation gave a small amount of a yellow oil which on silica gel chromatography gave a mixture of benzofuran-3-one (4%) and the known compound, di-(3,4-dichlorophenyl)methane (106) (11%).



(105)



(106)

While both reactions have given large quantities of uncharacterisable products they have nevertheless provided useful information concerning the decarbonylation stage for the isolation of (105) and (106) is once more consistent with the initial formation of a benzyl ether intermediate.

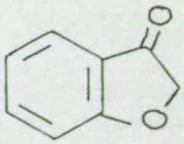
The formation of extensive quantities of tarry products when these solvents are used may be due to the formation of reaction products which are themselves more nucleophilic than the solvent. Therefore in the presence of solvents which do not readily acylate or alkylate the products formed in the initial stages of the reaction are more likely to be attacked by the acid chloride. For this reason nitrobenzene was not used as a reaction solvent.

(vi) Conclusions from the Initial Study

The product distributions obtained in benzene, p-xylene, and anisole are consistent with a unimolecular decarbonylation of phenoxyacetyl chloride; it follows that the phenoxy group acts as an electron donor and clearly this effect must be considerable for the acid chloride is primary.

The experimental evidence also suggests that the initial decarbonylation product is the corresponding phenyl benzyl ether (107). While a comparison of the product distributions obtained from the decarbonylation of the acid chloride and the rearrangement of the benzyl ether has only been possible when the solvent was benzene, the formation of the intermediate (107) may also be assumed from the nature of the diarylmethanes (108) obtained in other solvents.

The following competitive scheme is therefore likely.



$PhOCH_2COAr$

slow
unimolecular

slow
bimolecular
ArH

$PhOCH_2\overset{+}{C}O\ \overset{-}{AlCl_4}$

$-CO$ slow
unimolecular

$Ph\overset{+}{O}CH_2\ \overset{-}{AlCl_4}$

fast
ArH

$PhOCH_2Ar$

$AlCl_3$

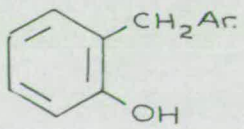
(107)

ArH

rearrangement

$PhOH + Ar_2CH_2$

(108)



(b) The Reactions of 2- and 4-substituted Phenoxyacetyl Chlorides with Aluminium Chloride in Aromatic Solvents

(i) General Introduction

A series of 2- and 4-substituted phenoxyacetyl chlorides were reacted with $AlCl_3$ (1 molar equivalent) in benzene (15-20 molar equivalents) at 5-10°C. over 1½ hours; in a few cases the reaction was repeated in p-xylene at 10-15°C., the higher temperature being necessary to prevent solidification of the solvent. The scheme was not extended to the other solvents used in the initial study (page 54) since these have been shown to lead to the formation of isomeric products or uncharacterisable tars. The influence of such substituents on the competing Friedel-Crafts acylation and decarbonylation reactions of aryloxyacetyl chlorides were thus determined.

The general isolation procedure was as follows:-

After hydrolysis of the reaction mixture, the organic layer was washed with sodium bicarbonate solution to remove any unreacted acid and the I.R. and N.M.R. spectra of the crude non-acidic product recorded to establish the absence of unhydrolysed acid chloride. The isolation procedure varied with the nature of the major component, necessitated by the tendency of certain benzofuranones to undergo self-condensation in alkali. Fortunately the N.M.R. spectrum of the crude product gave an accurate estimate of the product distribution for the chemical shifts of the methylene groups of the intermolecular ketone (5τ), the benzofuranone (5.5τ) and the decarbonylation products (6τ) were widely separated and were largely independent of substituent effects.

When the nucleus of the acid chloride contained electron withdrawing substituents the major product was invariably the intermolecular ketone, a single recrystallisation removing much of this component. The residue from the filtrate was dissolved in ether and washed successively with dilute

sodium hydroxide and 35% alcoholic potassium hydroxide solution. The neutral component was analysed for diphenylmethane and further amounts of the intermolecular ketone by silica gel chromatography; using a similar technique the sodium hydroxide soluble fraction was examined for the presence of the parent phenol and the cyclic ketone, the latter usually being essentially stable to alkali. The benzyl phenolic fraction obtained from the alcoholic potassium hydroxide layer was carefully analysed for the presence of isomeric products by N.M.R. spectroscopy and silica gel chromatography.

The reactions of aryloxyacetyl chlorides containing electron donating groups led to the formation of the cyclic ketone as the major component (when an ortho-position was vacant), the majority of which was removed by a single recrystallisation. Unfortunately these cyclic ketones appeared to be less stable to alkali than those containing electron withdrawing substituents and in consequence the above extraction procedure could not be used. Instead the residue from the filtrate was divided into three portions:-

(i) Silica gel chromatography generally gave both diphenylmethane and a benzylphenolic fraction, the latter again investigated for isomeric components by N.M.R. spectroscopy; a fraction which contained the cyclic ketone was always eluted after these components and was contaminated with uncharacterisable side products.

(ii) Steam distillation and silica gel chromatography on the volatile fraction gave a further quantity of diphenylmethane and the cyclic ketone as a pure sample.

(iii) The final portion was washed extensively with sodium hydroxide solution and the washings rejected. The organic layer was then extracted with alcoholic potassium hydroxide solution, the former examined for diphenylmethane and the intermolecular ketone and the latter for benzylphenols in the normal manner.

Table V , page 153 , gives the yields of each product obtained using the above procedures. When the cyclic ketone or the intermolecular ketone was a minor product but could not be isolated the yield quoted was that estimated from the integrated N.M.R. spectrum of the crude non-acidic product. When decarbonylation occurred, while diphenylmethane was always isolated, it was not always possible to isolate small amounts of the benzyl phenol or even estimate the yield of the latter since the methylene resonances of the decarbonylation products were practically degenerate.

In cases where decarbonylation occurred in benzene and where the molar ratio of diphenylmethane to benzyl phenol was established by their isolation the corresponding aryl benzyl ether was prepared and was reacted with $AlCl_3$ in benzene under conditions identical to those used in the acid chloride reaction. After hydrolysis of the reaction mixture, extraction of the organic layer with dilute sodium hydroxide and alcoholic potassium hydroxide removed the parent phenol and the benzyl phenol respectively leaving a neutral component which then contained only diphenyl methane. Therefore by comparing the nature of the benzyl phenolic fractions obtained from both the ether rearrangement and the acid chloride decarbonylation it has been possible to show that the initial decarbonylation product is indeed the corresponding aryl benzyl ether. Moreover this will be substantiated by comparing the corresponding ratios of diphenylmethane to benzyl phenol obtained.

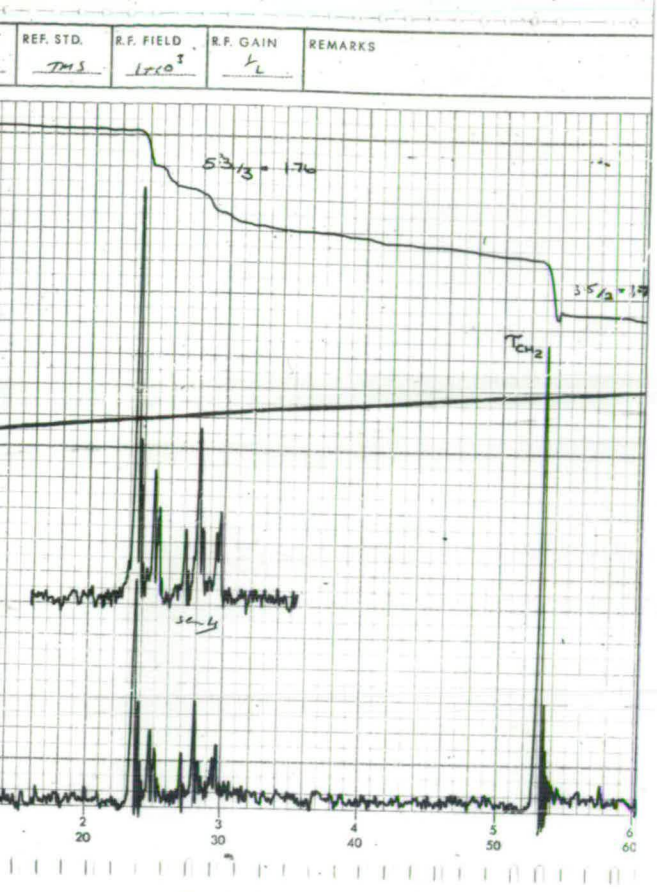
Since a detailed study of the $AlCl_3$-catalysed rearrangement of aryl benzyl ethers has not been carried out and since the mechanism is necessary for a complete study of the decarbonylation scheme, this aspect of the work was studied as comprehensively as the reactions of the acid chlorides.

In view of the wide range of products obtained it is fortunate that their characterisation has been relatively simple. In most cases the intermolecular

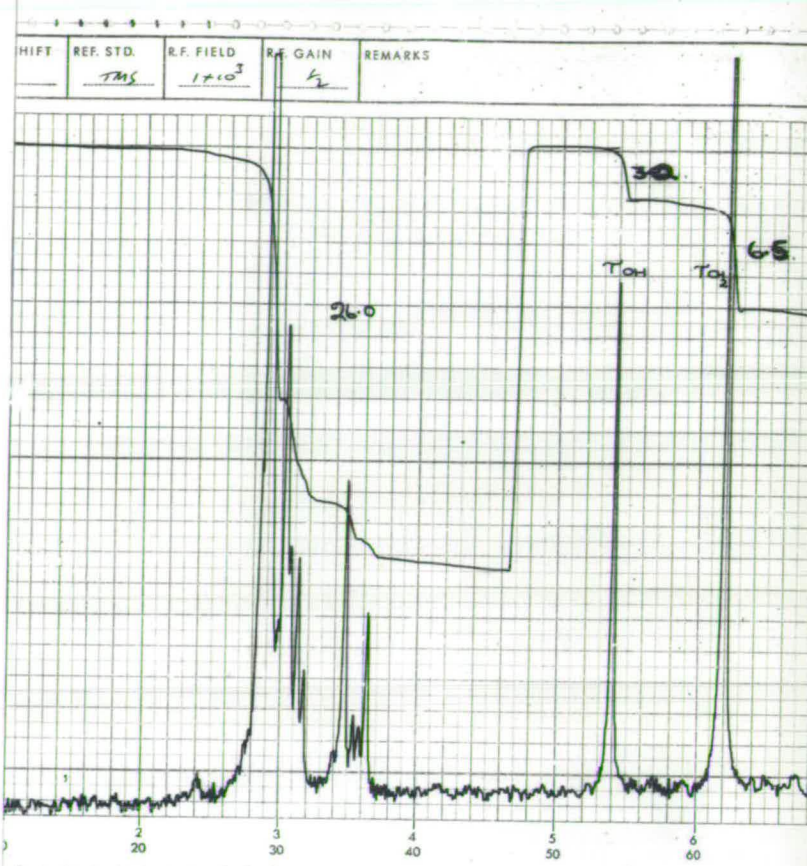
ketones, the aryloxyacetophenones (109) were known compounds although the majority have been prepared by other methods, the most widely used synthetic route comprising the reaction of a phenol (sodium salt) with 2-bromoacetophenone.[58] Such compounds are readily identified by spectroscopic methods for the I.R. carbonyl stretching vibration (ν co) lies within the 1680 $cm.^{-1}$-1700 $cm.^{-1}$ region of the spectrum and the N.M.R. spectrum shows a characteristic singlet at 4.6-4.9τ, assigned to the methylene group (τCH_2). The spectral features of this series of products are given in table VI, page 156, in the experimental section.

The majority of the cyclic ketones, the benzofuranones (110), prepared in this study have also been reported in the literature and invariably by the same method, for the Friedel-Crafts intramolecular acylation of aryloxyacetyl chlorides, in inert or aromatic solvents, is a well-established synthetic route to these compounds.[12.13.14.63] Again these are readily identified by their I.R. and N.M.R. spectra, the carbonyl stretching vibration being in the 1700-1720 $cm.^{-1}$ region and the chemical shift of the methylene group lying in the 5.3-5.5τ range. Table VII, page 158, illustrates this.

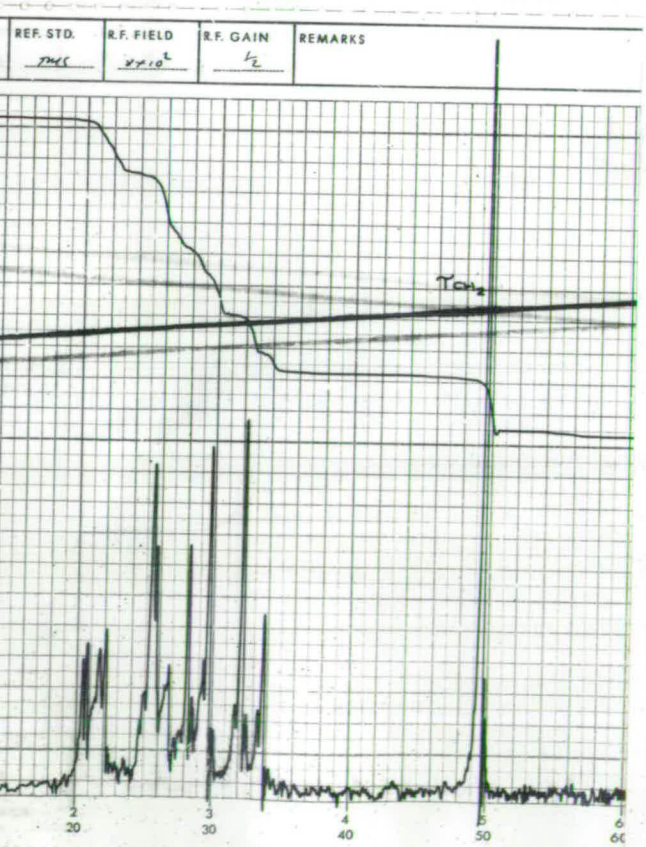
The products derived from the decarbonylation of the acid chloride and the rearrangement of the corresponding benzyl ether were identical in every case, the parent phenol and diphenylmethane (τCH_2 = 6.1) being characterised by comparison with authentic (commercial) samples. The benzyl phenolic fraction was always a single component, the 2-benzylphenol (111), when an ortho-position was vacant in the acid chloride or ether. Again these were generally known compounds, prepared by the method of Claisen in which the sodium salt of a phenol is treated with a benzyl halide in toluene solution.[31.32] It is interesting to note that the reaction is known to proceed via a benzyl ether intermediate and gives exclusively the 2-benzylphenol.



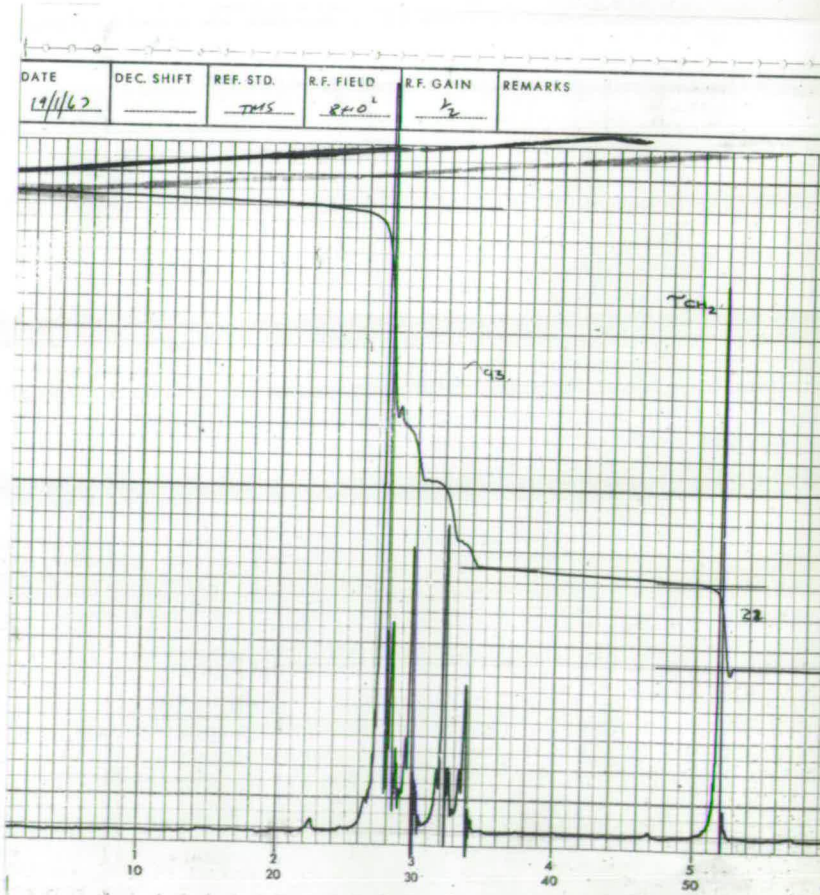
244-01 for 468-1112 5-Chlorobenzofuran-3-one



244-01 for 468-1112 4-Chloro-2-benzylphenol

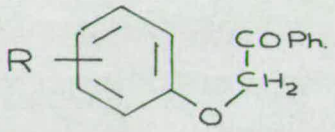


244-01 for 468-1112 2-(4-Chlorophenoxy) acetophenone



244-01 for 468-1112 4-Chlorophenyl Benzyl Ether

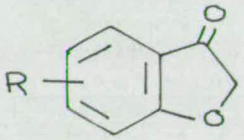
The N.M.R. spectra of the benzyl phenols prepared all showed a singlet due to the methylene group at 6.0-6.2 τ and hydroxyl absorption between 4.0 and 6.0 τ, the latter appearing to be remarkably independent of solvent or concentration effects. The spectral characteristics are given in Table VIII, page 161 .



(109)

τ_{CH_2} 4.6-4.9 τ

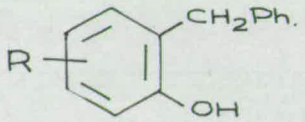
ν_{CO} 1680-1700 cm^{-1}



(110)

τ_{CH_2} 5.3-5.5 τ.

ν_{CO} 1700-1720 cm^{-1}



(111)

τ_{CH_2} 6.0-6.2 τ.

τ_{OH} 4.0-6.0 τ.

(ii) Reactions involving Acylation only

2- and 4-Nitro-phenoxyacetyl chlorides were reacted with $AlCl_3$ in benzene at 5-10°C. over 1½ hours and led to the exclusive formation of their corresponding 2-(nitrophenoxy)acetophenones (109; R = 2-NO_2 and 4-NO_2 respectively) in yields of 18% and 21% respectively. In each case the N.M.R. spectrum indicated the absence of side products and the acid recovered accounted for the remainder of the material. At 20°C. and over 2 hours the same products were obtained, again exclusively, and the yields were increased to 50%. Minton and Stephen[63] have reported the failure of these acid chlorides to acylate benzene but the reaction conditions were not given; it is possible that the high molar ratio of solvent used is responsible for the success of the present procedure.

2-(2-Cyanophenoxy)acetophenone (109; R = 2-CN) and 2-(3-methyl-2-nitrophenoxy)acetophenone (109; R = 3-CH_3-2-NO_2) were the sole reaction products

obtained from their corresponding phenoxyacetyl chlorides with $AlCl_3$ in benzene at 5-10°C.; the yields were 30% and 33% respectively. In contrast, 2,4-dichlorophenoxyacetyl chloride gave the acetophenone (109; R = 2,4-Cl_2) in 85% yield, and the N.M.R. spectrum indicated the presence of a trace amount of 5,7-dichlorobenzofuran-3-one (110; R = 5,7-Cl_2) although the latter could not be isolated.

Based on the yields obtained under similar conditions, it would appear that the (qualitative) rates of acetophenone formation decrease with progressive electron withdrawal by the nucleus. Since the presence of such substituents increase the electrophilic character of the carbonyl group and in consequence retard the rate of complex formation it is possible that the latter is the rate determining stage. Solubility effects are not thought to be significant for each acid chloride readily dissolved in the quantity of solvent used.

It has previously been established that the above acid chlorides readily eliminated carbon monoxide and gave the aryloxymethyl chloride in inert solvents. Clearly the relative rates of acylation of these acid chlorides in benzene are much greater than their relative rates of decarbonylation, whether unimolecular or bimolecular. Indeed it is fortunate that this is so for both mechanisms could formally result in the formation of an aryl benzyl ether, the latter by direct attack by the solvent or via an aryloxymethyl chloride precursor. However their failure to decarbonylate in benzene under conditions in which phenoxyacetyl chloride gives the benzyl ether is once more consistent with a unimolecular decarbonylation of the latter.

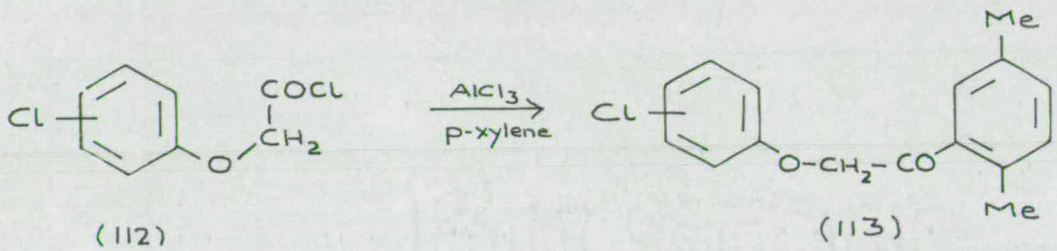
(iii) Reactions involving Acylation and Decarbonylation

Halogeno-phenoxyacetyl Chlorides

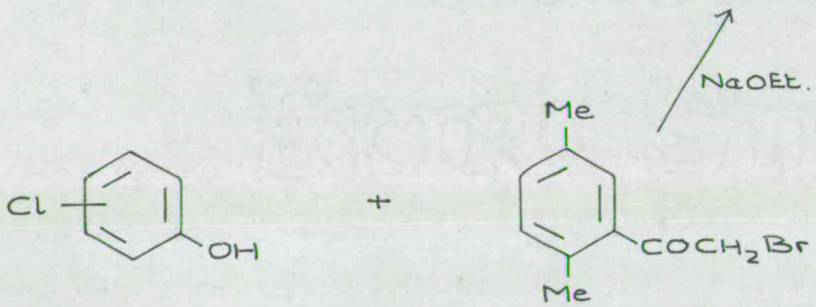
3,4-Dichlorophenoxyacetyl chloride in benzene as solvent gave the aryloxyacetophenone (109; R = 3,4-Cl_2) in high yield, the cyclic ketone not being detected in the N.M.R. spectrum of the crude non-acidic product. Equimolar amounts of diphenylmethane (4%) and 3,4-dichlorophenol (3%) were isolated, consistent with a benzyl ether intermediate, although the corresponding 2-benzylphenol was not obtained.

Each of the 2-halogenophenoxyacetyl chlorides studies in benzene gave the aryloxyacetophenone (109; R = 2-F; 2-Cl; 2-I) as the major product and these were isolated in yields greater than 50%; the N.M.R. spectra of the crude non-acidic products showed that the corresponding 7-halogeno-benzofuran-3-one (110; R = 7-F; 7-Cl; 7-I) was always formed and were estimated to be present in less than 10% yield. The known 7-chloro-benzofuran-3-one (110; R = 7-Cl) was isolated in 8% yield and had previously been prepared from 2-chlorophenoxyacetyl chloride in carbon disulphide as solvent; 7-iodobenzofuran-3-one (110; R = 7-I), obtained in 7% yield, had not been reported in the literature and this product did not give a sharp melting point (ca. 180°C.). However its I.R., N.M.R., and U.V. spectra (ν_{co} 1710cm.$^{-1}$; τ CH_2 5.3; $\lambda_{max.}$ 330mμ) were those of a typical benzofuran-3-one and the sample gave a satisfactory analysis. While approximately equimolar amounts (5-7%) of diphenylmethane and the parent phenol were always obtained, a benzyl phenolic fraction was isolated only from the reaction of 2-iodophenoxyacetyl chloride; this was an uncharacterisable mixture and it was thought that de-iodination had occurred at some point in the decarbonylation stage for both acylation products were formed with retention of the halogen yet much iodine was liberated in the reaction.

The reaction of 2-chlorophenoxyacetyl chloride (112; R = 2-Cl) was repeated in p-xylene and the sole product formed was 2',5'-dimethyl-2-(2-chlorophenoxy)acetophenone (113; R = 2-Cl), characterised by microanalysis and by its independent synthesis from 2-chlorophenol (114; R = 2-Cl) and 2',5'-dimethyl-2-bromoacetophenone (115).



(112) (113)



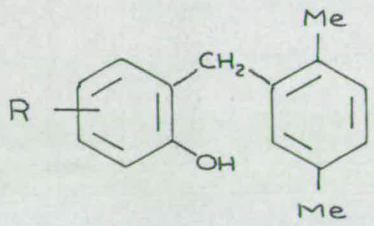
(114) (115)

The reactions of 4-halogenophenoxyacetyl chlorides in benzene gave the appropriate aryloxyacetophenones (109; R = 4-F; 4-Cl; 4-Br; 4-I) as the major products and these were isolated in yields of 30-40%. While the corresponding acylic ketones were always detected by N.M.R. spectroscopy they were present in small amounts and only 5-chlorobenzofuran-3-one (110; R = 5-Cl) was obtained as a pure sample; this was a known compound and had already been prepared from the acid chloride (112; R = 4-Cl) by its cyclisation in carbon disulphide solution.

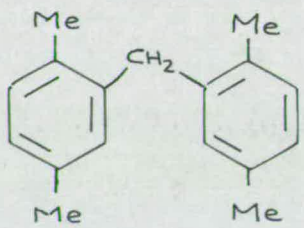
The decarbonylation products were formed in sufficient amounts to allow an isolation of each component; thus equimolar quantities (15-25%) of

diphenylmethane and the parent phenol were obtained together with a benzyl phenolic fraction. The latter was always a single product, the 2-benzyl-4-halogenophenol (111; R = 4-F; 4-Cl; 4-Br) with the exception that the corresponding fraction obtained from the reaction of 4-iodophenoxyacetyl chloride was an uncharacterisable mixture; again de-iodination was thought to be responsible for its complexity.

The reactions of 4-chloro- and 4-fluoro-phenoxyacetyl chlorides were repeated in p-xylene and both gave excellent yields (>90%) of the corresponding 2',5'-dimethyl-2-(4-halogenophenoxy)acetophenones; these gave satisfactory analyses and the former (113; R = 4-Cl) was further characterised by its synthesis from 4-chlorophenol (114; R = 4-Cl) and (115). Di-(2,5-xylyl)methane (117) was isolated from both reactions (in trace amounts) and impure samples of 4-chloro- and 4-fluoro-2-(2',5'-dimethylbenzyl)phenols (116; R = 4-Cl; 4-F) were obtained, characterisation being only by N.M.R. spectroscopy (τ_{CH_2} 6.1-6.2τ; $\tau_{2'\text{-}CH_3}$ 7.6-7.7τ; $\tau_{5'\text{-}CH_3}$ 7.7-7.8τ).



(116)



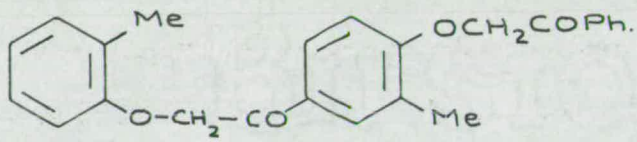
(117)

Methylphenoxyacetyl Chlorides

From the reaction of 4-methylphenoxyacetyl chloride in benzene was isolated 5-methylbenzofuran-3-one (110; R = 5-Me) as the main product (40%) together with smaller amounts of diphenylmethane (6%) and a benzyl phenolic fraction (17%) which contained only 2-benzyl-4-methylphenol (111; R = 4-Me). The N.M.R. spectrum of the crude non-acidic product showed a single peak at 4.9 τ and indicated the presence of 2-(4-methylphenoxy)acetophenone (109; R = 4-Me), in an estimated yield less than 5%, but this could not be isolated. This acid chloride was also reacted in p-xylene and gave 2',5'-dimethyl-2-(4-methylphenoxy)acetophenone in 58% yield; 5-methylbenzofuran-3-one was only detected in the N.M.R. spectrum of the crude non-acidic product as a minor component. After removing the bulk of the acetophenone from the crude reaction product by recrystallisation, silica gel chromatography on the residue led to the isolation of equal amounts (5%) of di-(2,5-xylyl)methane, 4-methylphenol, and 4-methyl-2-(2',5'-dimethylbenzyl)phenol (116; R = 4-Me); the latter was a non-recrystallisable oil and was characterised by converting it to its solid phenylurethane derivative. This gave a satisfactory analysis.

The crude non-acidic product from the reaction of 2-methylphenoxyacetyl chloride in benzene on recrystallisation gave the main product, 7-methylbenzofuran-3-one (110; R = 7-Me); silica gel chromatography on the residue gave diphenylmethane (6%) and a benzyl phenolic fraction (8%) which contained only 2-benzyl-6-methylphenol (111; R = 6-Me). A third fraction was also obtained which, after alcoholic potassium hydroxide extraction, gave a neutral component and was expected to be 2-(2-methylphenoxy)acetophenone (109; R = 2-Me). The N.M.R. spectrum showed however a minimum of four peaks in the 5 τ ($O-CH_2-CO$) region and fractional recrystallisation of this mixture gave a single product whose spectrum indicated the presence of two methylene groups (τ_{CH_2} = 4.6

and 4.8τ), two "aromatic" methyl groups (τCH_3 = 7.65 and 7.7τ) and an aromatic multiplet equivalent to 12 protons. This product analysed for $C_{24}H_{22}O_4$ and its I.R. carbonyl absorption was that of a typical acetophene (ν_{CO} = 1695 cm.$^{-1}$). Since the aromatic substitution pattern could not be determined by spectroscopy the most likely structure was thought to be (118), a result of the attack of the acid chloride on the initially formed 2-methylphenoxyacetophenone.



(118)

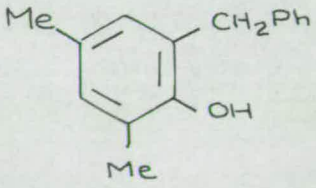
While 2,4-dimethylphenoxyacetyl chloride in benzene gave 5,7-dimethylbenzofuran-3-one (110; R = 5,7-Me_2) as the sole acylation product in 83% yield both diphenylmethane (6%) and 2-benzyl-4,6-dimethylphenol (4%) (111; R = 4,6-Me_2) were isolated.

When cyclisation was precluded by the presence of electron-donating groups in the ortho-positions of phenoxyacetyl chloride decarbonylation was almost quantitative. In consequence the reactions of 2,6-dimethyl- and 2,4,6-trimethyl-phenoxyacetyl chlorides in benzene gave only trace amounts of the intermolecular ketones; these could only be detected by N.M.R. spectroscopy and were estimated to be present in less than 3% yield. Using the normal alkaline extraction procedure equimolar amounts of diphenylmethane and the parent phenol were isolated and in both cases a benzylphenolic fraction was obtained, their N.M.R. spectra indicating that these were essentially mixtures of mono-benzyl phenols. Their characterisation is now discussed.

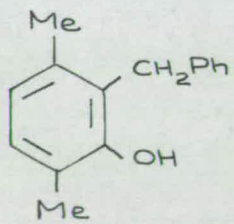
All attempts to separate the benzyl phenolic fraction obtained from the reaction of 2,6-dimethylphenoxyacetyl chloride, by fractional recrystallisation or silica gel chromatography, led only to the isolation of a trace amount of a dibenzylxylenol; the characterisation of this compound will be discussed at a later stage. It was therefore necessary to characterise the residue spectroscopically, by comparison with known samples.

The N.M.R. spectrum was consistent with a mixture of two mono-benzyl xylenols (τ CH_2 = 6.1 and 6.2τ) in a molar ratio of 3:1; moreover the phenolic ring protons showed a 5-line spectrum which comprised a singlet, equivalent to 2 protons, and a pair of ortho-split doublets (J = 8c/s), each equivalent to one proton. It was therefore possible to ascertain that one isomer was 1,2,3,5-tetrasubstituted, the other 1,2,3,4-tetrasubstituted.

The results so far have indicated that there is a definite tendency for ortho-substituted benzyl phenols to appear as final decarbonylation products; in this case the formation of such compounds by methyl migration could therefore not be discounted. For this reason 2-benzyl-4,6-dimethylphenol (119) and 2-benzyl-3,6-dimethylphenol (120) were prepared as reference samples by the $AlCl_3$-catalysed rearrangement of the appropriate xylyl benzyl ethers (64; R = 2,4-Me_2 and 2,5-Me_2)



(119)

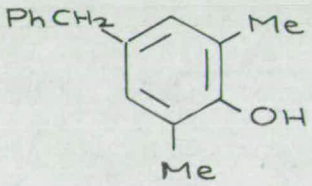


(120)

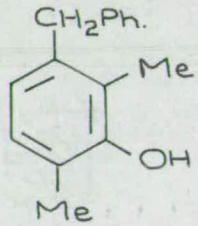
Quantitative I.R. and N.M.R. spectroscopy conclusively showed the absence of these ortho-benzylxylenols and since these products are those most likely

to be formed by ortho-benzylation and subsequent methyl migration it is reasonable to assume that such a mechanism is not of primary importance.

Assuming that methyl migration has not occurred the benzylxylenol fraction must be a mixture of 4-benzyl-2,6-dimethylphenol (121) and 3-benzyl-2,6-dimethylphenol (122); in an attempt to establish the presence of the former this was synthesised by the $AlCl_3$-catalysed benzylation of 2,6-xylenol with benzyl chloride in petroleum as solvent.[57]



(121)

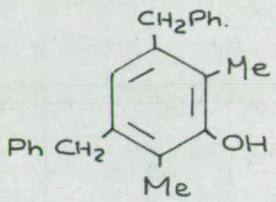


(122)

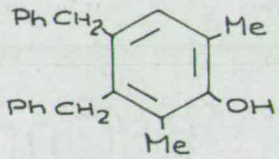
The crude reaction product was separated into a mono-benzyl-2,6-xylenol fraction (b.pt. 200-210°C./14mm.) and a dibenzyl-2,6-xylenol fraction (b.pt. 255-260°C./14mm.), recrystallisation of the former giving 4-benzyl-2,6-dimethylphenol. By quantitative I.R. and N.M.R. spectroscopy this product was shown to be the minor isomer present in the mixture obtained from the acid chloride and the major isomer formed in the mono-benzylation of 2,6-xylenol.

Moreover the spectra of these mixtures showed differences in relative intensities only and therefore both reactions have led to the same products although in different proportions. Since in the direct benzylation of 2,6-xylenol there is no apparent driving force for methyl migration the minor component is likely to be 3-benzyl-2,6-dimethylphenol and suggests this to be the major benzyl phenolic product derived from the decarbonylation of

2,6-dimethylphenoxyacetyl chloride. The same dibenzyl xylenol was obtained from the benzylation of 2,6-xylenol and the decarbonylation of the acid chloride; the N.M.R. spectrum showed methylene singlets at 6.1τ and 6.2τ and aromatic methyl singlets at 7.8τ and 7.9τ. The symmetrical 3,5-dibenzyl-2,6-dimethylphenol (123) can be discounted and the product was characterised as 3,4-dibenzyl-2,6-dimethylphenol (124).

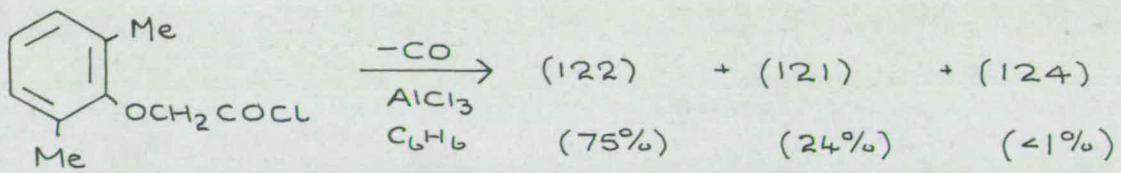


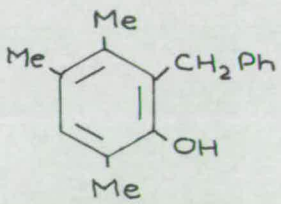
(123)



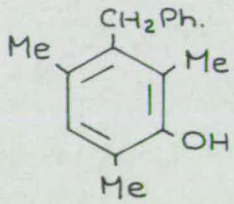
(124)

In conclusion, since the same benzyl phenolic products have been formed in the acid chloride decarbonylation and in the benzylation of the corresponding phenol it is most likely that the former has resulted in the following product distribution.





(125)

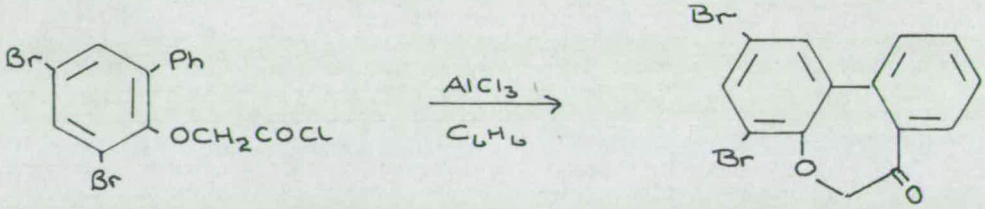


(126)

The benzyl phenolic fraction obtained from the decarbonylation of 2,4,6-trimethylphenoxyacetyl chloride was shown by N.M.R. spectroscopy and microanalysis to be a single mono-benzyl-trimethylphenol. A reference sample of 2-benzyl-3,4,6-trimethylphenol (125) was prepared by the rearrangement of 2,4,5-trimethylphenyl benzyl ether (64; R = $2,4,5\text{-Me}_3$) and its physical and spectral properties showed that this was not the unknown phenol. In view of the high proportion of meta-substitution obtained from the mono-benzyl-2,6-xylenol fraction the product was characterised as 3-benzyl-2,4,6-trimethylphenol (126). An identical product (m.pt. 59°C; phenylurethane 134°C.) has been reported to be a reaction product in the direct benzylation of 2,4,6-trimethylphenol.[64]

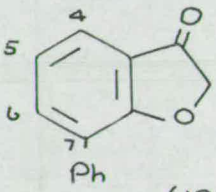
Phenylphenoxyacetyl Chlorides

The reaction of 4,6-dibromo-2-phenylphenoxyacetyl chloride (127) in benzene (and in carbon disulphide) gave a single product in high yield, 1',3'-dibromodibenz(b,d)oxepin-7(6H)-one (128), characterised by I.R. and N.M.R. spectroscopy (ν_{CO} = 1680 cm.$^{-1}$; τ CH_2 = 5.2) and by microanalysis.

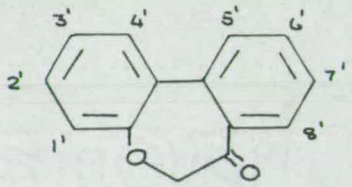


(127) (128)

The reactions of 2-phenylphenoxyacetyl chloride in both benzene and carbon disulphide also led to the exclusive formation of a cyclic ketone in high yield. Microanalysis was consistent with this product being 7-phenylbenzofuran-3-one (129) or dibenz(b,d)oxepin-7(6H)-one (130) and I.R. or N.M.R. spectroscopy (at 60 Mc/s) could not differentiate between these with any certainty (ν_{CO} = 1680 cm.$^{-1}$; τCH_2 = 5.2τ).

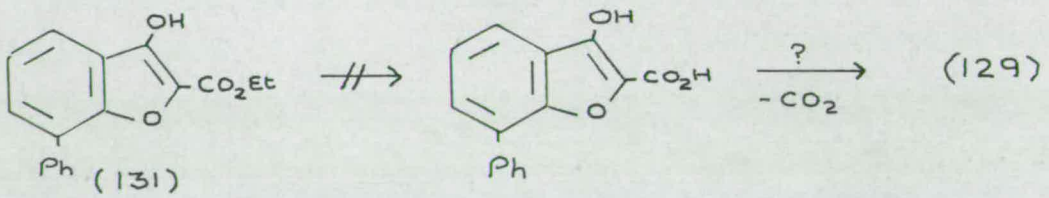


(129)



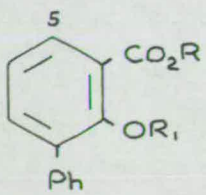
(130)

To resolve this problem an unambiguous synthesis of 7-phenylbenzofuran-3-one was attempted[65] but the resistance of 2-carbethoxy-3-hydroxy-7-phenylbenzofuran (131) to alkaline hydrolysis could not be overcome.

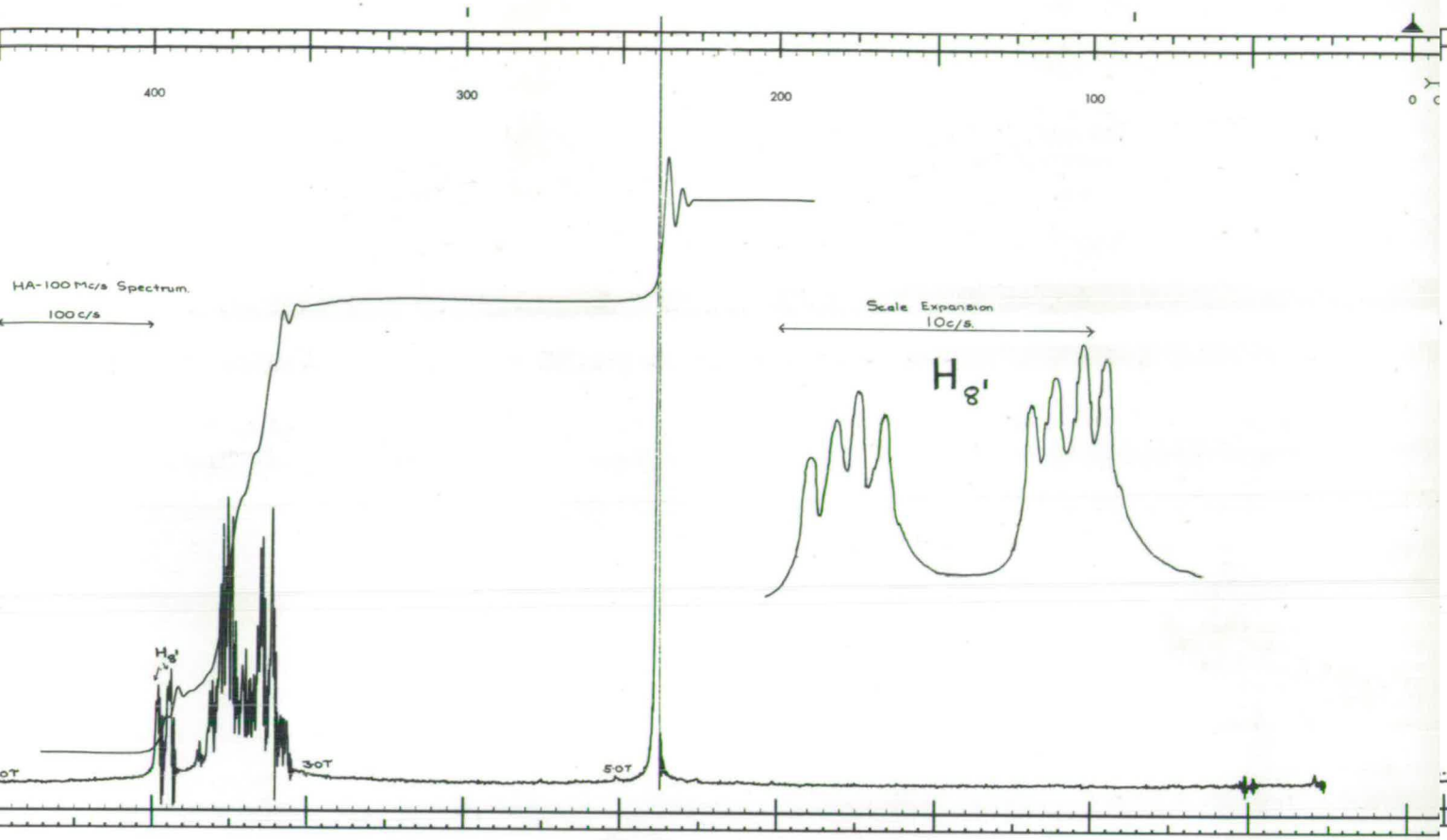


In the synthesis of (131) a series of 6-substituted derivatives of 2-phenylphenol were prepared (132a-c).

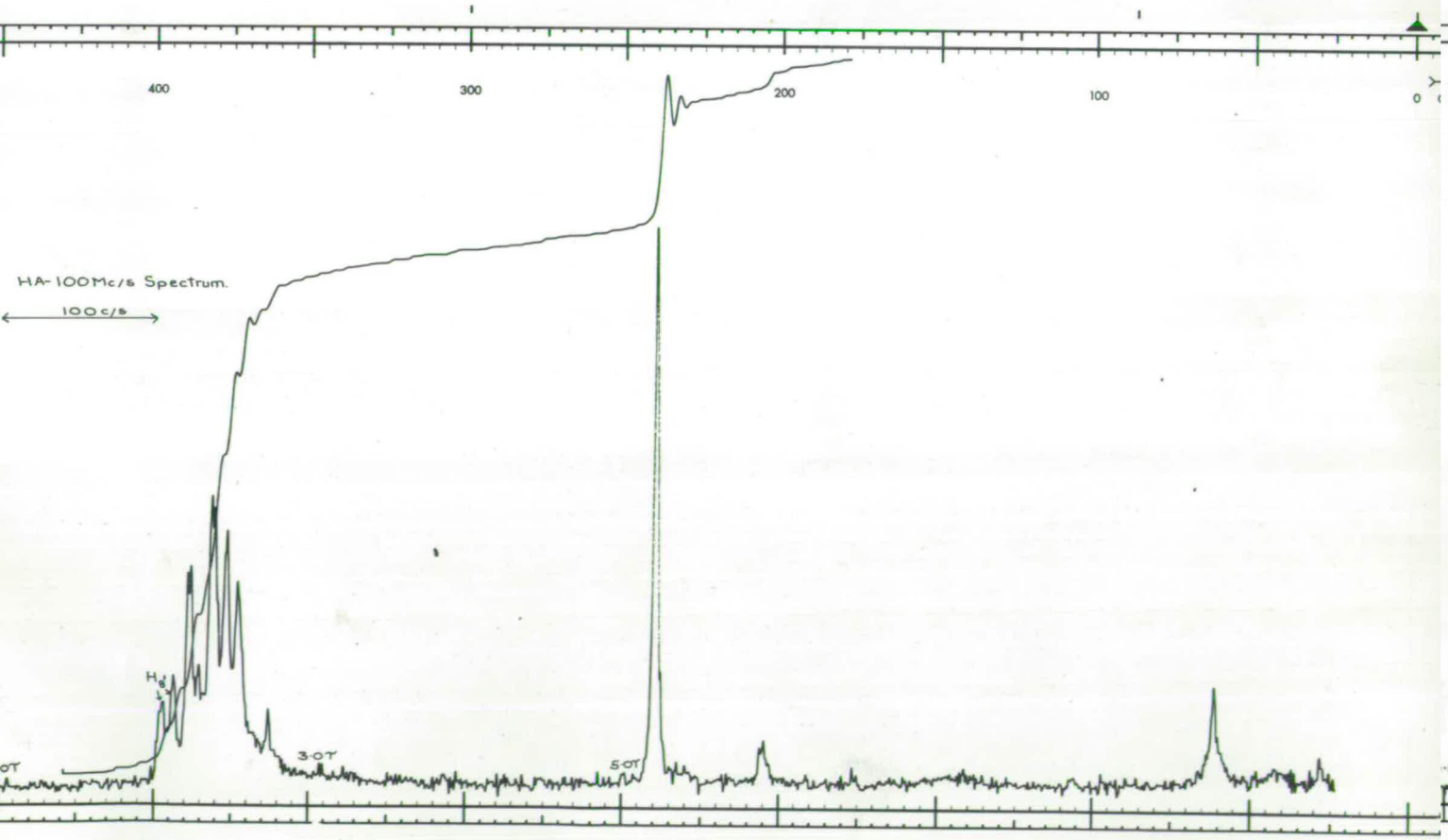
(132)



a. R=R$_1$=H.
b. R=Et ; R$_1$=H
c. R=Et ; R$_1$= CH_2CO_2H.



Dibenz (b,d) oxepin-7(6H) one (130)



1',3'-Dibromodibenz (b,d) oxepin-7(6H) one (128)

The N.M.R. spectra at 60 Mc/s of these compounds (132) showed that the deshielding effect of the 6-carboxyl group was sufficient to lower the chemical shift of the 5-proton relative to the remaining aromatic multiplet. In all cases this proton (H_5) was identified as a pair of meta-split ortho-doublets centred at approximately 2τ from which $J_{45} \simeq 8$ c/s and $J_{35} \simeq 2$c/s. Since a similar effect is shown in the N.M.R. spectra of 7-substituted benzofuran-3-ones (~~1333~~) then it may be expected that 7-phenylbenzofuran-3-one (129) would exhibit a low-field quartet due to a single proton (H_4) from which J_{46} and J_{45} could be readily calculated.

While the 60 Mc/s N.M.R. spectrum of the cyclisation product derived from 2-phenylphenoxyacetyl chloride gave a low-field multiplet centred at 2.1τ due to a single proton this did not appear to be a quartet. Recording the spectrum at 100 Mc/s showed that this was essentially a first-order octet, consistent with the proton being coupled by protons in positions ortho-, meta- and para- to it (J_{ortho} = 7c/s; J_{meta} = 1.8c/s; J_{para} = 0.7c/s). Clearly the observed multiplicity cannot be due to the 4-proton in 7-phenylbenzofuran-3-one and the additional para-coupling allows the multiplet to be assigned to the 8'-proton of dibenz(b,d)oxepin-7(6H)-one (130).

The 60 Mc/s N.M.R. spectrum of 1'3'-dibromodibenz(b,d)oxepin-7(6H)-one (128) indicates that the corresponding multiplet at 2.15τ is similar to that of (130); at present we are awaiting a 100 Mc/s N.M.R. spectrum of this compound and a detailed analysis of the low-field spectrum should further indicate that the assignment of (130) as the cyclic ketone obtained from 2-phenylphenoxyacetyl chloride is correct.

By comparing the U.V. spectrum of this cyclic ketone with that of the known oxepinone (128) and with those of a series of 7-substituted benzofuran-3-ones it has also been possible to assign its structure as dibenz(b,d)oxepin-

7(6H)-one (130); the U.V. spectral data are given in Table VII A, page 160, in the experimental section.

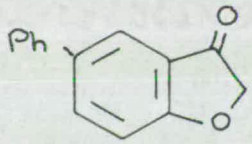
The long wavelength absorptions in benzofuran-3-ones (λ max. = 320-340mμ) are due to a $\pi \rightarrow \pi^*$ transition involving the carbonyl group and are shown to be subject to the normal bathochromic (and presumably hypsochromic) effects of nuclear substituents. The introduction of a phenyl group in the 7-position of benzofuran-3-one ($\lambda_{max.}$ = 325mμ) may be expected to give rise to two competing effects, a resulting increase in conjugation (dependent on the degree of coplanarity between the aromatic rings) being offset by a steric inhibition to the conjugative effect of the hetero-atom with the benzofuran nucleus.

Beaven et. al.[66] have shown that the non coplanarity of the phenyl groups in the diphenyl 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'-dibromodiphenyl ($\lambda_{max.}$ = 207mμ) has an U.V. spectrum similar to that of bromobenzene (λ_{max} = 210mμ). However in 2-substituted diphenyls non-coplanarity is not significant and the spectrum is that of a typical diphenyl. That 2-phenyl-anisole (λ_{max} = 246mμ) shows a large bathochromic shift relative to anisole (λ_{max} = 217mμ) and a small hypsochromic shift relative to diphenyl (λ_{max} = 248mμ) 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 (129) would therefore show a distinct bathochromic shift relative to benzofuran-3-one.

However, since the long-wavelength carbonyl $\pi \rightarrow \pi^*$ absorptions in both the oxepinone (128) ($\lambda_{max.}$ = 300mμ) and the unknown cyclic ketone ($\lambda_{max.}$ = 307mμ) show a large hypsochromic shift relative to the corresponding absorption in benzofuran-3-one ($\lambda_{max.}$ = 325mμ) there can be little doubt

that the product obtained by the cyclisation of 2-phenylphenoxyacetyl chloride is dibenz(b,d)oxepin-7(6H)-one.

Since the reaction of 4-phenylphenoxyacetyl chloride in benzene gave only a small amount (29%) of 5-phenylbenzofuran-3-one (133) together with considerable quantities of decarbonylation and intermolecular ketonic products, while in carbon disulphide no cyclic ketone was formed, it is clearly difficult to rationalise the ready cyclisation of 2-phenylphenoxyacetyl chloride to 7-phenylbenzofuran-3-one (129) in either steric or electronic terms. The extreme difference in the reactivities of the 2- and 4-phenylphenoxyacetyl chlorides to cyclisation is therefore more consistent with the formation of the 7-membered ketone (130) from the former.



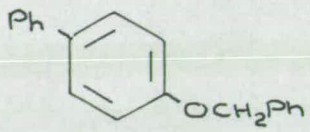
(133)

6. Mechanism of the Decarbonylation Stage

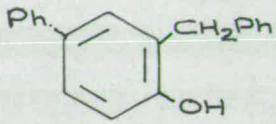
(a) Nature of the Intermediate

The preliminary study has shown that the decarbonylation of phenoxyacetyl chloride in benzene is consistent with the initial formation of phenyl benzyl ether and its subsequent $AlCl_3$-catalysed decomposition is thought to be a competitive intermolecular attack by the solvent and intramolecular rearrangement. To establish the generality of such a mechanism in the decarbonylation of the substituted phenoxyacetyl chlorides studied a series of aryl benzyl ethers were reacted with $AlCl_3$ in benzene. It may be expected that, if the aryl benzyl ether is a precursor to the final decarbonylation products, a similar product range and distribution should result from the decarbonylation of the acid chloride and decomposition of the corresponding benzyl ether.

Since the present discussion does not require a knowledge of the mechanism of the decomposition of aryl benzyl ethers (this aspect will be discussed at a later stage) it is sufficient to state that in every case an equimolar mixture of the parent phenol and diphenylmethane was obtained (in benzene as solvent); moreover, when the aryl groups contained a vacant ortho-position the benzyl phenolic fraction was always a single compound, the corresponding 2-benzylphenol, and this product was identical to that obtained from the decarbonylation of the appropriate aryloxyacetyl chloride. In general, the molar ratios of 2-benzylphenol to diphenyl methane compared favourably with those obtained from the acid chloride reactions, the sole exception being the rearrangement of (4-phenyl)phenyl benzyl ether (134) which gave exclusively a mixture of diphenylmethane and 4-phenylphenol although a small amount of 2-benzyl-4-phenylphenol (135) was formed in the decarbonylation of 4-phenylphenoxyacetyl chloride.[65]



(134)

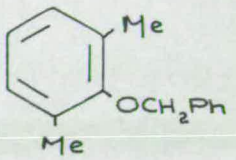


(135)

Tables V and XII, pages 153 and 174, give a comparison of the product distributions obtained from the decarbonylation of the acid chloride and rearrangement of the corresponding benzyl ether.

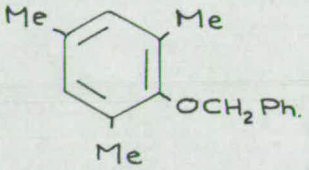
Perhaps the most conclusive evidence for a benzyl ether intermediate is shown from the reactions of 2,6-dimethyl- and 2,4,6-trimethyl-phenoxyacetyl chlorides and their corresponding benzyl ethers.

The benzyl phenolic fraction, obtained in 53% yield, from the decarbonylation of 2,6-dimethylphenoxyacetyl chloride in benzene has already been shown to comprise a mixture of 3- and 4-benzyl-2,6-dimethylphenols in a molar ratio of 3:1. The reaction of 2,6-dimethylphenyl benzyl ether (136) with $AlCl_3$ in benzene gave a crude benzyl phenolic fraction in 55% yield and its I.R. and N.M.R. spectra showed that this was identical in composition to that obtained from the acid chloride reaction; that is the major component was again 3-benzyl-2,6-dimethylphenol. Since both reactions have resulted in the same benzyl phenolic mixture and have given an unexpectedly high proportion of meta-substituted 2,6-dimethylphenol, in contrast to the direct benzylation of 2,6-dimethylphenol,[57] there can be little doubt that the decarbonylation of the acid chloride involves the initial formation of the benzyl ether.



(136)

$\xrightarrow[C_6H_6]{AlCl_3}$ (122) + (121)



(137)

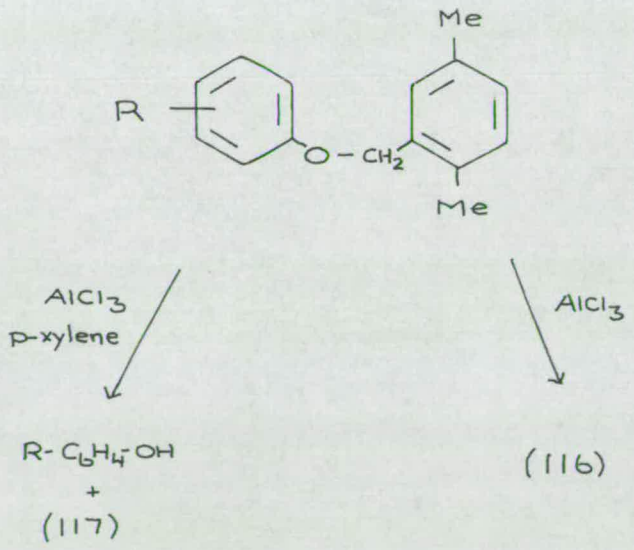
$\xrightarrow[C_6H_6]{AlCl_3}$ (126)

The crude benzyl phenolic fractions obtained from the reactions of 2,4,6-trimethylphenoxyacetyl chloride and 2,4,6-trimethylphenyl benzyl ether (137) were also identical and each contained a single product, 3-benzyl-2,4,6-trimethylphenol. These fractions were isolated in yields of 66% and 70% respectively and further indicated the readiness with which meta-substitution occurs when the ortho-positions already contain substituents.

The reaction of 4-iodophenyl benzyl ether (64; R = 4-I) in benzene resulted in the liberation of considerable amounts of iodine and, although giving an equimolar mixture of diphenylmethane and the parent phenol, the benzyl phenolic fraction was an uncharacterisable complex mixture. It was thought that de-iodination had occurred in the intramolecular rearrangement of this ether and it appeared likely that 4-benzylphenol would be a component of the benzyl phenolic fraction; however none was isolated or detected by spectroscopy. As stated previously, the reaction of 4-iodophenoxyacetyl chloride in benzene also liberated iodine and while the acylation products

were formed without loss of iodine the benzyl phenolic fraction was a complex mixture. The benzyl phenolic fractions obtained from both reactions were shown by I.R. and N.M.R. spectroscopy to be identical. It is therefore probable that the liberation of iodine in the reaction of 4-iodophenoxyacetyl chloride (and presumably the 2-iodo-acid chloride also) was a result of the rearrangement of the benzyl ether intermediate.

There is therefore considerable evidence to show that the decarbonylation of aryloxyacetyl chlorides in benzene proceed in general via a benzyl ether intermediate; in the few cases that the aryloxyacetyl chlorides were reacted in p-xylene the formation of di-(2,5-xylyl)methane (117) and the corresponding 2-(2',5'-dimethylbenzyl)phenol (116) is consistent with the formation of an aryl 2',5'-dimethylbenzyl ether intermediate (138) although such ethers were not prepared or rearranged.



While it is most likely that the decarbonylation of aryloxyacetyl chlorides involves the initial formation of the transient aryloxymethylene carbonium ion

complex which is attacked by the solvent to give the aryl benzyl ether

$$ArOCH_2\overset{+}{C}O\ \overset{-}{AlCl_4} \xrightarrow{-CO} ArO\overset{+}{C}H_2\ \overset{-}{AlCl_4} \xrightarrow{Ar'H} ArOCH_2Ar'$$

it is theoretically possible that the formation of the benzyl ether could occur by an initial decarboxymethylation reaction. The latter would be similar to the mechanism postulated by Armarego for the decarboxymethylation of 2,4-dichlorophenoxyacetic acid with phosphorous pentoxide in benzene[15] where it has been established by carbon-14 labelling studies that initial reaction proceeds as follows:

$$ArOCH_2CO_2H \xrightarrow{P_2O_5} ArOH + \left[\overset{+}{C}H_2CO_2H\right]$$

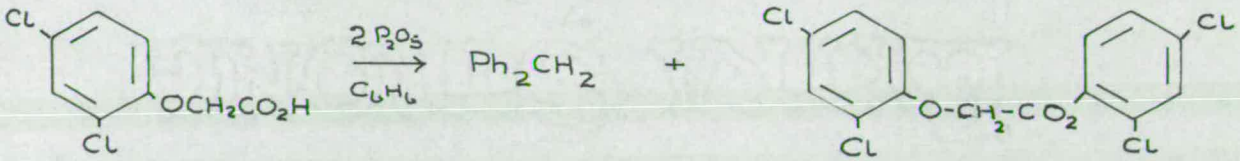
$$\left[\overset{+}{C}H_2CO_2H\right] \xrightarrow[H^+]{C_6H_6} Ph\overset{+}{C}H_2 + CO + H_2O \qquad \text{(via a formaldehyde type intermediate).}$$

It was reported that the benzyl carbonium did not attack the phenol and only reacted with a further molecule of the solvent to give diphenylmethane and that the phenol preferrentially attacked the unreacted acid to give an ester; clearly benzyl ether formation is not favoured.

$$ArOCH_2CO_2H + ArOH \xrightarrow{P_2O_5} ArOCH_2CO_2Ar$$

$$Ph\overset{+}{C}H_2 + C_6H_6 \longrightarrow PhCH_2Ph$$

However, the reaction of 2,4-dichlorophenoxyacetic acid with phosphorous pentoxide in benzene was re-investigated and the reaction product was exhaustively analysed for the presence of benzyl phenols and 2,4-dichlorophenyl benzyl ether. With one molar equivalent of the Lewis acid only the starting acid was recovered while in the presence of a molar excess of phosphorous pentoxide the reaction products were solely diphenylmethane and (2,4-dichlorophenyl)2,4-dichlorophenoxyacetate (140).



(140)

From these reactions the following conclusions may be made:-

(1) 2 molar equivalents of the Lewis acid are necessary to effect decarboxymethylation, presumably because the acidic function (rather than the "ether" oxygen) preferrentially complexes the Lewis acid.

(2) The high yields of the decarboxymethylation products are due to the inability of the acid complex to act as an acylating agent.

(3) The aryl benzyl ether is not formed under these conditions since the benzyl carbonium ion initially formed preferrentially attacks the solvent.

The reaction of 2,4-dichlorophenoxyacetyl chloride in benzene with 2 molar equivalents of $AlCl_3$ was studied in an attempt to effect a similar decarboxymethylation reaction; only the intermolecular ketone, 2-(2,4-dichlorophenoxy)acetophenone (109; R = $2,4\text{-}Cl_2$) was formed. Thus decarboxymethylation would appear to be of no consequence when in competition with acylation and this has been substantiated by the exclusive decarboxymethylation of this acid chloride with $AlCl_3$ (2 moles) in nitrobenzene as solvent,[15] the sole reaction product being the ester (140). Since it has been shown that aryloxyacetyl chlorides eliminate carbon monoxide in the presence of <u>one</u> molar equivalent of $AlCl_3$ under conditions in which acylation is favoured and that the decarbonylation products are consistent with the <u>sole</u> formation of the

corresponding aryl benzyl ether a decarboxymethylation mechanism is not favoured.

(b) The Effects of Nuclear Substituents

While it has been established that the decarbonylation of aryloxyacetyl chlorides involves the initial formation of a benzyl ether it is necessary to confirm the preliminary indications that this is a unimolecular process and that the decarbonylation stage is a result of the electron donating properties of the aryloxy group. This aspect of the mechanism may be determined by considering the variations in the product distributions obtained from the reactions of aryloxyacetyl chlorides in benzene and in p-xylene.

Since the (molar) product ratios obtained from the integrated N.M.R. spectra of the crude reaction products are a more accurate estimation than those isolated, the former data will be used in the following discussion and are given in the following Tables.

Product ratios from the reactions of Aryloxyacetyl Chlorides

(1) In benzene

$R = {}^{R}A$	P_1^R %	P_2^R %	P_3^R %	P_1^R/P_3^R	P_2^R/P_3^R
H	15	50	35	0.4	1.4
2,4-Cl_2	90	3	7	13.0	0.4
3,4-Cl_2	93	-	7	13.3	-
4-F	39	6	55	0.7	0.1
2-F	79	3	18	4.4	0.2
4-Cl	46	8	46	1.0	0.2
2-Cl	80	8	12	6.7	0.7
4-Br	49	7	44	1.1	0.2
4-I	40	10	50	0.8	0.2
2-I	66	11	23	2.9	0.5
4-Me	5	50	45	0.1	1.1
2-Me	13	67	20	0.7	3.4
2,4-Me_2	3	82	15	0.2	5.5
2,6-Me_2	3	-	97	0.03	-
2,4,6-Me_3	1	-	99	0.01	-
4-Ph	12	29	59	0.2	0.5
2-Ph	-	100	-	-	-
2-Ph-4,6-Br_2	-	100	-	-	-

(2) In p-xylene

A^R R =	P_1^R %	P_2^R %	P_3^R %	P_1^R/P_3^R	P_2^R/P_3^R
H	86	7	7	12.3	1.0
4-F	91	2	7	13.0	0.3
4-Cl	94	2	4	23.5	0.5
2-Cl	99	~1	<1	>100	~1.0
4-Me	68	14	18	3.7	0.7

Notes
- A^R = aryloxyacetyl chloride (R denotes substituent)
- P_1^R = yield aryloxyacetophenone (R denotes substituent)
- P_2^R = yield benzofuranone (R denotes substituent)
- P_3^R = yield decarbonylation products (R denotes substituent)

From the nature of the products obtained there can be little doubt that a common intermediate, the acid chloride complex, is involved. Since the product ratio obtained in any competitive study gives a measure of the relative rates of formation of the individual products it is possible to assess the effects of nuclear substituents on the decarbonylation stage, though only in a qualitative manner, from the observed variations of the product ratios. Hence in the above tables the ratio P_1^R/P_3^R gives a measure of the rate of formation of the aryloxyacetophenone relative to the rate of decarbonylation and the ratio P_2^R/P_3^R, the rate of cyclisation relative to decarbonylation.

When comparing the values of the above ratios for different acid chlorides the unimolecular or bimolecular nature of any competing stage must be considered; however since each acid chloride was studied under standard conditions (using a molar ratio of acid chloride:$AlCl_3$:solvent equal to 1:1:20) the differences in product ratios obtained are a reflection of the influence of the nuclear substituents rather than different concentration effects on bimolecular reactions.

In cases where the acid chlorides were reacted in both benzene and p-xylene the relative rate of acetophenone formation to decarbonylation (P_1/P_3) was substantially greater in the latter solvent; since this was not paralleled by a similar increase in the relative rate of cyclisation to decarbonylation (P_2/P_3) it follows that the decarbonylation stage is probably unimolecular. This is consistent with a slow rate determining elimination of carbon monoxide followed by a rapid attack by the solvent on the aryloxymethylene carbonium ion complex to give the aryl benzyl ether

$$ArOCH_2\overset{+}{C}O\ \overset{-}{AlCl_4} \xrightarrow{-CO\ \text{slow}} ArO\overset{+}{C}H_2\ \overset{-}{AlCl_4} \xrightarrow{Ar'H\ \text{fast}} ArOCH_2Ar'.$$

Since the elimination of carbon monoxide is a unimolecular process it is probable that the aryloxy group acts as an electron donor and this is also indicated from the variation in the relative rate ratios P_1/P_3 and P_2/P_3 observed in the reactions of aryloxyacetyl chlorides in benzene.

It is reasonable to assume that the influence of any nuclear substituent is greatest at the nucleus, smaller at the methylene group and least at the carbonyl group. It follows that the observed decrease in the relative rates of intermolecular ketone formation to decarbonylation (P_1/P_3) as the nucleus contains progressively stronger electron donating groups can only be consistent with a decarbonylation mechanism involving electron donation by the nucleus;

clearly the paralleled increase in the relative rate of cyclisation to decarbonylation (P_2/P_3) does not preclude such a mechanism. In consequence the decarbonylation reaction can be inhibited by the presence of electron withdrawing nuclear substituents, leading to high relative rates of intermolecular ketone formation, and by the presence of electron donating groups, leading to high relative rates of cyclisation; in both cases decarbonylation was the alternative reaction and this is evidence that the effects of nuclear substituents on the decarbonylation stage are marked.

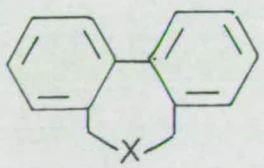
It is perhaps rather unexpected that the 4-halogenophenoxyacetyl chlorides consistently showed a much greater tendency to decarbonylate than the corresponding 2-isomers. It is more likely that these differences were due to their differing reactivities to decarbonylation rather than to intermolecular ketone formation. The ratios P_1/P_3 and P_2/P_3 showed that the 4-halogen was always a weaker electron withdrawing group than the 2-halogen and it is possible that this may be a reflection of the greater -I effect of the 2-halogen or the greater ability of the 4-halogen to exert its +E effect on the hetero atom. Steric effects were not thought to be of primary importance for the difference in reactivity to decarbonylation between corresponding pairs of 2- and 4-halogeno-acid chlorides, as measured from their P_1/P_3 ratios, did not increase with an increase in steric size. A similar effect was shown by the 2- and 4-methylphenoxyacetyl chlorides, the latter more readily promoting decarbonylation relative to cyclisation. This result cannot be explained in terms of inductive effects and, assuming steric effects to be unimportant, it is possible that differences in their rates of cyclisation may be responsible.

The reactions of the 2- and 4-phenylphenoxyacetyl chlorides followed a similar pattern; however the failure of the former to decarbonylate is more

readily explained, the high relative rate of cyclisation being due to the ease with which the 7-membered ketone, dibenz(b,d)oxepin-7(6H)-one (130) is formed. The exclusive formation of such a product is however worthy of comment for on first principles there is no apparent reason for its preferrential formation. Thus from consideration of both proximity and ring strain effects the 5-membered ketone, 7-phenylbenzofuran-3-one, may be expected to be favoured. Similarly, the benzofuran-3-one should be favoured on electronic grounds for the electron donating effect of the hetero-atom is known to activate the nucleus to cyclisation.

The reaction of 4-phenylphenoxyacetyl chloride has shown that the formation of a phenyl-substituted benzofuran-3-one is not favoured; this, together with the fact that dibenz(b,d)oxepins of the form (141) or (142) are readily formed by the cyclisation of 2,2'-substituted diphenyls, allows a rationalisation of the ease with which 2-phenylphenoxyacetyl chloride cyclises to the 7-membered oxepinone.

Since it has been shown[66] that the oxepins (141) and (142) have strainless configurations when the ring plane angle is approximately 50° it would appear that the formation of the 7-membered ketone is a result of the non-coplanarity of the diphenyl system allowing the extreme proximity of the carbonyl group and the cyclisation site in the transition state.



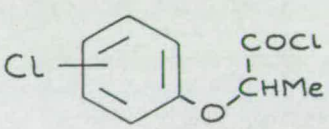
(141; X=O) (142; X= -CH-CO_2R)

The high relative rate of cyclisation (to the benzofuran-3-one) was instrumental in inhibiting the decarbonylation of 2,4-dimethylphenoxyacetyl chloride for the relative rate of intermolecular ketone formation to decarbonylation was low. Consequently in 2,6-dimethyl- and 2,4,6-trimethylphenoxyacetyl chlorides, where cyclisation is precluded, the almost quantitative decarbonylation of these acid chlorides again suggests the decarbonylation stage to involve electron donation by the aryloxy groups.

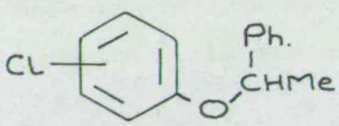
(c) Effects of Side Chain Substituents

To assess the effects of electron-donating side-chain substituents on the decarbonylation of aryloxyacetyl chlorides the reactions of 2-aryloxypropionyl chlorides (143) were studied briefly.

The reaction of 2-(2-chlorophenoxy)propionyl chloride (143; R = 2-Cl) with $AlCl_3$ in benzene gave exclusively an equimolar mixture of 2-chlorophenol and 1,1-diphenylethane (145); 2-(4-chlorophenoxy)propionyl chloride (143; R = 4-Cl) under similar conditions gave only 4-chlorophenol and 1,1-diphenylethane. These decarbonylation products are once more consistent with the formation of the corresponding chlorophenyl α-phenylethyl ethers (144).



(143)



(144)

Ph_2CHMe

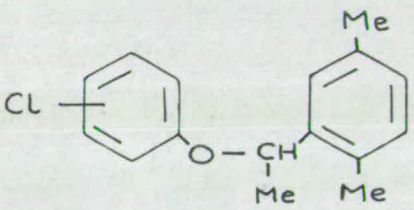
(145)

While 4-chlorophenyl α-phenylethyl ether (144; R = 4-Cl) with $AlCl_3$ in benzene gave predominantly 4-chlorophenol and (145) in equimolar amounts, a small quantity of 4-chloro-2-(α-phenylethyl)phenol was also formed. There

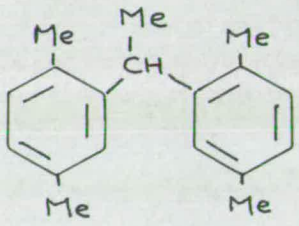
is however little doubt that the decarbonylation of the above acid chlorides (143) involve the initial formation of the corresponding ethers (144).

The acid chlorides (143; R = 2-Cl; 4-Cl) were also reacted in p-xylene; in both cases decarbonylation was quantitative and the phenolic fraction contained only the parent phenol. However the N.M.R. spectra of the crude neutral fractions, although identical, showed the absence of products of the diarylethane type and di-(2,5-xylyl)methane was isolated in 70% and 84% yield respectively.

The only factor which is inconsistent with the formation of the aryl ethers (146) as initial decarbonylation products in p-xylene is the formation of di-(2,5-xylyl)methane rather than 1,1-di-(2,5-xylyl)ethane (147).



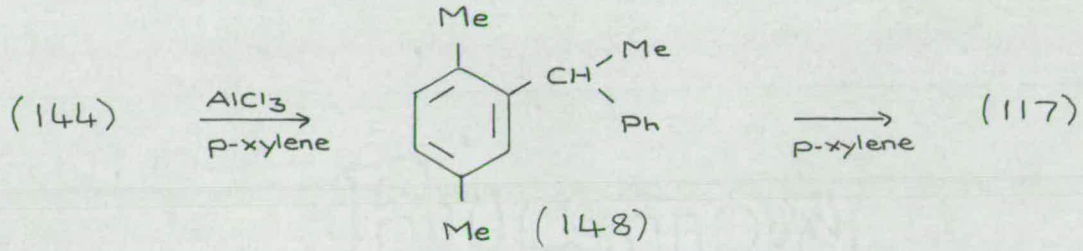
(146)



(147)

Clearly the syntheses of these ethers and their rearrangement in p-xylene would solve this problem. It has been possible however to determine the fate of the methyl group from a study of the rearrangement of 4-chlorophenyl α-phenylethyl ether (144; R = 4-Cl) with $AlCl_3$ in p-xylene. After hydrolysis of the reaction mixture the organic layer was washed with alcoholic potassium hydroxide solution and the phenolic fraction gave only 4-chlorophenol. The organic layer was distilled, a sample of the recovered solvent taken and analysed by Gas Liquid Chromatography, and the presence of small amounts of benzene, toluene and trimethylbenzenes were established. The

residual neutral product was similarly analysed and was shown to contain only di-(2,5-xylyl)methane, this being confirmed by I.R. and N.M.R. spectroscopy. Clearly, the initial product formed (148) has exchanged both the methyl and phenyl groups with the solvent, the former probably involving a hydride ion transfer.

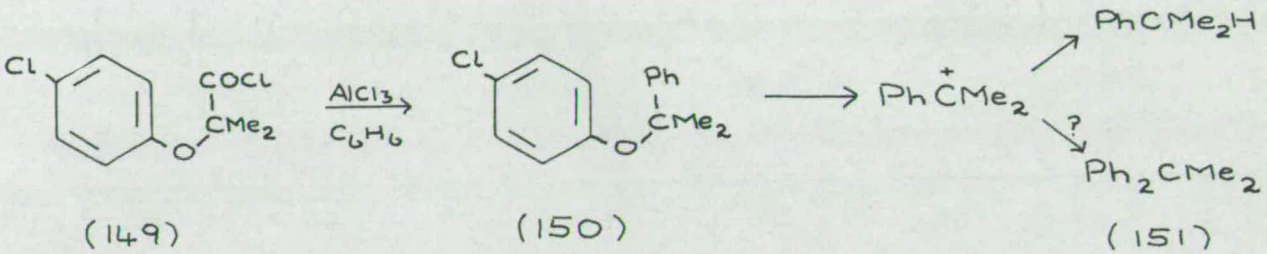


Neglecting the exchange of the phenyl group with p-xylene in (148), for this would be of no consequence in the methyl exchange of 1,1-di-(2,5-xylyl)ethane (147) with p-xylene, the formation of di-(2,5-xylyl)methane as a final product in the decarbonylation of 2-aryloxypropionyl chlorides in p-xylene probably does not preclude the initial formation of the corresponding benzyl ether (146).

The reaction of 2-(4-chlorophenoxy)isobutyryl chloride (149) with $AlCl_3$ in benzene was also studies and, as expected, decarbonylation was quantitative. 4-Chlorophenol was the sole phenolic product and the neutral fraction and a sample of the recovered solvent were analysed in the normal manner. The neutral fraction was an uncharacterisable mixture and 2,2-diphenylpropane (151) was not detected by N.M.R. spectroscopy or Gas Liquid Chromatography.

Since neither diphenylmethane nor diphenylethane could be detected in the residue it is possible that 2,2-diphenylpropane was not formed in large amounts; the presence of isopropylbenzene only in the solvent sample also indicated this for it is more likely to be derived by a hydride ion transfer

to the phenylisopropyl carbonium ion initially formed by cleavage of the ether (150). However no definite conclusions may be made in view of the large amounts of tarry products obtained.



(149) (150) (151)

The quantitative decarbonylation of the above side-chain substituted aryloxyacetyl chlorides in both benzene and p-xylene under conditions in which the corresponding primary acid chlorides give a high proportion of acylation products is consistent with a unimolecular elimination of carbon monoxide promoted by the electron donating effects of α-substituents. Since the secondary and tertiary acid chlorides also involve the formation of their corresponding benzyl ethers an identical decarbonylation mechanism is operative in all cases and the primary aryloxyacetyl chlorides differ from their secondary or tertiary analogues only in their reactivity to decarbonylation. The observed order of reactivity conclusively establishes the decarbonylation of the primary aryloxyacetyl chlorides to be a consequence of the electron donating properties of the aryloxy group.

(d) <u>The Rearrangement of Aryl Benzyl Ethers with Aluminium Chloride in Benzene</u>

While a comprehensive study of the Lewis acid-catalysed rearrangements of aryl benzyl ethers has not been carried out it is clear that such reactions may be classified as follows.

(1) Under heterogeneous conditions, the zinc chloride-catalysed rearrangement of 2-methylphenyl benzyl ether[33] (64; R = 2-Me) gives a mixture of 4- and 6-benzyl-2-methylphenols respectively, and 4,6-dibenzyl-2-methylphenol in a molar ratio of 2:1:1. Since the zinc chloride-catalysed benzylation of 2-methylphenol results in the same product distribution the rearrangement stage involves the preliminary ionisation of the complex (152) and the final products are formed by an intermolecular benzyl carbonium ion mechanism.

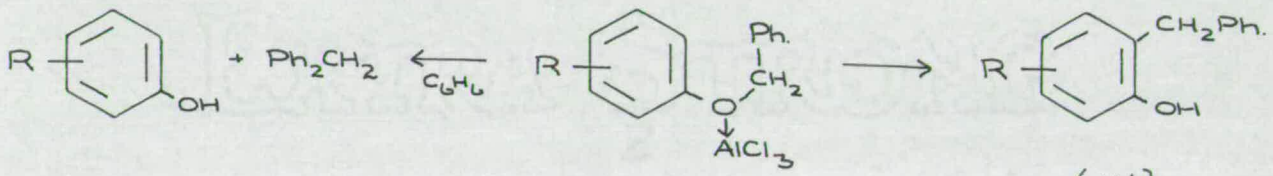
$$ArO\begin{matrix}\nearrow ZnCl_2 \\ \searrow CH_2Ph\end{matrix} \longrightarrow ArO\overset{-}{Z}nCl_2 + \overset{+}{P}hCH_2 \longrightarrow PhCH_2 - ArOH + \text{etc.}$$

(152)

(2) In contrast, the homogeneous $AlBr_3$-catalysed rearrangement of phenyl benzyl ether in chlorobenzene[34] results in the exclusive formation of 2-benzylphenol (67); equimolar amounts of phenol and di-(chlorophenyl)-methanes are also formed by a competitive intermolecular reaction of the complex with the solvent. This is of no consequence when considering the rearrangement stage which is clearly an intramolecular process and which does not involve the formation of a free carbonium ion, presumably because the preliminary ionisation of the complex is not favoured under homogeneous conditions in a non-polar solvent.

The product distributions obtained from the rearrangements of a series of 2- and 4-substituted aryl benzyl ethers with $AlCl_3$ in benzene at 5-10°C. are given in Table XII, page 174, in the experimental section. In each case an equimolar mixture of diphenylmethane and the parent phenol was formed together with a benzyl phenolic fraction which was carefully analysed for the presence of isomeric products. The exclusive formation of the corresponding ortho-benzylphenols in the rearrangement of phenyl and 2-methylphenyl benzyl

ethers establishes the intramolecular nature of the rearrangement stage. Similarly the rearrangements of the para-substituted aryl benzyl ethers gave only the ortho-rearrangement product; while this is not conclusive evidence for an intramolecular process the absence of poly-substituted benzylphenols is consistent with such a mechanism and is clearly identical to the $AlBr_3$ -catalysed rearrangement of phenyl benzyl ether. The product distributions are therefore a result of the competitive intramolecular rearrangement and intermolecular solvent attack of the intermediate complex (153).

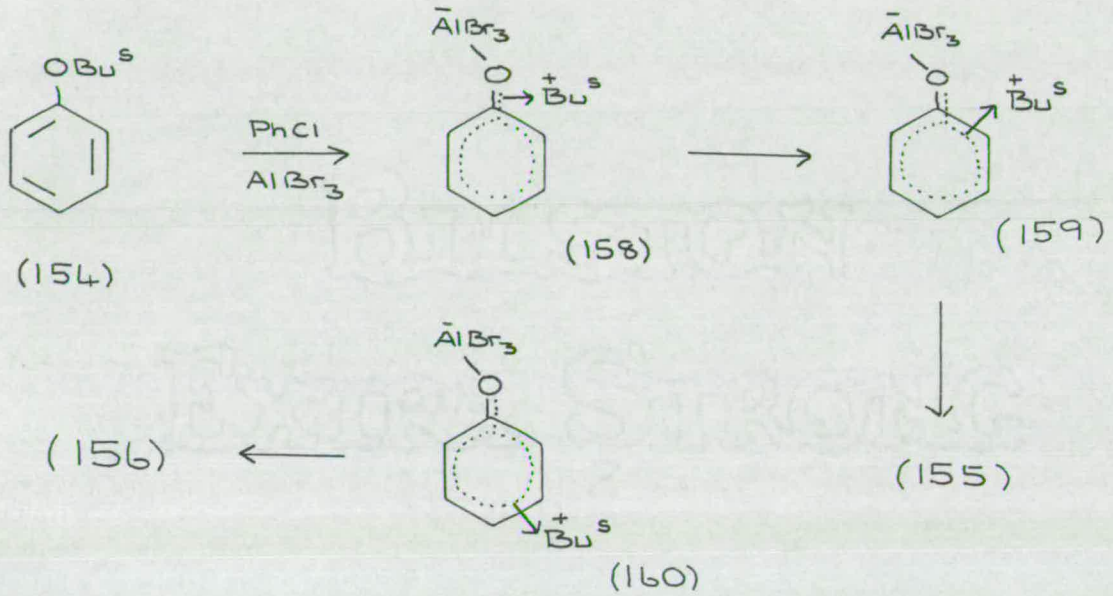


(153) (111)

In contrast with the intramolecular rearrangements of the above aryl benzyl ethers the $AlBr_3$-catalysed rearrangements of aryl alkyl ethers in chlorobenzene have been studied extensively.[62] In each case a phenolic fraction was obtained and while the major component was the ortho-substituted rearrangement product a small amount of the para-isomer was always present; thus the rearrangement of phenyl sec-butyl ether (154) gave a mixture of phenols which was shown to contain 2-sec-butyl phenol (91%) (155) and 4-sec-butylphenol (9%) (156). No meta-substituted product was formed.

Since the direct (intermolecular) sec-butylation of phenol gave predominantly 4-sec-butylphenol the rearrangement of these ethers must be intramolecular, at least in part.

The mechanism was stated to involve the formation of the π-complex (158), migration of the alkyl group leading to the isomeric alkyl phenols.

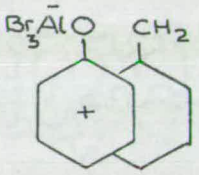


Since (159) is a precursor to (160) it is reasonable to assume that this mechanism leads to high o/p ratios, the product ratio being dependent on the migratory aptitude of the alkyl group.

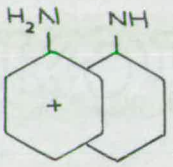
The failure of the aryl benzyl ethers to give para-substituted rearrangement products suggests that, if a simple π-complex mechanism is effected, the migratory properties of the benzyl group are low. Alternatively the benzyl group may play a specific role in the rearrangement stage. Thus when both ortho-positions are substituted the aryl benzyl ether rearranges to give a meta-substituted benzyl phenol in preference to the para-isomer. 2,6-Dimethylphenyl benzyl ether was shown to give a benzyl phenolic fraction

which contained 3-benzyl-2,6-dimethylphenol (75%) and 4-benzyl-2,6-dimethylphenol (24%). An intramolecular mechanism is still preserved since the direct (intermolecular) benzylation of 2,6-dimethylphenol gave predominantly para-substitution. The ease with which meta-substitution occurred was further demonstrated by the high molar ratio of 3-benzyl-2,4,6-trimethylphenol to diphenylmethane obtained in the rearrangement of 2,4,6-trimethylphenyl benzyl ether. Thus a simple π -complex is probably not involved.

Dewar has expressed the view that the intermediate π -complex may be a "sandwich" type structure (161) analogous to the postulated intermediate (162) which has successfully rationalised the product distributions obtained in the rearrangements of hydrazobenzene to benzidines, diphenylines, and semidines under acid conditions.[62]



(161)

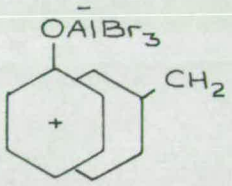


(162)

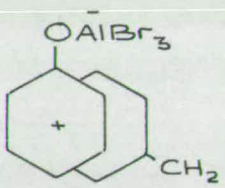
The intermediate (161) can be formally expressed to comprise the conjugate acid of the phenoxide ion and the benzyl carbonium ion, the positive charge on the latter being considered to become delocalised throughout the π system. In consequence these should be able to form a stable "sandwich" π -complex where the dative bond is formed by electron donation from the highest bonding molecular orbital of the phenol to the corresponding vacant molecular orbital of the benzyl group.

Molecular orbital calculations on the rotational isomers of (162) have shown that the rotational energy barriers are small. By analogy the

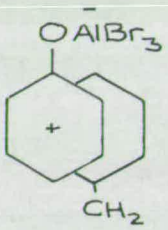
π -complex (161) may be expected to exhibit a similar effect giving rise to the rotational isomers (163), (164), (165) without substantially weakening the dative bond.



(163)



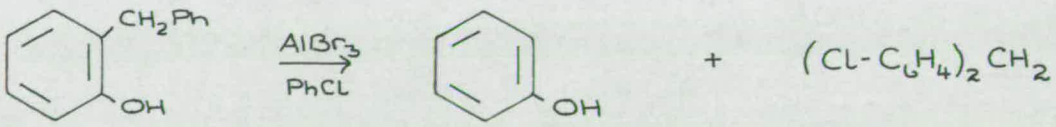
(164)



(165)

This mechanism would appear to rationalise the observed order of substitution (i.e. ortho > meta > para) although with the limited evidence available these results are claimed only to be an indication of the complex factors involved and not conclusive evidence for the formation of a "sandwich" type π -complex.

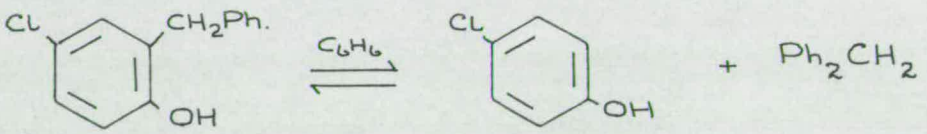
In a kinetic study of the $AlBr_3$-catalysed intramolecular rearrangement of phenyl benzyl ether[34] in chlorobenzene it was shown that the initial reaction was extremely rapid and was followed by a slow unimolecular conversion of the rearrangement product, 2-benzylphenol to a mixture of the parent phenol and the di-(chlorophenyl)methanes.



The molar ratio of diarylmethane to 2-benzylphenol therefore varies with the reaction time under these conditions; since the postulation of a benzyl

ether intermediate in the decarbonylation of aryloxyacetyl chlorides is dependent in part on this ratio, the significance of the secondary decomposition of the ortho-benzylphenol with $AlCl_3$ in benzene at 5-10°C. was assessed.

The reaction of 4-chlorophenyl benzyl ether (1 mole) with $AlCl_3$ (1 mole) in benzene (~ 20 moles) at 5-10°C. was studied. At reaction times between 15 minutes and 3 hours a sample of the reaction mixture was taken and the molar ratio of diphenylmethane to 4-chloro-2-benzylphenol determined, using the normal isolation procedure. A similar reaction was carried out in the presence of ~ 100 molar equivalents of benzene. In both cases the product ratio was constant over the reaction times stated. To finally eliminate the possibility that the observed molar ratios were not a consequence of the equilibrium (A), a solution of equimolar amounts of 4-chloro-2-benzylphenol and $AlCl_3$ in benzene was stirred at 5-10°C. over 3 hours. The absence of diphenylmethane in the neutral fraction showed the equilibrium (A) to be insignificant.



(A)

There is little doubt that the correlation of the molar ratio obtained from the acid chloride decarbonylation reaction and the corresponding benzyl ether rearrangement is due to the absence of secondary reaction involving the benzylphenol. It is possible that the use of $AlCl_3$ is responsible since it is a weaker Lewis acid than $AlBr_3$ and therefore less capable of promoting the acid-catalysed decomposition of the 2-benzylphenol.

EXPERIMENTAL PROCEDURE AND RESULTS

1. Melting points were taken on a Gallenkamp melting point apparatus (M.F.-370) and are uncorrected.

2. Microanalyses were by Weiler and Strauss of Oxford, and by Dr. Minnis of A. H. Baird Ltd., Edinburgh.

3. N.M.R. spectra were recorded by Mr. B. Semple, B.Sc., and Miss M. Methven using a Perkin-Elmer R.10 (60 Mc/s) nuclear magnetic resonance spectrometer using tetramethylsilane as an internal standard.

4. Infrared spectra were taken on a Unicam S.P. 200 Spectrophotometer.

5. Solutions were dried over anhydrous magnesium sulphate.

6. Boiling points are uncorrected.

1. Preparation of Phenols

(a) 3-methyl-6-nitrophenol and 3-methyl-4-nitrophenol[67]

The nitration of m-cresol with concentrated nitric acid (S.G. 1.5) in glacial acetic acid at -15°C. for 1½ hours gave a mixture of nitro-m-cresols which were precipitated on addition of water. Steam distillation gave 3-methyl-6-nitrophenol only.

m.pt. 56°C. (Et_2O); yield 25% theoretical.

The I.R. spectrum showed ν OH 3300cm.$^{-1}$ and ν NO_2 1540cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave singlets at -0.5 τ(OH) and 7.6 τ (3-CH_3). Also J_{45} = 9.0 c/s; J_{24} = 2.0 c/s.

The steam non-volatile component, after recrystallisation from ethanol gave only 3-methyl-4-nitrophenol.

m.pt. 128°C. (EtOH); yield 31% theoretical.

The I.R. spectrum gave ν OH 3320cm.$^{-1}$ and ν NO_2 1530cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave singlets at -0.3 τ (OH) and 7.45 τ (3-CH_3). Also J_{56} = 9.5 c/s.

(b) 3-methyl-2-nitrophenol[68]

The 4,6-disulphonation of m-cresol with 15% oleum at 50°C. gave a dark reaction mixture. This was treated with concentrated nitric acid (S.G. 1.5) in 15% oleum at 50-60°C. Subsequent dilution and steam distillation (at 160-180°C.) gave 3-methyl-2-nitrophenol which was purified by fractional distillation.

m.pt. 39°C.; yield 52% theoretical.

b.pt. 128-130°/20 mm.

The I.R. spectrum gave ν OH 3300cm.$^{-1}$ and ν NO_2 1540cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave singlets at -0.2 τ (OH) and 7.45 τ (3-CH_3). Also $J_{45} \simeq J_{56} \simeq 8$ c/s.

(c) 2-Cyanophenol (Salicylnitrile)[69.70.71]

Dehydration of salicylamide with P_2O_5[69] gave poor yields (15%) of 2-cyanophenol.

The dehydration of salicylaldoxime on treatment with (1) acetic anhydride and (2) sodium ethoxide gave a high conversion to 2-cyanophenol.[70.71]

m.pt. 97°C. (C_6H_6); yield 83% theoretical.

The I.R. spectrum gave ν OH 3300cm.$^{-1}$ and ν CN 2250cm.$^{-1}$.

(d) 2-(p-Toluenesulphonyl)phenol

Phenol (40gm., 0.43 moles) and p-toluenesulphonyl chloride (90gm., 0.46 moles) were dissolved in 250ml. 10% sodium hydroxide solution and 400ml. acetone added. After stirring for one hour, water was added and the precipitate filtered. Recrystallisation of the solid from ethanol gave a pure sample of phenyl p-toluenesulphonate.

m.pt. 95°C. (EtOH); yield 105gm. (98% theoretical).

Phenyl p-toluenesulphonate (100gm., 0.35 moles) was treated with anhydrous aluminium chloride (75gm., 0.56 moles) at 110°C.-130°C. for 15 minutes and cooled. The reaction mixture was decomposed with iced dil. hydrochloric acid, the product extracted with $CHCl_3$, and the organic phase washed with 2N. sodium hydroxide. Acidification of the sodium hydroxide extract gave an insoluble oil which was extracted with $CHCl_3$ and which, after removal of the solvent, gave a yellow oil. Addition of benzene and precipitation with petroleum (40/60) gave a solid product, which on recrystallisation from methanol gave pure 2-(p-toluenesulphonyl)phenol.

m.pt. 126°C. (MeOH); yield 26gm. (26% theoretical).

The I.R. spectrum gave ν OH 3300cm.$^{-1}$ and the N.M.R. spectrum gave, in $CDCl_3$, a singlet at 7.5 τ (4'-CH_3).

(e) 2-Nitro-1-Naphthol and 4-Nitro-1-Napthol[72]

The nitration of Acet-1-naphthalide with mixed acid at 15°C. and hydrolysis of the nitro acet-1-naphthalides by refluxing with 5% sodium hydroxide gave an isomeric mixture of nitro 1-naphthols. Steam distillation of the crude product gave 2-nitro-1-naphthol, purified by recrystallisation from ethanol.

m.pt. 128°C. (EtOH); yield 25% theoretical.

The N.M.R. spectrum (in $CDCl_3$) showed a singlet at -2.3 τ (OH) and J_{34} = 9.5 c/s. Inter-ring coupling was observed, with J_{48} = 0.5 c/s.

The steam non-volatile product was a dark yellow solid from which 4-nitro-1-naphthol was obtained by extraction with hot water, and was purified by recrystallisation from water or dilute ethanol.

m.pt. 164°C. (H_2O); yield 32% theoretical.

The N.M.R. spectrum (in $CDCl_3$/dimethylsulphoxide) gave J_{23} = 8.5 c/s and no inter-ring coupling was observed.

(f) 4,6-Dibromo-2-phenylphenol[73]

Dibromination of 2-phenylphenol with bromine in $CHCl_3$ solution at room temperature gave a single product, 4,6-dibromo-2-phenylphenol, in a high state of purity.

m.pt. 62°C. (Lit. 57°C.) (petroleum 40/60); yield 87% theoretical.

The N.M.R. spectrum (in CCl_4) gave a singlet at 4.6 τ (OH) and J_{35} = 2.5 c/s.

(g) 6-Phenylsalicylic acid

Kolbe-Schmidt carbonation of 2-phenylphenol (sodium salt) with CO_2 at 175-200°C. and 70 atm. for 6 hours gave a single acidic product, 2-phenylphenol 4,6-dicarboxylic acid.

m.pt. 296°C. (aq. EtOH); yield 16% theoretical.

The I.R. spectrum showed ν OH 3400cm.$^{-1}$ and ν CO 1680cm.$^{-1}$ and the N.M.R. spectrum (in dry dimethylsulphoxide (D.M.S.O.)) gave a singlet at -1.6τ (OH) equivalent to two protons. The phenyl group was a broad unresolved multiplet at 2.3τ, also J_{35} = 2 c/s.

Microanalysis $C_{14}H_{10}O_5$ requires: C, 65.1%; H, 3.9%

found: C, 64.9%; H, 4.1%.

Using the Marasse method outlined by Vorozcov,[74] 6-phenylsalicylic acid was the sole acidic product obtained by heating 2-phenylphenol, potassium carbonate and CO_2 at 180°C. and 40 atm. for 5 hours.

m.pt. 187°C. (EtOH); yield 82% theoretical.

The I.R. spectrum gave ν OH 3100cm.$^{-1}$ and ν CO 1680cm.$^{-1}$ and the N.M.R. spectrum gave (in $CDCl_3$/D.M.S.O.) a singlet at -0.1τ (OH); also $J_{45} = J_{34}$ = 7.4 c/s and J_{35} = 1.8 c/s.

(h) 4-Iodophenol[75]

Diazotisation of p-aminophenol in dil. sulphuric acid and warming the resulting solution with potassium iodide in the presence of copper bronze gave 4-iodophenol as a red solid. Purification was achieved by decolorising a benzene solution of the product with charcoal and recrystallisation from petroleum (40/60).

m.pt. 94°C. (petroleum 40/60); yield 71% theoretical.

The I.R. spectrum gave ν OH 3300cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave a singlet at 4.0τ (OH) and J_{23} = 9 c/s.

(i) 4-Bromophenol[76]

Monobromination of phenol with bromine in CS_2 at 0-5°C. for 2 hours gave on removal of the solvent, a crude bromination product, from which pure 4-bromophenol was obtained by fractional distillation and subsequent

recrystallisation from petroleum (40/60).

m.pt. 64°C. (petroleum)

b.pt. 136-8°C./25mm.; yield 78% theoretical.

The I.R. spectrum gave ν OH 3300cm.$^{-1}$ and the N.M.R. spectrum gave (in CCl_4) a singlet at 4.0 τ (OH) and J_{23} = 9 c/s.

(j) All other phenols cited in the text are commercial samples, their purity checked by melting point determination and by N.M.R. spectroscopy. Further purification was unnecessary.

2. Preparation of 2-Aryloxyacetic acids

(a) From the phenol and sodium chloroacetate

The general method used was as follows:

By refluxing an aqueous solution of a phenol, chloroacetic acid and sodium hydroxide pellets (molar ratio 1:1:2) for 4-6 hours and acidifying the cold solution a solid product was obtained. Extraction with $CHCl_3$ and washing the extract with sodium bicarbonate solution gave, on acidification of the aqueous phase, the 2-aryloxyacetic acid in a high state of purity. A single recrystallisation usually yielded the pure acid.

The following acids were prepared by the above method.

TABLE I

Physical Constants of 2-Aryloxyacetic Acids

Acid (77) R =	M.Pt. °C.	Solvent	Yield %
H	98,	H_2O	71
2,4,6-Me_3	153,	C_6H_6	66
2,6-Me_2	134,	EtOH	79
2,4-Me_2	142,	C_6H_6	76
4-Me	138,	EtOH	76
2-Me	158,	EtOH	83
2-Ph	100,	C_6H_6	77
4-F	104,	H_2O	88
2-F	139,	H_2O	85

Table I continued overleaf.

Table I continued:

Acid (77) R =	M.Pt. °C.	Solvent	Yield %
4-Cl	154,	H_2O	72
2-Cl	146,	H_2O	83
4-Br	158,	EtOH	84
4-I	160,	EtOH	83
2-I	136,	EtOH	84
3,4-Cl_2	140,	C_6H_6	81
4,6-Br_2-2-Ph (a)	134,	C_6H_6	50
2-Ts (b)	172,	C_6H_6	63
4-CHO	196,	EtOH	53
2-CHO	131,	EtOH	56
4-CN	176,	EtOH	65
2-CN	182,	EtOH	62
4-NO_2 (e)	186,	EtOH	50
3-NO_2 (e)	154,	H_2O	50
2-NO_2 (e)	157,	H_2O	40
3-Me-6-NO_2 (c),(e)	151,	H_2O	37
3-Me-2-NO_2 (d),(e)	195,	EtOH	76
1-Naphthoxy	193,	EtOH	61
2-Naphthoxy	156,	H_2O	64

NOTES

(a) $C_{12}H_8Br_2O$ requires: C, 43.6; H, 3.0; Br, 41.5%

found: C, 43.9; H, 3.5; Br, 41.6%

(b) $C_{15}H_{14}SO_5$ requires: C, 59.2; H, 4.2; S, 10.2%

found: C, 59.3; H, 4.5; S, 10.5%

(c) $C_9H_9NO_5$ requires: C, 51.2; H, 4.0; N, 6.6%

found: C, 50.9; H, 3.8; N, 6.7%

(d) $C_9H_9NO_5$ found: C, 51.2; H, 4.0; N, 6.4%

(e) Excess sodium chloroacetate required.

(b) 4-Phenylphenoxyacetic acid

4-Phenylphenol did not react with sodium chloroacetate using the above method,[46] the sodium salt being largely insoluble in the aqueous phase.

4-Phenylphenol (17gm., 0.1 moles) was dissolved in ethanolic sodium ethoxide (from 2.1gm. sodium (0.1 moles) in 150ml. ethanol). Ethyl bromoacetate (17gm., 0.11 moles) was added and the homogeneous solution refluxed for 4½ hours. On cooling ethyl 4-phenylphenoxyacetate precipitated as a colourless solid and was characterised spectroscopically without purification.

Yield 8gm. (33% theoretical).

The I.R. spectrum gave ν CO 1755cm.$^{-1}$.

The ester (8gm., 0.03 moles) was refluxed with 100ml. 10% sodium hydroxide containing 30ml. ethanol for 3 hours. The insoluble solid formed on cooling was collected, washed several times with water and refluxed with 50% hydrochloric acid for 2 hours. The solid product was filtered from the cold solution, washed with water and dried at 60°C. Recrystallisation from ethanol gave pure 4-phenylphenoxyacetic acid.

m.pt. 188°C. (EtOH); yield 7gm. (96% theoretical).

The I.R. spectrum gave ν CO 1700cm.$^{-1}$ and ν OH 3400cm.$^{-1}$ and the N.M.R. spectrum showed (in $CDCl_3$/D.M.S.O.) a singlet at 5.35τ (CH_2) and J_{23} = 9 c/s.

(c) 4-(p-Toluenesulphonyl)phenoxy acetic acid

Phenoxyacetic acid (52gm.) was refluxed with an excess of thionyl chloride until the solution was homogeneous. After removing excess thionyl chloride by vacuum distillation, the residual oil was treated with 100ml. dry methanol at 50°C. for 30 minutes, finally removing excess methanol by distillation. The residual oil was extracted with ether and washed with dilute sodium hydroxide solution. The ether extract was fractionated to give methyl phenoxyacetate as a colourless oil.

b.pt. 140-142°C./25mm.; yield 47gm., 83% theoretical.

The I.R. spectrum gave ν CO 1760cm.$^{-1}$ and the N.M.R. spectrum (CCl_4) showed singlets at 5.5τ (CH_2) and 6.3τ (CH_3O).

Methyl phenoxyacetate (42gm., 0.25 moles) was dissolved in 100ml. dry dichloroethane and added dropwise to a mixture of p-toluenesulphonyl chloride (49gm., 0.25 moles) and aluminium chloride (67gm., 0.5 moles) in 200ml. dichloroethane. The reaction mixture was stirred for 6 hours at 65-70°C., cooled, and decomposed with iced dilute hydrochloric acid. The products were extracted into ether and washed with 2N. sodium hydroxide solution. After removal of the solvent the residue rapidly solidified and recrystallisation from methanol gave a pure sample of methyl 4-(p-toluenesulphonyl)-phenoxyacetate.

m.pt. 151°C. (MeOH); yield 65gm., 81% theoretical.

The I.R. spectrum gave ν CO 1760cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave singlets at 5.3τ (CH_2), 6.2τ (CH_3O), 7.6τ (4'-CH_3); also J_{23} = 9 c/s and $J_{2'3'}$ = 8 c/s.

$C_{16}H_{16}SO_5$ requires: C, 60.0; H, 4.7; S, 10.0%

found: C, 60.1; H, 4.8; S, 10.2%.

Methyl 4-(p-toluenesulphonyl)phenoxyacetate (28gm.) was hydrolysed by refluxing for 2 hours in 250ml. 10% sodium hydroxide solution containing 100ml. methanol. After removing the methanol by distillation the solution was acidified and the precipitated solid was extracted with $CHCl_3$. Sodium bicarbonate extraction of the organic layer gave on acidification 4-(p-toluenesulphonyl)phenoxyacetic acid, purified by recrystallisation from methanol.

m.pt. 222°C. (MeOH); yield 25gm., 95% theoretical.

The I.R. spectrum gave ν CO 1715cm.$^{-1}$ and ν OH 3450cm.$^{-1}$ and the N.M.R. spectrum (in D.M.S.O.) gave singlets at 5.1 τ (CH_2) and 7.7 τ (4'CH_3). Also J_{23} = 9 c/s and $J_{2'3'}$ = 9 c/s.

$C_{15}H_{14}SO_5$ requires: C, 59.2; H, 4.2; S, 10.2%

found: C, 58.9; H, 4.3; S, 10.1%

(d) <u>2,4-Dinitrophenoxyacetic acid and 4-Chloro-2,6-dinitrophenoxyacetic acid</u>

Phenoxyacetic acid (20gm.) was added over 45 minutes to 68ml. nitric acid (S.G. 1.5) at 0°C. After stirring at room temperature for 45 minutes the homogeneous solution was poured into iced water and the yellow precipitate collected. Recrystallisation from ethanol gave 2,4-dinitrophenoxyacetic acid as a colourless solid.

m.pt. 148°C. (EtOH); yield 28gm., 88% theoretical.

The I.R. spectrum gave ν CO 1710cm.$^{-1}$, ν OH 3400cm.$^{-1}$ and ν NO_2 1535cm.$^{-1}$ and the N.M.R. spectrum showed (in D.M.S.O.) a singlet at 4.9 τ(CH_2); also J_{56} = 9 c/s and J_{35} = 2 c/s.

4-Chlorophenoxyacetic acid was nitrated in an identical manner and gave

4-chloro-2,6-dinitrophenoxyacetic acid.

m.pt. 146°C. ($CHCl_3$); yield 65% theoretical.

The I.R. spectrum gave ν CO 1700cm.$^{-1}$, ν OH 3350cm.$^{-1}$ and ν NO_2 1540cm.$^{-1}$ and the N.M.R. spectrum showed (in D.M.S.O.) a singlet at 5.3τ (CH_2) and an aromatic singlet at 1.5τ.

$C_8H_5ClN_2O_7$ requires: C, 34.7; H, 1.8; Cl, 13.0; N, 10.1%

found: C, 34.8; H, 1.7; Cl, 12.6; N, 10.3%.

(e) <u>1-Nitro-2-naphthoxyacetic acid and 4-nitro-1-naphthoxyacetic acid</u>

2-Naphthoxyacetic acid was nitrated with nitric acid (S.G. 1.5) in glacial acetic acid at 7-12°C. for 3 hours. The solution was poured into iced water and the precipitate, 1-nitro-2-naphthoxyacetic acid, was purified by recrystallisation from acetic acid.

m.pt. 190°C.; yield 66% theoretical.

The I.R. spectrum gave ν CO 1730cm.$^{-1}$, ν OH 3300cm.$^{-1}$ and ν NO_2 1530cm.$^{-1}$.

The N.M.R. spectrum showed (in D.M.S.O.) a singlet at 5.2τ (CH_2); J_{34} = 8 c/s.

4-Nitro-1-naphthol did not react with sodium chloroacetate under the above conditions.[46]

The nitration of 1-naphthoxyacetic acid under the conditions described for 2-naphthoxyacetic acid[77] gave only 4-nitro-1-naphthoxyacetic acid.

m.pt. 213°C. (50% AcOH); yield 82% theoretical.

The I.R. spectrum showed ν CO 1770cm.$^{-1}$, ν OH 3200cm.$^{-1}$ and ν NO_2 1520cm.$^{-1}$.

The N.M.R. spectrum gave (in D.M.S.O.) a singlet at 4.9τ (CH_2) and J_{23} = 8.8 c/s.

$C_{12}H_9NO_5$ requires: C, 57.6; H, 4.0; N, 6.0%

found: C, 58.0; H, 3.7; N, 5.7%.

3. Preparation of 2-Aryloxypropionic acids and 2-Aryloxyisobutyric acids

(a) 2-(4-Chlorophenoxy)propionic acid and 2-(2-Chlorophenoxy)propionic acid

Using the general method described above[46] but with 2-chloropropionic acid substituted for chloroacetic acid, 4-chlorophenol gave 2-(4-chlorophenoxy)propionic acid.

m.pt. 116°C. (C_6H_6); yield 41% theoretical.

The I.R. spectrum gave ν CO 1695cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave a quartet at 5.2τ (J = 7 c/s) (CH), a doublet at 8.35τ (J = 7 c/s) (CH_3) and a singlet at -1.0τ (OH). The aromatic protons showed a first-order p-disubstitution pattern with J_{23} = 9 c/s.

Using the same method 2-chlorophenol gave 2-(2-chlorophenoxy)propionic acid.

m.pt. 114°C. (C_6H_6); yield 48% theoretical.

The I.R. spectrum gave ν CO 1700cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave a quartet at 5.2τ (J = 7 c/s) (CH), a doublet at 8.3τ (J = 7 c/s) (CH_3) and a singlet at -1.2τ (OH).

(b) 2-(4-Chlorophenoxy)isobutyric acid[49]

4-chlorophenol and sodium hydroxide pellets (molar ratio 1:2) were dissolved in excess acetone, $CHCl_3$ added, and the heterogeneous mixture refluxed for 6 hours. The solvent was removed by distillation, the residue treated with dilute hydrochloric acid and the aqueous acidic solution extracted with $CHCl_3$. The organic layer was washed with saturated sodium bicarbonate solution, the aqueous phase acidified, and extracted with $CHCl_3$. This extract gave 2-(4-chlorophenoxy)isobutyric acid, purified by recrystallisation from benzene.

m.pt. 121°C. (C_6H_6); yield 17%

The I.R. spectrum gave ν CO 1695cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave singlets at -2.1τ (OH) and 8.4τ (CMe_2); also J_{23} = 8 c/s.

(c) 2-(2,4-Dinitrophenoxy)isobutyric acid

2-Phenoxyisobutyric acid was prepared from phenol, $CHCl_3$ and acetone as described above.[49]

m.pt. 99°C. (H_2O); yield 31% theoretical.

The I.R. spectrum gave ν CO 1690cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave singlets at 0.5τ (OH) and 8.4τ (CMe_2).

2-Phenoxyisobutyric acid was added to nitric acid (S.G. 1.5) at 0°C. and the homogeneous solution stirred for 1 hour. On pouring into iced water, collecting the precipitate and recrystallising from ethanol, 2-(2,4-dinitrophenoxy)isobutyric acid was obtained in 62% yield; m.pt. 136-7°C. (EtOH).

The I.R. spectrum gave ν CO 1730cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave singlets at 1.2τ (OH) and 8.2τ (CMe_2). Also J_{56} = 8 c/s and J_{35} = 3 c/s, the aromatic protons exhibiting a 1,2,4-trisubstitution pattern.

4. Preparation of 2-Arylthioacetic acids

(a) Phenylthioacetic acid and 2-Chlorophenylthioacetic acid[50]

Aniline was diazotised in hydrochloric acid solution with sodium nitrite at -5°C. and the solution added to an alkaline solution of potassium xanthate at 60°C. Extraction with ether gave the crude xanthate ester which was hydrolysed with 50% sodium hydroxide solution by refluxing for 3 hours. Sodium chloroacetate was added and the reaction mixture refluxed for a further 1½ hours to give phenylthioacetic acid.

m.pt. 62°C. (EtOH); yield 64% theoretical.

The I.R. spectrum gave ν CO 1700cm.$^{-1}$ and the N.M.R. spectrum gave (in acetone) a singlet at 6.3τ (CH_2).

In an identical manner 2-chloroaniline gave 2-chlorophenylthioacetic acid.

m.pt. 118°C. (H_2O); yield 60% theoretical.

The I.R. spectrum gave ν CO 1710cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$/D.M.S.O.) gave a singlet at 6.4τ (CH_2).

(b) 2-Nitrophenylthioacetic acid, 4-Nitrophenylthioacetic acid, and 2,4-Dinitrophenylthioacetic acid[51]

2-Chloronitrobenzene was treated with thioglycollic acid (di-sodium salt) by refluxing in aqueous ethanol. On removal of the solvent and addition of water the alkaline soluble component gave 2-nitrophenylthioacetic acid.

m.pt. 162°C. (H_2O); yield 40% theoretical.

The I.R. spectrum gave ν CO 1695cm.$^{-1}$ and the N.M.R. spectrum showed (in $CDCl_3$/D.M.S.O.) a singlet at 5.9τ (CH_2) and J_{34} = 8 c/s.

By the same method 4-chloronitrobenzene gave 4-nitrophenylthioacetic acid.

m.pt. 156°C. (H_2O); yield 35% theoretical.

The I.R. spectrum gave ν CO 1695cm.$^{-1}$ and the N.M.R. spectrum showed (in $CDCl_3$/D.M.S.O.) a singlet at 6.2τ (CH_2) and J_{23} = 8 c/s.

2,4-Dinitrophenylthioacetic acid was similarly prepared from 2,4-dinitrochlorobenzene in ethanolic sodium acetate solution.

m.pt. 168°C. (EtOH); yield 88% theoretical.

The I.R. spectrum gave ν CO 1710cm.$^{-1}$ and the N.M.R. spectrum gave (in $CDCl_3$/D.M.S.O.) a singlet at 6.05τ (CH_2); J_{56} = 9.0 c/s and J_{35} = 2.5 c/s.

5. The Reactions of 2-Aryloxyacetyl chlorides with $AlCl_3$ in non aromatic solvents

Preparation of Aryloxymethyl Chlorides

(a) 4-Nitrophenoxymethyl chloride

4-Nitrophenoxyacetic acid (15gm., .076 moles) was refluxed with excess thionyl chloride until a homogeneous solution was obtained and the excess thionyl chloride was removed by vacuum distillation. The I.R. spectrum of the residual oil showed complete conversion to the acid chloride had occurred (ν CO 1800cm.$^{-1}$). The acid chloride (used without purification) was added to 150ml. CS_2 (dried over P_2O_5) and 11gm. (.082 moles) $AlCl_3$ added. After refluxing for 4 hours (during which a dark insoluble complex was formed) and cooling, the reaction mixture was poured into iced dilute hydrochloric acid and stirred vigorously for 1 hour. $CHCl_3$ was added and the organic layer was washed with water, saturated sodium bicarbonate solution, 2N. sodium hydroxide solution, and dried.

Acidification of the sodium bicarbonate solution gave 3.0gm. (30%) recovered 4-nitrophenoxyacetic acid. No phenolic products were obtained on acidification of the sodium hydroxide solution. The organic layer gave 9.0gm. of a red oil which, on distillation gave 4-nitrophenoxymethyl chloride as the sole reaction product.

b.pt. 170-175°C./15mm.; yield 8.6gm., 61% theoretical.

The I.R. spectrum showed no carbonyl or hydroxyl absorption and gave ν NO_2 = 1520cm.$^{-1}$ and ν C-O 1060,1200cm.$^{-1}$.

The N.M.R. spectrum gave (in $CDCl_3$) a singlet at 4.0τ (CH_2) and J_{23} = 9 c/s.

4-Nitrophenoxymethyl chloride on refluxing with a solution of sodium p-nitrobenzoate in methanol gave (4-nitrophenoxymethyl)p-nitrobenzoate.

m.pt. 126°C. (EtOH). The I.R. spectrum gave ν CO = 1730cm.$^{-1}$.

(b) 2-Nitrophenoxymethyl chloride

2-Nitrophenoxyacetic acid (15gm., .076 moles) gave 2-nitrophenoxyacetyl chloride on treatment with thionyl chloride. The excess thionyl chloride was removed by vacuum distillation and the I.R. spectrum of the residual oil showed complete conversion to the acid chloride.

The acid chloride was dissolved in 150ml. CS_2 and $AlCl_3$ (11.0gm., .082 moles) added. After refluxing for 4 hours, cooling, and decomposing, the reaction mixture with iced dilute hydrochloric acid, the products were extracted into $CHCl_3$ and the organic layer washed with water, saturated sodium bicarbonate solution and 2N. sodium hydroxide.

The sodium bicarbonate solution, on acidification, gave 2.0gm. (13%) of recovered 2-nitrophenoxyacetic acid and the sodium hydroxide solution contained no phenolic products.

The organic layer gave a red oil from which a single fraction was obtained, shown to be 2-nitrophenoxymethyl chloride.

b.pt. 156-8°C./15mm.; yield 10.5gm., 73% theoretical.

The I.R. spectrum showed no carbonyl or hydroxyl absorption and gave ν NO_2 1540cm.$^{-1}$.

The N.M.R. spectrum (in CCl_4) gave a singlet at 4.05τ (CH_2) and the aromatic region showed J_{34} = 8 c/s, J_{45} = 7 c/s, J_{46} = J_{35} = 2 c/s.

2-Nitrophenoxymethyl chloride, on refluxing with a solution of sodium p-nitrobenzoate in methanol gave (2-nitrophenoxymethyl) p-nitrobenzoate.

m.pt. 125°C. (EtOH). The I.R. spectrum gave ν CO 1730cm.$^{-1}$.

(c) Preparation of 4-nitrophenoxymethyl chloride
Determination of optimum reaction conditions

The general method given in Part 5(a) was carried out and the molal concentration in all gases was 0.01 moles acid chloride/20ml. solvent.

The reaction mixture was decomposed with 50ml. dilute (2N.) hydrochloric acid by stirring for 1 hour at room temperature, the aqueous phase was extracted three times with 50ml. aliquots of $CHCl_3$, washed with 50ml. water, and dried. The residual crude product obtained on removal of the solvent was weighed accurately and quantitatively analysed as follows.

A weighed sample was dissolved in $CDCl_3$ or $CDCl_3$/D.M.S.O. and a known weight of 1,2-dibromoethane added as internal standard. From the integrated N.M.R. spectrum the molar proportions of 4-nitrophenoxymethyl chloride and 4-nitrophenoxyacetic acid (τCH_2 = 4.0 and 5.2 respectively) were determined relative to 1,2-dibromoethane (τCH_2 = 6.4) and from this the absolute yields calculated.

The results obtained are given in Table II.

TABLE II

Preparation of 4-Nitrophenoxymethyl Chloride (1)

Lewis Acid (moles)	Solvent	Reaction Temp., °C.	Reaction Time, Hrs.	4-Nitrophenoxy-Methyl Chloride %	4-Nitrophenoxy-Acetic Acid %
$AlCl_3$ (0.005)	CS_2	46	3	37	46
$AlCl_3$ (0.005)	CS_2	46	16	42	31
$AlCl_3$ (0.01)	CS_2	46	1	31	68
$AlCl_3$ (0.01)	CS_2	46	2	56	35
$AlCl_3$ (0.01)	CS_2	46	3	68	22
$AlCl_3$ (0.01)	CS_2	46	6	62	19
$AlCl_3$ (0.02)	CS_2	46	3	- (2)	-
$AlCl_3$ (0.01)	$MeNO_2$	0	3	0	98
$AlCl_3$ (0.01)	$MeNO_2$	25	3	35	65
$AlCl_3$ (0.01)	$MeNO_2$	25	16	40	38
$AlCl_3$ (0.005)	$MeNO_2$	25	16	41	53
$AlCl_3$ (0.01)	$MeNO_2$	50	3	- (3)	-
$AlCl_3$ (0.01)	CS_2/CH_2Cl_2	45	3	47	53
$AlCl_3$ (0.01)	CH_2Cl_2	40	3	0	96
$AlCl_3$ (0.01)	$(CH_2)_2Cl_2$	50	3	43	39
$AlCl_3$ (0.01)	C_6F_6	50	3	41	15
$SnCl_4$ (0.01)	CS_2	46	3	0	97
$SnCl_4$ (0.01)	$MeNO_2$	50	3	0	93
$SnCl_4$ (0.01)	$MeNO_2$	82	3	- (4)	-

NOTES

(1) From 0.01 moles acid chloride.

(2) No quantitative N.M.R. data since impurity peaks at ~ 4T . Preparative experiment gave 32% isolated.

(3) No quantitative N.M.R. data. Preparative experiment gave 23% isolated.

(4) Extensive side product formation.

(d) Determination of Carbon Monoxide in the reaction of 4-Nitrophenoxyacetyl Chloride with $AlCl_3$ in CS_2 at 46°C.

4-Nitrophenoxyacetyl chloride (1.90gm., 0.009 moles) was dissolved in 20ml. CS_2 and $AlCl_3$ (1.03gm., 0.009 moles) added. The reaction mixture was refluxed for 2 hours, the evolved gases passed through saturated sodium hydroxide solution, water, and concentrated sulphuric acid, and collected in a 500ml. Hempel pipette, using concentrated sulphuric acid as displacing medium. Carbon monoxide was determined by absorption with cuprous sulphate/2-naphthol/sulphuric acid as reagent.

Volume of carbon monoxide evolved, at N.T.P. = 106ml.

= 59% theoretical.

The reaction mixture was worked up in the usual manner and 4-nitrophenoxymethyl chloride determined by quantitative N.M.R. spectroscopy, with 1,2-dibromoethane as internal standard.

Yield 4-Nitrophenoxymethyl chloride = 56% theoretical

Yield 4-Nitrophenoxyacetic acid recovered = 39% theoretical

(e) 3-Nitrophenoxymethyl chloride

On refluxing for 3 hours a mixture of 3-nitrophenoxyacetyl chloride (from 20gm., 0.11 moles, the acid), $AlCl_3$ (15gm., 0.11 moles) and CS_2 (200ml.), and using the normal purification procedure, the following extracts were obtained.

Sodium bicarbonate extraction gave, on acidification, 3-nitrophenoxyacetic acid (13.1gm., 66% theoretical).

2N. Sodium hydroxide extraction gave, on acidification, 3-nitrophenol (0.6gm., 4% theoretical).

The $CHCl_3$ extract gave 2.1gm. of a red viscous oil.

The I.R. spectrum showed a weak carbonyl absorption at 1740cm.$^{-1}$ and the N.M.R. spectrum showed a well defined singlet at 4.05τ ($CDCl_3$) in addition to several peaks in the 3.9-5.4τ region. Sodium fusion test indicated chlorine present.

However no 3-nitrophenoxymethyl chloride was obtained by vacuum distillation, the product decomposing on heating.

(f) 3-Methyl-6-nitrophenoxymethyl chloride

On refluxing a mixture of 3-methyl-6-nitrophenoxyacetyl chloride (from 15gm., 0.07 moles the acid), $AlCl_3$ (9.4gm., 0.07 moles) and CS_2 (150ml.) for 4 hours, and isolating the products in the normal manner, the following extracts were obtained.

Sodium bicarbonate extraction gave, on acidification, 3-methyl-6-nitrophenoxyacetic acid, 8.9gm. (61% theoretical).

The 2N. sodium hydroxide extract gave no phenolic products on acidification and the $CHCl_3$ extract gave a red solid, 3-methyl-6-nitrophenoxymethyl chloride, purified by recrystallisation.

m.pt. 59-60°C. (petroleum 60/80); yield 3.0gm., 20% theoretical.

The I.R. spectrum gave νNO_2 1530cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) showed singlets at 4.05τ (CH_2) and 7.55τ (CH_3). Also J_{45} = 8 c/s and J_{24} = 1.5 c/s.

$C_8H_8ClNO_3$ required: C, 48.0; H, 4.0; N, 7.0; Cl, 17.5%

found: C, 48.5; H, 3.8; N, 6.5; Cl, 16.8%

p-nitrobenzoate derivative m.pt. 117°C. (MeOH)

The I.R. spectrum gave ν CO 1730cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave singlets at 3.9τ (CH_2) and 7.55τ (CH_3).

$C_{15}H_{12}N_2O_7$ requires: C, 54.1; H, 3.6; N, 8.4%

found: C, 54.1; H, 3.6; N, 8.3%

(g) 3-Methyl-2-nitrophenoxymethyl chloride

A mixture of 3-methyl-2-nitrophenoxyacetyl chloride (from 20gm., 0.09 moles the acid), $AlCl_3$ (14gm., 0.09 moles) and CS_2 (200ml.) was refluxed for 4 hours and the following extracts obtained.

3-Methyl-2-nitrophenoxyacetic acid (11.4gm., 58% theoretical) was obtained from acidification of the sodium bicarbonate extract.

3-Methyl-2-nitrophenol was shown, by I.R. spectroscopy, to be the major component of a red fiscous oil (0.2gm.), obtained on acidification of the 2N. sodium hydroxide extract.

The residue from the $CHCl_3$ extract gave a single fraction on vacuum distillation, 3-methyl-2-nitrophenoxymethyl chloride.

b.pt. 162-3°C./15mm.; yield 5gm., 26% theoretical.

The I.R. spectrum gave ν NO_2 = 1540cm.$^{-1}$ and the N.M.R. spectrum gave (in CCl_4) singlets at 4.15τ (CH_2) and 7.7τ (CH_3).

$C_8H_8ClNO_3$ requires: C, 48.0; H, 4.0; Cl, 17.5; N, 7.0%

found: C, 45.4; H, 4.6; Cl, 16.8; N, 8.1%

p-nitrobenzoate derivative m.pt. 143°C. (MeOH).

The I.R. spectrum gave ν CO 1750cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave singlets at 3.95τ (CH_2) and 7.7τ (CH_3).

$C_{15}H_{12}N_2O_7$ requires: C, 54.1; H, 3.6; N, 8.4%

found: C, 54.0; H, 3.7; N, 9.0%

(h) 2,4-Dinitrophenoxymethyl chloride

A mixture of 2,4-dinitrophenoxyacetyl chloride (from 5.6gm., 0.023 moles the acid), $AlCl_3$ (3.3gm., 0.023 moles) and CS_2 (56ml.) was refluxed for 3 hours and the following extracts obtained in the normal manner.

The sodium bicarbonate extract gave 2,4-dinitrophenoxyacetic acid (0.6gm., 10% theoretical) and the 2N. sodium hydroxide extract gave no phenolic products.

The $CHCl_3$ extract gave 2,4-dinitrophenoxymethyl chloride, purified by recrystallisation from benzene.

m.pt. 46°C. (C_6H_6); yield 3.3gm., 63% theoretical.

The I.R. spectrum gave ν NO_2 = 1530cm.$^{-1}$ and the N.M.R. spectrum (in $CCl_4/CDCl_3$) gave a singlet at 3.95τ (CH_2); also J_{56} = 9.2 c/s and J_{35} = 2.6 c/s.

$C_7H_5ClN_2O_5$ requires: C, 36.1; H, 2.2; Cl, 15.4; N, 12.0%

found: C, 36.9; H, 2.8; Cl, 15.0; N, 12.3%

p-nitrobenzoate derivative m.pt. 130°C. (C_6H_6).

$C_{14}H_9N_3O_9$ requires: C, 46.3; H, 2.5; N, 11.6%

found: C, 46.4; H, 2.7; N, 11.3%

Notes

(1) The yields of 2,4-dinitrophenoxymethyl chloride obtained under the above conditions varied between 5%-78% and high conversion was only effected by ensuring that both $AlCl_3$ and acid chloride were in the form of a fine powder and by stirring the reaction mixture vigorously. By taking these precautions and by increasing the reaction time to 5 hours a maximum yield of 84% was obtained.

(2) The p-nitrobenzoate was formed in less than 10% yield and the main product was 2,4-dinitrophenol. A derivative was not formed on heating with thiourea.

(i) 4-Chloro-2,6-dinitrophenoxymethyl chloride

A mixture of 4-chloro-2,6-dinitrophenoxyacetyl chloride (from 27.7gm., 0.1 moles, the acid), $AlCl_3$ (13.4gm., 0.1 moles) and CS_2 (270ml.) were refluxed for 3 hours and the following extracts obtained.

The sodium bicarbonate extract gave 4-chloro-2,6-dinitrophenoxyacetic acid (7.0gm., 26% theoretical) and the 2N. sodium hydroxide extract gave no phenolic products.

The residue from the $CHCl_3$ extract gave 4-chloro-2,6-dinitrophenoxymethyl chloride, purified by recrystallisation.

m.pt. 58°C. (40/60 petroleum); yield 15.5gm., 58% theoretical.

The I.R. spectrum gave νNO_2 = 1540cm.$^{-1}$ and the N.M.R. spectrum gave (in $CDCl_3$) singlets at 1.9τ (aromatic 3-H and 5-H) and 4.10τ (CH_2).

$C_7H_4Cl_2N_2O_5$ requires: C, 31.5; H, 1.5; Cl, 26.9; N, 10.5%

found: C, 31.9; H, 1.8; Cl, 26.8; N, 10.6%.

Notes

(1) Yields varied 18-58% and maximum yield, using finely powdered reagents and by refluxing with vigorous stirring for 5 hours, was 64%.

(2) No p-nitrobenzoate derivative. Only 4-Chloro-2,6-dinitrophenol (m.pt. 80°C.) formed.

(j) 2- and 4-Cyano-phenoxymethyl chlorides

A mixture of 4-cyanophenoxyacetyl chloride (from 27.6gm., 0.15 moles, the acid), $AlCl_3$ (21.0gm., 0.15 moles) and CS_2 (276ml.) was refluxed for 5 hours and gave the following extracts.

4-Cyanophenoxyacetic acid (15.2gm., 56%) was obtained from the sodium bicarbonate extract and the 2N. sodium hydroxide extract gave 0.2gm. (1%) 4-cyanophenol as a red oil.

The $CHCl_3$ extract gave a red oil from which a single fraction was obtained on vacuum distillation, 4-cyanophenoxymethyl chloride.

b.pt. 164-8°C./24mm.; yield 5.0gm., 29% theoretical.

The I.R. spectrum gave ν CN = 2250cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave a singlet at 4.05τ (CH_2); also J_{23} = 8 c/s.

p-nitrobenzoate derivative m.pt. 114°C. (EtOH).

The I.R. spectrum gave ν CN = 2250cm.$^{-1}$, ν CO 1740cm.$^{-1}$ and ν NO_2 = 1540cm.$^{-1}$.

The N.M.R. spectrum (in $CDCl_3$) gave a singlet at 3.90τ (CH_2) and J_{23} = 9 c/s.

$C_{15}H_{10}N_2O_5$ requires: C, 60.4; H, 3.3; N, 9.4%

found: C, 60.9; H, 3.2; N, 9.9%

Under the same conditions 2-cyanophenoxyacetyl chloride (from 27.6gm., 0.15 moles, the acid) gave 14gm. (51%) 2-cyanophenoxyacetic acid, 0.1gm. 2-cyanophenol and the $CHCl_3$ extract gave a red oil, from which 2-cyanophenoxymethyl chloride was obtained by vacuum distillation.

b.pt. 150-4°C./10mm.; yield 5.6gm., 33% theoretical.

The I.R. spectrum gave ν CN = 2240cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave a singlet at 4.05τ (CH_2).

p-nitrobenzoate derivative m.pt. 119°C. (MeOH).

The I.R. spectrum gave ν CN = 2250cm.$^{-1}$, ν CO = 1730cm.$^{-1}$ and ν NO_2 = 1530cm.$^{-1}$.

The N.M.R. spectrum (in $CDCl_3$) gave a singlet at 3.95τ (CH_2).

$C_{15}H_{10}N_2O_5$ requires: C, 60.4; H, 3.3; N, 9.4%

found: C, 60.2; H, 3.3; N, 9.5%

(k) 2- and 4-(p-Toluenesulphonyl)-phenoxymethyl chlorides

A mixture of 4-(p-toluenesulphonyl)phenoxyacetyl chloride (from 13.6gm., 0.043 moles the acid), $AlCl_3$ (5.9gm., 0.043 moles) and CS_2 (136ml.) was refluxed for 5 hours and gave 4-(p-toluenesulphonyl)phenol (0.1gm) and a red oil from the $CHCl_3$ extract. Recrystallisation from benzene/petroleum gave 4-(p-toluenesulphonyl)phenoxymethyl chloride.

m.pt. 109°C. (C_6H_6/petroleum, 40/60); yield 4.9gm., 37% theoretical.

The N.M.R. spectrum (in $CDCl_3$) gave singlets at 4.15τ (CH_2) and 7.7τ (4'-CH_3); also J_{23} = 9 c/s and $J_{2'3'}$ = 8 c/s.

$C_{14}H_{13}ClO_3S$ requires: C, 56.5; H, 4.4; Cl, 12.1; S, 10.8%

found: C, 56.4; H, 4.6; Cl, 11.8; S, 10.6%

p-nitrobenzoate derivative m.pt. 148°C. (MeOH).

The I.R. spectrum gave ν CO = 1730cm.$^{-1}$ and ν NO_2 = 1540cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave singlets at 3.9τ (CH_2) and 7.6τ (4'-CH_3); also J_{23} = $J_{2'3'}$ = 9 c/s.

$C_{21}H_{17}NO_6S$ requires: C, 59.0; H, 4.0; N, 3.3; S, 7.5%

found: C, 59.2; H, 4.3; N, 3.6; S, 7.4%

Under identical conditions 2-(p-toluenesulphonyl)phenoxyacetyl chloride (from 13.6gm., 0.043 moles, the acid) gave 2-(p-toluenesulphonyl)phenoxyacetic acid (10.3gm., 76%), recovered by acidification of the sodium bicarbonate extract, and a red oil (0.3gm.) was obtained from the $CHCl_3$ extract.

The I.R. spectrum gave a weak carbonyl absorption, ν CO = 1750cm.$^{-1}$, and the N.M.R. spectrum (in $CDCl_3$) gave singlets at 4.25τ (CH_2), 5.4τ (CH_2), and 7.7τ (4'-CH_3), a quartet at 5.9τ (CH_2) and a triplet at 8.8τ (CH_3). The integrated spectrum was consistent with a mixture of 2-(p-toluenesulphonyl)phenoxymethyl chloride (60%) and ethyl 2-(p-toluenesulphonyl)-phenoxyacetate (40%). No pure chloromethyl ether was obtained by fractional recrystallisation and attempts to prepare a p-nitrobenzoate derivative failed.

(1) Table IIA gives a comparison of the yields of the aryloxymethyl chlorides (prepared in sections 5(a)-(k)) obtained under standard conditions. The optimum reaction conditions determined in section 5(c) were chosen; that is from equimolar quantities of the acid chloride and $AlCl_3$ in CS_2 at 46°C. over 3 hours.

N.M.R. spectral data for the aryloxymethyl chlorides are also given, τCH_2 denoting the chemical shift of the methylene group relative to T.M.S.

TABLE IIA

Aryloxy-acetyl chloride (1) R =	Aryloxy-methyl chloride (2) %	CH_2	Aryloxy-acetic acid (77) %
2-NO_2	70	4.05	18
3-NO_2	5	4.05	71
4-NO_2	68	4.00	22
3-Me-6-NO_2	25	4.05	61
3-Me-2-NO_2	22	4.15	59
2,4-$(NO_2)_2$	63	3.95	26
4-Cl-2,6-$(NO_2)_2$	58	4.10	29
4-CN	24	4.05	66
2-CN	27	4.05	61
4-p-Tosyl	29	4.15	62
2-p-Tosyl	3	4.25	82

NOTE:- The yields of aryloxymethyl chlorides formed and aryloxyacetic acids recovered are those determined by quantitative N.M.R. spectroscopy, using 1,2-dibromoethane as an internal standard.

(m) The Reactions of Halogeno-Aryloxyacetyl Chlorides with $AlCl_3$ in CS_2

2-Chlorophenoxyacetyl chloride

From 2-chlorophenoxyacetyl chloride (from 20gm., 0.11 moles the acid), $AlCl_3$ (14gm., 0.11 moles) and CS_2 (200ml.) at 46°C. for 4 hours the following extracts were obtained.

Sodium bicarbonate extraction gave 2-chlorophenoxyacetic acid (12gm., 60%) and the 1N. sodium hydroxide extract gave a red oil (0.7gm.) which was shown to be predominantly 2-chlorophenol by I.R. spectroscopy.

The $CHCl_3$ extract gave a clear red oil (0.4gm.), the N.M.R. spectrum showing no singlet at ~ 4τ. Steam distillation gave 7-chlorobenzofuran-3-one.

m.pt. 110°C. (petroleum 40/60); yield 0.1gm.

The I.R. spectrum gave ν CO = 1720cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave a singlet at 5.35τ (CH_2); also $J_{45} = J_{56} = 7.5$ c/s and $J_{46} = 1.5$ c/s.

Note

The reaction was repeated at 25°C. in nitromethane as solvent when the only product isolated was the recovered acid in 22% yield. No benzofuranone or aryloxymethyl chloride was detected spectroscopically in the black viscous oil obtained from the $CHCl_3$ extract.

4-Chlorophenoxyacetyl chloride

From 4-chlorophenoxyacetyl chloride (from 20gm., 0.11 moles the acid), $AlCl_3$ (14gm., 0.11 moles) and CS_2 (200ml.) at 46°C. for 4 hours, the following extracts were obtained.

4-Chlorophenoxyacetic acid (10.4gm., 52%) was obtained by sodium bicarbonate extraction and the 1N. sodium hydroxide extract gave 0.3gm. impure 4-chlorophenol.

The $CHCl_3$ extract gave a red glass-like solid (0.7gm.) whose N.M.R. spectrum showed no singlet at ~ 4τ. Steam distillation gave 5-chloro-benzofuran-3-one.

m.pt. 113°C. (petroleum 40/60); yield 60mg.

The I.R. spectrum gave ν CO = 1700cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave a singlet at 5.35τ; also J_{67} = 8 c/s and J_{46} = 2 c/s.

3,4-Dichlorophenoxyacetyl chloride

From 3,4-dichlorophenoxyacetyl chloride (from 8.4gm., 0.038 moles, the acid), $AlCl_3$ (0.045 moles, 6gm.) and CS_2 (85ml.) at 46°C. for 4 hours, the following extracts were obtained.

Sodium bicarbonate extraction gave 3,4-dichlorophenoxyacetic acid (5.8gm., 68%) and the 1N. sodium hydroxide extract gave a red viscous oil (0.15gm.) which contained 3,4-dichlorophenol.

The $CHCl_3$ layer gave a glass-like solid (0.2gm.) from which no benzofuranone or aryloxymethyl chloride was detected by I.R. or N.M.R. spectroscopy.

2-Fluorophenoxyacetyl chloride

From 2-fluorophenoxyacetyl chloride (from 17gm., 0.1moles the acid), $AlCl_3$ (14gm., 0.11 moles) and CS_2 (170ml.) at 46°C. for 4 hours the following extracts were obtained.

2-Fluorophenoxyacetic acid (13gm., 76%) was obtained by sodium bicarbonate extraction and the 1N. sodium hydroxide extract gave a red oil (0.3gm.) which was mainly 2-fluorophenol.

The $CHCl_3$ extract gave 2gm. of a red oil which was shown by I.R. and N.M.R. spectroscopy to contain a small amount of unreacted acid chloride but not the benzofuranone or aryloxymethyl chloride.

4-Fluorophenoxyacetyl chloride

From 4-fluorophenoxyacetyl chloride (from 17gm., 0.1 moles, the acid), $AlCl_3$ (14gm., 0.11 moles) and CS_2 (170ml.) at 46°C. for 4 hours, 4-fluorophenoxyacetic acid was recovered, in 59% yield, by sodium bicarbonate extraction. The 1N. sodium hydroxide extract gave 0.1gm. impure 4-fluorophenol and the $CHCl_3$ layer gave 0.6gm. of a red oil, this product being mainly unhydrolysed acid chloride. No benzofuran-3-one or aryloxymethyl chloride was detected by N.M.R. spectroscopy.

(n) Attempted Unambiguous Synthesis of 2,4-Dinitrophenoxymethyl Chloride

(i) Phenol (9.4gm., 0.1 moles), sodium chloromethanesulphonate (15.3gm., 0.1 moles) and sodium hydroxide (4gm., 0.1 moles) were dissolved in the minimum volume of water and heated at 200°C., allowing the water to be removed by distillation. The temperature was finally raised to 220°C. and after a reaction period of 4 hours the solid mass was cooled, treated with water and any insoluble material removed by filtration. On addition of barium chloride a white amorphous solid was precipitated, barium phenoxymethanesulphonate. Yield 17gm.

16.5gm. of the phenoxymethanesulphonate salt was added in small portions over 30 minutes to 50ml. nitric acid (S.G. 1.5) and the reaction mixture was stirred at 25°C. over 2 hours. On pouring the homogeneous mixture into iced water a yellow precipitate was formed, showed by I.R. and N.M.R. spectroscopy to be solely 2,4-dinitrophenol.

Yield 8gm., 84% theoretical.

(ii) 2,4-Dinitrochlorobenzene (20gm., 0.1 moles) was refluxed with dry methanolic sodium methoxide (from 2.1gm. sodium and 100ml. methanol) for 30 minutes and the resulting precipitate of sodium chloride removed by filtration. The solvent was evaporated until crystallisation occurred and on cooling a pure

sample of 2,4-dinitroanisole was obtained.

m.pt. 87°C.; yield 19gm., 97% theoretical.

The N.M.R. spectrum in $CDCl_3$, gave a singlet at 5.9τ (OCH_3); also J_{56} = 8 c/s and J_{23} = 3 c/s.

On heating a mixture of 2,4-dinitroanisole (0.2 moles) and PCl_5 (0.01 moles) at 130°C. and passing chlorine gas over 2 hours no reaction was observed and the anisole was recovered unchanged. Repeating the experiment at 200°C. over 2 hours gave a red oil, obtained on addition of water to the reaction mixture and extraction into ether. The N.M.R. spectrum was extremely complex and the absence of peaks at 4τ and 5.8τ showed the absence of the aryloxymethyl chloride or the anisole. No characterisable products were obtained by chromatography on alumina.

(o) The Reactions of 1-Nitro-2-Naphthoxyacetyl Chloride with $AlCl_3$ in non-aromatic solvents

A mixture of 1-nitro-2-naphthoxyacetyl chloride (from 3.1gm., 0.01 moles the acid), $AlCl_3$ (1.6gm., 0.01 moles) and CS_2 (30ml.) was refluxed over 3 hours, the reaction mixture hydrolysed with dilute hydrochloric acid, and the products extracted into $CHCl_3$. Sodium bicarbonate extraction gave 2.7gm. (87%) 1-nitro-2-naphthoxyacetic acid and no phenolic products were obtained on extraction of the organic layer with 2N. sodium hydroxide solution.

The $CHCl_3$ layer gave a dark viscous oil whose N.M.R. spectrum showed a series of broad bands between 2.5 and 5.8τ and no characterisable products were obtained by chromatography on alumina.

The reaction was repeated in (i) 1,2-dichloroethane at 60°C. and (ii) nitromethane at 40°C.; in both cases the acid was recovered in 35-40% yield and the organic layer gave small amounts of a dark viscous oil

which was unable to be characterised, the N.M.R. spectrum showing no well-resolved peaks. Large quantities of an inextractable black solid was formed on hydrolysis of the reaction mixture.

(p) The Reactions of 4-Nitro-1-Naphthoxyacetic acid with $AlCl_3$ in non-aromatic solvents

A mixture of 4-nitro-1-naphthoxyacetyl chloride (from 1.02gm., 0.004 moles the acid), $AlCl_3$ (0.54gm., 0.004 moles) and CS_2 (11ml.) was refluxed (46°C.) for 3 hours. The evolved gases were collected in a Hempel pipette and analysed for carbon monoxide by absorption with cuprous sulphate/2-naphthol reagent in concentrated sulphuric acid and the reaction mixture was hydrolysed with dilute hydrochloric acid over 4 hours. The sodium bicarbonate extract gave 4-nitro-1-naphthoxyacetic acid (0.57gm., 56%) and the 2N. sodium hydroxide extract gave a red solid (0.04gm.) whose I.R. and N.M.R. spectra showed the presence of 4-nitro-1-naphthol.

The $CHCl_3$ extract gave a dark viscous oil (0.18gm.) whose N.M.R. spectrum showed no singlet at ~ 4τ, a low intensity singlet at 5.1τ being present. The I.R. spectrum showed a weak carbonyl absorption at 1800cm.$^{-1}$, confirming the presence of the unhydrolysed acid chloride.

40% of the theoretical volume of carbon monoxide (at N.T.P.) was liberated under the above conditions.

The reaction was repeated in nitromethane as solvent at 40-50°C. for 3 hours, using 1.8gm. (0.007 moles) the acid chloride. After a 4 hour hydrolysis period 1.5gm. of a black inextractable solid was obtained. The sodium bicarbonate extract gave 4-nitro-1-naphthoxyacetic acid (0.2gm., 11%) and the 2N. sodium hydroxide extract gave 30mg. of a glass-like solid whose I.R. spectrum showed that 4-nitro-1-naphthol was present.

The $CHCl_3$ extract contained 0.1gm. of a dark viscous oil; unhydrolysed acid chloride was detected by I.R. and N.M.R. spectroscopy while the N.M.R. spectrum showed no singlet at ~ 4 τ.

Less than 20% of the theoretical volume of carbon monoxide (at N.T.P.) was determined to be liberated in the reaction.

(a) The Reaction of 2,4-Dinitrophenoxyisobutyryl chloride with $AlCl_3$ in CS_2

A mixture of 2,4-dinitrophenoxyisobutyryl chloride (from 5.4gm., 0.02 moles, the acid), $AlCl_3$ (2.7gm., 0.02 moles), and CS_2 (55ml.) was refluxed (46°C.) for 4 hours and the reaction mixture hydrolysed with dilute hydrochloric acid over 3 hours.

The products were extracted into $CHCl_3$ and the organic layer washed several times with 2N. sodium hydroxide solution. The sodium hydroxide extract gave only 2,4-dinitrophenoxyisobutyric acid and only the unhydrolysed acid chloride could be detected in the $CHCl_3$ extract.

The total yield of acid and acid chloride recovered was in excess of 75% theoretical.

6. The Reactions of Arylthioacetyl Chlorides with $AlCl_3$ in Non-Aromatic Solvents

The experimental procedure used was identical to that described in the reactions of aryloxyacetyl chlorides with $AlCl_3$. The reaction mixture was hydrolysed for 4 hours and any inextractable solid removed by filtration.

The $CHCl_3$ extract was examined for arylthiomethyl chlorides by I.R. and N.M.R. spectroscopy but in each case the products were uncharacterisable viscous oils. The only identifiable material was the recovered arylthioacetic acid, obtained from the sodium bicarbonate extract, and the 2N. sodium hydroxide extract showed, in all cases, that the corresponding thiophenol was not formed in significant quantities.

Where stated, the evolved gases were analysed for carbon monoxide by absorption with cuprous sulphate/2-naphthol reagent in concentrated sulphuric acid.

Table III illustrates the amounts of recovered acid obtained under the reaction conditions used in the attempted preparation of arylthiomethyl chlorides.

TABLE III

Arylthio-acetyl chloride (91) R =	Solvent	Reaction Time (hrs.)	Reaction Temp. (°C.)	Arylthio-acetic acid
2-NO_2 a.	CS_2	3	46	79
2-NO_2 b.	$(CH_2)_2Cl_2$	3	80	21
2-NO_2 b.	C_6F_6	3	50	35
4-NO_2 a.	CS_2	3	46	72
4-NO_2 b.	$(CH_2)_2Cl_2$	3	80	29
4-NO_2	$MeNO_2$	3	35	83
4-NO_2	$MeNO_2$	3	55	69
4-NO_2	$MeNO_2$	3	65	72
4-NO_2 b.	$MeNO_2$	3	85	19
2,4-$(NO_2)_2$ c.	CS_2	13	46	95
2,4-$(NO_2)_2$	$(CH_2)_2Cl_2$	3	80	62
2,4-$(NO_2)_2$	$(CH_2)_2Cl_2$	3	50	75
2,4-$(NO_2)_2$	$MeNO_2$	3	30	88
2,4-$(NO_2)_2$ b.	$MeNO_2$	3	80	28

a. No carbon monoxide detected.

b. Much inextractable solid formed after hydrolysis.

c. No evidence of complex formation.

7. Nuclear Magnetic Resonance Spectra of Aryloxyacetyl Chlorides and Arylthioacetyl Chlorides

The chemical shift of the methylene group (τCH_2) of a number of aryloxyacetyl chlorides and arylthioacetyl chlorides, relative to tetramethylsilane (T.M.S.), at infinite dilution was determined as follows.

The acid chlorides were prepared from the corresponding acids in the normal manner, and were used without purification. The absence of unreacted acid was confirmed by I.R. spectroscopy. For each acid a series of solutions were prepared, in $CDCl_3$ containing T.M.S., in concentrations ranging between 10mg./ml. and 80mg./ml. The N.M.R. spectrum of each was recorded at 1c/s per chart unit and in this way the chemical shift of the methylene group (τCH_2) was determined, in cycles/second downfield of T.M.S., to within ±0.2 c/s. A graph of concentration against chemical shift gave a linear relationship and, by extrapolation to zero concentration, the chemical shift at infinite dilution ($\tau CH_2^{c \to 0}$) obtained. The results obtained are given in Table IV.

TABLE IV

Aryloxyacetyl Chloride (1)	$\tau\ CH_2^{C\rightarrow O}$ c/s	$\Delta\tau\ CH_2^{C\rightarrow O}$ c/s
R = 4-NO_2	302.8	+ 6.4
R = 3-NO_2	302.4	+ 6.0
R = 2-NO_2	304.8	+ 8.4
R = H	296.4	-
R = 4-Cl	294.8	- 1.6
R = 4-CH_3	294.6	- 1.8
Arylthioacetyl Chloride (91)	$\tau\ CH_2^{C\rightarrow O}$ c/s	$\Delta\tau\ CH_2^{C\rightarrow O}$ c/s
R = 4-NO_2	253.5	+ 11.0
R = 2-NO_2	256.0	+ 13.5
R = H	242.5	-

8. The Reactions of Aryloxyacetyl Chlorides with $AlCl_3$ in Aromatic Solvents

(a) Phenoxyacetyl chloride

(i) With $AlCl_3$ in Benzene

To a suspension of 19gm. (0.15 moles) $AlCl_3$ in 110ml. dry benzene at 5-10°C., was added a solution of phenoxyacetyl chloride (prepared from 20gm., 0.13 moles the acid) in 110ml. benzene over 45 minutes and with vigorous stirring. The reaction mixture was stirred for a further 1½ hours, poured into dilute hydrochloric acid, and the mixture hydrolysed over 1 hour. The products were extracted into ether and the organic layer washed with sodium bicarbonate solution, acidification of the latter giving 0.5gm. (2.5%) recovered phenoxyacetic acid.

The organic layer, on removal of the solvent, gave a red oil (20.8gm.) which partially solidified. The I.R. and N.M.R. spectra were recorded and the absence of phenoxyacetyl chloride confirmed.

Recrystallisation of the crude product from ethanol containing 60/80 petroleum gave a pale yellow solid, benzofuran-3-one.

m.pt. 99°C.; yield 6.0gm.

The I.R. spectrum gave ν CO = 1720cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave a singlet at 5.5τ (CH_2).

The residue obtained from the filtrate was steam distilled, the distillate extracted and the organic layer washed with 2N. sodium hydroxide.

The product from the organic layer gave the following fractions obtained by silica gel chromatography.

Fraction 1 (Eluate benzene); Diphenylmethane.

m.pt. 26°C.; yield 1.2gm. (No melting point depression in admixture with an authentic sample).

The I.R. spectrum showed only the typical C-C and C-H absorptions of an

aromatic hydrocarbon and the N.M.R. spectrum (in $CDCl_3$) showed singlets at 2.9τ (10 aromatic protons) and 6.1τ (CH_2).

Fraction 2 (Eluate benzene); 2-benzylphenol, as a colourless oil. Yield 0.7gm.

The I.R. spectrum gave ν OH = 3500cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave an aromatic multiplet (9 protons), and singlets at 4.2τ (OH) and 6.1τ (CH_2).

Phenylurethane derivative: m.pt. 117°C. (petroleum 60/80).

Fraction 3 (Eluate 50% benzene/ether); 2-phenoxyacetophenone. m.pt. 71°C. (EtOH); yield 0.5gm. (No melting point depression in admixture with authentic sample).

The I.R. spectrum gave ν CO = 1710cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave a singlet at 4.8τ (CH_2); also $J_{2'3'}$ = 8 c/s and $J_{2'4'}$ = 2 c/s. The sodium hydroxide extract gave, on acidification, a red oil, silica gel chromatography giving the following fractions.

Fraction 1 (Eluate benzene); 2-benzylphenol (0.9gm.)

Fraction 2 (Eluate 50% benzene/ether); benzofuran-3-one (1.8gm.)

Fraction 3 (Eluate chloroform); phenol (0.2gm.).

The steam non-volatile component (3.1gm.) was a viscous red oil. Silica gel chromatography gave a further 0.2gm. 2-benzylphenol and the other component obtained was a red oil (0.9gm.) from which no characterisable products were obtained by fractional recrystallisation or further silica gel chromatography.

The I.R. spectrum of this product showed ν CO = 1720cm.$^{-1}$ (broad), ν OH = 3400cm.$^{-1}$ and strong aromatic C-H deformations at 700 and 740cm.$^{-1}$. The N.M.R. spectrum (in $CDCl_3$) gave singlets at 4.85, 4.95, 6.05 and 6.1τ and the aromatic region included a multiplet at 2.1 and a high-intensity singlet at 2.9τ.

Thus from the above separation separation scheme was isolated,

Phenoxyacetic acid	(2.5%),	0.5gm.
Benzofuran-3-one	(44%),	7.8gm.
Diphenylmethane	(5%),	1.2gm.
2-Benzylphenol	(7%),	1.8gm.
2-Phenoxyacetophenone	(2%),	0.5gm.
Phenol	(1%),	0.2gm.

(ii) With $AlCl_3$ in p-Xylene

Phenoxyacetyl chloride (from 10gm., 0.06 moles the acid) was dissolved in 60ml. p-xylene and added over 45 minutes to a stirred suspension of $AlCl_3$ (9.5gm., 0.07 moles) in 60ml. p-xylene at 10-15°C., the reaction mixture stirred at 10-15°C. for 1½ hours and hydrolysed with dilute hydrochloric acid over 1 hour. The products were extracted in ether, the organic layer washed with sodium bicarbonate solution, the latter on acidification giving phenoxyacetic acid (0.4gm., 4%). The organic layer, on removal of the solvent, gave a red viscous oil, whose I.R. and N.M.R. spectra confirmed the absence of acid chloride. The oil was dissolved in ether and washed with 2N sodium hydroxide.

The ether layer gave a red oil, which on recrystallisation from 40/60 petroleum gave 2-phenoxy-2',5'-dimethylacetophenone.

m.pt. 70°C.; yield 8.1gm. (No melting point depression in admixture with an authentic sample).

The I.R. spectrum gave ν CO = 1700cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave singlets at 4.9τ(CH_2), 7.55τ(2'-CH_3) and 7.65τ(5'-CH_3).

$C_{16}H_{16}O_2$ requires: C, 80.0; H, 6.9%

found: C, 79.9; H, 6.7%

The residue from the filtrate gave the following fractions, obtained by silica gel chromatography.

Fraction 1 (Eluate benzene); di-(2,5-xylyl)methane m.pt. 62°C. (EtOH); yield 50mg. (No melting point depression in admixture with an authentic sample).

The N.M.R. spectrum (in $CDCl_3$) gave singlets at 6.2 τ(CH_2) and 7.8 τ (2- and 5-CH_3).

Fraction 2 (Eluate 50% benzene/ether); 2-phenoxy-2'5'-dimethyl-acetophenone. Yield 1.4gm.

A red oil obtained from the 2N. sodium hydroxide extract gave only benzofuran-3-one on silica gel chromatography.

Yield 0.4gm., 5% theoretical.

The above separation scheme gave the following products.

Phenoxyacetic acid	0.4gm.	(4%)
Benzofuran-3-one	0.4gm.	(5%)
2-Phenoxy-2'5'-dimethylacetophenone	9.5gm.	(65%)
Di-(2,5-xylyl)methane	50mg.	(< 1%)

(iii) With $AlCl_3$ in Anisole

Phenoxyacetyl chloride (from 5gm., 0.03 moles the acid) was dissolved in 30ml. (0.28 moles) anisole, added over 45 minutes to a suspension of $AlCl_3$ (4.7gm., 0.04 moles) in 30ml. (0.28 moles) anisole at 5-10°C., the reaction mixture stirred at 5-10°C. for 1½ hours and hydrolysed over 1 hour with dilute hydrochloric acid. The products were extracted into ether and the organic layer washed with sodium bicarbonate solution, the latter, on acidification, giving phenoxyacetic acid (2.8gm., 56%).

2N. sodium hydroxide extraction of the organic layer gave no products on acidification.

The organic layer, on removal of the solvent, gave a yellow oil, a single

fraction (2.0gm.) being obtained by silica gel chromatography.

The I.R. spectrum gave ν CO = 1695cm.$^{-1}$ and the N.M.R. spectrum (in CCl_4) gave singlets at 4.85τ(CH_2), 4.9τ(CH_2), 6.25τ(OCH_3) and 6.3τ(OCH_3), consistent with an isomeric mixture of 2'- and 4'-methoxy-2-phenoxy-acetophenones. Fractional recrystallisation gave a pure sample of 4'-methoxy-2-phenoxyacetophenone.

m.pt. 65°C. (60/80 petroleum); yield 0.7gm.; 9% theoretical. (The other isomer was not obtained as a pure sample).

The I.R. spectrum gave ν CO = 1695cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave singlets at 4.85τ(CH_2) and 6.25τ(4'-OCH_3); also $J_{2'3'}$ = 9 c/s.

The yield of isomeric acetophenones obtained after chromatography was 2.0gm., 25% theoretical, and the integrated N.M.R. spectrum showed the ortho: para ratio to be 1:2.

The reaction was repeated using (a) phenoxyacetyl chloride (0.03 moles) $AlCl_3$ (0.04 moles) and anisole (0.28 moles), and (b) phenoxyacetyl chloride (0.03 moles), $AlCl_3$ (0.08 moles) and anisole (0.56 moles). Using the same experimental procedure outlined above the following results were obtained.

Phenoxyacetic acid recovered	(a) 26%	(b) 20%
Yield isomeric acetophenones	(a) 46%	(b) 52%
Ortho:para ratio	(a) 1:2	(b) 1:2

(iv) With $AlCl_3$ in m-Dimethoxybenzene

From phenoxyacetyl chloride (11.4gm., 0.07 moles), $AlCl_3$ (9.5gm., 0.07 moles) and m-dimethoxybenzene (125ml., 1.3 moles) at 5-10°C. for 2 hours, the following extracts were obtained.

The sodium bicarbonate extract gave phenoxyacetic acid (4.8gm., 48%) and no products were obtained from the 2N. sodium hydroxide extract.

The organic layer, on removal of the solvent (b.pt. 71-72°C./1.5mm.) gave a solid product, which on recrystallisation gave 2',4'-dimethoxy-2-phenoxyacetophenone.

m.pt. 115°C. (benzene/petroleum 60/80); yield 3.0gm., 17% theoretical.

The I.R. spectrum gave ν CO = 1660cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave singlets at 4.8τ(CH_2), 6.1τ(2'-OCH_3) and 6.15τ(4'-OCH_3); also $J_{5'6'}$ = 8 c/s, $J_{3'6'}$ = 0.5 c/s, and $J_{3'5'}$ = 2 c/s.

Silica gel chromatography on the residue obtained from the filtrate gave a single fraction, eluted with 50% benzene/ether.

m.pt. 100-102°C. (EtOH); yield 2.6gm.

The I.R. spectrum gave ν CO = 1660cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave singlets at 4.8τ(CH_2), 7.8τ(aromatic CH_3?) and 4 singlets between 6.0 and 6.15τ(OCH_3). The spectra indicated 2',4'-dimethoxy-2-phenoxyacetophenone to be a component, a mixed m.pt. of 109°C. confirming this. Fractional recrystallisation or silica gel chromatography did not lead to further separation.

(v) With $AlCl_3$ in Chlorobenzene

From phenoxyacetyl chloride (13.5gm., 0.08 moles), $AlCl_3$ (11gm., 0.08 moles) and chlorobenzene (140ml.), at 5-10°C. for 2 hours, the following extracts were obtained.

Sodium bicarbonate extraction gave phenoxyacetic acid (1.0gm., 8%) and the organic layer gave 9.0gm. of a viscous oil, steam distillation of which gave a yellow oil (3.9 gm.)

Silica gel chromatography gave the following fractions.

Fraction 1 (Eluate benzene). A clear yellow oil (1.8gm.) was obtained, whose I.R. spectrum showed no hydroxyl or carbonyl absorption. The N.M.R. spectrum (in CCl_4) gave singlets at 5.9, 6.0 and 6.2τ (CH_2), the complex aromatic region being equivalent to 8 protons.

The spectra were consistent with an isomeric mixture of di-(chlorophenyl)-methanes. Fractional recrystallisation or silica gel chromatography failed to give a single product.

Yield 9% theoretical.

Fraction 2 (Eluate 50% benzene/ether); benzofuran-3-one.

Yield 1.1gm; 10% theoretical.

Fraction 3 (Eluate chloroform); phenol.

Yield 0.1gm.; 1% theoretical.

No isolable products were obtained from the steam non-volatile component by silica gel chromatography.

(vi) With $AlCl_3$ in o-Dichlorobenzene

From phenoxyacetyl chloride (10.6gm., 0.06 moles), $AlCl_3$ (9.4gm., 0.07 moles) and o-dichlorobenzene (108ml.), at 5-10°C. for 2 hours, the following products were obtained.

After a 4 hour hydrolysis period a dark inextractable solid (5.0gm.) was obtained, whose I.R. spectrum indicated this product to be polymeric.

Sodium bicarbonate extraction of the organic layer gave phenoxyacetic acid (1.0gm., 10%).

The organic layer gave a red viscous oil (5.5gm.) which on steam distillation gave a yellow oil (3.7gm.).

Silica gel chromatography on this product gave the following fractions.

Fraction 1 (Eluate benzene); di-(3,4-dichlorophenyl)methane.

m.pt. 116°C. (EtOH); yield 2.3gm., 11% theoretical.

The I.R. spectrum showed no hydroxyl or carbonyl absorption and the N.M.R. spectrum (in CCl_4) gave a singlet at 6.1τ (CH_2); also $J_{56} = J_{5'6'} =$ 8 c/s and $J_{26} = J_{2'6'} = 2$ c/s.

Fraction 2 (Eluate 50% benzene/ether); benzofuran-3-one.

Yield 0.4gm.; 4% theoretical.

Fraction 3 (Eluate 50% benzene/ether).

This fraction (0.6gm.) was a viscous oil whose I.R. spectrum gave ν OH = 3400cm.$^{-1}$ and ν CO = 1700cm.$^{-1}$. The N.M.R. spectrum (in CCl_4) gave singlets at 5.4τ (CH_2), 6.2τ (CH_2) and 4.0τ (OH). A small amount of benzofuran-3-one was detected, by spectroscopy, but the major product was not obtained as a pure sample on further silica gel chromatography.

The steam non-volatile component was an uncharacterisable viscous oil, whose I.R. spectrum suggested this product to be polymeric.

(b) Substituted Phenoxyacetyl Chlorides

(1) With $AlCl_3$ in benzene

A solution of the aryloxyacetyl chloride in benzene (0.1 moles per 100ml. solvent) was added to a stirred suspension of $AlCl_3$ in benzene (0.1 moles per 100ml. solvent) at 5-10°C. over 30-45 minutes. The reaction mixture was stirred at this temperature for a further 1½ hours and was hydrolysed by pouring into iced dilute hydrochloric acid. The products were extracted (ether) and the organic phase washed with saturated sodium bicarbonate solution. The I.R. and N.M.R. spectra of the crude non-acidic product were recorded, the absence of unhydrolysed acid chloride and the product distribution being estimated in this way.

The general separation scheme was as follows:

A single recrystallisation generally gave the major component (aryloxyacetophenone (109) or benzofuranone(110)) as a pure sample and the residue from the filtrate was divided into three equal portions.

(i) Silica gel chromatography gave diphenylmethane and in many cases the 2-benzylphenol (111).

(ii) Steam distillation and silica gel chromatography on the steam volatile component gave diphenylmethane and the benzofuranone (occasionally the parent phenol was also isolated).

(iii) The final portion was dissolved in benzene or ether and was washed thoroughly with 2N. sodium hydroxide and alcoholic potassium hydroxide solution (35gm. KOH, 25ml. H_2O, 75ml. MeOH). The neutral fraction obtained from the organic layer gave the aryloxyacetophenone and diphenylmethane, separated by silica gel chromatography and the potassium hydroxide extract gave, on acidification, the benzylphenol. The 2N. sodium hydroxide extract generally gave the parent phenol

although when the benzofuranone (110) was present as the major product this extract was always contaminated with uncharacterisable self-condensation products derived from (110). In consequence the parent phenol was not always isolated by silica gel chromatography on this fraction.

Table V gives the products isolated using the above scheme.

TABLE V

Reactions of 2-Aryloxyacetyl chlorides (1) with $AlCl_3$ in Benzene at 5-10°C.

Acid Chloride (1) R =	Acetophenone (109) %	Benzofuranone (110) %	Diphenylmethane %	Phenol %	2-Benzyl Phenol (111) %	Notes
4-NO_2	49	-	-	-	-	(1)
2-NO_2	52	-	-	-	-	(2)
3-Me-2-NO_2	33	-	-	-	-	(3)
2-CN	30	-	-	-	-	(4)
2,4-Cl_2	85	1	-	-	-	(5) (15)
3,4-Cl_2	76	-	4	3	-	-
4-F	28	4	26	21	19	(5)
2-F	78	4	7	3	-	(5)
4-Cl	39	8	15	16	12	-
2-Cl	66	8	4	1	-	-
4-Br	40	6	17	13	10	(5)
4-I	28	6	15	11	10-20	(5) (6)
2-I	53	7	6	5	5-10	(7)
H	2	44	4	1	7	-
4-Me	5	40	8	1	17	(8)
2-Me	1	60	6	1	8	(9)
2,4-Me_2	-	83	6	-	4	-
2,6-Me_2	-	-	32	32	53	(10)
2,4,6-Me_3	-	-	27	27	66	(11)
2-Ph	-	70	-	-	-	(12)
2-Ph-4,6-Br_2	-	85	-	-	-	(13)
4-Ph	9	16	15	23	16	(5) (14)

TABLE V NOTES

(1) Reaction at 20°C.; 43% recovered acid.

(2) Reaction at 20°C.; 40% recovered acid.

(3) Reaction at 5-10°C.; 59% recovered acid.

(4) Reaction at 5-10°C.; 70% recovered acid.

(5) The benzofuranone was not isolated and the yield quoted is that estimated from the N.M.R. spectrum ofthe crude non-acidic product.

(6) Much iodine was liberated during the reaction; a crude benzyl phenolic fraction was obtained but no single component was isolated. The N.M.R. spectrum showed singlets at 6.1 and 6.2τ (CH_2). The yield was estimated from the N.M.R. spectrum of the crude non-acidic product.

(7) Much iodine was liberated during the reaction; a crude benzyl phenolic fraction was obtained but no single component was isolated. The N.M.R. spectrum showed several singlets between 6.1 and 6.3τ (CH_2). The yield was estimated from the N.M.R. spectrum of the crude non-acidic product.

(8) 2-(4-methylphenoxy)acetophenone was not isolated and the yield was estimated from the N.M.R. spectrum of the crude non-acidic product.

(9) 2-(2-methylphenoxy)acetophenone was not isolated from the neutral fraction (after removal of diphenylmethane) whose N.M.R. spectrum showed a minimum of four peaks between 4.6 and 5.0τ. A single component was isolated by fractional recrystallisation.

m.pt. 130°C. (MeOH)

The I.R. spectrum gave ν CO = 1700cm.$^{-1}$ and the N.M.R. spectrum, in $CDCl_3$, showed singlets at 4.6τ (CH_2), 4.8τ (CH_2), 7.6τ (CH_3) and 7.7τ (CH_3); the aromatic region was complex and was equivalent to 12 protons.

$C_{24}H_{22}O_4$ requires: C, 76.9; H, 5.9%

found: C, 76.0; H, 5.8%

(10) The benzyl phenolic fraction was shown, by quantitative I.R. and N.M.R. spectroscopy to be a mixture of

3-benzyl-2,6-dimethylphenol (75%)

4-benzyl-2,6-dimethylphenol (24%).

3,4-dibenzyl-2,6-dimethylphenol (1%) was isolated by recrystallisation.

(11) The benzyl phenolic fraction contained only 3-benzyl-2,4,6-trimethylphenol.

(12) Dibenz(b,d)oxepin-7(6H)-one was formed exclusively.

(13) 1',3'-Dibromodibenz(b,d)oxepin-7(6H)-one was formed exclusively.

(14) Reference 65.

(15) 2-(2,4-dichlorophenoxy)acetophenone was the sole product formed (in 90% yield) using a molar excess of $AlCl_3$.

TABLE VI

Physical Constants of 2-Aryloxyacetophenones (109)

Acetophenone (109) R =	m.pt. °C. (a)	N.M.R. Spectrum τ CH_2 (c)	I.R. Spectrum ν CO($cm.^{-1}$) (d)	Notes
4-NO_2	144	4.6	1680	
2-NO_2	118	4.55	1690	
3-Me-2-NO_2	88	4.7	1690	(1)
2-CN	140	4.6	1690	(2)
2,4-Cl_2	74	4.9	1695	
3,4-Cl_2	96	4.75	1690	(3)
4-F	102 (b)	4.95	1705	(4)
2-F	102	4.7	1690	(5)
4-Cl	98	4.9	1695	
2-Cl	102	4.75	1700	(6)
4-Br	108	4.8	1690	
4-I	102	4.95	1700	(7)
2-I	114	4.7	1695	(8)
H	72	4.9	1700	
4-Me	-	4.8	-	(9)
4-Ph	-	4.9	1720	(10)

TABLE VI NOTES

(a) Solvent ethanol.

(b) Solvent petroleum (60/80).

(c) τ CH_2 denotes the chemical shift of the 2-methylene group relative to T.M.S. Solvent $CDCl_3$.

(d) I.R. spectra recorded as Nujol mulls.

(1) $C_{15}H_{13}NO_4$ requires: C, 66.4; H, 4.8; H, 5.2%

found: C, 64.7; H, 4.5; N, 4.8%

(2) $C_{15}H_{11}NO_2$ requires: C, 75.8; H, 4.6; N, 5.9%

found: C, 74.5; H, 4.6; N, 6.2%

(3) $C_{14}H_{10}Cl_2O_2$ requires: C, 59.8; H, 4.0; Cl, 25.2%

found: C, 59.9; H, 4.1; Cl, 24.9%

(4) $C_{14}H_{11}FO_2$ requires: C, 72.9; H, 4.8; F, 8.3%

found: C, 72.4; H, 4.8; F, %

(5) $C_{14}H_{11}FO_2$ found: C, 73.0; H, 4.8; F, 9.1%

(6) $C_{14}H_{11}ClO_2$ requires: C, 68.1; H, 4.6; Cl, 14.4%

found: C, 68.4; H, 5.1; Cl, 14.2%

(7) $C_{14}H_{11}IO_2$ requires: C, 49.7; H, 3.3; I, 37.7%

found: C, 50.0; H, 3.4; I, 37.5%

(8) $C_{14}H_{11}IO_2$ found: C, 49.5; H, 3.3; I, %

(9) Spectral evidence only.

(10) Reference 65.

TABLE VII

Physical Constants of Benzofuranones (110)

Benzofuranone (110) R =	m.pt. °C.	N.M.R. Spectrum τ CH_2 c.	I.R. Spectrum ν CO ($cm.^{-1}$) d.	Notes
5,7-Cl_2	-	5.5	-	(1)
5-F	-	5.5	1700	(1)
7-F	-	5.45	-	(1)
5-Cl	113 a.	5.4	1710	
7-Cl	110 a.	5.35	1720	
5-Br	-	5.55	-	(1)
5-I	-	5.5	1705	(1)
7-I	180 b.	5.3	1710	(2)
H	98 b.	5.4	1720	
5-Me	54 b.	5.55	1710	
7-Me	87 b.	5.5	1700	
5,7-Me_2	80 b.	5.5	1710	
5-Ph	-	5.4	1700	(1)
(A)	80 a.	5.2	1680	(3)
(B)	189 a.	5.2	1680	(4) (5)

TABLE VII NOTES

a. Solvent petroleum (60/80).

b. Solvent ethanol.

c. τ CH_2 denotes the chemical shift of the 2-methylene group relative to T.M.S. Solvent $CDCl_3$.

d. I.R. spectra recorded as Nujol mulls.

(1) Product not isolated; spectral evidence only.

(2) $C_8H_5IO_2$ requires: C, 36.9; H, 1.9; I, 49.0%

found: C, 37.2; H, 2.1; I, 48.5%

(3) Product (A); dibenz(b,d)oxepin-7(6H)-one.

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

found: C, 79.5; H, 4.9%

(4) Product (B); 1',3',-dibromodibenz(b,d)oxepin-7(6H)-one.

$C_{14}H_8Br_2O_2$ requires: C, 45.6; H, 2.2; Br, 43.4%

found: C, 45.6; H, 2.7; Br, 43.1%

(5) Reference 65.

TABLE VIIA

U.V. Spectra of Benzofuran-3-ones (110)

Benzofuran-3-one (110) R =	λ max. (mμ) (Solvent Ethanol) (ε x 10^{-3})		
H	210 (24.5)	250 (11.8)	325 (4.9)
7-Me	214 (21.6)	255 (9.0)	328 (4.6)
5,7-Me_2	216 (22.3)	257 (9.5)	340 (4.8)
7-Cl	215 (26.8)	256 (9.0)	327 (5.4)
7-I	220 (17.5)	265 (4.6)	330 (5.0)

U.V. Spectra of Dibenz(b,d)oxepin-7(6H)-ones

Oxepinone R =	λ max. (mμ) (Solvent Ethanol) (ε x 10^{-3})			
H	209 (18.0)	236 (21.0)	258 (10.5)	307 (3.3)
1',3'-Br_2	205 (21.4)	222 (30.2)	260 (10.1)	300 (3.1)

TABLE VIII

Physical Constants of 2-Benzyl phenols (111)

2-Benzyl-Phenol (111)	m.pt.[a.] or b.pt. °C.	N.M.R. Spectrum[b.]		Notes
		τ CH_2[c.]	τ OH[d.]	
R = 4-F	10	6.1	4.8	(1)
R = 4-Cl	48	6.2	5.4	
R = 4-Br	210/10mm.	6.15	4.7	
R = H	10	6.1	4.2	(2)
R = 4-Me	36	6.15	5.1	
R = 6-Me	50	6.1	5.6	
R = 4,6-Me_2	67	6.15	5.9	
(C)	66	6.3	5.8	(3)
(D)	-	6.2	5.4	(3)
(E)	116	6.1,6.2	5.7	(3)
(F)	59	6.1	5.2	(4)
R = 4-Ph	84	6.0	5.2	(5)

TABLE VIII NOTES

a. Solvent petroleum (60/80).

b. Solvent CCl_4.

c. τ CH_2 denotes the chemical shift of the methylene group relative to T.M.S.

d. τ OH denotes the chemical shift of the hydroxyl proton relative to T.M.S.

(1) Phenylurethane derivative m.pt. 155°C. (benzene).

$C_{20}H_{16}FNO_2$ requires: C, 74.5; H, 5.3; F, 5.9; N, 4.4%

found: C, 74.5; H, 5.1; F, 6.1; N, 4.5%

(2) Phenylurethane derivative m.pt. 117°C. (petroleum (60/80)

(3) Reaction products from 2,6-dimethylphenoxyacetyl chloride.

Product C, 4-benzyl-2,6-dimethylphenol

Product D, 3-benzyl-2,6-dimethylphenol

Product E, 3,4-dibenzyl-2,6-dimethylphenol

$C_{22}H_{23}O$ requires: C, 87.1; H, 7.5%

found: C, 86.7; H, 7.4%

(4) Reaction product from 2,4,6-trimethylphenoxyacetyl chloride.

Product F, 3-benzyl-2,4,6-trimethylphenol

$C_{16}H_{18}O$ requires: C, 85.0; H, 7.9%

found: C, 84.4; H, 7.9%

Phenylurethane derivative m.pt. 134°C.

(5) Reference 65.

(2) With $AlCl_3$ in p-Xylene

Using the reaction scheme and isolation procedure outlined in Part 8 (a) (ii), the following products were obtained.

TABLE IX

The Reactions of 2-Aryloxyacetyl Chlorides with $AlCl_3$ in p-Xylene

Acid Chloride (1) R =	Aryloxy-2',5'-dimethyl-acetophenone %	Benzo-furanone (110) %	Di-(2,5-xylyl)-methane (117) %	Phenol %	2-(2',5'-dimethyl-benzyl) phenol (116) %	Notes
4-F	90	2	7	7	1	(1) (2)
4-Cl	90	2	1	-	1	(1) (2)
2-Cl	93	-	-	-	-	
H	65	5	1	-	-	
4-Me	58	9	5	4	5	(3)

TABLE IX NOTES

(1) The benzofuranone was not isolated and was estimated from the N.M.R. spectrum of the crude non-acidic product.

(2) The 2-(2',5'-dimethylbenzyl)phenol was not isolated as a pure sample; spectral evidence from the crude benzyl phenolic fraction 4-Fluoro-2-(2',5'-dimethylbenzyl)phenol.

I.R. spectrum; ν OH 3500cm.$^{-1}$.

N.M.R. spectrum: τ CH_2 6.2τ, τ 2'-Me 7.7τ, τ 5'-Me 7.8τ.

4-Chloro-2-(2',5'-dimethylbenzyl)phenol.

I.R. spectrum; ν OH 3400cm.$^{-1}$.

N.M.R. spectrum; τ CH_2 6.1τ, τ 2'-Me 7.7τ, τ 5'-Me 7.75τ.

(3) 4-Methyl-2-(2',5'-dimethylbenzyl)phenol isolated as an oil

I.R. spectrum; ν OH 3400cm.$^{-1}$.

N.M.R. spectrum; τ CH_2 6.2τ; also singlets at 7.7, 7.8 and 7.85 τ (2'-Me, 5'-Me, 4-Me).

Phenylurethane derivative m.pt. 105°C. (petroleum 60/80).

$C_{23}H_{23}NO_2$ requires: C, 79.7; H, 6.9; N, 4.0%

found: C, 79.3; H, 7.0; N, 3.5%

TABLE X

Physical Constants of 2-Aryloxy-2',5'-dimethylacetophenones

2',5'-Dimethyl-acetophenone R =	m.pt. °C.	N.M.R. Spectrum f.			I.R. Spectrum	Microanalysis
		τ CH_2 c.	τ 2'-CH_3 d.	τ 5'-CH_3 e.	ν CO ($cm.^{-1}$)	
4-F	86 a.	5.1	7.6	7.7	1700	$C_{16}H_{15}FO_2$ requires: C, 74.3; H, 5.8; F, 7.4% found: C, 73.8; H, 5.7, F, %
4-Cl	107 a.	4.9	7.5	7.6	1690	$C_{16}H_{15}ClO_2$ requires: C, 69.8; H, 5.5; Cl, 12.8% found: C, 69.8; H, 5.8; Cl, 12.7%
2-Cl	76 a.	4.9	7.6	7.7	1680	$C_{16}H_{15}ClO_2$ found: C, 69.9; H, 5.2; Cl, 12.6%
H	70 b.	4.9	7.5	7.6	1700	$C_{16}H_{16}O_2$ requires: C, 80.0; H, 6.7% found: C, 79.9; H, 6.9%
4-CH_3	80 b.	5.1	7.6	7.7	1680	$C_{17}H_{18}O_2$ requires: C, 80.3; H, 7.1% found: C, 80.6; H, 6.9%

TABLE X NOTES

a. Solvent ethanol.

b. Solvent petroleum (60/80).

c. τ CH_2 denotes the chemical shift of the 2-methylene group, relative to T.M.S.

d. τ 2'-CH_3 denotes the chemical shift of the 2'-methyl group, relative to T.M.S.

e. τ 5'-CH_3 denotes the chemical shift of the 5'-methyl group, relative to T.M.S.

f. Solvent $CDCl_3$.

(c) The Reaction of 2,4-Dichlorophenoxyacetic acid with P_2O_5 in Benzene[15]

2,4-Dichlorophenoxyacetic acid (10gm., 0.05 moles) was dissolved in benzene (120ml.), 13gm.(0.09 moles) P_2O_5 added, the reaction mixture refluxed with stirring for 1½ hours and hydrolysed with dilute hydrochloric acid over 1 hour.

The products were extracted into ether and the organic layer washed with sodium bicarbonate solution, 2N. sodium hydroxide, and alcoholic potassium hydroxide.

The sodium bicarbonate extract gave, on acidification, 2,4-dichlorophenoxyacetic acid (1.7gm., 17%).

No products were obtained on acidification of the alkaline extracts.

The organic layer gave a yellow oil which was separated into the following fractions by silica gel chromatography.

Fraction 1 (Eluate benzene) Diphenylmethane.

Yield 2.3gm.; 66% theoretical.

Fraction 2 (Eluate ether) (2,4-dichlorophenyl) 2,4-dichlorophenoxyacetate. m.pt. 112°C. (EtOH); yield 6.0gm., 70% theoretical.

The I.R. spectrum gave ν CO = 1760cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave a singlet at 5.05τ (CH_2).

The I.R. and N.M.R. spectrum of the crude non-acidic product indicated the absence of 2-(2,4-dichlorophenoxy)acetophenone, and 5,7-dichlorobenzofuran-3-one.

The above reaction was repeated with 0.05 moles 2,4-dichlorophenoxyacetic acid, 0.05 moles P_2O_5 and 120ml. benzene. Under identical reaction conditions and following the same separation scheme, the only component isolated was the recovered 2,4-dichlorophenoxyacetic acid in 95% yield.

9. Unambiguous Syntheses of 2-Aryloxyacetophenones

(a) 2-Phenoxyacetophenone[58]

Sodium (0.95gm., 0.04 moles) was reacted with methanol (100ml.) and phenol (3.9gm., 0.04 moles) was added. A solution of 2-bromoacetophenone (phenacyl bromide) (8.2gm., 0.04 moles) in methanol (75ml.) was added and the reaction mixture refluxed, with stirring, for 3 hours, after which time the methanol was removed by distillation. 2N. Sodium hydroxide solution was added and the neutral products were extracted into ether.

The organic layer, on removal of solvent, gave a yellow oil which, after three recrystallisations from 40/60 petroleum, gave 2-phenoxyacetophenone.

m.pt. 72°C.; yield 6.1gm., 72% theoretical.

(b) 2-Phenoxy-2',5'-dimethylacetophenone

(1) 2',5'-Dimethylacetophenone[78]

p-Xylene (26gm., 0.25 moles) was dissolved in CS_2 (260ml.) and $AlCl_3$ (33gm., 0.25 mole) added. The mixture was stirred, and cooled to -10°C. A mixture of acetyl chloride (20gm., 0.25 moles) in CS_2 (260ml.) was added to the stirred solution at such a rate that the internal temperature did not exceed -4°C., the reaction mixture stirred at -10°C. to -4°C. for a further 6 hours, and decomposed with iced dilute hydrochloride over 1 hour.

The organic layer was separated, washed with 2N. sodium hydroxide, and the residue from the organic layer fractionally distilled, collecting the fraction, b.pt. 100-110°C./10mm.

This fraction, on re-distillation, gave a pure sample of 2',5'-dimethyl-acetophenone.

b.pt. 104°C./11mm.; yield 30gm., 81% theoretical.

The I.R. spectrum gave ν CO = 1680cm.$^{-1}$ and the N.M.R. spectrum (in CCl_4) gave singlets at 2.6τ (6'-H), 3.0τ (3'-H, 4'-H), 7.6τ (2'-CH_3, 2-CH_3) and 7.7τ (5'-CH_3).

(2) 2-Bromo-2',5'-dimethylacetophenone

2',5'-Dimethylacetophenone (11.5gm., 0.08 moles) was dissolved in glacial acetic acid (15ml.), warmed to 50°C. and a solution of bromine (12.8gm., 0.08 moles) in glacial acetic acid (15ml.) added dropwise over 1 hour. The reaction mixture was stirred at 50°C. for 1½ hours, cooled, poured into water, and extracted into ether. The organic layer gave a green oil which, on recrystallisation from 40/60 petroleum, cooling the solution to -20°C., gave a colourless solid, 2-bromo-2',5'-dimethylacetophenone. This product liquified at room temperature,

Yield 12gm., 67% theoretical.

This compound was characterised only by I.R. and N.M.R. spectroscopy, comparing its spectral properties with those of 2-bromoacetophenone.

2-Bromoacetophenone

The I.R. spectrum gave ν CO = 1680cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) gave a singlet at 5.7τ (2-CH_2).

2-Bromo-2',5'-dimethylacetophenone

The I.R. spectrum gave ν CO = 1680cm.$^{-1}$ and the N.M.R. spectrum gave (in CCl_4) singlets at 2.6τ (6'-H), 2.9τ (3'-H, 4'-H), 5.75τ (2-CH_2), 7.6τ (2'-CH_3) and 7.7τ (5'-CH_3).

(3) 2-Phenoxy-2',5'-dimethylacetophenone

Sodium (1.1gm., 0.05 moles) was reacted with methanol (75ml.) and phenol (4.7gm., 0.05 moles) added. To this solution was added a solution of 2-bromo-2',5'-dimethylacetophenone (7gm., 0.03 moles) in methanol (25ml.). The reaction mixture was refluxed with stirring, for 3 hours and in the

normal manner was obtained 2-phenoxy-2',5'-dimethylacetophenone as a colourless solid.

m.pt. 70°C. (petroleum 60/80); yield 6.0gm., 83% theoretical.

I.R. and N.M.R. spectroscopy and mixed m.pt. showed this product to be identical to the sample prepared from the reaction of p-xylene with 2-phenoxyacetyl chloride and $AlCl_3$.

(c) 2-(2-Chlorophenoxy)-2',5'-dimethylacetophenone

From 2-chlorophenol, 2-bromo-2',5'-dimethylacetophenone in methanolic sodium methoxide was prepared, 2-(2-chlorophenoxy)-2',5'-dimethylacetophenone

m.pt. 75°C. (EtOH); yield 88% theoretical.

I.R. and N.M.R. spectroscopy and mixed m.pt. showed this product to be identical to the sample prepared from the reaction of p-xylene with 2-(2-chlorophenoxy)acetyl chloride and $AlCl_3$.

(d) 2-(4-Chlorophenoxy)-2',5'-dimethylacetophenone

From 4-chlorophenol, 2-bromo-2',5'-dimethylacetophenone in methanolic methoxide was prepared, 2-(4-chlorophenoxy)-2',5'-dimethylacetophenone

m.pt. 107°C. (EtOH); yield 76% theoretical.

I.R. and N.M.R. spectroscopy and mixed m.pt. showed this product to be identical to the sample prepared from the reaction of p-xylene with 2-(4-chlorophenoxy)acetyl chloride and $AlCl_3$.

10. Syntheses of Aryl Benzyl Ethers

The preparation of phenyl benzyl ether outlined below illustrates the general method of synthesis of aryl benzyl ethers given in Table XI.

2.5gm. (0.11 moles) sodium was reacted with ethanol (100ml.) and phenol (10.3gm., 0.11 moles) added. A solution of benzyl bromide (17.1gm., 0.1 moles) in 50ml. ethanol was added and the solution refluxed with stirring for 2 hours, during which time a precipitate of sodium bromide was formed. Most of the solvent was removed by distillation and 2N. sodium hydroxide was added to the cooled residue. The neutral products were extracted into ether, the residue from the organic layer giving, on recrystallisation from 40/60 petroleum, a pure sample of phenyl benzyl ether

m.pt. 39°C.; yield 12.0gm., 65% theoretical.

The I.R. and N.M.R. spectrum of the product was recorded and in all cases benzyl bromide or its hydrolysis or alcoholysis products, benzyl alcohol or benzyl ethyl ether, were shown to be absent.

TABLE XI

The Physical Constants of Aryl Benzyl Ethers

Aryl Benzyl Ether (64) R =	m.pt. or b.pt. °C.	Yield %	N.M.R. Spectrum a. τCH_2 b.	N.M.R. Spectrum a. τC_6H_5 c.	Notes
2,4-Cl_2	61	80	5.0	2.7	
4 - F	55	50	5.1	2.8	
4-Cl	75	64	5.2	2.8	
4-Br	64	67	5.1	2.7	
4-I	63	75	5.1 d.	2.7 d.	
H	39	65	5.25	2.9	
4-Me	42	56	5.2	2.8	
2-Me	194/45mm.	63	5.2	2.8	
2,4-Me_2	180/15mm.	75	5.25	2.8	
2,5-Me_2	171/14mm.	77	5.2	2.8	
2,6-Me_2	200/35mm.	79	5.35	2.8	
2,4,5-Me_3	46	69	5.1	2.8	(1)
2,4,6-Me_3	172/10mm.	36	5.25 d.	2.7 d.	
4-Ph	133	44	5.45 d.	2.7 d.	(2)

TABLE XI NOTES

a. Solvent CCl_4.

b. τCH_2 denotes the chemical shift of the methylene group relative to T.M.S.

c. τC_6H_5 denotes the chemical shift of the phenyl group protons which were always a broad singlet.

d. Solvent $CDCl_3$.

(1) $C_{16}H_{18}O$ requires: C, 85.0; H, 7.9%

found: C, 84.8; H, 7.9%

(2) Reference 65.

11. The Reactions of Aryl Benzyl Ethers with $AlCl_3$ in Benzene

(a) Phenyl benzyl ether

To a stirred suspension of $AlCl_3$ (3.9gm., 0.03 moles) in benzene (30ml.) at 5-10°C. was added a solution of phenyl benzyl ether (5.5gm., 0.03 moles) in benzene (30ml.) over 30 minutes. The reaction mixture was stirred at 5-10°C. for 1½ hours, hydrolysed with dilute hydrochloric acid, and extracted with ether.

The organic layer was washed thoroughly with 2N. sodium hydroxide and alcoholic potassium hydroxide solution.

Acidification of the 2N. sodium hydroxide extract gave a single product, phenol (1.2gm., 45%) and the alcoholic potassium hydroxide extract, on acidification, gave 2-benzylphenol (2.9gm., 54%).

The residue from the organic layer gave diphenylmethane (2.3gm., 45%).

NOTES

(1) The above method illustrates the general scheme used for the reactions of aryl benzyl ethers with $AlCl_3$ in benzene. The results obtained are given in Table XII.

(2) In all cases the crude product obtained from the 2N. sodium hydroxide extract was examined by I.R. and N.M.R. spectroscopy for the presence of benzyl phenols and the crude neutral product examined for the presence of unreacted aryl benzyl ether, in the same manner.

(3) The benzyl phenols prepared by this method were in all cases spectroscopically identical to those formed in the reactions of 2-aryloxyacetyl chlorides with $AlCl_3$ in benzene.

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

TABLE XII

Aryl Benzyl Ether (64) R =	Diphenyl-methane %	Phenol %	2-Benzyl-phenol (111) %	Notes
2,4-Cl_2	48	46	45	
4-F	70	67	30	
4-Cl	62	59	34	
4-Br	60	56	36	
4-I	47	37	-	(1)
H	45	45	54	
4-Me	38	32	53	
2-Me	43	33	55	
2,4-Me_2	51	45	48	
2,5-Me_2	55	51	42	(2)
2,6-Me_2	40	40	55	(3)
2,4,5-Me_3	33	33	65	(4)
2,4,6-Me_3	29	29	70	(5)
4-Ph	70	70	0	(6)

TABLE XII NOTES

(1) Iodine was liberated during the reaction and the benzyl phenolic fraction was a complex mixture of products from which a single product was not obtained by silica gel chromatography.

(2) 2-Benzyl-3,6-dimethylphenol.

m.pt. 72°C. (petroleum 40/60).

I.R. Spectrum; ν OH 3400cm.$^{-1}$

N.M.R. Spectrum; τ CH_2 6.1τ, τ OH 5.6τ (in CCl_4)

$C_{15}H_{16}O$ requires: C, 84.9; H, 7.5%

found: C, 84.5; H, 7.3%

(3) The benzyl phenolic fraction was shown by quantitative I.R. and N.M.R. spectroscopy to be a mixture of

3-benzyl-2,6-dimethylphenol (75%), and

4-benzyl-2,6-dimethylphenol (25%).

(4) 2-Benzyl-3,4,6-trimethylphenol

m.pt. 90°C. (petroleum 40/60).

I.R. spectrum: ν OH 3400cm.$^{-1}$

N.M.R. spectrum: τ CH_2 6.0τ, τ OH 5.8τ.

$C_{16}H_{18}O$ requires: C, 85.0; H, 7.9%

found: C, 84.8; H, 7.8%

(5) 3-Benzyl-2,4,6-trimethylphenol formed.

(6) Reference 65.

(c) A Study of the Reaction of 4-Chlorophenyl Benzyl Ether with $AlCl_3$ in Benzene at 5-10°C.

(i) To a stirred suspension of $AlCl_3$ (13.3gm., 0.1 moles) in benzene (150ml.) at 5-10°C. was added rapidly a solution of 4-chlorophenyl benzyl ether (21.9gm., 0.1 moles) in benzene (180ml.). At given intervals 50ml. aliquots of the homogeneous reaction mixture were removed and, using the normal separation scheme, analysed for the benzyl ether, diphenylmethane, 4-chlorophenol and 2-benzyl-4-chlorophenol.

Table XIII gives the results obtained.

TABLE XIII

Reaction time (minutes)	4-Chloro-phenyl benzyl ether %	Diphenyl-methane % a.	4-Chloro-phenol % a.	4-Chloro-2-benzyl-phenol % a.
15	0	66	65	33
22	0	66	66	34
30	0	65	65	34
40	0	66	65	34
110	0	65	64	35
180	0	65	63	35

NOTE a. Mole fraction of total expressed as a percentage.

(ii) The reaction was repeated with 4-chlorophenyl benzyl ether (2.2gm., 0.01 moles), $AlCl_3$ (1.4gm., 0.01 moles) and benzene (100ml.) at 5-10°C. Analysis of the products in the normal manner gave a mixture of diphenyl-methane (68%), 4-chlorophenol (66%) and 2-benzyl-4-chlorophenol (30%).

(iii) A mixture of 2-benzyl-4-chlorophenol (4.4gm., 0.02 moles), $AlCl_3$ (2.6gm., 0.02 moles) and benzene (50ml.) was stirred at 5-10°C. for 3 hours.

Following the normal separation scheme 2-benzyl-4-chlorophenol (4.2gm., 9%) was recovered unchanged from the alcoholic potassium hydroxide extract, no products (diphenylmethane or 4-chlorophenol) being obtained from the organic layer or the 2N. sodium hydroxide extract.

12. The Reactions of 2-Aryloxypropionyl Chlorides with $AlCl_3$ in aromatic solvents

(a) 2-(4-chlorophenoxy)propionyl chloride in benzene

To a stirred suspension of $AlCl_3$ (7.2gm., 0.05 moles) in benzene (70ml.) at 5-10°C. was added a solution of the acid chloride (from 8.8gm., 0.04 moles, the acid) in benzene (30ml.) over 30 minutes. The reaction mixture was stirred at 5-10°C. for 1½ hours, hydrolysed over 1 hour with dilute hydrochloric acid, and the products extracted into ether.

The organic layer was washed with sodium bicarbonate solution from which 2-(4-chlorophenoxy)propionic acid was recovered on acidification.

Yield 0.4gm., 5% theoretical.

The residue from the organic layer was a yellow oil (12.2gm.), the I.R. spectrum showing no carbonyl absorption and the N.M.R. spectrum showing no peaks in the 4τ to 5.5τ region, both confirming the absence of the aryloxy-acetophenone derivative or the cyclic ketone.

The crude product was dissolved in ether and washed with 2N. sodium hydroxide and alcoholic potassium hydroxide solutions. Acidification of the 2N. sodium hydroxide extract gave 4-chlorophenol (4.2gm., 74%), characterised by I.R. and N.M.R. spectroscopy, while the alcoholic potassium hydroxide extract gave, on acidification, a viscous oil (0.2gm.) whose I.R. and N.M.R. spectra showed this product to be mainly 4-chlorophenol.

The residue from the organic layer gave a single fraction on distillation at atmospheric pressure, 1,1-diphenylethane.

b.pt. 260-265°C.; yield 6.3gm., 79% theoretical.

The N.M.R. spectrum (in CCl_4) showed a broad singlet at 2.95τ, a quartet at 5.9τ (CH) (J = 7 c/s.) and a doublet at 8.4τ (CH_3) (J = 7 c/s.).

(b) 2-(4-Chlorophenoxy)propionyl chloride in p-Xylene

To a stirred suspension of $AlCl_3$ (7.2gm., 0.05 moles) in p-xylene (70ml.) at 10-15°C. was added over 30 minutes a solution of the acid chloride (8.9gm., 0.04 moles) in 40ml. p-xylene. The reaction mixture was stirred at 10-15°C. for 1½ hours, hydrolysed with dilute hydrochloric acid over 1 hour and in the normal manner the following extracts were obtained.

Acidification of the sodium bicarbonate extract gave 0.2gm., 3% of the recovered 2-(4-chlorophenoxy)propionic acid and the 2N. sodium hydroxide extract gave 4-chlorophenol (4.6gm., 81%) on acidification. No products were obtained from the alcoholic potassium hydroxide extract.

The organic layer, on removal of the solvent, gave a yellow oil (10.0gm.).

The I.R. spectrum showed no carbonyl absorption or hydroxyl absorption and the N.M.R. spectrum (in CCl_4) showed three almost degenerate singlets at 6.2 to 6.3 τ, a singlet at 7.85 τ and several low-intensity absorptions between 7.3 and 9 τ.

Fractional distillation of this product gave a single fraction, di-(2,5-xylyl)methane, purified by recrystallisation from ethanol.

b.pt. 180-185°C./13mm.

m.pt. 62°C. (EtOH); yield 7.6gm., 84% theoretical.

This product was characterised by I.R. and N.M.R. spectroscopy and gave no melting point depression in admixture with an authentic sample.

(c) 2-(2-Chlorophenoxy)propionyl chloride in p-Xylene

From 2-(2-chlorophenoxy)propionyl chloride (5.5gm., 0.025 moles), $AlCl_3$ (4.8gm., 0.035 moles) and p-xylene (70ml.) at 10-15°C. for 1½ hours, under the conditions outlined above, the following extracts were obtained.

Both the sodium bicarbonate and alcoholic potassium hydroxide extracts

gave no products on acidification while the 2N. sodium hydroxide extract gave 2-chlorophenol (2.8gm., 85%).

The residue from the organic layer (6.0gm.) was a yellow oil, whose I.R. and N.M.R. spectra indicated the absence of the acetophenone derivative or cyclic ketone.

Distillation of this product again gave di-(2,5-xylyl)methane.

m.pt. 61°C. (EtOH); yield 3.9gm., 70% theoretical.

13. (a) Preparation of 4-Chlorophenyl α-Phenylethyl Ether

(i) α-Phenylethyl bromide[79]

Styrene (26gm., 0.25 moles) was added dropwise to a solution of hydrobromic acid in glacial acetic acid (45% w/v.) (250ml.) and allowed to stand overnight at room temperature. A yellow oil was precipitated on addition of water, and was extracted into chloroform, the residue from the organic layer giving α-phenylethyl bromide on fractional distillation.

b.pt. 90-93°C./10mm.; yield 34gm., 74% theoretical.

(ii) 4-Chlorophenyl α-Phenylethyl Ether

A solution of 4-chlorophenol (21gm., 0.15 moles), α-phenylethyl bromide (30gm., 0.16 moles) and sodium ethoxide (7.2gm., 0.15 moles) in ethanol (200ml.) was refluxed for 2 hours and the solvent removed by distillation. 2N. sodium hydroxide was added and the products were extracted into ether. The residue from the organic layer, on recrystallisation from 40/60 petroleum, gave 4-chlorophenyl α-phenylethyl ether.

m.pt. 70°C.; yield 25gm., 73% theoretical.

The N.M.R. spectrum (in CCl_4) gave a quartet (J = 6 c/s) at 4.9τ(CH) and a doublet (J = 6 c/s.) at 8.45τ(CH_3). The aromatic region showed the phenyl group as a singlet (2.8τ) and gave J_{23} = 9 c/s.

(b) The Reaction of 4-Chlorophenyl α-Phenylethyl Ether with $AlCl_3$ in Benzene

To a suspension of $AlCl_3$ (3.2gm., 0.024 moles) in benzene (40ml.) at 5-10°C. was added a solution of the ether (5.5gm., 0.024 moles) in benzene (30ml.) over 30 minutes. The reaction mixture was stirred at 5-10°C. for 1½ hours and hydrolysed with dilute hydrochloric acid. Following the

separation scheme outlines in Part II, section (a), the following extracts were obtained.

Acidification of the 2N. sodium hydroxide extract gave 4-chlorophenol (2.1gm., 69%). The alcoholic potassium hydroxide extract, on acidification gave a yellow oil, which on distillation gave a single fraction, 4-chloro-2-(α-phenylethyl)phenol.

b.pt. 175°C./10mm.; yield 1.0gm., 18% theoretical.

The I.R. spectrum gave ν OH = 3550cm.$^{-1}$ and the N.M.R. spectrum (in CCl_4) gave a singlet at 4.9τ (OH), a quartet (J = 6 c/s.) at 5.8τ(CH) and a doublet (J = 6 c/s.) at 8.5τ(CH_3). The aromatic region showed the phenyl group as a singlet (2.9τ) and gave J_{56} = 8 c/s. and J_{35} = 2 c/s.

The residue from the organic layer was shown, by I.R. and N.M.R. spectroscopy, to be 1,1-diphenylethane (3.0gm., 70%).

(c) The Reaction of 4-Chlorophenyl α-Phenylethyl Ether with $AlCl_3$ in p-Xylene

To a suspension of $AlCl_3$ (3.2gm.) in p-xylene (40ml.) at 10-15°C. was added a solution of the ether (5.5gm.) in p-xylene (40ml.) over 30 minutes. After stirring at 10-15°C. for 1½ hours the reaction mixture was hydrolysed with dilute hydrochloric acid and, using the normal separation scheme, gave 4-chlorophenol (2.6gm., 86%) and a neutral fraction; the latter on fractional distillation gave di-(2,5-xylyl)methane (3.6gm., 68%).

14. The Reaction of 2-(4-Chlorophenoxy)isobutyryl Chloride with $AlCl_3$ in Benzene

To a stirred suspension of $AlCl_3$ (7.2gm., 0.05 moles) in benzene (70ml.) at 5-10°C. was added a solution of the acid chloride (from 8.9gm., 0.04 moles the acid) in benzene (30ml.) over 30 minutes. The reaction mixture was stirred at 5-10°C. over 1½ hours, hydrolysed with dilute hydrochloric acid and the benzene layer separated. Sodium bicarbonate extraction of the organic layer led to the recovery of 2-(4-chlorophenoxy)isobutyric acid (0.2gm.) while 4-chlorophenol (4.5gm., 79%) was the sole product obtained by extraction with 2N. sodium hydroxide solution. The alcoholic potassium hydroxide extract gave a dark viscous oil (0.1gm.) whose I.R. and N.M.R. spectra showed this to be impure 4-chlorophenol.

The dried organic layer was distilled at atmospheric pressure finally removing the last traces of solvent under slightly reduced pressure. A sample of the collected solvent was analysed by Gas Liquid Chromatography and the presence of isopropylbenzene determined by comparison with an authentic sample.

The residue from the organic layer was a dark viscous oil (3.2gm.) whose I.R. spectrum showed no carbonyl or hydroxyl absorption and whose N.M.R. spectrum showed a complex aromatic multiplet at 2.9 to 3.3τ and several peaks in the 8.2-9.2τ region. The absence of diphenylmethane, 1,1-diphenylethane or 2,2-diphenylpropane was established by comparison with known samples and was confirmed by Gas Liquid Chromatography.

The oil was re-dissolved in benzene and after treatment with decolourising charcoal a clear yellow oil (0.7gm.) was the only product obtained from the solvent; this could not be characterised.

REFERENCES

1. Palmer, M.H., McVie, G.J., Tet. Lett., 1966, 51, 6405.
2. Kalinowski, M.L., Kalinowski, L.W., J. Amer. Chem. Soc., 1948, 70, 1970.
3. Loudon, J.D., Razdan, R.K., J. Chem. Soc., 1954, 4299.
4. Chakravarti, D., Dutta, J., J. Ind. Chem. Soc., 1939, 16, 639.
5. Johnson, W.S., Org. Reactions, 1944, II, 114.
6. Von Braun, J., Ber., 1928, 61, 448.
7. Von Braun, J., Manz, G., Ann., 1929, 468, 258.
8. Schubert, W.M., Sweeney, W.A., Latourette, H.K., J. Amer. Chem. Soc., 1954, 76, 5462.
9. Huisgen, R., Reitz, U., Tet., 1958, 2, 271.
10. Buu-Hoi, N.P., Hoan, N., Xuong, N.G., J. Chem. Soc., 1951, 3499.
11. Rothstein, E., J. Chem. Soc., 1951, 1459.
12. Palmer, M.H., Scollick, N.M., unpublished results.
13. Stoermer, R., Atenstadt, P., Ber., 1902, 35, 3562.
14. Higginbotham, L., Stephen, H., J. Chem. Soc., 1920, 117, 1534.
15. Armarego, W.L.F., Aust. J. Chem., 1960, 13, 94.
16. Rothstein, E., Saboor, M.A., J. Chem. Soc., 1943, 425.
17. Rothstein, E., Saville, R.W., J. Chem. Soc., 1949, 1946.
18. Rothstein, E., Saville, R.W., J. Chem. Soc., 1949, 1950.
19. Rothstein, E., Saville, R.W., J. Chem. Soc., 1949, 1954.
20. Rothstein, E., Saville, R.W., J. Chem. Soc., 1949, 1959.
21. Rothstein, E., Saville, R.W., J. Chem. Soc., 1949, 1961.
22. McKenzie, A., Roger, R., McKay, W.B., J. Chem. Soc., 1932, 2597.
23. Ramart-Lucas, P., Ann. Chim., 1913, 30, 349.
24. Grundy, M.E., Rothstein, E., Hsu, W., J. Chem. Soc., 1956, 4561.

25. Grundy, M.E., Rothstein, E., Hsu, W., J. Chem. Soc., 1958, 581.

26. Grundy, M.E., Rothstein, E., Hsu, W., J. Chem, Soc., 1960, 372.

27. Khalaf, A.A., Roberts, R.M., J. Org. Chem., 1966, 31, 89.

28. Rothstein, E., Schofield, W.G., J. Chem. Soc., 1965, 4566.

29. Von Braun, J., Blessing, G., Cahn, R.S., Ber., 1924, 57, 908.

30. Von Braun, J., Wirz, W., Ber., 1927, 60, 102.

31. Short, W.F., Stewart, M.L., J. Chem. Soc., 1929, 553.

32. Huston, R.C., Eldridge, R.F., J. Amer. Chem. Soc., 1931, 53, 2260.

33. Iddles, H.A., et al., J. Amer. Chem. Soc., 1952, 74, 545.

34. Tarbell, D.S., Petropoulos, J.C., J. Amer. Chem. Soc., 1952, 74, 244.

35. Dewar, M.J.S., "Molecular Rearrangements" (P. De Mayo, Editor), Part I, Ch. 5, Interscience Publications, 1963.

36. Hart, H., Elia, R.J., J. Amer. Chem. Soc., 1954, 76, 3031.

37. Boesken, J., Rec. Trav. Chim., 1901, 20, 102.

38. Cook, D., Can. J. Chem., 1959, 37, 48.

39. Susz, B.P., Wuhrmann, J.J., Helv. Chim. Acta., 1957, 40, 971.

40. Baker, E.B., et al., J. Amer. Chem. Soc., 1962, 84, 2733.

41. Brown, H.C., Young, H.L., J. Org. Chem., 1957, 22, 719, 724.

42. Jensen, F.R., Brown, H.C., J. Amer. Chem. Soc., 1958, 80, 3039.

43. Calloway, N.O., J. Amer. Chem. Soc., 1937, 59, 1474.

44. Yamase, Y., Bull. Chem. Soc. Japan, 1961, 34, 480.

45. Brown, H.C., Marino, G., Stock, L.M., J. Amer. Chem. Soc., 1959, 81, 3310.

46. Hayes, N.V., Branch, G.E.K., J. Amer. Chem. Soc., 1943, 65, 1555.

47. Kovacic, P., Hiller, J.J., J. Org. Chem., 1965, 30, 1581.

48. Brown, H.C., Jensen, F.R., J. Amer. Chem. Soc., 1958, 80, 4042, 4046.

49. Bargellini, G., Gazz. Chim. Ital., 1906, 36_2, 334.

50. Dalgleish, C.E., Mann, F.G., J. Chem. Soc., 1945, 893.

51. Friedlander, P., Chwala, A., Monatsch., 1907, 28, 247.

52. Barber, H.J., et al., J. App. Chem., 1953, 3, 253, 259, 266.

53. Brodie, A.C., Palmer, M.H., unpublished results.

54. McIntyre, P.S., Palmer, M.H., unpublished results.

55. Behaghel, O., J. Prakt. Chem., 1926, 114, 287.

56. Barber, H.J., Fuller, R.F., Green, M.B., J. App. Chem., 1953, 3, 409.

57. Elkobaisi, F.M., Hickinbottom, W.J., J. Chem. Soc., 1959, 1873.

58. Mohlau, R., Ber., 1882, 15, 2497.

59. Welch, C.H., Smith, H.A., J. Amer. Chem. Soc., 1951, 73, 4391.

60. Gore, P.H., "Friedel-Crafts and Related Reactions" (G.A. Olah, Editor) Vol.III, Ch. 31.

61. Kovacic, P., Hiller, J.J., J. Org. Chem., 1965, 30, 1581.

62. Dewar, M.J.S., Puttnam, N.A., J. Chem. Soc., 1959, 4090.

63. Minton, T.H., Stephen, H., J. Chem. Soc., 1922, 121, 1591, 1598.

64. Elkobaisi, F.M., Hickinbottom, W.J., J. Chem. Soc., 1960, 1286.

65. Leitch, D.S., Palmer, M.H., unpublished results.

66. Beaven, G.H., et al., J. Chem. Soc., 1952, 854,
1955, 2708,
1956, 4637.

67. Khotinsky, E., Jacopson-Jacopmann, W., Ber., 1909, 42, 3097.

68. Gibson, G.P., J. Chem. Soc., 1923, 123, 1269.

69. Spiker, A., Ber., 1889, 22, 2772.

70. Brady, O.L., Dunn, F.P., J. Chem. Soc., 1914, 825.

71. Beckmann, E., Ber., 1893, 26, 2621.

72. Hodgson, H.H., Kilner, E., J. Chem. Soc., 1924, 808.

73. Bell, F., Robinson, P.H., J. Chem. Soc., 1927, 1127.

74. Vorozcov, N.N., Troshchenko, A.T., J. Gen. Chem. U.S.S.R., 1938, 432.

75. Org. Syn., 1935, 15, 39.

76. Org. Syn., 1921, 1, 39.

77. Lees, F. H., Shedden, F., J. Chem. Soc., 1903, 83, 758.

78. Nightingale, D.V., Hucker, H.B., J. Org. Chem., 1953, 18, 1529.

79. Ashworth, F., Burkhardt, G.N., J. Chem. Soc., 1928, 1798.