STUDIES   IN   CYCLISATION   REACTIONS:

THE   PREPARATION   OF   TRICYCLIC   KETONES

BY   INTRAMOLECULAR   ACYLATION

by

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TO MY PARENTS AND SHEILA

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I N D E X

EXPERIMENTAL

SUMMARY

The interaction of some twenty-four aryloxyacetyl chlorides and in particular 1- and 2-naphthyloxyacetyl chlorides, under Friedel-Crafts conditions with aluminium chloride in benzene has been investigated.

'Angular' cyclisation to the naphtho[1,2-b]furan-3(2H)one has been confirmed to be the dominant reaction of 1-naphthyloxyacetyl chloride and demonstrated to occur with seven nuclear substituted derivatives with electron releasing substituents, as well as with the side chain alkylated 2-(1-naphthyloxy)isobutyryl chloride. Chlorides with -E, -M groups, however, acylate the solvent and peri ring closure has been confirmed to occur when the 2-position is blocked by halogen.

2-Naphthyloxyacetyl chloride cyclises to the 'angular' ketone, naphtho[2,1-b]furan-1(2H)one, and similar 2,1 ring closure has been shown to occur with 7- and 8- substituted derivatives with no trace of the isomeric linear ketones. 1- Substituted acid chlorides in this series do not undergo intramolecular acylation, but acylate the solvent and eliminate carbon monoxide to give rise to divers alkylation products.

1-Phenanthryloxyacetyl chloride has been shown to ring close to the 6-membered ring peri condensed ketone and not to the 5-membered ring product.

An attempt has been made to rationalise these results in terms of steric electronic and conformational effects.

The present investigation has also included a study of the three isomeric monomethoxyphenoxyacetyl chlorides and it has been shown that while the substituent at the 3-position gives rise to exclusive acylation with cyclisation dominant, a methoxyl group in the 2- or 4-positions promotes extensive decarbonylation and these latter reactions are not accompanied by ring closure.

The acetylation of four dimethoxynaphthalenes in benzene has been examined and a reversible system demonstrated to operate in the acetylation of 2,7-dimethoxynaphthalene with aluminium chloride in benzene or nitrobenzene.

An improved synthesis of 3-iodo-1-naphthol prepared in admixture with 3-chloro-1-naphthol is reported together with a means of product separation.

Finally, the preparation of 1-oxaphenalen-3(2H)one and its 6-methoxy- derivative have been carried out. A synthesis of the former has since been recorded in the literature.

INTRODUCTION
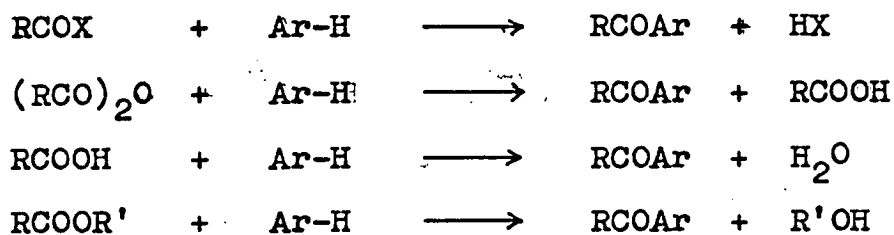
The Friedel-Crafts Reaction

With time it has become a generally accepted concept that any organic reaction brought about by the catalytic action of anhydrous aluminium chloride, or a related catalyst, is a Friedel-Crafts reaction.   The scope of the reaction by this definition, then, is considerable.   More specifically, but still in fairly broad terms, the Friedel-Crafts reaction involves attack by electrophilic carbon promoted by the action of a catalyst.   The electron accepting catalytic species may be a Lewis acid type acidic halide such as aluminium chloride or boron trifluoride, or a proton acid in the Bronsted-Lowry sense such as hydrogen fluoride or sulphuric acid.

The reaction may be applied to aromatic, aliphatic and alicyclic substrates.   Nevertheless it remains in the aromatic field where the reaction has received the greatest attention and it is in this connection that the present investigation is concerned.

In a generalised sense all Friedel-Crafts reactions can be divided into two main categories;   alkylations and acylations. The alkylation reaction as the name implies involves the intro-:duction or other reaction brought about by an alkyl group provided by the action of the catalyst on a typical alkylating agent such as an alkyl halide, alkene or alcohol.   Little more will be said of these alkylations here since it is the acylation reaction which is pertinent to the present work and more particularly its application to aromatic substrates.

Aromatic Ketone Synthesis

The Friedel-Crafts acylation of aromatic compounds leads to the formation of aromatic ketones. The acylating agents employed are usually acyl halides, acid anhydrides, esters or acids, and their reactions may be represented in the following manner :

$$RCOX + Ar\text{-}H \longrightarrow RCOAr + HX$$

$$(RCO)_2O + Ar\text{-}H \longrightarrow RCOAr + RCOOH$$

$$RCOOH + Ar\text{-}H \longrightarrow RCOAr + H_2O$$

$$RCOOR' + Ar\text{-}H \longrightarrow RCOAr + R'OH$$

Intermolecular acylations, where one molecule of the acyl component interacts with an aromatic molecule, have been of considerable synthetic importance. Apart from the obvious ease of formation of aromatic ketones with a carbonyl group adjacent to the ring, reduction of the carbonyl function by either the Clemmensen or Wolf-Kishner reductions gives ready access to alkyl aromatics which may be difficult to prepare by the Friedel-Crafts alkylation reaction which is often accompanied by polysubstitution and isomerisation of the side chain. Isomerisa-:tion of this sort is rare in acylations and once an acyl group has been introduced the electron withdrawing effect of the carbonyl group generally deactivates the aromatic nucleus to further electrophilic attack.
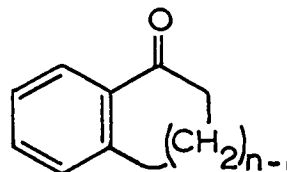
An important application of the acylation reaction is the preparation of cyclic ketones by an intramolecular reaction

involving an aromatic ring with an attached side chain. The
cyclisation of β-phenylpropionic acid (1) and the chloride of
γ-phenylbutyric acid (3) to 1-hydrindone (2) and 1-tetralone (4)
respectively are two simple examples.
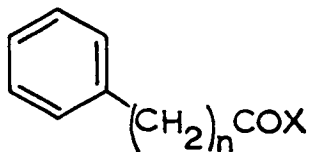
(1) n = 2, x = OH
(3) n = 3, x = Cl

(2) n = 2
(4) n = 3

These reactions may be carried out by heating the acid with
a suitable condensing agent such as sulphuric acid, hydrogen
fluoride or stannic chloride as in (1) to (2), or by first
converting the acid into its chloride and treating the latter
with a Lewis acid such as aluminium chloride as in (3) to (4).

Intramolecular acylations have been fairly extensively
investigated and diverse types of arylaliphatic acids with
substituents both in the aromatic nucleus and in the side chain
have been cyclised and hydroaromatic and heterocyclic systems
synthesised. Several factors have been found to influence these
cyclisations with respect to both the nature and yield of the
product or products formed. Clearly the size of the ring to be
formed, the nature of substituents and the position of these
substituents in the aromatic ring or in the side chain are of
importance. The condensing agents too and even the reaction

conditions for a particular catalyst have also been observed on occasions to give rise to different products. Many of these factors will be discussed in later sections.

Purpose of the Present Investigation

The present investigation is concerned with the products obtained from the treatment of a number of aryloxyacetyl chlorides under Friedel-Crafts conditions. The major part of the work has been directed at studying the products arising from cyclisation of nuclear substituted 1- and 2-naphthyloxyacetyl chlorides, (5) and (6) respectively, where ring closure may give rise to one or both of two isomeric tricyclic ketones for each series. These ketones may be represented by the formulae (7) to (10) below.
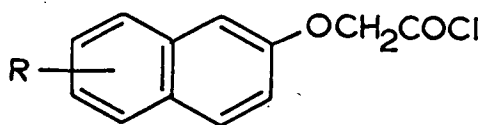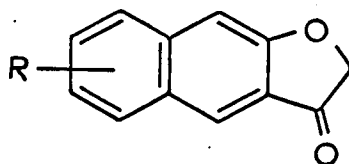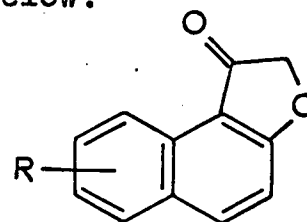
(5)   (7)   (8)
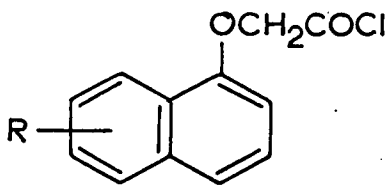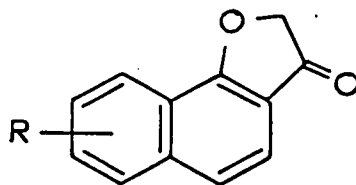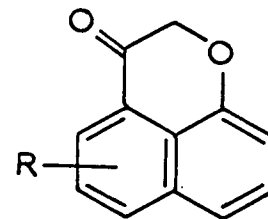
(6)   (9)   (10)

Cyclisation of 2-naphthyloxyacetyl chloride (5, R = H) has been effected by Ingham, Stephen and Timpe who obtained as the sole ketonic product the angular ketone naphtho[2,1-b]furan-1(2H)one (8, R = H).[1]

The absence of the linear ketone naphtho [2,3-b] furan-3(2H)one
(7, R=H) has been recently verified by comparison of its Infra
Red and Nuclear Magnetic Resonance spectra with those of the
crude product from cyclisation.[2]

Ingham et al.[1] also investigated the unsubstituted acid
chloride (6, R=H) on reaction with aluminium chloride in benzene
and obtained the 1,2-ring closed product naphtho [1,2-b] furan-3
(2H)one (9, R=H). The peri ring closed ketone 1-oxaphenalen-3 (2H)
one (10, R=H) was not observed in this reaction.

Peri ring closure has however been reported by O'Brien and
Smith[3] in the cyclisation of 2-chloro-1-naphthyloxyacetyl chloride
with aluminium chloride, blocking of the ortho position ensuring
peri cyclisation. This reaction was performed with benzene as
solvent and it is interesting that none of the intermolecular
ketone (11) was reported from solvent acylation.
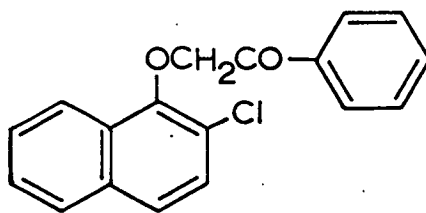
(11)

The cyclisations of the unsubstituted acid chlorides (5 and
6, R=H) were also conducted in benzene and no solvent acylation
is reported in these cyclisations. Clearly intramolecular
acylation in both series is likely to occur readily in the absence
of strongly deactivating influences.

The object then was to investigate a number of suitably substituted chlorides of (5) and (6) (R various) with a view to providing electronic activation at the ring closure sites not attacked in the case of the unsubstituted chlorides. Alternative approaches to obtaining the 'abnormal' ketones were specific deactivation of the 2-position of the 1-naphthoxyacetyl chloride, the site normally substituted in this series, and provision of a bulky substituent in the 8-position in the β-series to give rise to a large steric effect to acetylation at the adjacent α-site.

Although these studies form the major part of the work a number of other factors have been investigated, the more important ones being listed below.

i) Reaction of the three isomeric methoxyphenoxyacetyl chlorides with aluminium chloride in benzene and rearrangement of the corresponding aryl benzyl ethers under similar conditions.

ii) Acylation studies with acetyl and chloroacetyl chlorides on methoxynaphthalene derivatives where this has been considered useful in connection with the cyclisation of naphthyloxyacetyl chlorides.

iii) Investigations into reversibility in Friedel-Crafts systems.

Interaction of Phenoxyacetyl Chlorides with Aluminium Chloride

In recent years extensive investigations have been carried out in this Department concerning the interaction of various phenoxyacetyl chlorides with aluminium chloride in both aromatic and non-aromatic solvents.[2,4]   Those data pertinent to the present research, which is obviously closely related, are summarised briefly below.

Palmer and McVie [4,5] were able to show that reaction of phenoxyacetyl chloride (12) with aluminium chloride in a molar ratio of unity at 5 - 10° C. over 1.5 hours in benzene (15 moles) led to the formation of some five products as well as the recovery (10%) of phenoxyacetic acid after hydrolysis.   Isolated and characterised were the major product benzofuran-3(2H)-one (13) from intramolecular acylation and the intermolecular ketone, 2-phenoxyacetophenone (14), in low yield.   As well as these acylation products, small amounts of phenol (19) o-benzylphenol (17) and diphenylmethane (18) were obtained.   The last three products are considered to arise from unimolecular loss of carbon monoxide from the acylium ion (or other reactive species) followed by alkylation of the solvent and rearrangement of the resulting benzyl phenyl ether (16) to the observed products.

Benzyl phenyl ether was shown to be unstable to the conditions used in the reaction and to give rise to products (17), (18) and (19).   The product distributions in the ether

rearrangement with aluminium chloride and the acid chloride
experiment were shown to be similar and justified the postulate
that benzyl phenyl ether was the initial decarbonylation product.
Similar relationships were observed with nuclear substituted
acid chlorides and the corresponding aryl benzyl ethers.[4,6]
The entire scheme may be represented in the following way:-
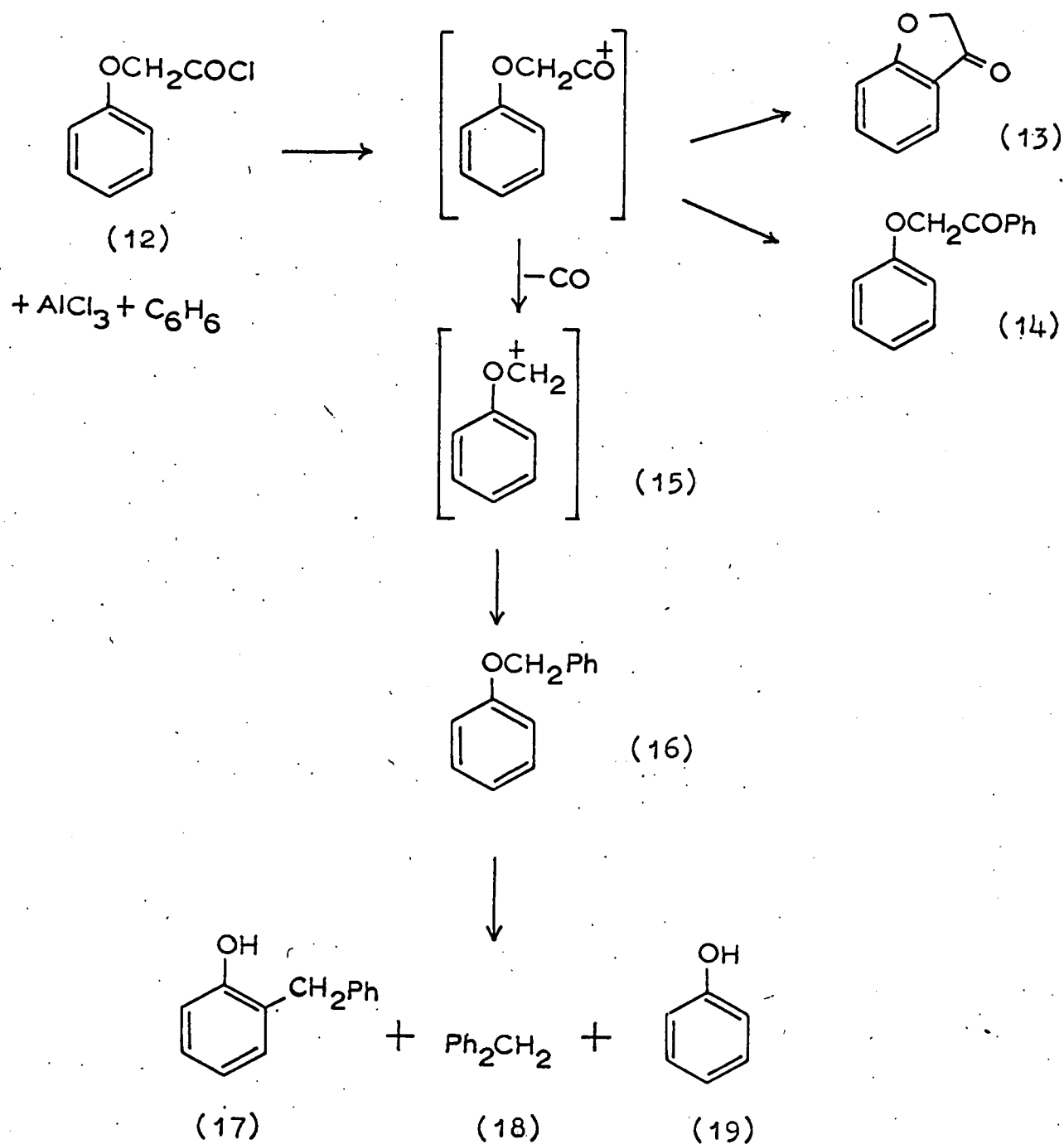
From a study of nineteen nuclear substituted phenoxyacetyl chlorides under similar conditions the effect of the substituent groups was determined. Strongly electron attracting substituents (-E, -M resonance polar effects) in the 2- or 4-position of (12) (12, with 2-NO$_2$, 4-NO$_2$, 2-CN) gave exclusively the corresponding 2-phenoxyacetophenones (analogues of 14) in 30 - 50% yield, the remaining material being accounted for as unreacted starting material isolated as the acid after hydrolysis. The low conversion is likely to be due to electron withdrawal from the aromatic nucleus decreasing the rate of formation of acylium ions by reducing the basicity of the chlorocarbonyl group in (12). This would imply, of course, that acylium ion formation is rate determining. The deficiency of nuclear electrons also accounts for the lack of decarbonylation products since the cationic species (15) would be expected to be stabilised to a lesser extent by resonance with the aromatic ring.

In carbon disulphide, nitromethane and other inert solvents, however, it has been demonstrated that phenoxyacetyl chlorides with -E -M groups in the 2- or 4-positions lose carbon monoxide exclusively and the major product from these reactions is the chloromethyl ether (20).[4, 7]

OCH$_2$COCl

AlCl$_3$ in CS$_2$

OCH$_2$Cl

(20)

R = 2-NO$_2$, 4-NO$_2$, 2-CN etc.
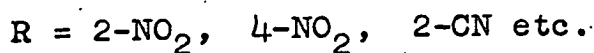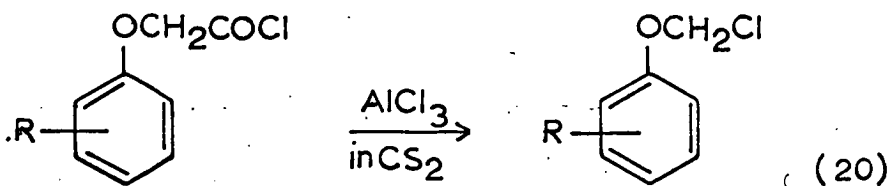
The failure of 2,4-dinitrophenoxyisobutyroyl chloride to yield a similar product suggested a bimolecular loss of carbon monoxide from nucleophilic attack by chloride or tetrachloro- aluminate ions on the acylium ion:
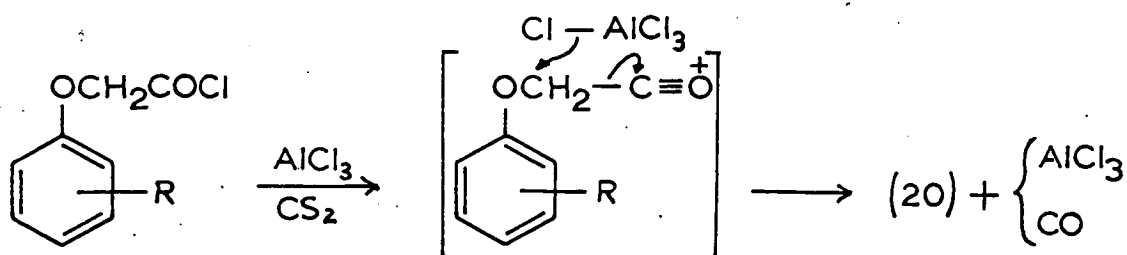
2- and 4-Halogeno-phenoxyacetyl chlorides also gave the intermolecular ketone as the major product in all cases in yields of 30 - 80%. The cyclic ketone and decarbonylation products were also observed in these instances and the overall conversion to products high as indicated by the low recovery of acid. In these instances then net deactivation of the ring is still the important feature although offset to some extent by electron release from the halogen.

With alkyl substituted phenoxyacetyl chlorides the cyclic ketones were obtained as the dominant products. With 3- and 3,4- disubstituted chlorides Palmer and Scollick [2, 8,] frequently observed mixtures of the isomeric intramolecular ketones arising from ring closure at both the available ortho sites. An example is the cyclisation of 3,4-dimethyl- phenoxyacetyl chloride (21) which gave the linear product (22)

as the major isomer

(21)   24%   76%   (22)
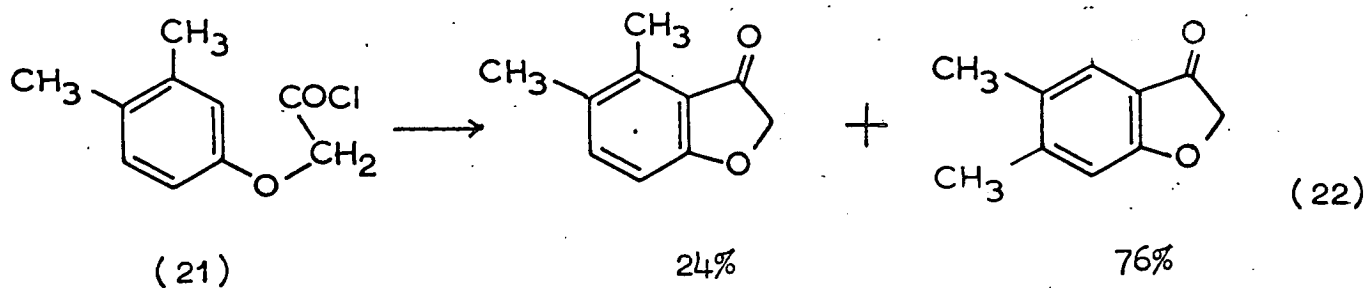
An interesting observation by these workers was the fact that with the polymethylene substituted acid chlorides of the type (23) while for n = 3, 5 and 6 the linear product (24) was the major one, for n = 4 the angular isomer (25) predominated. This is a further extension of the Mills-Nixon Effect.

(23)   (24)   (25)
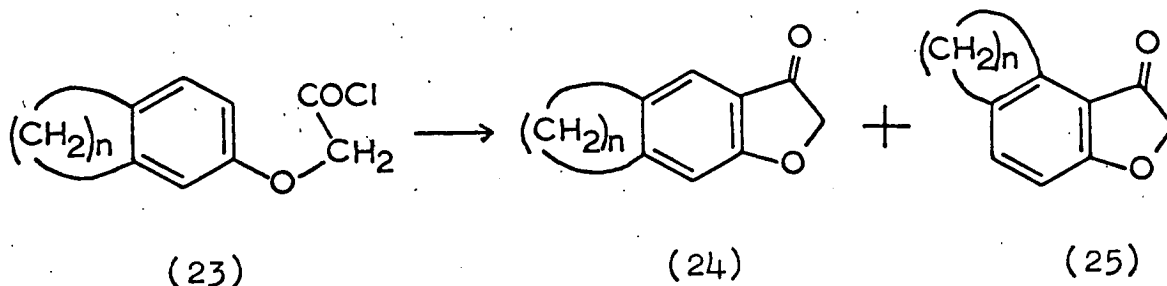
Treatment of phenoxyacetyl chlorides with aluminium chloride in aromatic solvents other than benzene, and in this respect p-xylene, anisole, m-dimethoxybenzene have been used, indicated a higher proportion of intermolecular acylation over both cyclisation and decarbonylation with respect to benzene.[4, 9] Increasing the nucleophilic character of the solvent had enhanced intermolecular acylation, a result to be expected, and implied a unimolecular loss of carbon monoxide in decarbonylation with aromatic solvents.

With chlorobenzene and o-dichlorobenzene, solvents which do not readily acylate or alkylate, tarry products were obtained which were largely intractable and thought to be due to further acylation of the initial products formed which were themselves more nucleophilic than the solvent. A similar but worse situation was envisaged with nitrobenzene as solvent and for this reason its use was not investigated.

The benzofuranones, although fairly stable to acid, have been shown to be susceptible to attack under basic conditions on account of the reactive methylene group. This has been demonstrated by the ready ease of formation of the 2-benzylidene derivative (26) from benzofuran-3(2H)one on condensation with benzaldehyde.

PhCHO

(26)
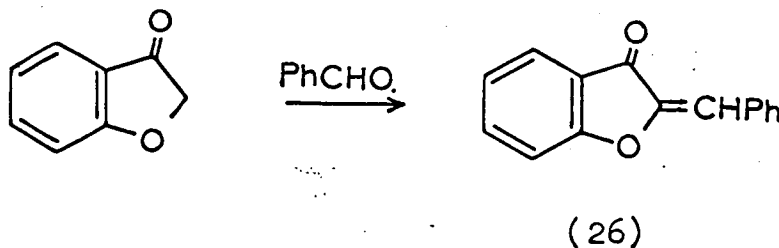
These ketones have also been shown to be susceptible to self condensation under alkaline conditions. Thus the fairly rapid dimerisation of the ketone (27) to (28) is observed in sodium methoxide solution on gentle warming. Immediate formation of the anion of the enol form was observed by following the reaction by N.M.R. spectroscopy.[10]

(27)　　　　　　　　　　　　　　(28)
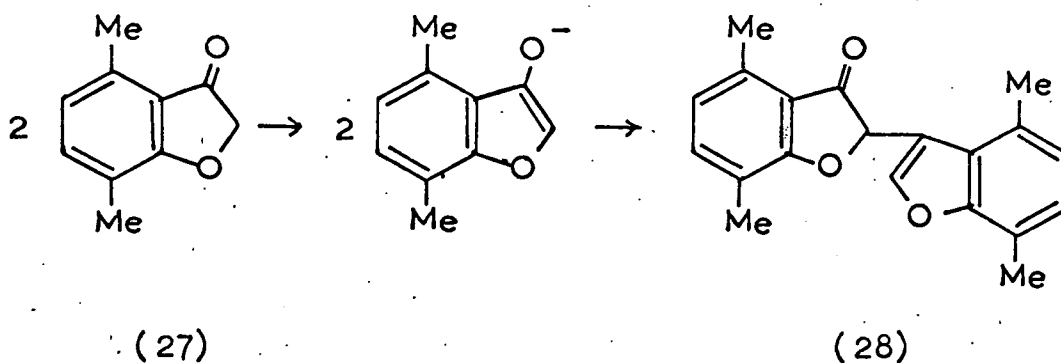
Syntheses of Tricyclic Ketones

Two aspects only of tricyclic ketone synthesis are considered here. The first section deals with the oxygen containing ketones represented by the general formulae (7), (8), (9) and (10) and is a survey of the preparative routes which have been applied in their syntheses. A second section surveys the cyclisation of a number of naphthyl acids or acid chlorides of the general formulae (29) and (30) and is thus restricted to acylations.
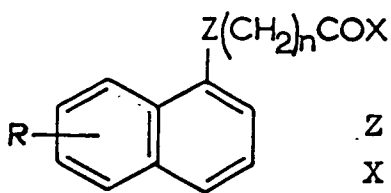
$Z = CH_2$, S
$X = OH$, Cl
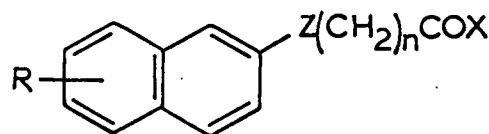
(29)　　　　　　　　　　　　　　(30)

It is not designed to be an exhaustive survey of all such

recorded acylations but merely to illustrate a number of features pertinent to the principal theme of the current investigation.

a) Syntheses of (7), (8), (9) and (10)

These compounds, in common with very many other heterocyclic systems, are most conveniently prepared from the intact naphthalene skeleton with addition of the heterocyclic ring.   Three types of syntheses may be identified and represented in the following manner, the broken line indicating the final bond formation
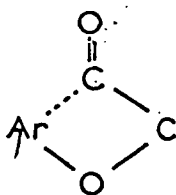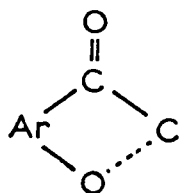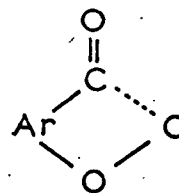
Type A   Type B   Type C

Type A syntheses are, of course, intramolecular acylations and form the basis of the present investigation.   Three ketones, naphtho [1,2-b] furan-3(2H)one (9, R=H)[1], naphtho[2,1-b] furan-1(2H)one (8, R=H)[1] and 9-chloro-1-oxaphenalen-3(2H)one (10, R=9Cl)[3] are reported to be synthesised by this method.

Anand and Venkataraman[11] have synthesised naphtho[1,2-b] furan-3(2H)one starting from 1-hydroxy-2-naphthoic acid (31) and proceeding through the diazoketone (32)

(31)　　　　　　　　　　　　　(32)

(9)

(R = H)
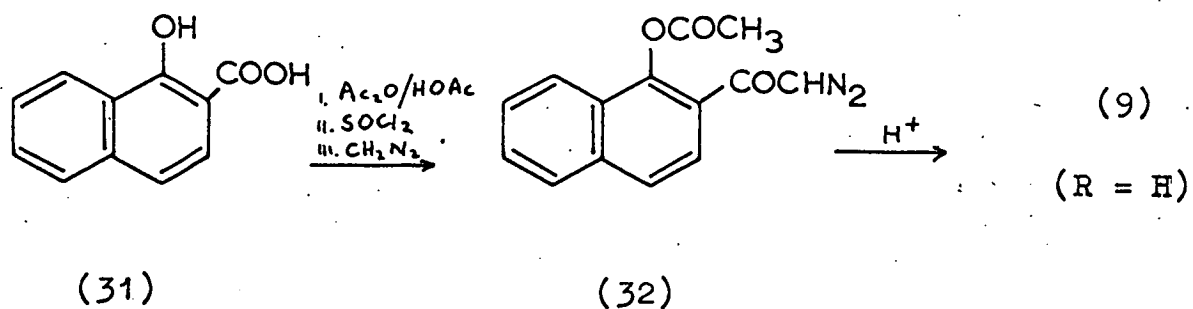
This unambiguous synthesis of Type B gave a product of identical melting point to that obtained by Ingham and his co-workers[1] from the cyclisation of 1-naphthyloxyacetyl chloride. A similar synthesis has given rise to the linear ketone (34) from 3-methoxy-2-naphthyl diazomethyl ketone (33)[12]

(33)　　　　　　　　　　　　　(34)
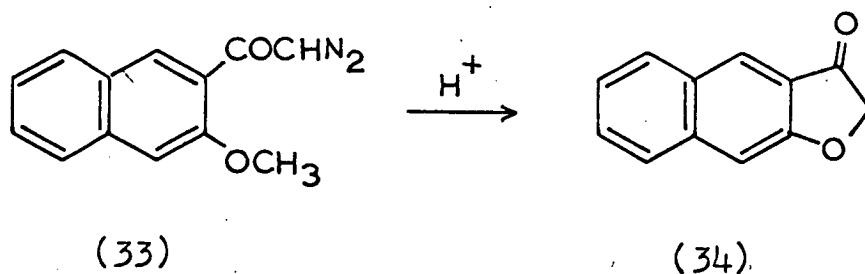
The synthesis of the ketone (36), 5-methoxynaphtho[1,2-b]furan-3(2H)one, from 1,4-dimethoxynaphthalene has been reported by the following sequence[13]

(35)　　　　　　　　　　　　　(36)
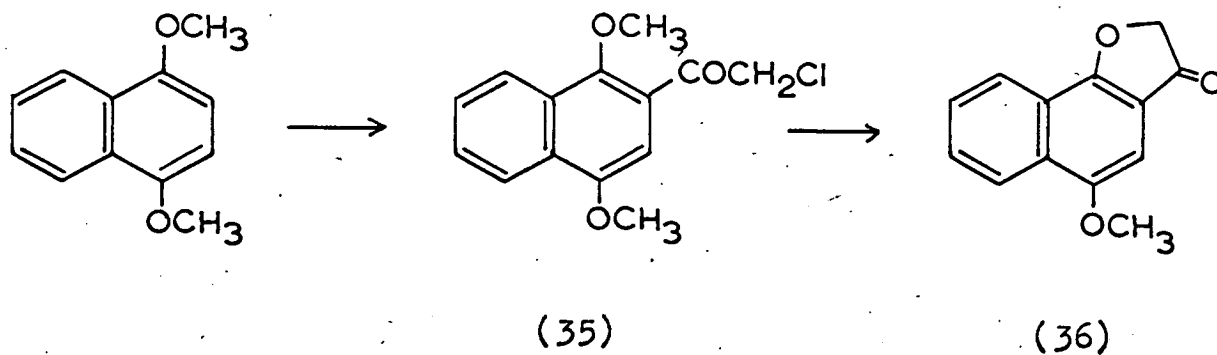
Treatment of the chloromethyl ketone (35) in boiling methanol with an aqueous suspension of calcium carbonate the author claimed led to demethylation and cyclisation to (36) although no yield is given for this stage. This sequence of reactions is similar to that employed by von Auwers and Pohl[14] in the synthesis of the methoxybenzofuranones (37) and (38)
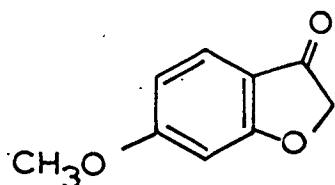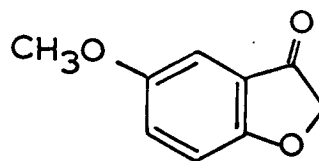
(37)   (38)

In the syntheses of the benzofuranones, treatment of both m- and p-dimethoxybenzene with chloroacetyl chloride in a Friedel-Crafts reaction gave the phenolic chloromethyl ketones (39) and (40) respectively where ether fission had occured in the position ortho to substitution
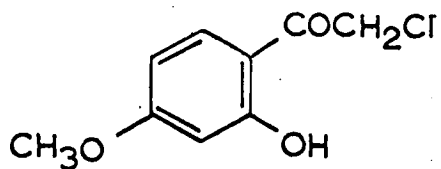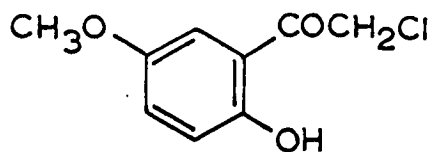
(39)   (40)

Both the above chloromethyl ketones cyclised readily and in good yield to the benzofuranones (37) and (38).

It might reasonably have been expected by analogy that

acylation of 1,4-dimethoxynaphthalene with chloroacetyl chloride would have given the partially demethylated species (41), which could ring close readily, rather than (35)

OH
COCH₂Cl
(41)
OCH₃
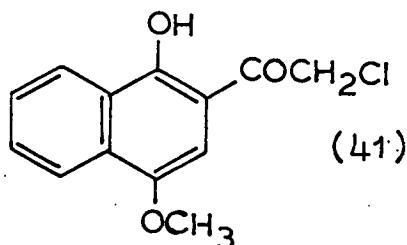
Type C syntheses have been applied in the unambiguous preparation of both the linear naphthofuranone (7, R=H) and 1-oxaphenalen-3(2H)one (10, R=H). Intermediates in syntheses of this sort are the diacids such as (42) or diesters such as (43) where $R^1=R^2=$alkyl.

OCH₂COOH

COOH

(42)

(7, R = H)

R²OOC   OCH₂COOR'
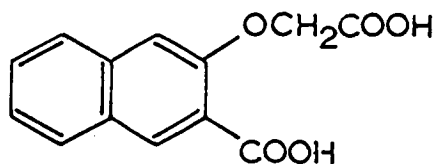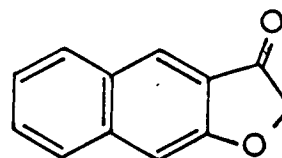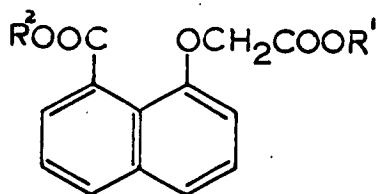
(43)
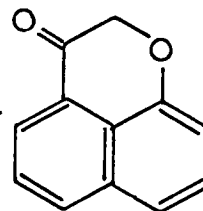
(10, R = H)

Emmot and Livingstone[15] prepared the linear ketone from the diacid (42) by first converting it into the enol acetate (44)

followed by hydrolysis of the cyclic acetate with base.
Acidification yielded the cyclic ketone.

(42) → $\xrightarrow[\text{NaOAc}]{\text{Ac}_2\text{O}}$ → (44) → $\xrightarrow[\text{ii. H}^+]{\text{i. OH}^-}$ → (7, R = H)
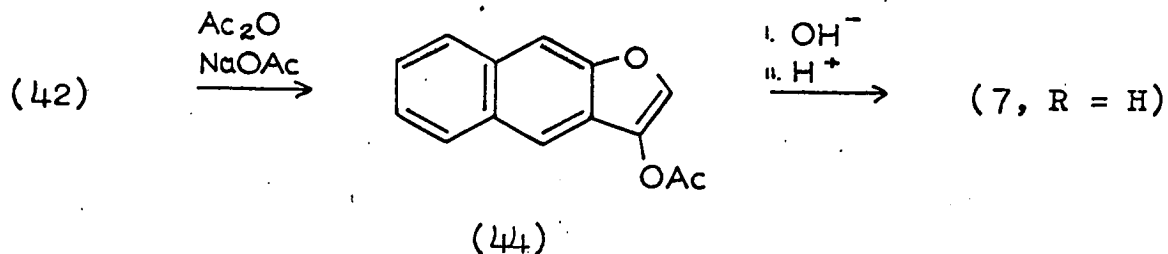
Possible mechanisms for the ring closure and hydrolysis
steps are suggested in the Discussion.

The diester (43, R^1 = Et, R^2 = Me) has recently been converted
by Alderson and Livingstone[16] into 1-oxaphenalen-3-one through a
Dieckmann cyclisation, an internal Claisen condensation, to
ethyl 3-oxo-2,3-dihydro-1-oxaphenalene-2-carboxylate (45).
Hydrolysis and decarboxylation of this yields the oxaphenalenone
(10, R=H)

(43)
(R^1 = Et,
R^2 = Me) → $\xrightarrow[\text{C}_6\text{H}_6]{\substack{\text{Na} \\ \text{EtOH}}}$ → (45) → $\xrightarrow[\text{ii. H}^+]{\text{i. OH}^-}$ → (10, R = H)
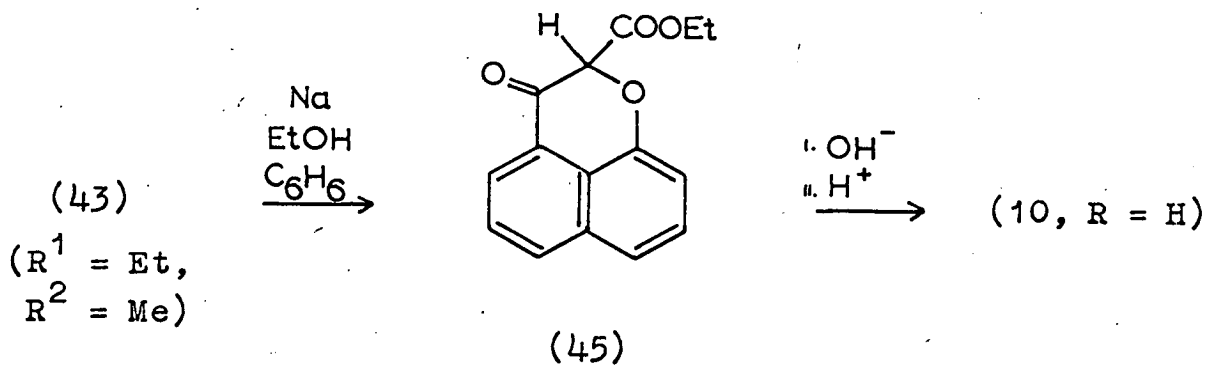
These workers also report the synthesis of (10, R=H) from
the diacid (43, R^1 = R^2=H) through 1-oxaphenalen-3-yl acetate.[16]

b) <u>Intramolecular acylations of compounds of type (29) and (30)</u>

The cyclisations of a large number of 1- and 2-naphthylalkanoic acids, which may be represented by the general formulae (46) and (47), have been reported in the literature either by cyclodehydration of the free acids themselves or by cyclodehydrohalogenation of the acid chlorides.

(46)   (47)
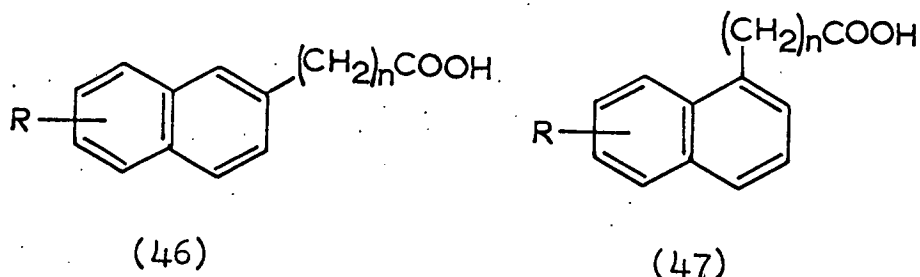
The nature of the cyclic products obtained is outlined below.

In the 2-naphthyl series the unsubstituted acids (46, R=H) and their chlorides have been reported to ring close at the neighbouring α-position for n=2, 3, 4, 5 and 6.[17-20]   The corresponding angular ketones (48, R=H, n=2-5) then are the products of these cyclisations.

(48)   (49)
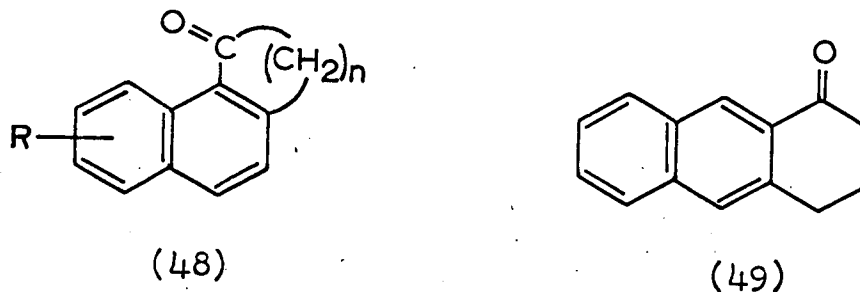
In all the reported cyclisations of these chain lengths the

angular ketones are claimed as the sole products with but one exception. Bavin[19] has observed that cyclisation of γ-(2-naphthyl)-butyric acid (46, R=H, n=3) with hydrogen fluoride at room temperature and subsequent dehydrogenation with palladised charcoal of the crude product gave a mixture which analysed by U.V. spectroscopy to be 2% anthracene. This was a clear indication that the linear ketone (49) was in fact formed in the cyclisation since phenanthrene, the dehydrogenation product from the angular ketone was not isomerised under the conditions employed for dehydrogenation.

Huisgen and Rietz [20] have reported a rather different type of heteronuclear cyclic ketone with the higher homologues of (46) where cyclisation of the acid chloride with n=10 gave annellation at the 8-position to yield the ketone (50). The lauric and myristic acid chlorides (46, R=H, n=11 and 13) as well as giving the ketones from ring closure at the 8-position, also gave detectable amounts of the 2,6-naphthocyclanones (51).

(50)   (51)
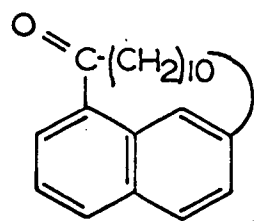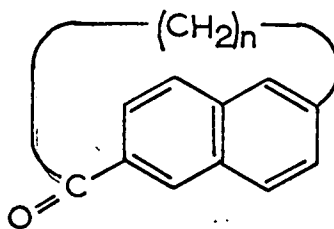
n = 11 and 13

Thus in large ring systems where the variation in ring strain with ring size is not significant, a proximity effect of the acylium ion (or other reactive species) to the site of sub-

:stitution seems to be all important in their syntheses. A proximity effect, too, probably plays a part in the formation of the smaller ring 1,2-substituted ketones although in the latter case a ring strain effect may be rather more significant. The effect of ring size on cyclisation products will be dealt with later in greater detail.

Peri effects precluding 1,2 cyclisation have been observed and the ketones substituted at 3-position of the naphthalene nucleus obtained. Thus the cyclisation of γ-(8-methyl-2-naphthyl)butyric acid (52) gives 1-keto-1,2,3,4-tetrahydro-5-methylanthracene (53) and not the ketophenanthrene derivative (54).[21]

(53)   (52)   (54)
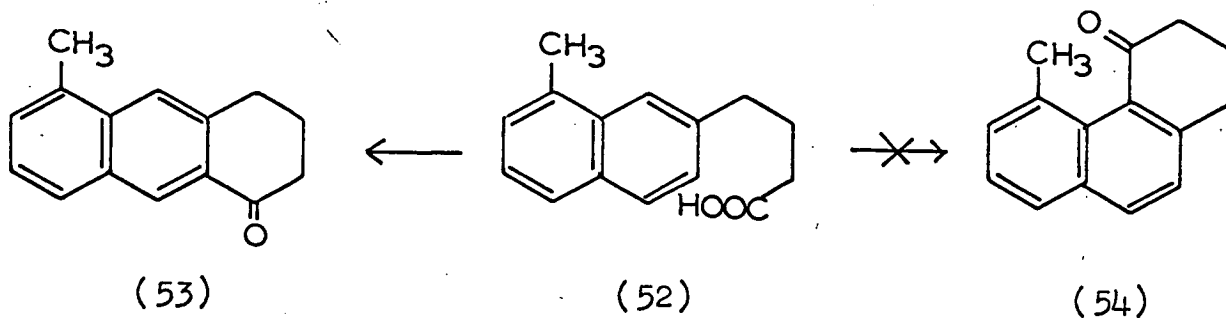
The relatively small methyl group is sufficient to cause a prohibitive steric effect to angular cyclisation. Indeed the steric effect of the peri hydrogen appears to have been sufficient to direct the cyclisation with polyphosphoric acid of the ketone (55) to the linear 1-ethylanthracene (56) rather than the expected 4-ethylphenanthrene (57).[22] This last reaction is however an alkylation and not an acylation and hence a different sort of

mechanism operates.

(55) (56) (57)
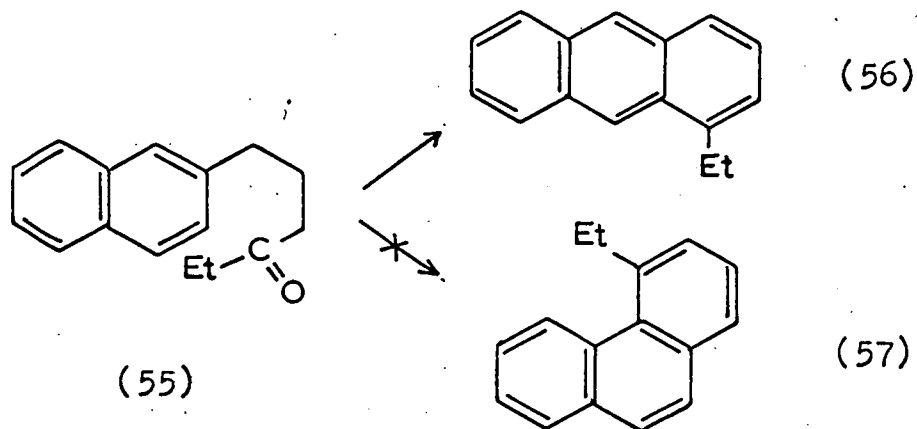
The cyclisation of 1-naphthylacetic acid derivatives appears
to occur exclusively at the peri-position giving acenapthenones.
1, 2 cyclisation would lead to a severely strained four membered
ring ketone and hence it is not surprising that ketones of this
sort have not been observed.   A number of substituted
1-naphthylacetic acids and their chlorides have been successfully
cyclised showing the method to be a convenient way to preparing
acenaphthenones.   The observation by Green and Hey,[23] however,
of the failure of both 4- and 6-methoxy-1-naphthylacetic acids
to cyclise with a number of condensing agents is interesting.
An electronic effect seems to be operating in these cases
deactivating the peri position to electrophilic substitution
since the unsubstituted acid is cyclised readily under mild
conditions.   The acids substituted with a 5- or 7-methoxyl
group did cyclise readily and this is expected since electron
donating alkoxyl groups in these positions would be expected to
increase the reactivity of the peri-position.

The cyclisation of β-(1-naphthyl)propionic acids (47, n=2) and their derivatives has been shown to lead to three types of products. The cyclic ketones (58) and (59) have been observed in these cyclisations arising from peri- and ortho-acylation respectively. A third product (60), a phenalenone (peri-naphthenone), has also been isolated in some instances.
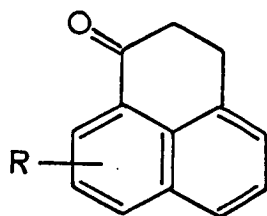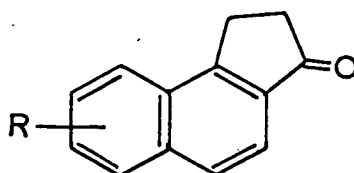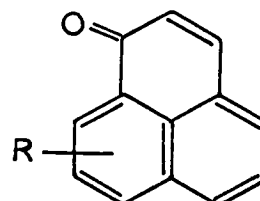
(58)   (59)   (60)

Phenalenone formation has been shown to be due to dehydro-genation in situ of the initially formed dihydro- compound (58).[24] The course of the reaction appears to be considerably affected by the cyclisation conditions employed. Thus with the unsubstituted propionic acid Fieser and Gates [25] isolated 2,3-dihydrophenalenone (58, R=H) in 81% yield together with a small amount of the 4,5-benzindanone (59, R=H) with hydrogen fluoride as condensing agent. Use of stannic chloride or aluminium chloride, however, in addition to the above compounds gave about 40% of phenalenone (60, R=H).[25, 26] Nonetheless the proportion of angular ketone with the unsubstituted acid is never more than 5%. Similar results were noted by Wenham and Whitehurst[24] on studies of the 7-alkyl series. These authors found that with a single catalyst (polyphosphoric acid) increasing the reaction time from fifteen

minutes to forty-five minutes and the temperature from 110° to 140° resulted in different products being obtained. At the lower temperature the alkyl-perinaphthanones were favoured but at higher temperature the dehydrogenation products (60, R=7-alkyl) were obtained in high yield. It was also found that cyclisation occurred almost exclusively at the peri-position for the acids (47, n=2, R=7 Me, 7 Et, 7-Pr^i) with a variety of condensing agents and only traces of the benzindanone derivatives were formed. It is interesting particularly that the 7-isopropyl substituted acid should give the peri ketone; a clear indication that the inductive activation of the peri position by the bulky isopropyl group is more than sufficient to offset its steric effect.

With the 7-tertiary butyl substituted acid, however, the benzindanone derivative was formed in preference to the peri-condensed ketone, a manifestation of the dominating steric effect.[27]

With both 5-methoxy and 7-methoxy-(1-naphthyl) propionic acids and their chlorides with a variety of catalysts and conditions, Green and Hey only obtained the peri-cyclised ketones with no trace of the benzindanones.[23] Clearly specific activation by the substituents of the 8-position over the 2-position accounts for this. The 6-methoxy substituted acid, however, cyclised to 3'-methoxy-4,5,benzindan-1-one (61) exclusively, presumably due to an amphi-effect, where the methoxyl is able to assist in delocalisation of the charge of the incoming acylium group in the manner depicted in (62). Nonetheless since the unsubstituted acid did give a small amount of the angular ketone it is not solely

an amphi-effect which operates.

(61)   (62)
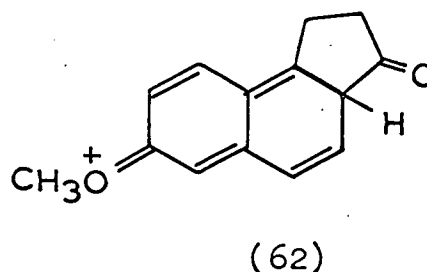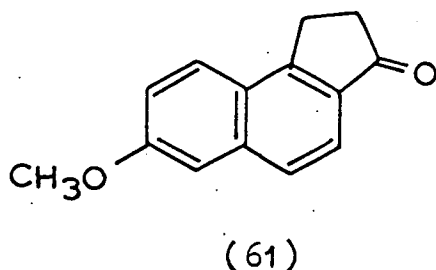
With the 1-naphthyl propionic acids then the inherent
tendency is for peri-ring closure and a plausible explanation is
the preference for six--rather than five- membered ring formation.

Cyclisation of the acid chloride of γ-(1-naphthyl)butyric
acid (47, R=H, n=3) with aluminium chloride gives only the angular
ketophenanthrene derivative.[28]   Peri-cyclisation has however
been observed with the butyric acids either with a 2-substituent
blocking the ortho cyclisation site[29] or with a methoxyl group
in the 5- or 7-positions.   Gilmore and Horton isolated the
homophenalenone (63) in 18% yield from the cyclisation of the
acid chloride of γ-(7methoxy-1-naphthyl)butyric acid with
aluminium chloride although the major product (64) was that from
1,2 ring closure in 78% yield.[29]   A similar cyclisation with
aluminium chloride of the isomeric 5-methoxy acid chloride is
reported[30, 31] to yield the dihydrohomophenalenone (65) whereas
the use of stannic chloride on the free acid affords the
ketophenanthrene.   Later Lockett and Short[32] reported only the
peri-product by either method and a subsequent investigation[23]
with the added refinement of the application of U.V. spectroscopy

has confirmed this.
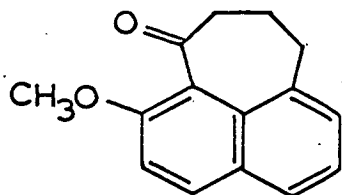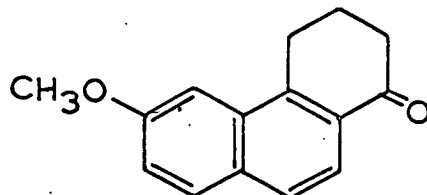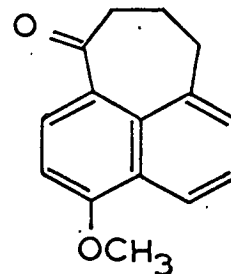
(63)   (64)   (65)

The preferential formation of a seven-membered peri ring over an energetically more favoured six-membered one across the 1,2-positions is rationalised by considering the activation at the peri-position by the 5-methoxyl group which appears to be just sufficient to overcome the additional ring strain. The 7-methoxyl on the other hand is not quite sufficient and this might at least in part be due to a proximity effect of the substituent to the peri-position giving rise to a steric inter- action in the intermediate for peri ring closure.

As with the 2-naphthylalkanoic acids of longer chain length, Huisgen and Rietz have reported non-neighbouring ring closures with the higher homologues of the 1-naphthyl acids.[33] For n=6, 7, 8 and 9 in (66) high dilution Friedel-Crafts acylation of these chlorides gave the 1, 7 cyclised products (67). For n=9 the 1,4-naphthocyclanone (68) was also detected.
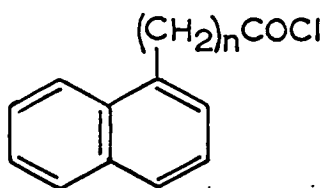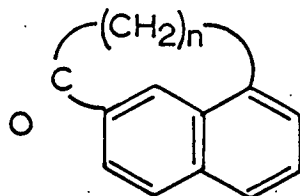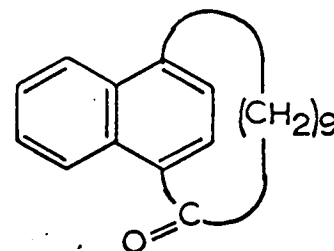
n = 6,7,8,9   n = 6,7,8,9
(66)   (67)   (68)

Truce and Toren have investigated inter alia the cyclisation of 1-naphthylalkanesulphonyl chlorides (69) in the presence of aluminium chloride in nitrobenzene solution. The products obtained for n=2, 3 and 4 were only the 1,2 ring closed sulphones (70) and no peri-annellation was detected.[34]
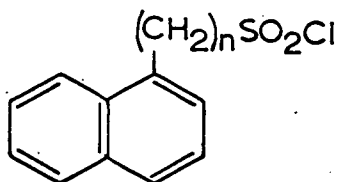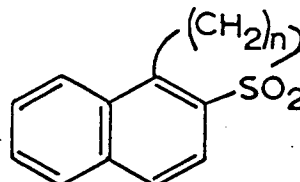
(69)　　　　　　　　　　　　　　(70)

A number of derivatives with sulphur in the peri ring have been reported. Russian investigators claim that cyclisation of 1-naphthylthioacetic acid (71, R=H) with aluminium chloride in chlorobenzene at temperatures in excess of 100° gives the peri ketone (72, R=H).[35] Using stannic chloride in the same solvent at 80° the 1,2 cyclised product (73, R=H) is also formed.[36] Unfortunately no yields are recorded. Leandri reports a 90% conversion to the peri ketone (72, R=7,9-$(NO_2)_2$) on cyclisation with aluminium chloride of the chloride of the 2,4-dinitro substituted acid (71, R=2,4-$(NO_2)_2$).[37]
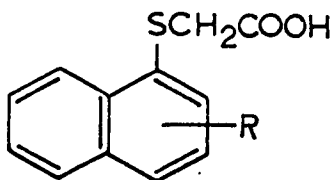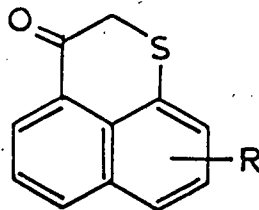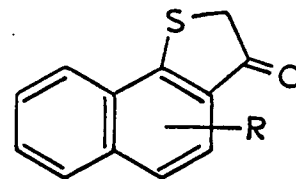
(71)　　　　　　　　　　(72)　　　　　　　　　　(73)

In this connection it is of interest that cyclisation of
β-(1-naphthylthio)propionic acid chloride with stannic chloride
in benzene took place entirely in to 1,2 direction to give (74).[38]

(74)
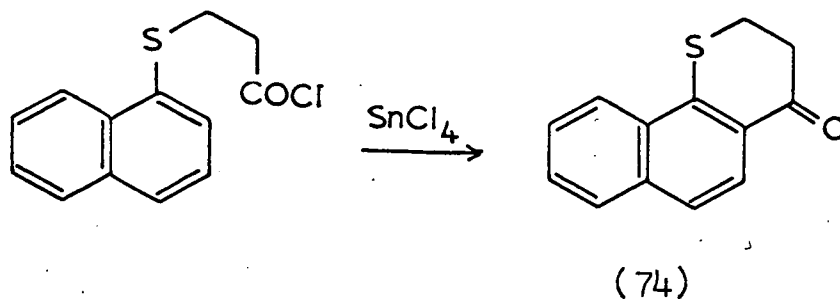
A high conversion to the thianaphthene derivative (76) is
obtained on cyclisation of 6-ethoxy-1-naphthylthioacetyl chloride
(75) indicating a distinct preference for angular rather than
linear condensation in accord with the corresponding oxygen and
methylene analogues.
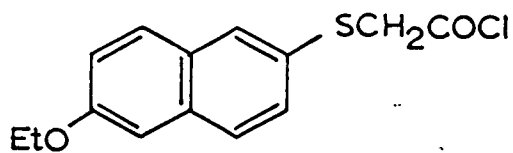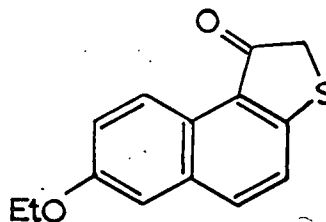
(75)   (76)

Factors influencing Friedel-Crafts Cyclisations

A number of factors have been reported to affect both
products formed and their distributions in acylation reactions.
Ring size is clearly an important consideration in cyclisation
reactions and reference has been made to this in earlier sections
concerning the cyclisation of naphthylalkanoic acids and their
chlorides.   Fairly extensive studies have been carried out on
the ring closure of arylaliphatic acid derivatives in general
and the following points are relevant.

Since both benzoyl chloride (77) and phenylacetyl chloride
(78) fail to cyclise under Friedel-Crafts conditions, it is
generally assumed that both three- and four-membered rings are
not favoured due to the high ring strain involved
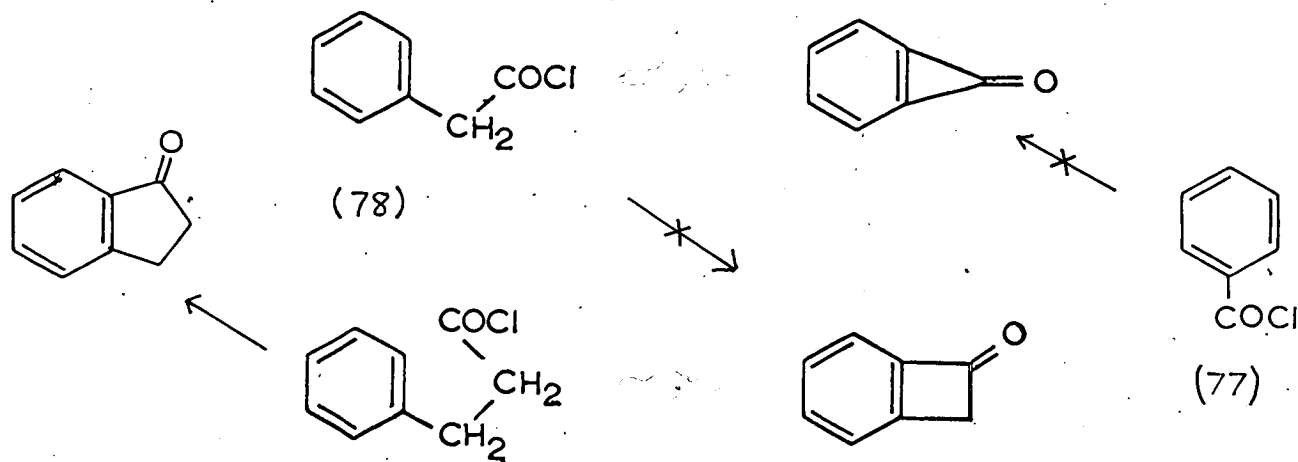
Five-, six- and seven-membered ring ketones, however, are
all fairly readily formed and examples of cyclisations leading

to the formation of these have been already given.   When there
is a choice between formation of a five- or six-membered ring
the latter generally appears to be formed.   Thus the cyclisation
of the diacid (79) with anhydrous hydrogen fluoride gives the
acidic ketone (80) as the sole product of reaction[40] - a clear
indication of the preference for the formation of the six-
membered ring tetralone rather than the five-membered ring
indanone derivative (81)
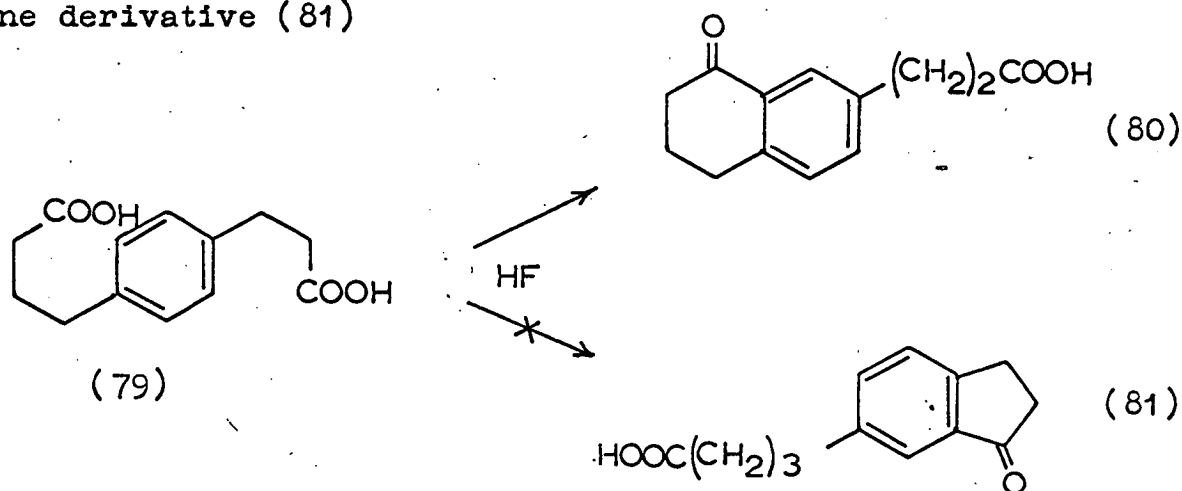
The cyclisation of β-(1-naphthyl)propionic acid to give the
perinaphthanone (58, R=H) as the major product with only a trace
of the angular five-membered ring ketone substantiates the
preference for six-membered rings over five-membered ones.

Seven-membered ring suberone derivatives are known to be
formed readily in cyclisations, however results obtained with
diacid cyclisations would indicate that these are formed less
readily than tetralones and indanones. β-Benzyladipic acid
(82) for example yielded on cyclisation only the tetralone
derivative (83) and none of the suberone derivative (84).[41]
Likewise α-benzylglutaric acid on cyclisation gave the indanone

derivative (85) rather than seven membered ring formation.[42]

(82)

(83)

(84)

(85)
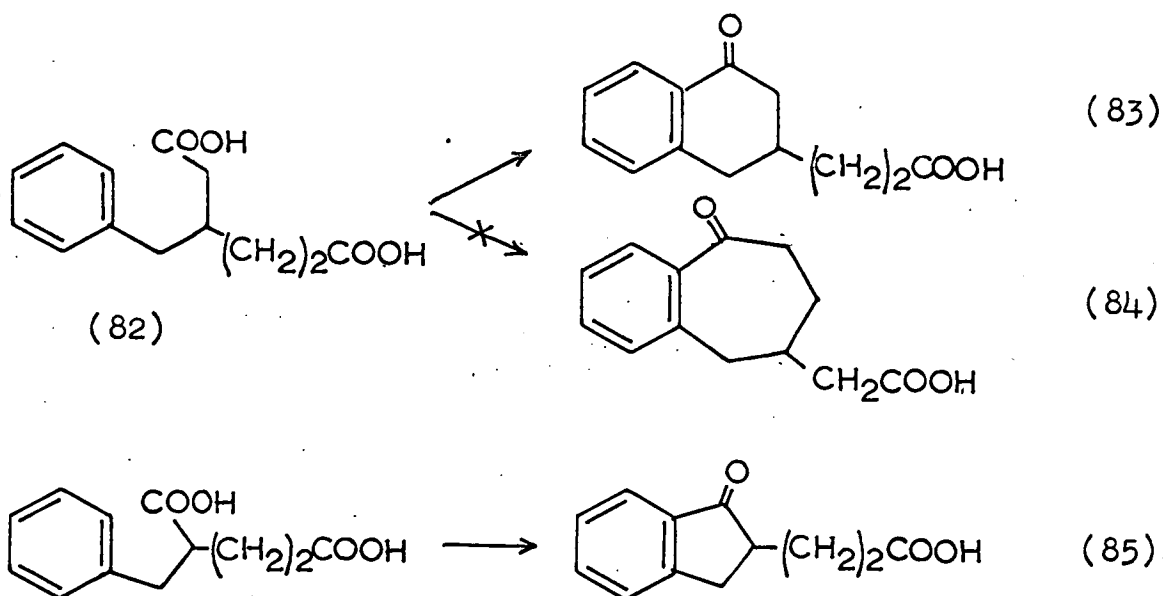
Diacid cyclisations of this sort do not imply that certain ring systems are inherently more stable than others but are merely manifestations of rates of reaction, assuming, of course, that both acyl groups are equally reactive.

In the absence of comparable data it is difficult to assess the ring size effect in the cyclisations of aryloxyaliphatic acid and their derivatives.   There is, however, much evidence indicating that both five-membered furanone derivatives and six-membered chromanone derivatives are readily formed. It would be unwise to assume that cyclisation of 1-naphthyloxyacetyl chloride (6, R=H) to the naphthofuranone (9, R=H), and not the six-membered peri ketone (10, R=H), is necessarily evidence in favour of universal preference for five-membered ring formation over six. The 2-position at which ring closure occurs is almost certainly

activated towards electophilic attack by electron release from
the ether oxygen. Interesting however is the observation that
the chloride of 2-phenylphenoxyacetic acid cyclises with
aluminium chloride to the seven-membered ring oxepinone (86)
rather than five-membered ring benzofuranone derivative.[43]

(86)
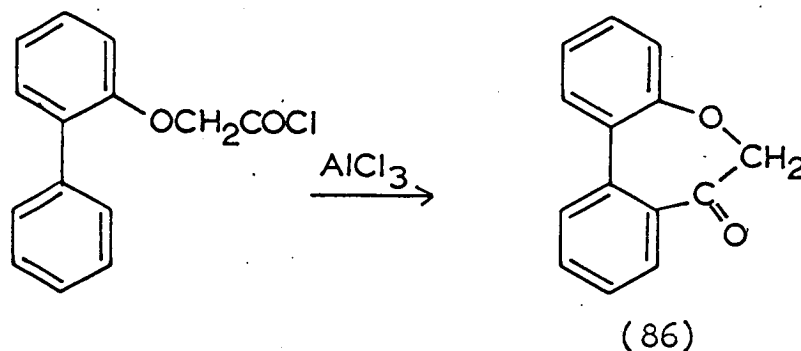
It is thought to be possible that oxepinone formation is
favoured on account of a proximity effect of the reactive tail
to the phenyl substituent which has two effective ring closure
sites. Perhaps, too, there are fewer interactions in the
transition state of the non-planar seven-membered ring.

The effect of nuclear substituents on cyclisation is
similar to other substitution reactions. The presence of an
ortho/para directing group ortho or para to the point of ring
closure activates the nucleus and in consequence cyclisation
occurs readily. Bulky substituents ortho to the acylation site
have been claimed to inhibit cyclisation as exemplified by the
acid (87). Fieser and Bradsher were only able to achieve
cyclisation with hydrogen fluoride in 16% yield and reported complete
failure to cyclise with a number of other condensing agents.[44]
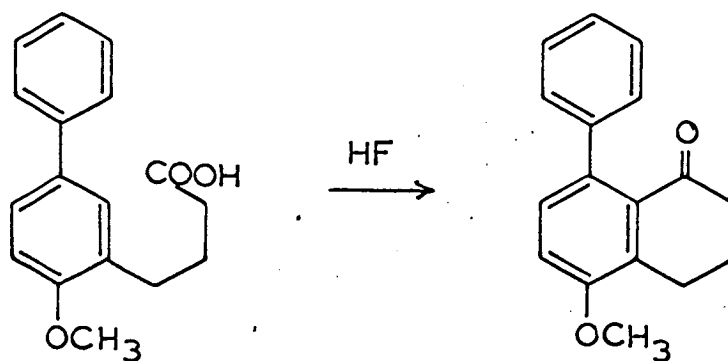
(87)

The reluctance to cyclise in this instance may well, in part, be due to the bulky phenyl group ortho to the point of ring closure, but a more likely inhibiting factor is the methoxyl group. The following certainly is suggestive of this being so.

Several workers have reported the failure of γ-(2,4-dimethoxyphenyl)butyric acid (88) to ring close with a variety of condensing agents, although more recently its cyclisation has been achieved with polyphosphoric acid on a 3g scale[45] in 4-6% yield to give a somewhat impure product. Increasing the scale of the reaction,however, led to no tetralone formation. Obviously the 2,4-dimethoxy acid is reluctant to cyclise.

(88) $R_1 = R_3 = OCH_3$, $R_2 = H$

(89) $R_1 = OCH_3$, $R_2 = R_3 = H$

(90) $R_1 = R_2 = H$, $R_3 = OCH_3$

(91) $R_1 = OH$, $R_2 = R_3 = H$
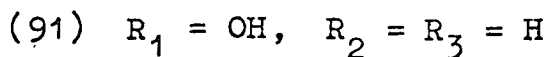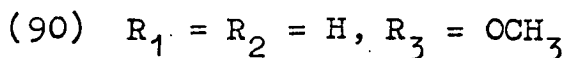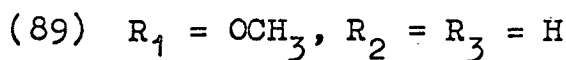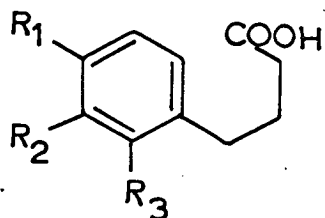
The 4-methoxy substituted acid (90) cyclises readily through its chloride with aluminium chloride[45] however γ-(2-methoxyphenyl)-butyric acid (89) did not cyclise under these conditions, although

it has been cyclised in moderate yield under more vigorous conditions.[46]   Clearly the 2-substituent has the greater deactivating influence at the site meta to itself, presumably on account of the adjacent side chain.   Whether this is a geometric or electronic effect is none too clear.

A similar observation has been made by Mitter and De who failed to cyclise γ-(2-hydroxyphenyl)butyric acid (91).[47] Indeed deactivation of the position meta to an electron donating substituent seems to occur on account of the aforementioned failure of 6-methoxy-1-naphthylacetic acid to cyclise and the observation that β-(6-methoxy-1-naphthyl)propionic acid cyclises to give predominantly 3'-methoxy-4,5-benzindan-1-one.(61)

The presence of electron-withdrawing substituents, such as nitro and carbonyl, deactivates the molecule in general towards electrophilic attack.   This does not, however, preclude the possibility of cyclisation since the chloride of the nitro acid (92) has been cyclised in over 70% yield to the indanone derivative (93) with aluminium chloride;   the p-nitro isomer on the other hand could not be cyclised.[48]   In both instances ring closure would be meta to the substituent - the least deactivated position.

(92)   (93)
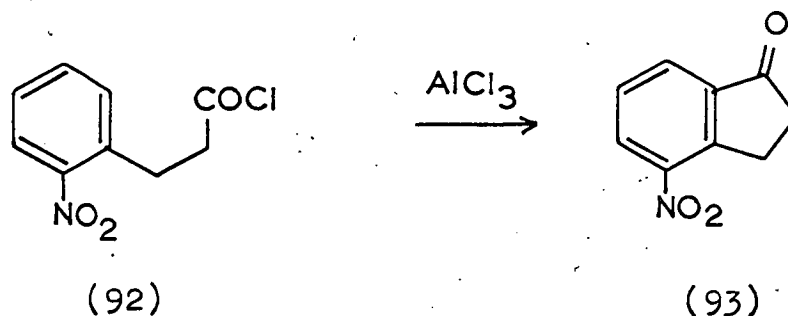
This difference in reactivity can be readily attributed to a lack of coplanarity of the 2-nitro group with the aromatic nucleus on account of the steric effect of the acidic side chain resulting in reduced resonance deactivation of the ring. The inductive effect alone is insufficient to prevent acylation.

Although an acyl group once introduced tends to deactivate the nucleus to further electrophilic substitution a number of double cyclisations have, however, been reported. With simple systems attempted double ring closures have only given low yields of the diketones or monocyclisation exclusively, although with polycyclic systems, notably the phenanthrene series, yields have been much higher in cases where the ring closures occur at distant points of the molecule.

Thus cyclisation of the diacid (94) with sulphuric acid, or its dichloride with stannic chloride or aluminium chloride, gave only the keto acid (95).[49] This keto acid has however been reported to cyclise with an excess of aluminium chloride together with a little sodium chloride to give about 5% of the tricyclic diketone (96) together with much unchanged keto acid, and this is effectively a double ring closure.[50]
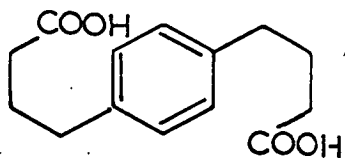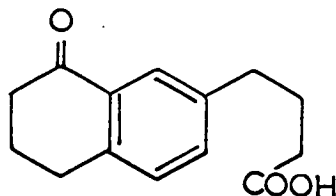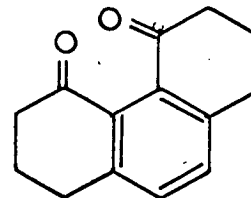
(94)   (95)   (96)

The phenanthrene derivative (97) however, with poly-phosphoric acid or stannic chloride is reported by Phillips to give mainly (98) together with some 29% of the isomer (99).[51]

(97)   (98)   (99)
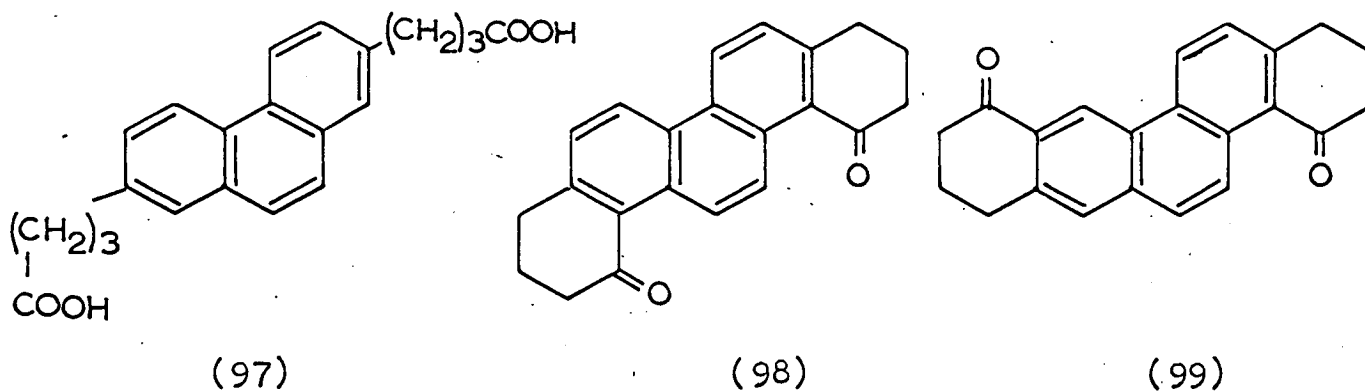
A number of instances have been recorded where the condensing agent clearly influences the course of cyclisation and not merely the yields of products formed.   A striking example of this is the cyclisation of ɣ-2-phenanthrylbutyric acid (100) which with hydrogen fluoride gives the benzanthracene derivative (101) in 78% yield, yet with stannic chloride yields 74% of the chrysene derivative (102).[52]

(100)   (101)   (102)
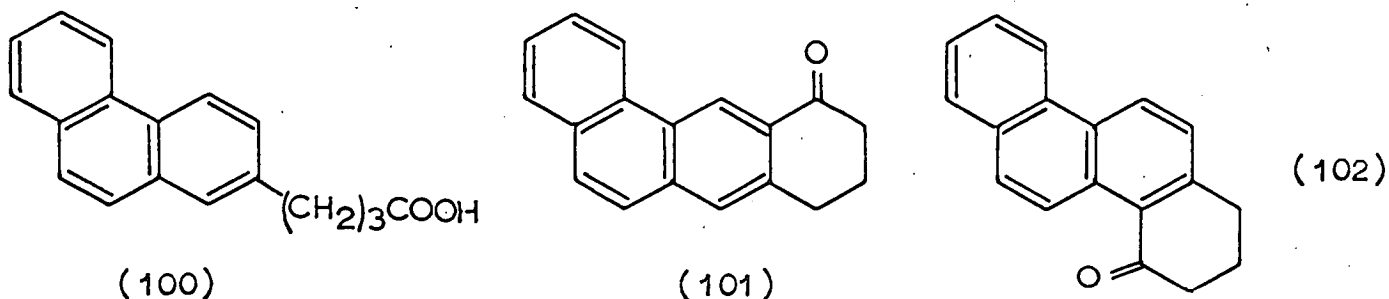
In this particular cyclisation a possible explanation is that the stannic chloride induced condensation at the 1-position of the

phenanthrene nucleus in the 'normal' course of ring closure on account of the higher bond order of the 1,2 bond compared with the 2,3 bond. This would seem reasonable by analogy with the lower homologues of the 2-naphthylalkanoic acids which show a distinct preference towards angular cyclisation, presumably a direct consequence of the shorter 1,2 bond length (higher bond order). That the angular ketone (102) is formed in high yield with hydrogen fluoride may be accounted for by initial addition of H-F across the 9,10 bond which is well established to display a considerable degree of olefinic character, and that subsequent cyclisation at the 3-position of the adduct (103, a or b) is now preferred.
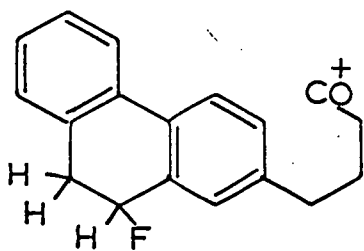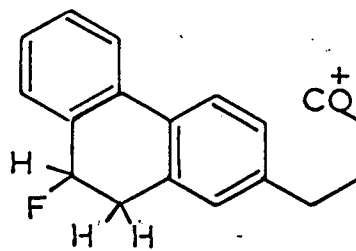
(a)   (b)

(103)

Either adduct, depending on the orientation of H-F addition, can reasonably account for predominant 3-acylation; (103 a) on account of a -I effect from the nearby fluorine atom and (103 b) from its similarity to a toluene derivative where the ortho/para ratios for substitution are generally low. In addition, both structures would be expected to provide an increased peri-effect

over the phenanthrene and might reasonable have 1,2 and 2,3 bond orders of similar magnitude, due to their likeness to biphenyl. Such an explanation, of course, depends on H-F elimination at a later stage, this quite likely being able to occur during the alkaline conditions used to work up the reaction.

Such large differences in product distribution with different condensing agents are rare and concerned in the main with the polycyclic systems.   Smaller variations are much more usual and reasonable, but when these depend on actual isolation of products, unless the accountability of material is high, the results must be treated with some degree of caution.   Unfortunately this condition has not often been met in reported studies. Quantitative evaluations of crude products by G.L.C. analysis, spectroscopic methods or other similar means, combined with unequivocal identification of the components would also be desirable, but as yet have been but rarely applied to cyclisations.

Mechanism of the Friedel-Crafts Acylation Reaction

Despite the fact that numerous studies have been directed at elucidating the mechanism of the Friedel-Crafts acylation reaction, there still exists some doubts as to the precise role of the catalyst and the nature of the acylating species. Although no attempt has been made in the present study to investigate either of these subjects, it is pertinent to discuss briefly at this point the current views held over these and other aspects of the reaction. Most of the studies have been concerned with the aluminium halide catalysed reaction of acyl halides with aromatic compounds, although the considerations can often be extended with slight modification to acylation with other species.

Since the reaction is catalysed by acids and on account of directive influences, there is little doubt that acylation involves electrophilic aromatic substitution. The role of the Lewis acid in acylation with acyl halides is clearly to act on the chlorocarbonyl group $-C\diagup^{\displaystyle O}_{\diagdown Cl}$ of the acyl halide in such a way as to render the acyl carbon atom more electrophilic. The precise nature of the acylating complex, however, has been the subject of much speculation. Two major structural possibilities are favoured, both having been substantiated by experimental evidence. These are the polarised donor-acceptor complex (A) and the acylium ion (B)

$$R - C\diagup^{\displaystyle O \longrightarrow MX_n}_{\diagdown X} \qquad\qquad R - \overset{+}{C} = O \quad MX_{n+1}^{-}$$

$$\text{(A)} \qquad\qquad\qquad\qquad \text{(B)}$$
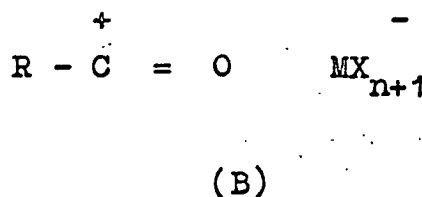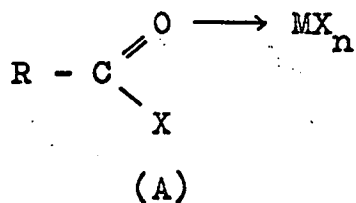
Other structures have also been proposed in the past, although no substantial evidence indicating their existence has been forthcoming, quite in contrast with (A) and (B).

Structural determinations of these acylating complexes have, of course, made an important contribution to the understanding of the mechanism of acylation. In this respect spectroscopic methods have become increasingly important in the study of such acyl halide-Lewis acid primary complexes.

Cook, on the basis of infra-red studies on the aluminium chloride-acetyl chloride system, inferred the presence of both the donor-acceptor complex (C) and the ionic species (D) [53]

$$CH_3 - C \underset{Cl}{\overset{O \longrightarrow AlCl_3}{<}} \qquad CH_3 - \overset{+}{C} = O \qquad \overset{-}{AlCl_4}$$

$$(C) \qquad\qquad\qquad (D)$$
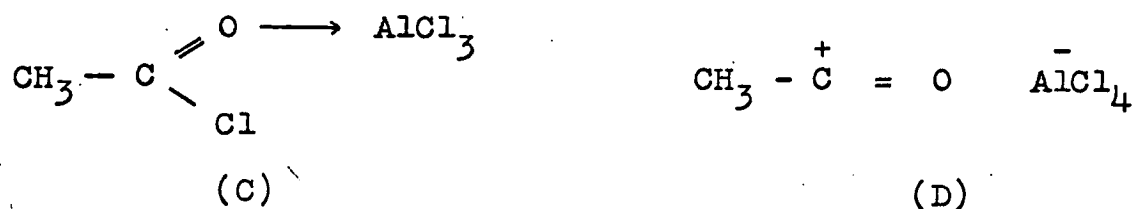
With nitrobenzene, a liquid of high dielectric constant, as solvent, the complex was shown to exist as both (C) and (D), whereas in chloroform, which has a relatively low dielectric constant, only the donor-acceptor complex appeared to be present.

The structures of a number of other complexes have also been investigated in recent years and the results have indicated as above that in some instances the complexes exist as acylium salts (B) and in other instances with metal atoms bonded to the carbonyl oxygen (structure A). Mixtures too have frequently been observed where the distribution depends on the physical state of the sample (whether a solid or a liquid) as well as on the nature of the

solvent, if in solution. Olah and his co-workers were able to show by high resolution proton and fluorine resonance spectroscopy that while the addition complexes of SbF_5, PF_5, AsF_5 and BF_3 with acetyl, propionyl and benzoyl fluorides existed as acylium salts of the form $RCO^+ MF^-_{(4 \text{ or } 6)}$ in the solid state, in solution the strongly polarised complexes of the sort (E) were favoured.[54]

$$R - \overset{\delta+}{\underset{\underset{F}{|}}{CO}} ------ \overset{\delta-}{MF_n} \qquad (n=3,5)$$

(E)
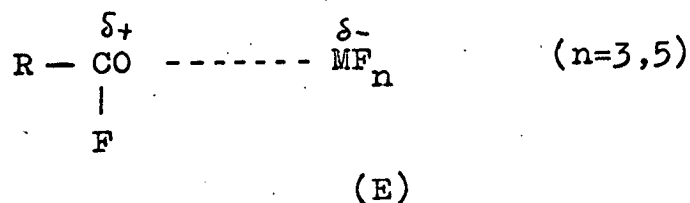
From the preceding discussion and the observation that Friedel-Crafts acylations with acyl halides are known to proceed readily in solvents of both high and low dielectric constant, it is likely that both the polarised complex (A) and the acylium ion structure (B) are active entities in acylations, the more effective one in a given case depending on the reaction conditions. In relatively non-polar solvents, which would not easily accommodate a high energy cation, acylium ions are not detected, hence acylations may well proceed via polarised complexes. In those solvents where both complexes exist there is uncertainty as to which, if either, is the more successful acylating agent. It may be that steric and electronic effects in the transition state leading to the final products is critical. There is also the possibility that the reactive intermediate may be some other species present only in low concentration and in support of this

a third species resembling the acylium ion and thought to differ
from it by the amount of interaction between anion and cation has
been inferred. However, no adequate explanation regarding its
structure has been offered.

On the basis that the potential acylating species is either
a donor-acceptor complex or the acylium ion, two mechanisms have
been postulated:

i) A carbonyl addition mechanism -
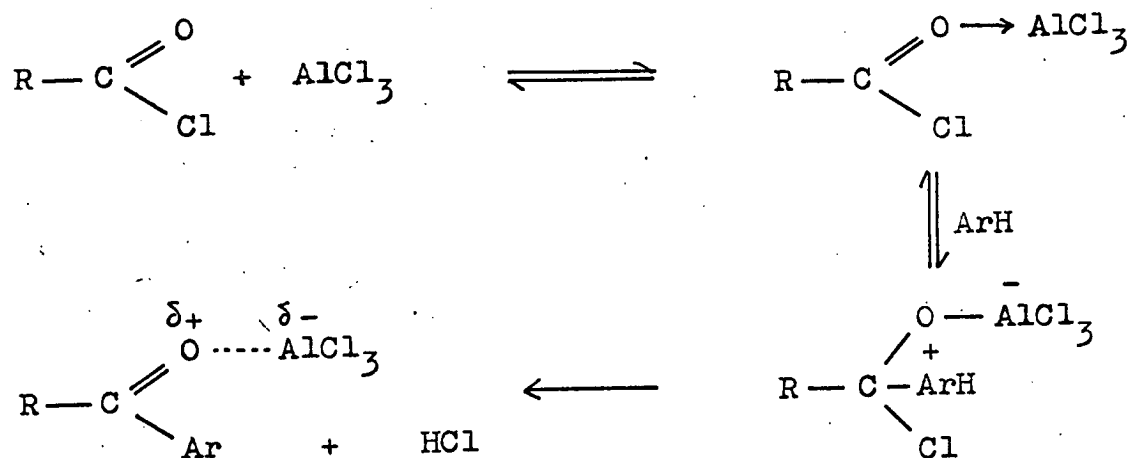
ii) An acyl-carbonium ion mechanism -
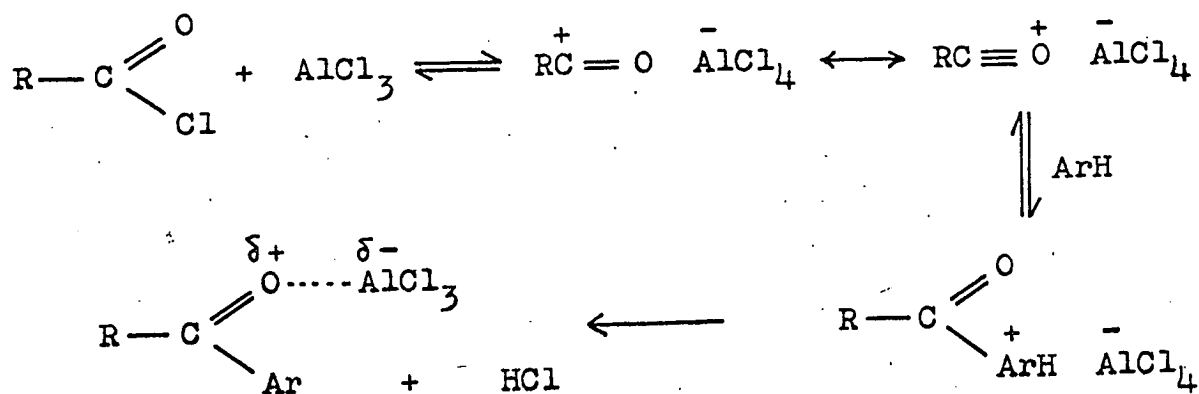
The essential features of these pathways i) and ii) were first proposed by Pfeiffer and Meerwein respectively. [55,56] It should be stressed that although these pathways differ in the reactive intermediate - either an oxonium compound or an acylium ion - the mechanisms allow for a rapid mobile equilibrium between both forms, so that regardless of the principal form of the addition complex in solution, either mechanism may operate for reaction. There exists considerable evidence that both of the pathways may operate in acylation reactions, although surprisingly it has not been possible to ascribe a particular mechanism to any one acylation.

The fact that acylation reactions are able to occur with hindered acyl halides, that constant isomer distributions have been observed with various catalysts, and that parallels can be drawn between sulphonylation reactions, which are known to occur by sulphonylium ions, and acylations, have been taken to indicate the operation of an acylium ion mechanism.

Features in accord with a carbonyl addition mechanism include high sensitivity to steric hindrance in the aromatic substrate which is suggestive of a bulky complex, and that chloride exchange in the phosgene-aluminium chloride complex (a powerful acylating agent) occurs only very slowly.

Although two possible mechanisms are thought to exist, it is likely true that the more consistent pattern for the reaction involves the acyl cation as the reactive intermediate, and this is borne out by frequent reference to this sort of intermediate in the literature. In accord with this convention, reactive Friedel-Crafts

intermediates will be represented and referred to as acylium ions throughout this work.

Acylation with carboxylic acids, their esters and anhydrides has been less extensively investigated. Mechanisms have been postulated consistent with experimental observations and these generally involve the acylium ion as the acylating agent.

DISCUSSION

The Preparation of Phenols

The most important series of reactions studied has been the cyclisation under Friedel-Crafts conditions of naphthyloxyacetyl chlorides, these chlorides being readily prepared from the corresponding acids. The acids were generally derived from the phenols, hence a number of substituted 1- and 2-naphthols were required to be synthesised.

1) Substituted 1-naphthols

a) 2-Chloro- and 4-chloro-1-naphthols

2-Chloro and 4-chloro-1-naphthols were prepared in admixture by the chlorination in chloroform of 1-naphthol with sulphuryl chloride as chlorinating agent. The principal electrophile is probably molecular sulphuryl chloride, which has recently been shown to be the effective electrophile in the chlorination of some aromatic ethers and alkylbenzenes,[57] although molecular chlorine, formed by the pre-equilibrium

$$SO_2Cl_2 \rightleftharpoons SO_2Cl\cdot + Cl\cdot \rightleftharpoons SO_2 + Cl_2$$
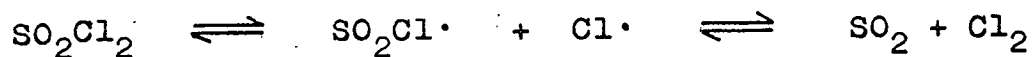
or the species Cl^+ from the ionisation

$$SO_2Cl_2 \rightleftharpoons Cl^+ + SO_2Cl^-$$
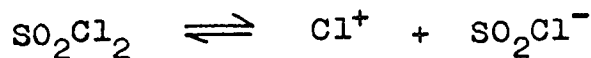
may also contribute. The 4-chloro isomer readily separated from the reaction mixture on cooling, however isolation of the 2-chloro product in a pure state proved troublesome. Steam distillation of the reaction mixture, after removal by filtration of the deposited 4-chloro- product and also of solvent by

distillation, yielded material highly enriched in 2-chloro-1-naphthol. The latter, however, could not be obtained in a pure state free of the 4-chloro isomer by fractional crystallisation as claimed by Lesser and Gad.[58] The presence of the 4-chloro- substituted product in these mixtures was readily inferred from their N.M.R. spectra, the 2H of the 4-chloro material absorbing as an ortho doublet at τ 3.04 (in acetone) with $J_{2,3}$ = 8.2 c.p.s. All protons in the 2-chloro isomer absorbed below τ2.70.

Pure 2-chloro-1-naphthol was obtained by preparing the mixed tosyl esters of the steam distillate, recrystallisation of this material twice from methanol, after which time no 4-chloro ester was detected in the N.M.R. spectrum, and alkaline hydrolysis of the now pure 2-chloro ester.

b) 3-Nitro, 3-chloro- and 3-iodo-1-naphthols

m- Disubstituted naphthalenes generally are not readily accessible hence their preparation frequently necessitates multi-stage syntheses. The route considered initially in the preparation of the 3-halogeno-1-naphthols was from 3-nitro-1-naphthol by reduction to the β-naphthylamine and substitution of the amino group through diazotisation and replacement by the required halogen.

3-Nitro-1-naphthol was successfully synthesised in low overall yield from 1,2,3,4-tetrahydronaphthalene (tetralin) in nine stages by the combined methods of Ward and Coulson,[59] and Morrison.[60] This route, outlined on the following page, required the synthesis

(104)   (105)

(106)   (107)

(108)   (109)   (110)

(111)   (112)
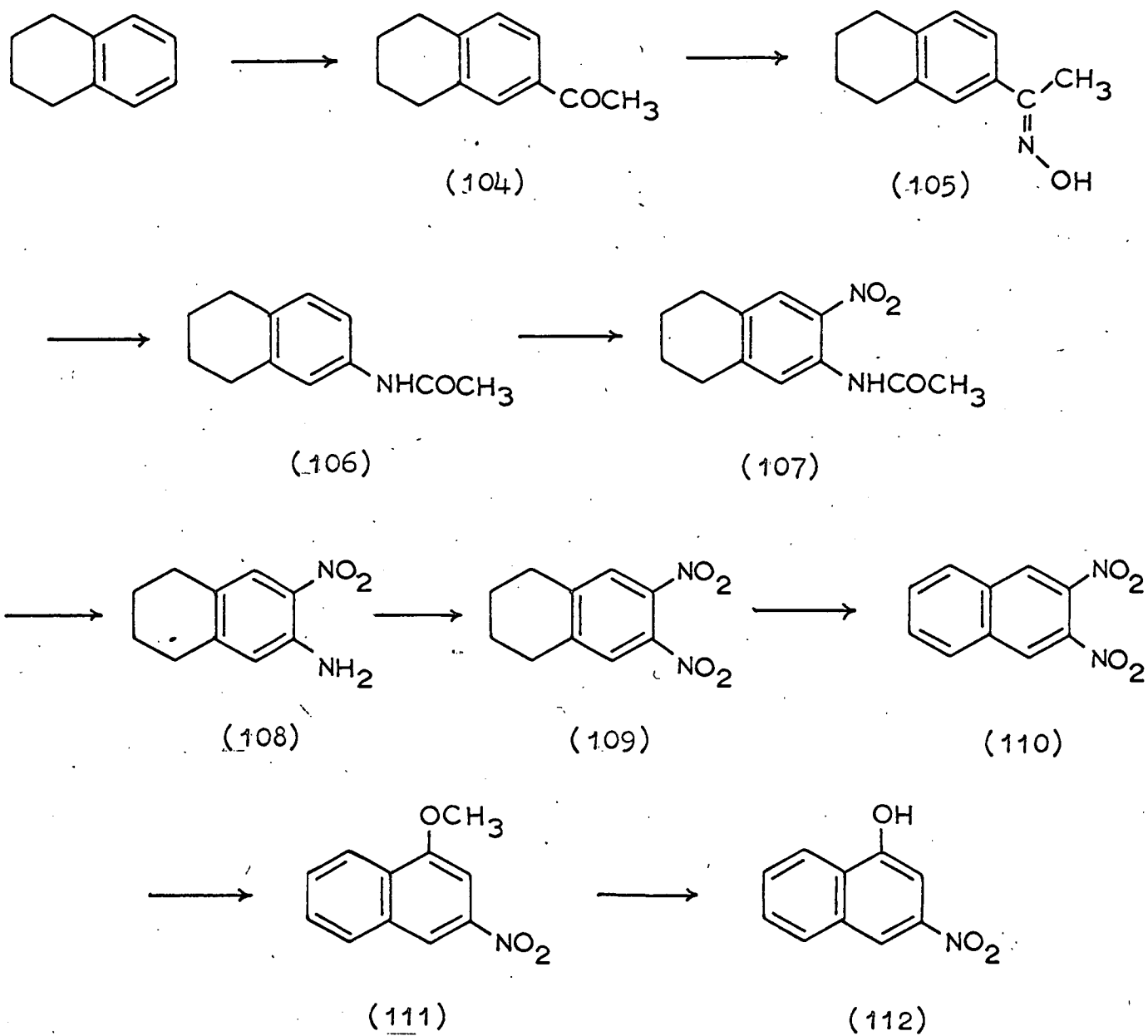
of 2,3-dinitronaphthalene (110) as a key intermediate and this was
achieved in 3% overall yield from tetralin. Ward and Coulson claim
an optimum yield of ca. 15% for these stages and the reduced yield
in the present investigation arises principally from two of the
seven stages.

Nitration of 6-acetamido-1,2,3,4-tetrahydronaphthalene (106) (110 g.) with nitric acid/acetic anhydride mixture, where the active species may be either the nitronium ion (NO_2^+)[61] or protonated acetyl nitrate $(AcONO_2H^+)$,[62] to the 7-nitro- derivative (107) was achieved in only 29% yield. Although lower than the yield of 38% claimed by Ward and Coulson who operated on a 5 g. scale, the present yield may be considered good in view of these investigators' claim of 'drastic reductions' in yield on scaling up the reaction.

Replacement by nitro of an amino group in (108) through diazotisation and treatment of the isolated diazonium sulphate with a cupro-cupri sulphate solution in saturated aqueous sodium sulphite gave only a 21% conversion to the dinitrotetralin (109).(cf. literature value of 55%). An eight-fold increase in the scale of the reaction in the present investigation is the most likely cause of the reduced yield being a direct consequence of harmful local heating and presumably preferential side reactions.

An attempt to improve this stage by using peracetic acid for the oxidation led to no improvement in yield. An impure product was obtained from which the pure dinitro product was isolated by fractional recrystallisation from methanol in 19% yield.

An interesting reaction in the synthesis is the rearrangement and displacement which results from treatment of 2,3-dinitro-naphthalene (110) with an excess of sodium methoxide in methanol. Morrison[60] has shown that the direct displacement can be effected by using dilute methoxide solutions, although the rearranged product is always present to a greater or lesser extent. He has

also shown that simple displacement does not precede rearrangement since 2-methoxy-3-nitronaphthalene is stable to hot concentrated methoxide solutions.   Morrison suggests that the reaction is an example of a ciné substitution implying loss of HNO_2 to yield the aryne intermediate (110).[a]

(110)[a]
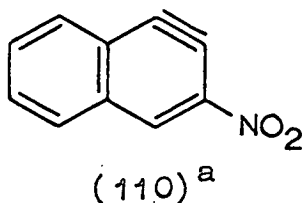
.That addition of methanol is specific with strong base, giving only the α-methoxy naphthalene (111) may be accounted for by a large steric effect provided by the 3-nitro- substituent so that the methoxyl moiety is more readily accommodated at the less hindered α-position of the nucleus.   An alternative mechanism is probably required to explain the direct displacement reaction with dilute methoxide solutions.

A previous attempt to prepare 3-nitro-1-naphthol from 3-nitro-1-naphthylamine was abandoned in view of the failure to obtain the latter compound on partial reduction of 1,3-dinitronanpthalene. The conditions employed for the reduction were those successfully used by Rosenblatt and his co-workers with sodium sulphide as the reducing agent.[63]   Only 1,3-naphthalenediamine, however, was isolated in the present work despite repeating the experiment.

A small amount of 1-methoxy-3-nitronaphthalene (111) was reduced with aqueous sodium dithionite to 4-methoxy-2-naphthylamine.

Attempted conversion of this into the hitherto unknown 4-methoxy-2-naphthol by warming the diazonium salt solution with 50% w/w sulphuric acid afforded a moderate amount of acidic material, the N.M.R. spectrum of which possessed no methoxyl resonance indicating extensive demethylation. Lack of success in achieving this conversion has been reported previously, but unfortunately no details are recorded.[59]

The purpose of synthesising 4-methoxy-2-naphthol was to identify positively the two materials from monomethylation of naphthalene-1,3-diol, since neither product is recorded in the literature and N.M.R. spectral identification would be indecisive and likely impossible. In fact, naphthalene-1,3-diol was methylated with rather more than one molar equivalent of dimethyl sulphate with potassium carbonate in acetone and a tarry mixture of monomethylated species (in the ratio 2 : 1) obtained as readily seen from the N.M.R. spectrum. Attempted separation by distillation under reduced pressure and by silica gel chromatography were both unsuccessful, and neither attempt led to any substantial enrichment. The experiment was abandoned particularly in view of the difficulty in structure determination even if separation were successful.

Since it was apparent that very little 3-chloro-1-naphthol would be obtainable from 3-nitro-1-naphthol, an earlier report of the formation of the former by Franzen and Stauble[64] from 2,3,4-trichloro-1-naphthol on treatment with hydriodic acid in acetic acid was considered. This synthesis had previously been

neglected on two particular counts. In the first instance it would not lead to the required 3-nitro- product and secondly the evidence for the product appeared dubious. In this respect the analysis data gave a slightly high halogen content, and a melting point of 134° C. was recorded. This contrasted markedly with the value of 143° C. observed by Hodgson and Elliot[65] (prepared from 3-chloro-1-naphthylamine via the diazo-compound) and a more recent value of 108° C. by Bryson and Matthews[66] (similarly prepared from the halonaphthylamine). Nevertheless since the required 3-nitro- compound had been prepared and since 2,3,4-trichloro-1-naphthol appeared to be fairly readily accessible by the method of Zincke,[67] this synthesis was attempted.

2,3,4-Trichloro-1-naphthol was prepared in 30% overall yield from 1-naphthol

(112)   (113)
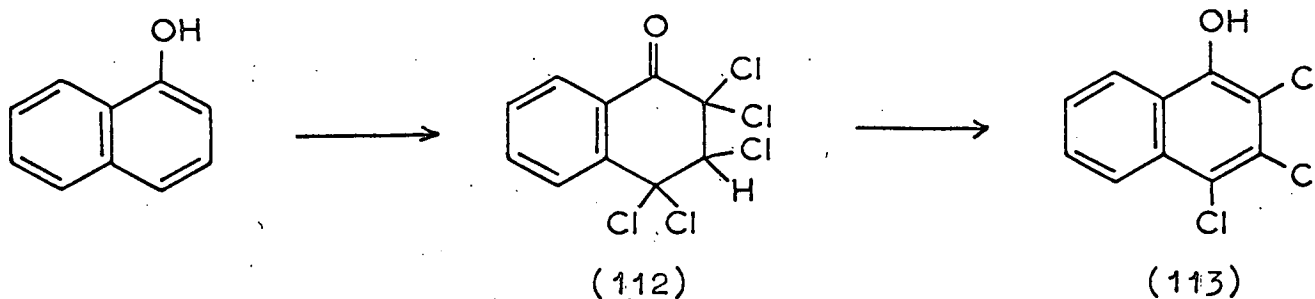
This route required the complete chlorination of 1-naphthol in glacial acetic acid solution with dry chlorine gas in the cold over several hours to give a yellow solid deposit of a pentachloroketo compound, suspected by Zincke to be (112). The N.M.R. spectrum of this material was consistent with this structure - although (114) is equally possible - having four degenerate aromatic protons to one other, the latter being a sharp

singlet at $\tau3.82$ (in acetone).   There was no OH peak in the

N.M.R. spectrum nor in the I.R. spectrum.

Reduction followed by oxidation (i.e. aromatisation) of the

pentachloro compound (112) to the trichloronaphthol (113) proceeded

readily with aqueous sodium sulphite in hot acetic acid solution,

the product depositing as a white solid.   The most probable

mechanism involves the reduced intermediate species (115),

aromatised by 1,4 and 2,3 elimination of HCl.   The analogous

carbinol from (114) is able to provide the trichloronaphthol by

1,2 and 3,4 loss of HCl.

(114)   (115)
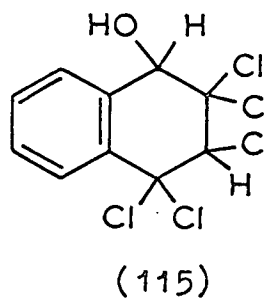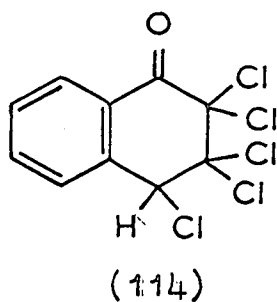
Reaction of 2,3,4-trichloro-1-naphthol with hydriodic acid

in acetic acid at reflux over 7 hours according to the conditions

originally employed by Franzen and Stauble, gave a solid product,

which melted over a fairly wide range (106 - 119° C.).   The

N.M.R. spectrum of this material was almost identical to a

portion recrystallised several times from light petroleum

(b.p. 60 - 80°), or carbon tetrachloride.

The spectrum in acetone displayed a broad OH resonance near

$\tau1.2$, removed by shaking with D_2O, and which integrated 1 : 6 against

the aromatic region.   This was a clear indication of the loss of

two chlorine atoms and replacement by hydrogens.   In the aromatic

region a downfield multiplet at $\tau 1.80$ was clearly visible and integrated for one proton. Such a resonance is quite characteristic of the peri proton (8H) in 1-naphthol ($\tau 1.82$ in $CDCl_3$). In this respect, hydroxyl, alkoxyl and amino groups as α-substituents have all been observed to give downfield shifts of the peri proton of about o.5 p.p.m. from the normal α-resonance near $\tau 2.20$. It is believed that such a considerable deshielding of the peri proton in these instances is due to the substituent assuming a preferred trans arrangement leading to the lone pair electrons of the oxygen or nitrogen lying within 2.40 Å from the peri proton.

The large melting point range implied a mixture and this was readily seen to be so from the upfield end of the aromatic region where two sharp meta-split doublets, which when taken together integrated to one proton, were readily discernible. These doublets at $\tau 2.73$ ($J_{meta} = 1.5$ c.p.s.) and $\tau 3.10$ ($J_{meta} = 1.7$ c.p.s.) clearly belonged to two separate 3-substituted 1-naphthols and were certain to be the 2H signals from each. (It is well established that the 2H resonances in 1-naphthols are shifted considerably upfield on account of the electron release from the adjacent oxygen atoms.)

It seemed not unreasonable that these materials were the expected 3-chloro- product and the 3-iodo analogue. N.M.R. data relating to halogenoquinolines[71] supported this possibility, and these data collected below for two quinaldine derivatives are pertinent :
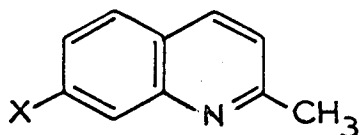
X	$6H(CS_2)$	$J_{6,8}$
Cl	$\tau 2.70$	2.0 c.p.s.
I	$\tau 2.35$	1.7 c.p.s.

It is clear that for a β-iodine substituent, the adjacent β-proton absorbs some 21 c.p.s. downfield from the corresponding signal for a proton similarly disposed to a chlorine atom.   This compares well with the observed difference in chemical shift with the naphthols of 22.2 c.p.s. and would further suggest the iodonaphthol 2H resonance is the lower of the two meta-doublets i.e. that at $\tau 2.73$.   The meta coupling constants across the halogens too are in agreement - a smaller constant being observed for the bulkier iodo- substituent.

Attempts to separate the mixture by column chromatography on silica gel, alumina and alumina deactivated with 7% w/w addition of water failed, both compounds being eluted together, and rapidly, with benzene.   (benzene : chloroform, 4 : 1 with deactivated alumina).   Separation was however achieved by slow distillation under reduced pressure using a short Vigreux column, the lower molecular weight chloronaphthol, as expected, being the more volatile component.   The iodonaphthol could either be distilled or alternatively obtained from the distillation residue after complete removal of the chloro- compound.

Several experiments were carried out to investigate the

variation in the crude product ratio with time.   With a seven
hour reaction time, the iodonaphthol was the dominant product
(ca. 70%) as seen by the N.M.R. integration, however after two
hours the ratio of chloro- : iodo- was approximately 1 : 1.
Shorter reaction times gave rather complex mixtures apparently
containing di- and possibly tri-halogeno components.   A 48 hour
reaction time gave very little of the chloronaphthol although
the crude product was clearly contaminated by spectroscopically
non-identifiable materials.   These were not further investigated.
Replacing hydriodic acid by hydrobromic or concentrated
hydrochloric acids led to no halogen removal or replacement,
only starting material being recovered unchanged even on prolonged
heating.

Formation of the 3-chloro-1-naphthol is merely an example of
protodehalogenation, a process which has been well established to
be an electrophilic substitution from observed kinetic isotope
effects[72] and the ease of deiodination with hydriodic acid of
substituted iodophenols.[73, 74]   The mechanism for such reactions
is thought to be the exact reverse of the mechanism for halogenation,
and in this case replacement of the 2-chlorine substituent may be
represented in the following manner :
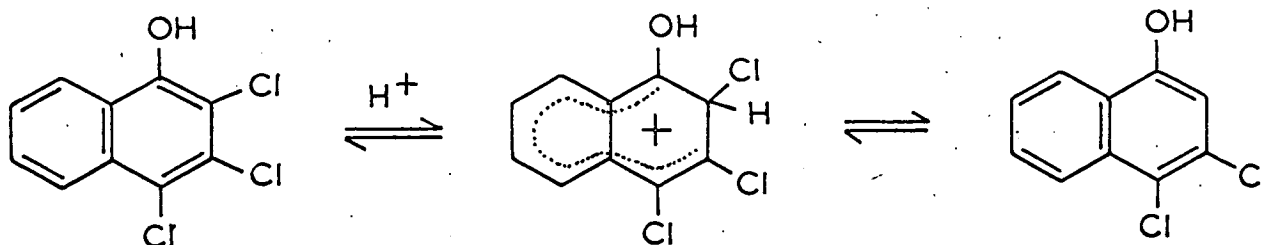
Data relating to Figure 1.

Figure 1 on the facing page illustrates spectroscopically the effect of time on the reaction of 2,3,4-trichloro-1-naphthol with hydriodic acid in acetic acid. Spectrum (a) is the aromatic region of the N.M.R. spectrum of the crude product after 1.5 hours reaction. Spectrum (b) is the crude material obtained after 2 hours and (c) the product after 7 hours.

The meta-split doublet denoted by A is the 2H in 3-iodo-1-naphthol and its proportion relative to B - the 2H in 3-chloro-1-naphthol - is readily seen to increase with time.

Figure 1. Partial N.M.R. Spectra of 3-Halogeno-1-Naphthols
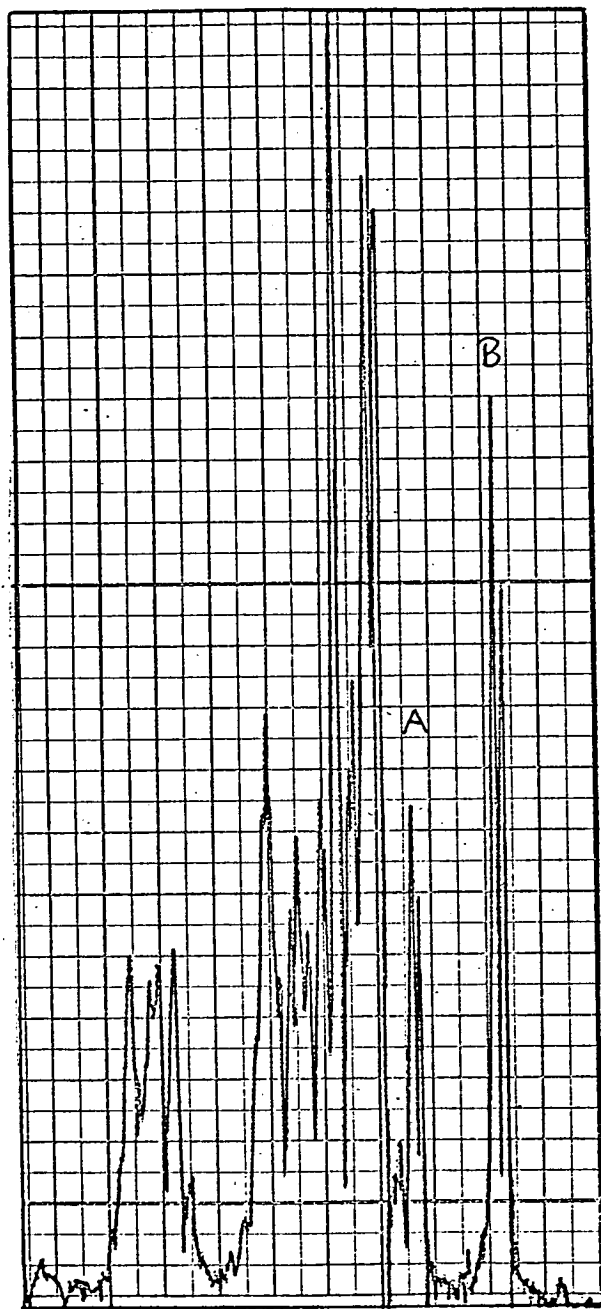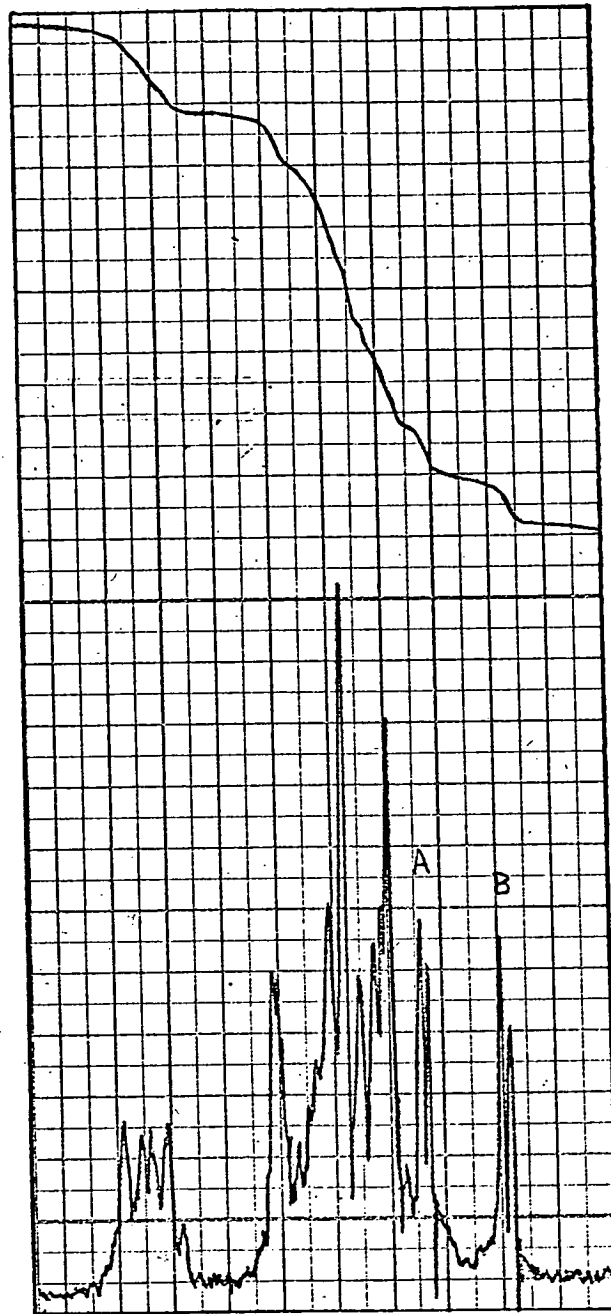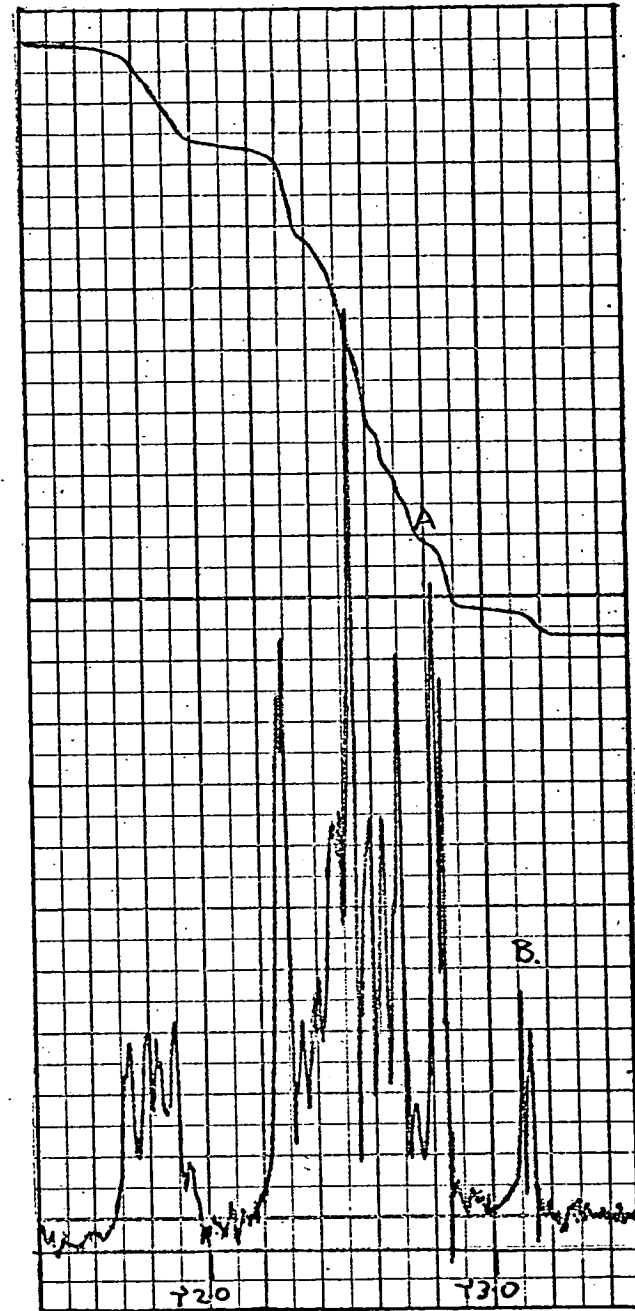
The finding that the proportion of 3-iodo-1-naphthol in the product mixture increased with time indicated that its formation occurred from the 3-chloro species by halogen replacement. A possible mechanism for this stage involves the keto- intermediate (116) and Markovnikov addition of HI, with subsequent loss of HCl.

(116)

(117)
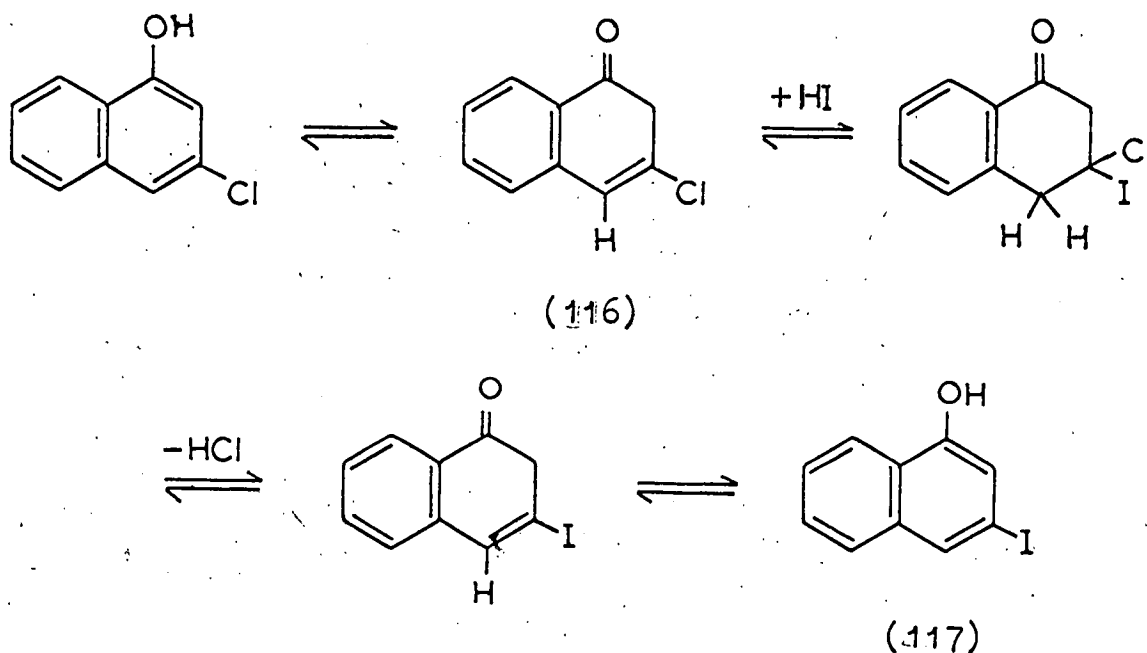
The high concentration of iodide present would account for the reaction being forced from left to right. Such a mechanism, however, scarcely explains the failure of halogen replacement with HBr and also demands that HI addition is either synchronous, or alternatively involves nucleophilic addition, since initial electrophilic attack by H^+ would be expected to occur at the β-position to give greater stabilisation of the resultant carbonium ion by resonance with the aromatic ring. (cf. addition to styrene).

More likely is that addition of free iodine occurs and that

net halogen replacement arises from subsequent loss of iodine
monochloride from the adduct (118).
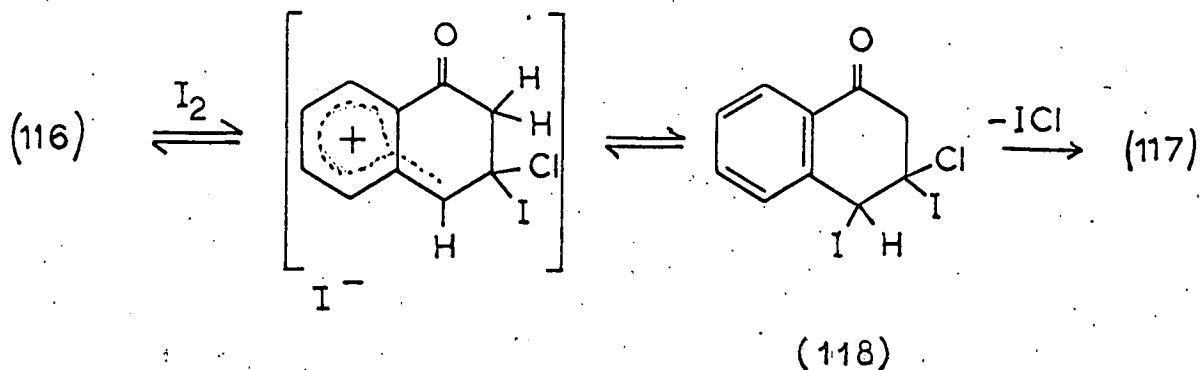
c) <u>Methoxy- and alkyl- substituted 1-naphthols</u>

5-Methoxy-1-naphthol was readily prepared from the symmetrical
1,5-diol with dimethyl sulphate in aqueous alkali.   A similar but
unsuccessful attempt to prepare the monomethoxy-1- and 2-naphthols
from the unsymmetrical 1,3-diol has already been described.

7-Methoxy-, 5,6,7-trimethoxy- and 7-methyl-1-naphthols were
all prepared by a similar route, starting from the substituted
benzenes.   The scheme may be represented in the following general
fashion:
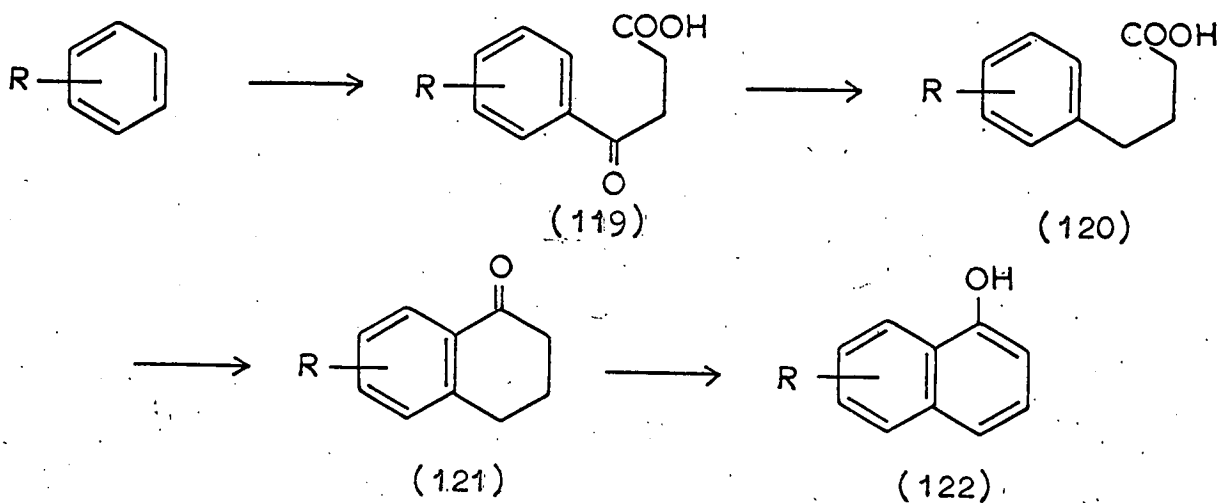
Syntheses of this type involving succinoylation of an aromatic, followed by reduction of the ketopropionic acid (119) to the substituted butyric acid (120) and ring closure of this or its chloride to the tetralone (121) are fairly standard in the preparation of additional rings. Dehydrogenation of the tetralone to the naphthol (122) may be achieved by any one of three routes: by the use of sulphur, palladium on charcoal, or selenium. Only sulphur and palladised charcoal were used in the present investigation at temperatures of 240 - 260° C. and 300 - 320° C. respectively in the absence of solvent. Reaction times were short (30 - 40 minutes) with sulphur, however 3 - 4 hour periods were used in the catalytic dehydrogenations where 30% preparations of palladium on charcoal were used.

It is interesting that dehydrogenation of 5,6,7-trimethoxy-1-tetralone (121, R = 5,6,7-$(OCH_3)_3$) could not be effected with palladium on charcoal, only a small amount of alkali soluble product being isolated as an uncharacterisable tar after acidification. The ketone was largely recovered unchanged from the neutral material. Dehydrogenation was successful, however, with sulphur, although a mixture of acidic products was obtained. An attempt to purify by distillation with diminished pressure was abandoned since there was a clear indication of decomposition before distillation. The mixture was treated with chloroacetic acid in alkaline solution in an attempt to prepare the aryloxyacetic acid, however, the contaminant - the corresponding thionaphthol - reacted preferentially and on removing the carboxylic acid product

by bicarbonate extraction, the recovered starting material was found to be very highly enriched in the naphthol.   That the contaminant was the thionaphthol was seen readily from the N.M.R. spectrum of the acidic product which displayed a large CH_2 resonance at $\tau 6.45$ – a characteristic value for $-S-CH_2-COOH$.[4] This acid product also displayed a smaller CH_2 peak near $\tau 5.2$ showing it to contain the aryloxyacetic acid.   Recycling the recovered and now enriched naphthol with chloroacetate in alkali gave the aryloxyacetic acid, which was obtained in a pure state by recrystallisation from benzene/light petroleum (b.p. 60 – 80°).

In other sulphur dehydrogenations the thionaphthols were not detected, although the products were not examined spectroscopically until they had been purified by distillation.

Interesting by-products were however observed in the catalytic dehydrogenation of both the 7-methyl- and 7-methoxy-substituted 1-tetralones (121, R = 7-CH_3 and 7-OCH_3).   The naphthols were isolated from the reaction mixture by 2N. sodium hydroxide extraction and the neutral material distilled under reduced pressure to recover the tetralones.   In both instances the non-volatile and semi solid residues after distillation yielded crystalline solids on trituration with a small amount of acetone.   These materials on recrystallisation from acetone displayed sharp melting points and were suspected to be single compounds.   The infra-red spectra of both showed total absence of carbonyl and hydroxyl stretching frequencies, but were clearly highly aromatic.

The N.M.R. spectra of both (reproduced on facing page 64) integrated in the ratio of 5 : 3 for aromatic : aliphatic (as CH_3 or OCH_3 singlets). No other lines were present. That the two compounds were not analogous was apparent on comparison of the aromatic regions of the spectra. The material obtained from the methyltetralone gave a remarkably simple aromatic expansion consistent with five discrete protons, however the methoxyl-containing material gave a rather more complex pattern consistent with ten different protons.

In the absence of mass spectrometric facilities at the time, molecular weights of 300 ± 3 for the methyl-containing material, and 330 ± 3 for the methoxylated product were obtained by vapour pressure osmometry, clearly indicating the molecules to be dimeric. These molecular weight values were later found to be in excellent agreement with values of 296 and 328 respectively from the parent peaks in the mass spectra.

From the N.M.R. spectral evidence that ten aromatic protons were present in the dimethoxy- compound it was clear that it at least was dimeric, however in the case of the dimethyl- substituted material, which had only five identifiably different protons, the dimer evidence from the molecular weight was of considerable significance since it implied a symmetrical structure. Indeed the difference between the two products was considered to be most likely due to this symmetry or lack of it.

Three basic structures appeared to be probable and able to be formed in a dimerisation; either a dinaphtho [1,2-b :2',1'-d]furan

(123), a dinaphtho[1,2-b :1',2'-d]furan (124) or a
dibenzo[c,k l] xanthene (125).
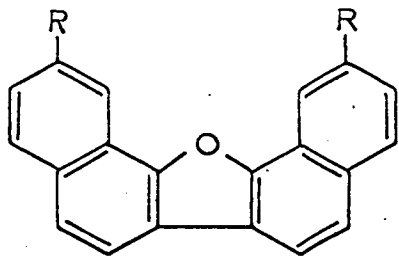
(123)
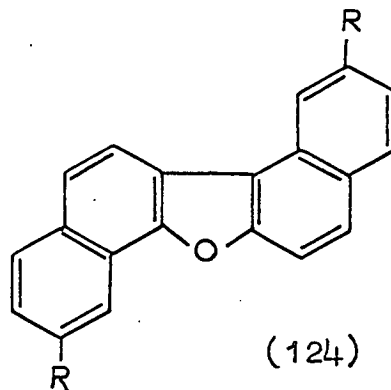
(124)
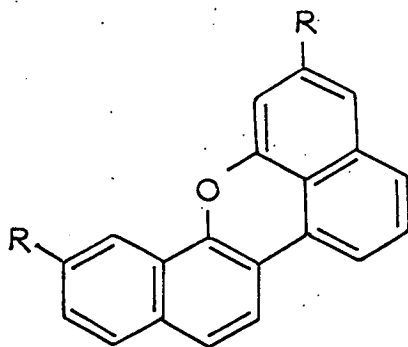
(125)

Of these structures only (123) possesses a plane of
symmetry and hence is the most likely structure for the methyl
dimer.

It was shown that the dimer obtained from 7-methoxy-1-tetralone
was most likely to be (124, R = OCH_3) by an independent synthesis
described below, and also on the basis of N.M.R. spectral
interpretation.

By saturating 1-tetralone with dry gaseous hydrogen chloride
and heating the mixture on a steam bath for 4 days, ca. 17% of a
white solid of melting point 133 - 135°C. was obtained together
with recovery of 59% of 1-tetralone by distillation under reduced
pressure.   This product had previously been isolated and
described by Friedel and Orchin[75] by a similar method, and these

investigators claimed its structure to be 1-keto-2(1⁻tetralylidene)-1,2,3,4-tetrahydronaphthalene (126).
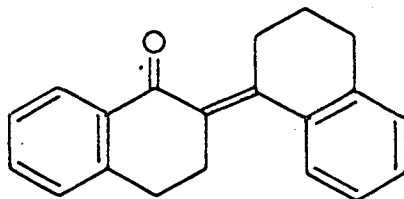
(126)

The N.M.R. spectrum however, was not consistent with this structure since it displayed a single vinyl proton (τ4.22, triplet) as well as seventeen others (eight aromatic and nine aliphatic). Clearly since there is but one olefinic proton, the double bond must be connected to the ring junctions giving rise to two possibilities, (127) and (128), for its structure.
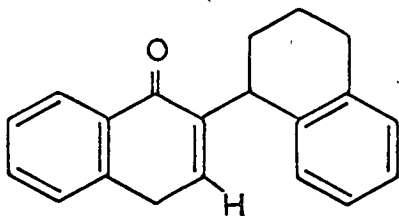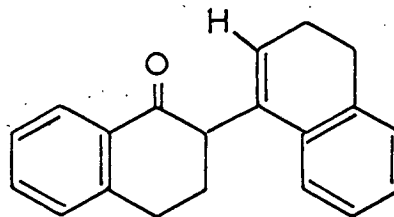
(127)   (128)

Of these structures, (128) was favoured on account of the carbonyl stretching frequency in the infra-red spectrum. Structure (127), where the carbonyl is conjugated both with an aromatic ring and an $\alpha\beta$-double bond, would be expected to display a bathochromic shift of ca. 35 cm.$^{-1}$ relative to 1-tetralone (ν_{co} 1695 cm.$^{-1}$)   A $\beta\gamma$-double bond, as exists in (128), would lead to a much smaller shift and indeed the value

observed (1695 cm.$^{-1}$) was identical to 1-tetralone.

A similar product was obtained with 7-methoxy-1-tetralone on treatment with gaseous hydrogen chloride and it was shown to display the characteristic vinyl triplet near τ4.2.   Treatment of this latter product with 30% palladium on charcoal for 45 minutes at 300 - 350° C. and chromatography on alumina/celite of the neutral product after extraction with strong alkali to remove phenolic material, gave on elution with benzene a small amount (11%) of material identical to that obtained in the original dehydrogenation of 7-methoxy-1-tetralone.

Since in this latter preparation one bond between the two aromatic ring systems was fixed prior to dehydrogenation, and assuming this bond to be stable, only one of two possibilities exists for the structure;   either the dinaphthofuran (124, R = OCH$_3$) or the dibenzoxanthene (125, R = OCH$_3$) depending on whether the oxygen at C_1 bonds with $C_{2'}$ or $C_{8'}$ respectively.

Close examination of the N.M.R. spectrum clearly indicated the structure to be the dinaphthofuran (129).

(129)
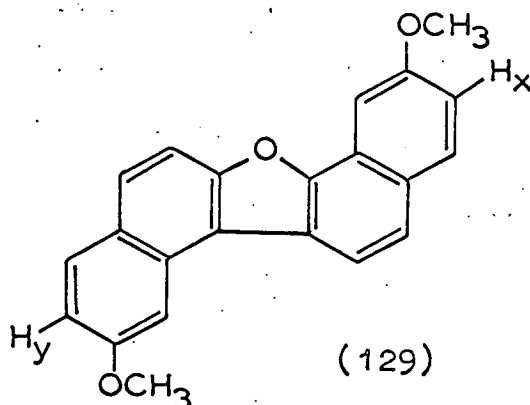
7,7'-Dimethyldinaphtho[1,2-b:2',1'-d]furan
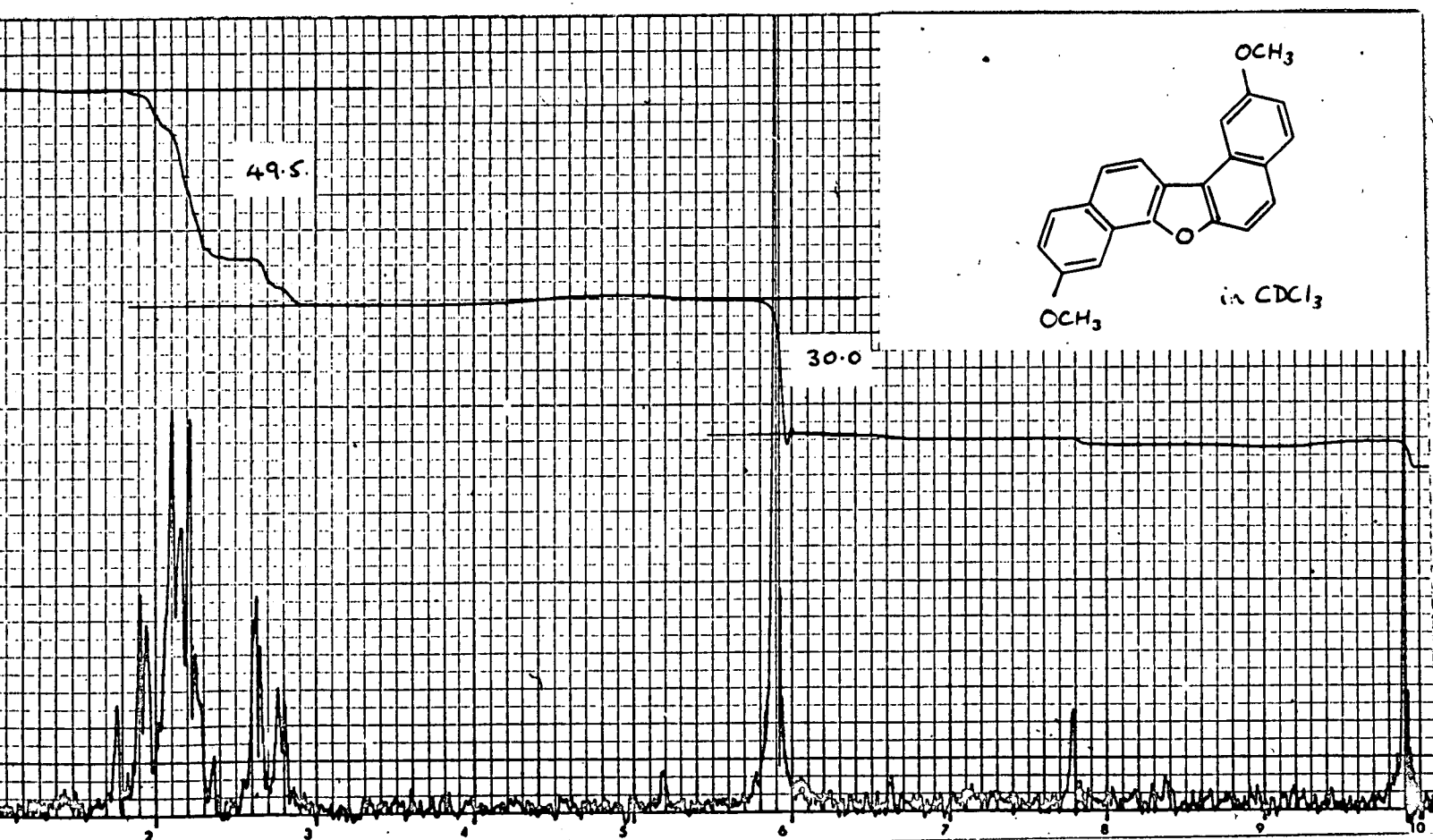
7,7'-Dimethoxydinaphtho[1,2-b:1',2'-d]furan

The following data is pertinent in this assignment of structure. Two apparently ortho-meta split quartets were visible at the upfield end of the aromatic region, which in deuterochloroform were nearly, but not quite, superimposed. Re-running the spectrum in acetone gave complete superposition of these signals indicating clearly that they were quartets. It is quite reasonable that these protons, by virtue of their chemical shifts ($\tau 2.8$), are adjacent to methoxyl groups and are consistent with the β-protons H_x and H_y in (129). Such a situation does not occur with the xanthene derivative, and on this basis alone differentiation is possible.

A similar two-stage reaction was attempted with 7-methyl-1-tetralone, although it was not possible to isolate a single component by chromatography as before. Nonetheless it was apparent by spectroscopic examination of the fractions obtained that the dimer produced in the catalytic dehydrogenation of 7-methyl-1-tetralone was not obtained, and presumably not formed, in the dehydrogenation of the intermediate species (dimethyl analogue of (128)).

It is thought possible that the dinaphthofurans formed during the dehydrogenations of the 7-substituted tetralones arise from the corresponding naphthols and not necessarily from intermediates such as (128), although proof is lacking. In this respect Woroshtzow[76] claims similar yields of some 30% for the dinaphthofuran (124, R = H) on treatment of either 1-tetralone or 1-naphthol with selenium under identical conditions supporting the above view.

5,7-Dimethoxy-1-naphthol, which is not described in the literature, was a much sought after compound. Its synthesis from m-dimethoxybenzene according to the route outlined on page 57 involving succinoylation, reduction, and ring closure to the tetralone followed by dehydrogenation to the naphthol has not been effected owing to the extreme difficulty encountered in ring closure of γ -(2,4-dimethoxyphenyl)butyric acid.

The only successful closure is reported by Davies et al.[77] using polyphosphoric acid with an optimum yield of less than 6% and necessitating small scale experimentation. These investigators also claim[78] total failure with either hydrogen fluoride on the acid, or stannic chloride on the acid chloride, confirming previous unsuccessful ring closures with these and other condensing agents.[79, 80]

In view of the requirement of several grams of the tetralone on account of the stages to follow, the polyphosphoric acid cyclisation was considered to be impracticable, and other syntheses were sought.

It was observed that the procedure employed by Lockett and Short[46] in the preparation of 5-methoxy-1-tetralone in good yield from the corresponding butyric acid and employing phosphorus oxychloride as the condensing agent had never been reported to be attempted with the dimethoxy- substituted acid (120, R = 2,4-$(OCH_3)_2$).

This was attempted in the present investigation, however, none of the tetralone was formed as seen from N.M.R. and I.R. spectral examination of the crude product. No other ring closures of this

sort were attempted.

The possibility of preparing 5,7-dimethoxy-1-tetralone by hydrolysis and decarboxylation of the β-ketoester formed from a Dieckmann condensation of the diester (130, R^1 and R^2 = alkyl) was considered.
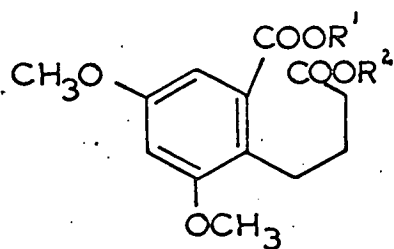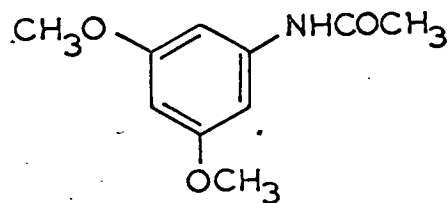
(130)   (131)

The most accessible synthesis of the required diester seemed to be from succinoylation of 1-acetamido-3,5-dimethoxybenzene (131) - rather than the corresponding deactivated benzoic acid or ester - and reduction of the ketopropionic acid formed.   Esterification and replacement of the acetamido group by an alkoxycarbonyl substituent would be required to follow to complete the synthesis. Attempted succinoylation of (131) in nitrobenzene with aluminium chloride, however, did not lead to the expected product but instead gave as the only isolable acidic material a phenol, the N.M.R. spectrum of which suggested its structure to be (132), and arising from methyl migration.   As a result this approach was not examined further.
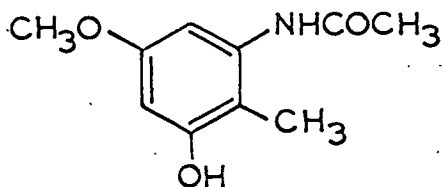
(132)

5,7-Dinitro-1-tetralone appeared to be a possible precursor in the synthesis of 5,7-dimethoxy-1-tetralone through reduction of both nitro groups to amino, replacement by hydroxyl and finally methylation. All attempts to prepare the dinitrotetralone, which is not described in the literature, by nitration of 1-tetralone failed. Mono-nitration was confirmed to give a mixture of the 5- and 7-nitro- substituted products,[81] where the latter is vastly dominant, however slightly more vigorous conditions gave rise to an exothermic reaction and the major product (the only one seen to be present by N.M.R. spectroscopy) was the oxidation product β-(2-carboxy-4-nitrophenyl)propionic acid.

Haworth et al. were able to oxidise, although in very low yield, the trimethoxytetralin (133) with chromium trioxide to a mixture of both trisubstituted 1-tetralones (134) and (135), separated chromatographically as the 2,4-dinitrophenylhydrazones.[83]

(133)   (134)   (135)
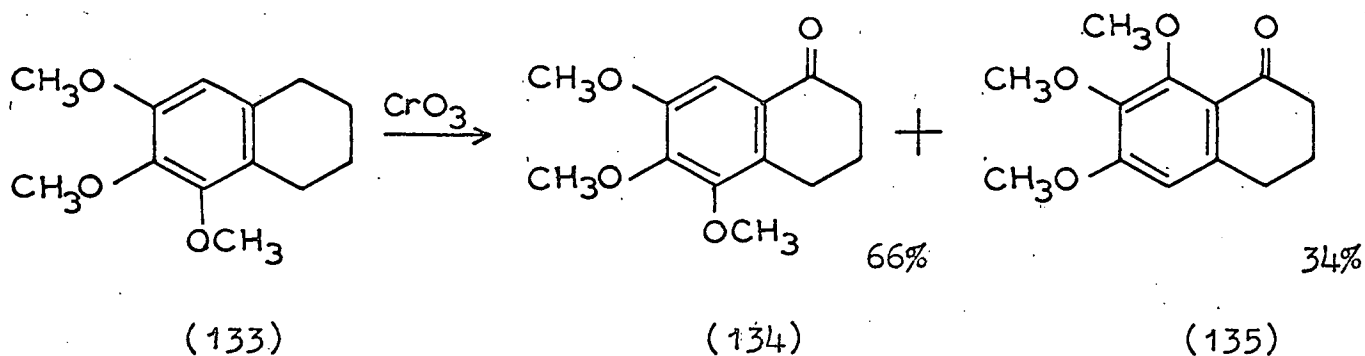
An analogous reaction was considered with m-dimethoxytetralin as substrate, however the latter's synthesis was not achieved. Catalytic reduction of 5,7-dinitro-1,2,3,4-tetrahydronaphthalene with Raney nickel or with palladium on charcoal in an atmosphere of hydrogen under pressure afforded only low yields of the diamine,

and subsequent acid hydrolysis of this in an autoclave at 200 - 250° C. gave only trace amounts of the impure diol.

The only reasonable synthesis of 5,7-dimethoxy-1-naphthol from a naphthalene derivative appears to be from 1-naphthylamine-5,7-disulphonic acid by alkali fusion of both sulphonate groups to give the dihydroxynaphthylamine, thence the di-O-methyl ether on methylation and finally the required naphthol on replacement of the amino group by hydroxyl. Since this synthesis involves alkali fusion to give a 1,3-dihydroxynaphthalene derivative it is unlikely to be successful on account of such compounds being unstable in alkali and rupturing to give o-toluic acid derivatives.[82] As a result this synthesis was not seriously attempted, although a preliminary experiment to replace the α-sulphonic acid group was carried out. Only a small amount of 5-amino-1-naphthol-3-sulphonic acid was obtained on fusion at 160 - 180° C. over several hours with strong caustic soda solution. The difficulty in maintaining a constant temperature throughout and in finding an ideally suitable reaction vessel were thought to be the main causes for the poor conversion.

2) Substituted 2-naphthols

a) 8-Substituted-2-naphthols

7-Methoxy-1-tetralone, prepared from anisole in the manner outlined on page 57, was used as a precursor in the preparation of 8-methyl-, 8-isopropyl- and 8-phenyl-2-naphthols. The scheme given on the following page indicates the route employed, which

required initial addition of a suitable Grignard reagent to the ketone, dehydration of the resultant carbinol (137) with dilute acid to yield the olefin (138) which was dehydrogenated catalytically with palladium on charcoal to give the methyl naphthyl ether (139). Demethylation of the ether was achieved by using hydriodic acid in acetic acid - a fairly standard reagent.

(137)   (138)

(139)

R = CH$_3$, Pr^i, Ph

In this way 8-methyl-2-naphthol was obtained in 41% overall yield from the tetralone and 8-phenyl-2-naphthol in 61% yield. The lower yield in the former case arose from apparent disproportionation in the dehydrogenation of the olefin necessitating distillation of the naphthyl ether. A low overall yield of 13% was obtained in the preparation of the isopropylnaphthol and here too disproportionation contributed to the poor conversion, however the initial Grignard addition, despite recycling the material and using an excess of reagent, was disappointingly poor. It was

found helpful to follow these reactions by N.M.R. spectroscopy and to purify products whenever necessary.

Spectroscopic examination was also useful in an unsuccessful attempt to prepare the hitherto unknown 8-t-butyl-2-naphthol. The initial Grignard reaction gave a complex mixture which was dehydrated and dehydrogenated without purification. Silica gel chromatography at this point afforded a small amount (ca. 10-15% accountability) of a mixture of apparently 1-t-butyl-7-methoxynaphthalene and 2-methoxynaphthalene in the ratio 1 : 1 eluted together with benzene. Further bands were eluted with chloroform/benzene but these were mixtures and unidentifiable. Re-chromatographing the binary mixture containing the required material gave no separation. This mixture after demethylation in the usual manner afforded a phenolic fraction identified by its N.M.R. spectrum as being the required t-butylnaphthol and 2-naphthol. It was apparent, however, that the proportion of alkylated naphthol, which accounted for less than 10% of the mixture, was much less than expected indicating drastic loss of the t-butyl group during reaction. At this point the synthesis was abandoned, since even if the required naphthol had been isolated in a pure state it was unlikely that sufficient material would be obtained for subsequent reactions.

b) 1-Methyl-2-naphthol

1-Methyl-2-naphthol was prepared in one step in moderate yield on Clemmensen reduction of the commercially available

2-hydroxy-1-naphthaldehyde.

3.) Methoxyphenols

m- and p-Methoxyphenols were prepared by monomethylation of the corresponding diols with rather more than one molar equivalent of dimethyl sulphate in aqueous alkali. o-Methoxyphenol (guaiacol) was obtained commercially.

The Preparation of Aryloxyalkanoic Acids and their Chlorides

1) Aryloxyacetic acids

In practically all cases these acids were prepared from the corresponding phenols according to the general procedure of Hayes and Branch, whereby the sodium salt of the phenol is heated at reflux with sodium chloroacetate in aqueous solution.[68] The reaction is probably a bimolecular nucleophilic substitution:

$$\text{Ar}-\text{O}^- \quad \underset{\text{CH}_2-\text{Cl}}{\overset{\text{COO}^-}{|}} \quad \longrightarrow \quad \text{Ar}-\text{O}-\underset{\text{CH}_2}{\overset{\text{COO}^-}{|}} \quad + \quad \text{Cl}^-$$
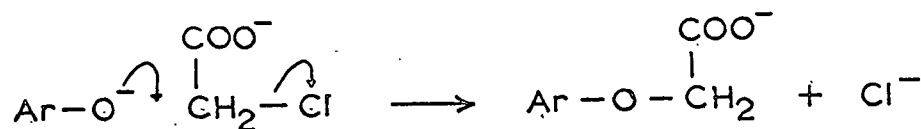
The time of reaction varied from three to five hours, hence conditions were not standard and optimum yields were not sought. Conversion to the acids, either obtained as an insoluble sodium salt or by bicarbonate extraction, was generally adequate. It was observed also that better yields were obtained in the main from 2-naphthols than from 1-naphthols, presumably a manifestation of the familiar steric effect of the peri-hydrogen in the case of the latter. Best yields were obtained by maintaining the pH of the reaction mixture just alkaline (pH 7-8), an excess of alkali giving somewhat reduced amounts of product most probably on account of destruction of the chloroacetate by hydrolysis to glycolic acid.

2-Chloro-1-naphthyloxyacetic acid was prepared using the more reactive ethyl bromoacetate on the dry sodium salt of the phenol.

Alkaline hydrolysis of the isolated ester provided the acid in high yield. A previous reported attempt to prepare the acid using the sodium chloroacetate route had given only low conversion.[3] This low reactivity is presumably due to the steric effect caused by the 2-substituent as well, of course, as the peri-effect of the 8-hydrogen atom.

2-Nitro-1-naphthyloxyacetic acid similarly is not able to be prepared using sodium chloroacetate on the naphthol,[69] and it was found in the present study to be inaccessible by the ethyl bromoacetate procedure, even on refluxing the dry salt of the naphthol in excess reagent with copper bronze over several hours. The reduced basicity of the naphthoxide ion in this case is likely to be critical and reinforced by a considerable steric factor.

4-Nitro-1-naphthyloxyacetic acid was best prepared by nitration of 1-naphthyloxyacetic acid with concentrated nitric acid in glacial acetic acid at low temperature. The sole product of reaction has recently been shown on the basis of N.M.R. analysis to be the 4-nitro isomer.[4]

7-Methoxy-2-naphthyloxyacetic acid was synthesised from naphthalene-2,7-diol through 7-hydroxy-2-naphthyloxyacetic acid and methylation

2) 2-(1-Naphthyloxy)isobutyric acid

This was the only acid investigated which was substituted in the aliphatic side chain. It was prepared by the method of

Bargellini in over 90% yield.[70]   This procedure involves heating
at reflux 1-naphthol, potassium hydroxide and chloroform in a molar
ratio of 1 : 1 : 2 in excess of acetone.   Two mechanisms are
possible for the reaction and both involve the epoxide intermediate
(140).   This species can either arise directly from dichlorocarbene
addition to acetone or alternatively from trichloromethyl carbanion
attack to give initially the carbinol (141).

$$CHCl_3 \xrightarrow{KOH} \bar{C}Cl_3 \xrightarrow{Me_2CO} Me_2C{\overset{O^-}{\underset{CCl_3}{<}}} \quad (141)$$

$$CHCl_3 \xrightarrow{KOH} :CCl_2 \xrightarrow{Me_2CO} Me_2C \overset{CCl_2}{\underset{O}{\triangle}} \quad (140)$$

$$\overset{OH^-}{\underset{}{}}\searrow^{ArO^-}$$

$$ArOCMe_2COOH$$
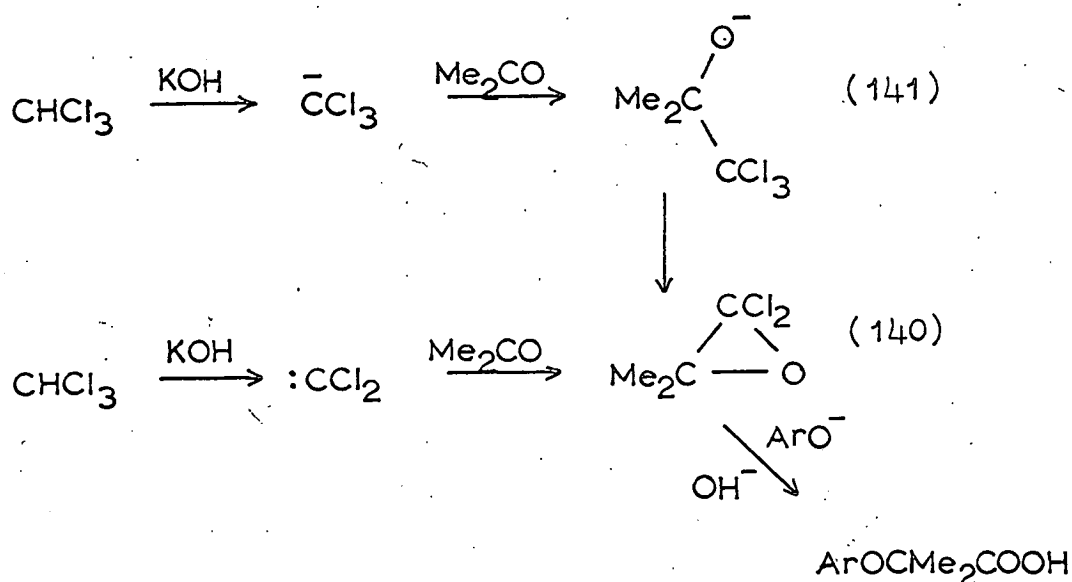
3) Acid chlorides

A recent unsuccessful attempt[2] at the cyclisation of
3-methoxyphenoxyacetic acid through its chloride with aluminium
chloride in benzene prompted a re-investigation of this reaction.

It was found that with thionyl chloride both as reagent and
solvent, and consequently present in considerable excess, in the
preparation of the acid chloride from the acid, as well as the
expected replacement of hydroxyl by halogen at the carboxylic

function, aromatic substitution had also occurred to the extent of apparent complete replacement of one aromatic proton. This was readily seen from the N.M.R. spectrum of the crude acid chloride which integrated in the ratio of 3 : 2 : 3 for aromatic : CH_2 : OCH_3. That cyclisation had not accompanied this reaction was evident from an examination of the infrared spectrum of the product which displayed a single carbonyl stretching absorption at 1798 cm.$^{-1}$ Such a frequency is well established to be characteristic of an acyl chloride and not of a benzofuranone, the latter invariably displaying a carbonyl vibration at 1700 - 1715 cm.$^{-1}$ The N.M.R. spectrum, on account of two CH_2 and two CH_3 resonances of roughly similar intensity and separated in each case by 2 - 3 c.p.s., indicated a mixture of two components. The aromatic region was consistent with this observation and by comparison of the multiplicity of the resonances and a comparison of chemical shifts with those of the starting acid it was clear that two possibilities existed. Either the mixture was one of isomers substituted at the 4- and 6-positions, or alternatively it was a mixture of non-isomeric compounds dissimilarly substituted either at the 4- or 6-positions. The esters of this mixture were prepared but separation of these by column chromatography on silica gel proved impossible. It was not possible then to determine the precise nature of the mixture although the failure to achieve separation would suggest than an isomeric mixture is more likely.

A similar quantitative substitution reaction occurred with 5-methoxy-1-naphthyloxyacetic acid when refluxed in excess thionyl

chloride for 1 - 2 hours and it could be determined from the N.M.R. spectrum that the substituent had entered an α-position, although it was not possible to state which of the two vacant sites had reacted.

To determine the nature of the incoming group in these reactions, 1,5-dimethoxynaphthalene was examined and it was found that on warming this latter material to 30 - 35° C. in excess thionyl chloride for only a few minutes, quantitative conversion to 4-chloro-1,5-dimethoxynaphthalene occurred.

It is most probable then that chlorination accompanies conversion to the acid chlorides. Clearly on directive influences, electrophilic attack occurs, possibly by Cl^+ from the dissociation

$$SOCl_2 \longrightarrow Cl^+ + SOCl^-$$
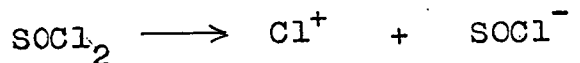
The observation that 1-naphthyloxyacetic acid when heated at reflux over several hours in thionyl chloride only underwent a small amount of ring substitution (from N.M.R. spectral integration) suggests that a peri effect may assist the facile substitutions. Thus with 1,5-dimethoxynaphthalene, for example, where the preferred orientation of substituents is trans with the molecule planer,[111] it may be that the non-bonding electrons at the oxygen assist electrophilic substitution at the peri position in similar fashion to the 'dipole effect' of 1-nitronaphthalene which nitrates predominantly at the 8-position.

In view of these observations, acid chlorides were prepared

in benzene with 1.3 molar equivalents of thionyl chloride and
this was found to be satisfactory in giving exclusive reaction
at the carbonyl function.   Deactivated acids, i.e. those with
nitro- substituents, were best prepared with an excess of
reagent in the absence of solvent.

The Reactions of Aryloxyacetyl Chlorides with Aluminium Chloride

1) General experimental considerations

An early study[2] of the Friedel-Crafts acylation reaction when applied to substituted phenoxyacetyl chlorides in aromatic solvents established that the presence of weakly electron-donating substituents in the aromatic nucleus resulted in exclusive, or near exclusive, formation of the intramolecular acylation product, excepting those cases where the aromatic solvent was itself more reactive to electrophilic attack than the acylating species. In these latter instances intermolecular acylation was observed.

It was further established that optimum yields of the cyclic ketones were obtained with aluminium chloride as the Lewis acid catalyst, and in this respect the use of zinc chloride, stannic chloride and antimony pentachloride were investigated, and that the best conditions involved dry benzene as solvent, whereby intermolecular acylation was minimal, at temperatures of 5 - 10° C. over 1 - 3 hours.

For this reason these conditions for acylation were duplicated with little modification in the initial stages of the present investigation into the preparation of tricyclic ketones from naphthyloxyacetyl chlorides. Satisfactory results were obtained in these preliminary experiments confirming that the choice of reaction conditions was an entirely suitable one. In consequence other Lewis acid catalysts were not investigated in

the current study. The use of other condensing agents, such as sulphuric acid and polyphosphoric acid, on the free acids was however examined, but more will be said of these elsewhere.

As far as preparative aspects of the aluminium chloride catalysed acylation are concerned, only a little need be said.

The sequence of addition of reactants was invariable and involved final addition of the substrate in dry benzene to a stirred, chilled suspension of powdered anhydrous aluminium chloride in a further quantity of dry benzene. The molar proportion of acid chloride : aluminium chloride : benzene was kept constant at 1 : 1.1 : 30. The addition was carried out drop-wise over 15 - 30 minutes to minimise local heating effects. The heterogeneous dark blue, green, or red reaction mixture was then stirred for 2.5 - 3 hours before terminating the reaction by decomposing the complex with crushed ice and dilute hydrochloric acid and stirring the mixture for 0.5 - 1 hour. These conditions were generally sufficient to hydrolyse unreacted acid chloride to the carboxylic acid which was recovered by extraction into saturated bicarbonate solution and subsequent acidification.

The crude product, after removal of the aryloxyacetic acid, was examined carefully by N.M.R. and I.R. spectroscopy. Spectral examination was critical since it was considered desirable to account for the entire range of products present.

The usefulness of infra-red spectroscopy lay primarily in its identification of carbonyl stretching frequencies. The

cyclic ketones are characterised by carbonyl stretching bands near, and generally slightly above, 1700 cm.$^{-1}$, whereas the intermolecular acylation products display such absorptions between 1680 and 1700 cm.$^{-1}$. Unhydrolysed acid chloride was inferred by the presence of an absorption, generally broad, near 1800 cm.$^{-1}$, and residual aryloxyacetic acid by one or two lines between 1710 and 1750 cm.$^{-1}$. The region near 3500 cm.$^{-1}$ was also examined, particularly with solution spectra, for the presence of hydroxyl stretching bands.

The infra-red spectrum by itself was of limited value but was used in the main to supplement data collected from the N.M.R. spectrum. The latter not only provided evidence of the number of species present on account of the number of lines observed for a particular resonance (-O-CH$_2$-CO-, or CH$_3$ if a methyl or methoxyl resonance were present), but also gave an indication of the proportions of such products. The identity of these products, too, was often possible on account of observed chemical shifts. Thus cyclic ketones are characterised by a CH$_2$ resonance between τ 5.0 and τ 5.4, whereas the intermolecular ketones absorb further downfield, generally between τ 4.6 and τ 4.9. These latter ketones also display a characteristic multiplet near τ 1.8 - 2.0, corresponding to the two protons in the positions ortho to the carbonyl function.

The nature of the work up procedure for the crude reaction mixtures depended largely upon the range and nature of the products inferred spectroscopically. These procedures and

product identification are described in some detail in the sections which follow.

2) 1-Naphthyloxyacetyl chlorides
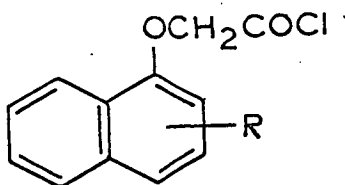
(6)

(a) R = H
(b) R = 2-Cl
(c) R = 3-Cl
(d) R = 4-Cl
(e) R = 7-CH$_3$
(f) R = 4-OCH$_3$
(g) R = 5-OCH$_3$
(h) R = 7-OCH$_3$
(i) R = 4-NO$_2$
(j) R = 3-NO$_2$
(k) R = 3-I
(l) R = 6-OCH$_3$
(m) R = 5,6,7-(OCH$_3$)$_3$

Acylation of the 1-naphthyloxyacetyl chlorides (6a - 6h), inclusive, gave crude products, obtained in the manner outlined in the preceding section, whose N.M.R. spectra indicated, with but two exceptions, the presence of a single component on the basis of one CH$_2$ resonance near $\tau 5.2$, which inferred that this was a cyclic ketone consistent with the integration ratio. The I.R. spectra, too, all displayed carbonyl absorptions at, or slightly above 1700 cm.$^{-1}$, corroborating this inference. Only in the cyclisations of 5-methoxy- and 7-methoxy-1-naphthyloxyacetyl chlorides (6g and 6h) was there evidence of a second component from a CH$_2$ resonance (singlet) at $\tau 4.8$ and $\tau 4.7$ respectively.

Separate methoxyl resonances were also observable corresponding
to these peaks as well as multiplets near $\tau 2.0$.   These
components were confidently predicted to be the intermolecular
ketones on the above evidence, and in the case of the 7-methoxy-
substituted acid chloride cyclisation a small amount of material,
whose integrated N.M.R. spectrum corresponded to such a product
was isolated by chromatography on silica gel.   Elution was
effected with benzene/chloroform (9 : 1 by volume), the material
being eluted slightly ahead of the main component, a cyclic ketone.
No separation was achieved on similar chromatography of the
5-methoxy product mixture.

In all eight cycliacylations the cyclic ketones were obtained
in a pure state by a single re-crystallisation from a suitable
solvent (usually ethanol).   Identification of the cyclic product
was based on interpretation of the aromatic region of the N.M.R.
spectrum and showing it to be consistent with the angular ketone
(9, R various), except in the case of (6b) where cyclisation was
only possible at the peri position.   The spectrum in this latter
instance, although displaying a degenerate aromatic region, was
nevertheless consistent with the product being the peri-acylated
ketone (10, R = Cl).   The following N.M.R. spectral data are
presented in accord with assignments of structure.

That the unsubstituted acid chloride (6a) cyclised to the
angular ketone was evident from a comparison of the product
spectrum with that of the acid (or acid chloride).   The acid
spectrum (in DMSO) shows a 2H resonance at $\tau 3.10$ (quartet) and

8H signal at τ1.70 (multiplet), these chemical shifts being a direct consequence of the O-alkyl side chain.   In the ketone the naphthalene 2H resonance is absent on account of substitution, whereas the 8H of the naphthalene nucleus (9H in the naphthofuranone) is still evident and absorbs at τ1.82 (in $CDCl_3$).

A similar argument held for the cyclisation product from 3-chloro-1-naphthyloxyacetyl chloride (6c) which has an obvious 9H multiplet at τ1.85 (in $CDCl_3$) - cf. the corresponding 8H at τ1.65 in acetone for the acid - and absence of the 2H resonance clearly visible as a meta-split doublet near τ3.0 in the acid. Further proof of structure came from the 5H resonance of the ketone which appears as a single line at τ2.57 in the whole spectrum, yet on expansion is a doublet with an observable inter-ring coupling of 0.8 c.p.s.

That the 4-chloro- substituted chloride (6d) gave the angular ketone was amply evident from a singlet attributable to the 4H, and two groups of multiplets, each multiplet corresponding to two protons, arising from the remaining α- (6H and 9H) and β- (7H and 8H) protons.   A similar arrangement of α- and β- protons appears in the spectra of 4-chloro-1-naphthol and O-alkylated derivatives.

Conclusive evidence in favour of angular cyclisation in the case of the 7-methyl-, 4-methoxy- and 7-methoxy- substituted acid chlorides (6e,6f and 6h respectively) came from the loss of the naphthalene nucleus 2H which in all spectra of the acids and their chlorides appears as the most upfield aromatic resonance. A complete first order analysis was possible for the aromatic
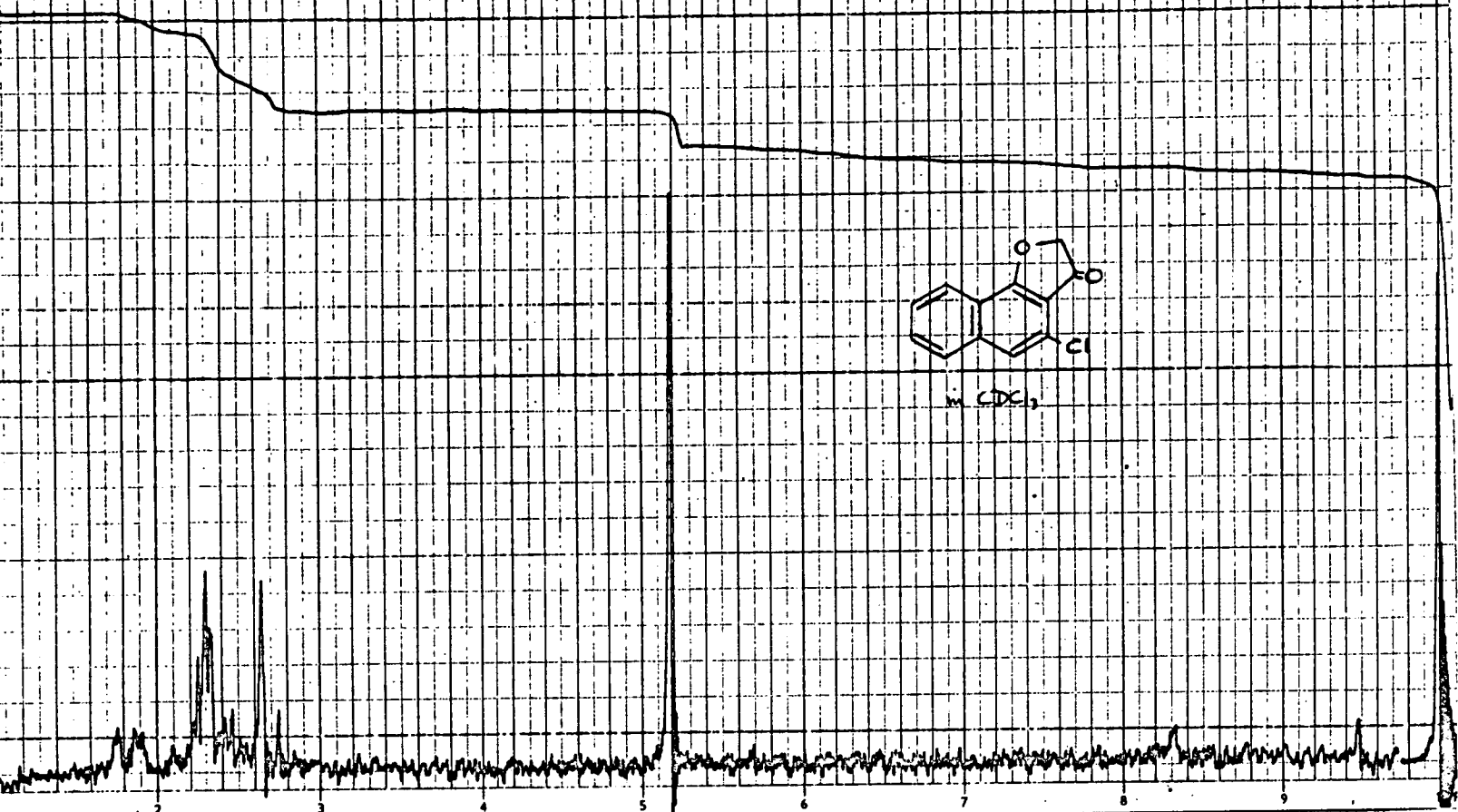
4-Chloronaphtho [1,2-b] furan-3(2H)one
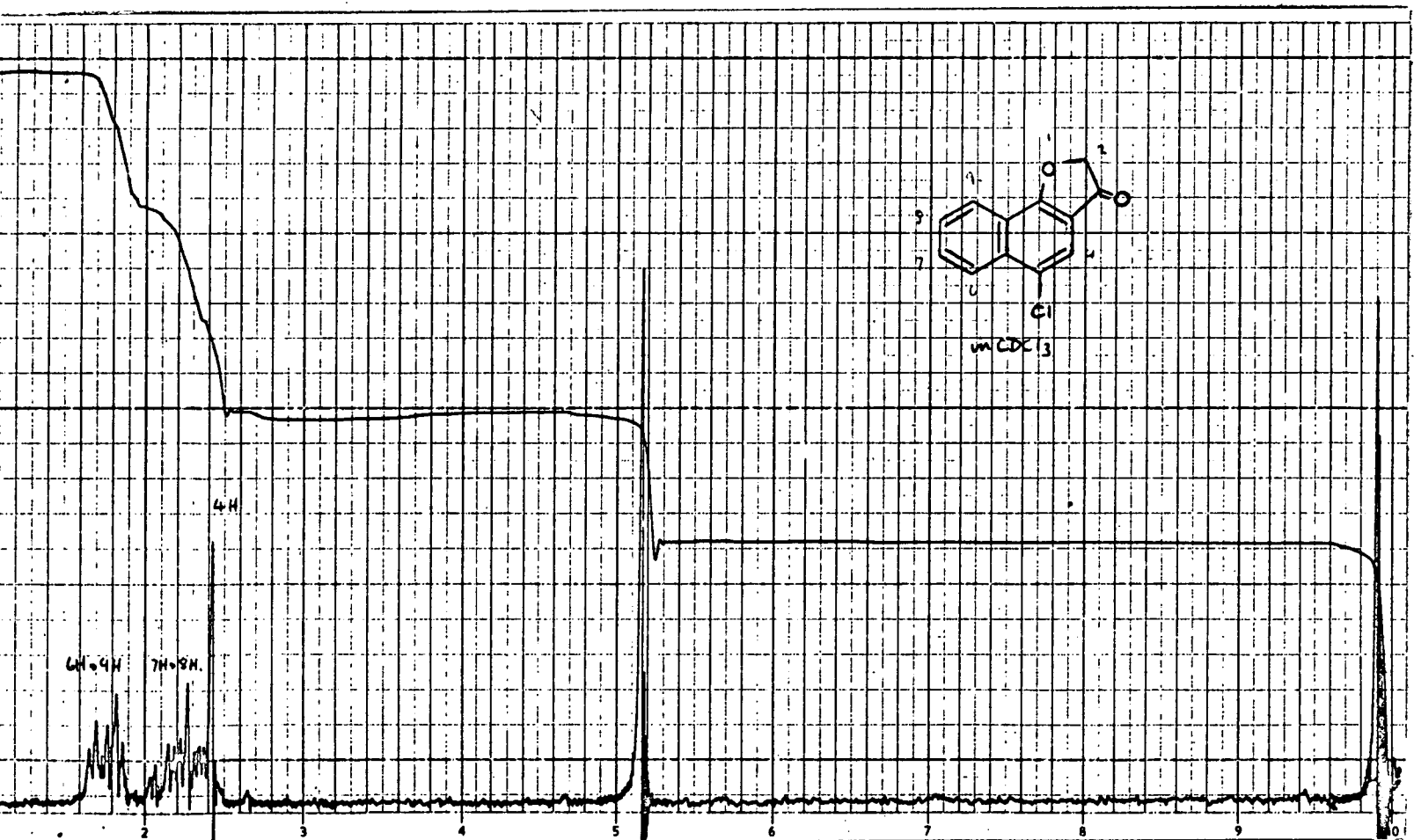
5-Chloronaphtho [1,2-b] furan-3(2H)one
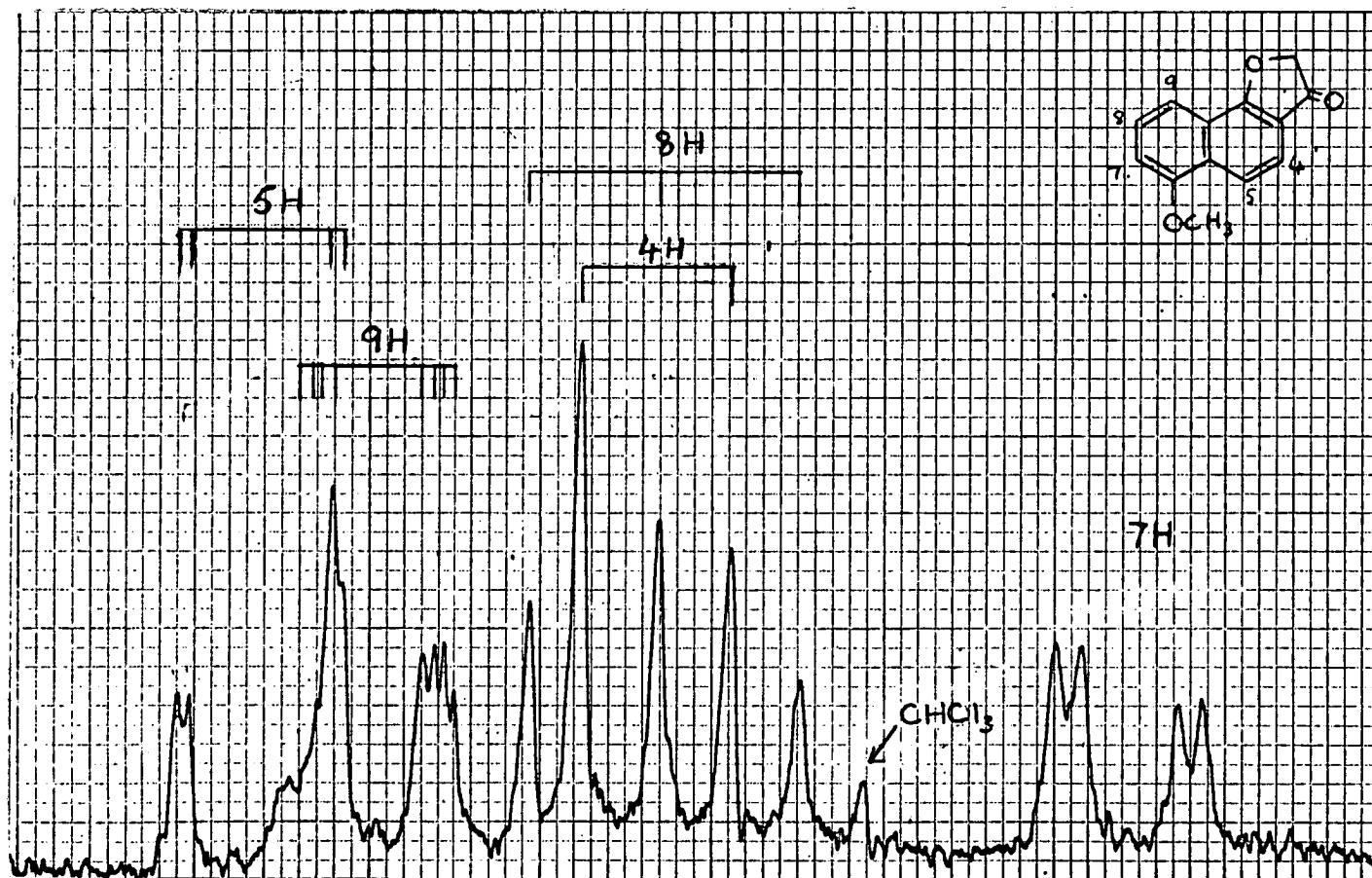
6-Methoxynaphtho[1,2-b]furan-3(2H)one
and Aromatic Expansion

expansion of the ketone from the cyclisation of 5-methoxy-1-naphthyloxyacetyl chloride (6g). The whole spectrum and expansion are reproduced on the facing page. From the loss of one of the β- protons from the position ortho to an O-alkyl substituent, and the presence of an inter-ring coupling, it was quire clear that angular cyclisation had occurred. Synthesis of the corresponding peri ketone, vide infra, and showing it to be different, confirmed the assignment of structure.

Two cyclisations were attempted where the aromatic nucleus was deactivated towards electrophilic attack on account of the presence of a nitro- substituent at C_3 or C_4. In these instances the intermolecular ketones were the sole products of reaction although conversion to products was in each case low and less than 20%. Only in the case of the 4-nitro cyclisation was the product obtained in a pure state, since in working up the reaction mixture of the 3-substituted isomer, chloroform was added to the system which gave rise of a quantity of the ethyl ester. (Ethanol is added as a stabiliser to solvent chloroform). That the ester had been formed was readily seen from the N.M.R. spectrum (ethyl triplet and quartet resonances at typical ester chemical shifts and associated $O-CH_2-CO$ singlet) and from the I.R. spectrum (ν_{co} 1755 cm.$^{-1}$). An attempt to hydrolyse the ester with warm 10% aqueous sodium hydroxide and a little ethanol decomposed the intermolecular ketone and no material was isolated to be positively identified. A repeat of the reaction on a very

small scale (0.2 g.), but at reflux over 2 hours in an endeavour to increase the yield, gave an intractable tar with a complex N.M.R. spectrum, presumably on account of decarbonylation or further acylation of initially formed products at increased temperature.

It was found that in those acylations of nitro-substituted substrates carried out at low temperature and where the major component after reaction was unreacted acyl halide, the normal conditions of decomposition and hydrolysis (ca. 3 - 4 N. hydrochloric acid at room temperature for 1 hour) were insufficient to effect complete hydrolysis of the acid chloride to the acid. Stirring for many hours (overnight) at room temperature, or 4 - 6 hours at 60 - 70° C. with the same strength of acid, or alternatively for 0.5 - 1 hour with 2N. aqueous sodium hydroxide at room temperature were required.

Cyclisation of 3-iodo-1-naphthyloxyacetyl chloride (6k) prodeeded smoothly to give a mixture of three components after complete removal of chloride and acid. The three products seen to be present all had singlets characteristic of $O-CH_2-CO$ resonances in the N.M.R. spectrum at shifts of τ 4.44, 4.98 and 5.03. Unfortunately on account of the exceedingly low solubility of the crude product a good spectrum was not possible, and the above values are for a weak solution in dimethylsulphoxide.

The major component (CH_2 at τ4.98) was readily isolated from the mixture on recrystallisation from benzene. A further recrystallisation from the same solvent afforded material of

sharp melting point which analysed for a cyclic ketone and which
displayed a carbonyl absorption at 1698 cm.$^{-1}$ (nujol mull) in the
infra-red spectrum.   A satisfactory N.M.R. spectrum was obtained
with a dilute solution in DMSO at 100 Mc/sec. consistent with the
material being the angular ketone, on account of a sharp singlet
at τ1.85, integrating for one proton,which could only be the
5H in the angular product.   The four adjacent aromatic protons
in the second ring in such a structure would be expected to be
degenerate and this too was consistent with the observed spectrum.

Initially structure assignment was dubious on account of a
second singlet at τ2.60, too far from the other aromatic
absorptions to be coupled to them, however this was shown to be
due to a trace of benzene (solvent for recrystallisation) which
had been retained stongly in the crystal structure.   It was
removed entirely by drying at 150° C. for two hours.   The
evaporated filtrate from the first recrystallisation was applied
to a short column of silica gel in a large quantity of benzene
but no material was able to be eluted, even with neat methanol.
The major product did however account for more than 50% of that
material which had reacted.   Assignments of structure to the
two minor components cannot be made with any certainty however
the likeliest structures would be the intermolecular ketone and
the peri-condensed cyclic ketone.   The further downfield of the
two CH_2 absorptions (τ4.44) is characteristic of the former and
the absorption at τ5.03 is most probably a reasonable value for
the latter.   A meta-split doublet at τ2.80 in the mixture could

arise from either structure, being the proton in the position ortho to both the halogen and the oxygenated substituent. This signal however, was clearly present in only one of the minor products by integration, yet both structures would require its presence. A further possible product would be the unsubstituted angular cyclic ketone from loss of iodine either before or after cyclisation, but this was excluded with certainty on comparison with the N.M.R. spectrum of an authentic sample. Decarbonylation too seemed unlikely, since no diphenylmethane was detected.

Cyclisation of 6-methoxy-1-naphthyloxyacetyl chloride (61) was attempted on three occasions under identical conditions, each run being characterised by considerable, unaccountable loss of material. Non-reproducible results were also typical and the only common feature was an apparent excess of OCH_3 resonances over CH_2. On account of the low amounts of material obtained (ca. 15 - 40mg. from 1 - 2 g. of acid) as mixtures, no attempt was made to isolate and identify components.

The trimethoxy- substituted acid chloride (6m) on reaction with 1.1 molar equivalents of aluminium chloride in the usual manner afforded a product mixture identified spectroscopically as being at least 85% acid chloride. Two other components with CH_2 resonances near $\tau 4.7$ (acetophenone?) and near $\tau 5.0$ (a cyclic ketone?) were evident and seemed to account for the remainder of the material. The product mixture was re-cycled with 2.5 molar equivalents of aluminium chloride, for it was thought possible that the low conversion to products was due to the catalyst

5-Methoxynaphtho [1,2-b] furan-3(2H)one
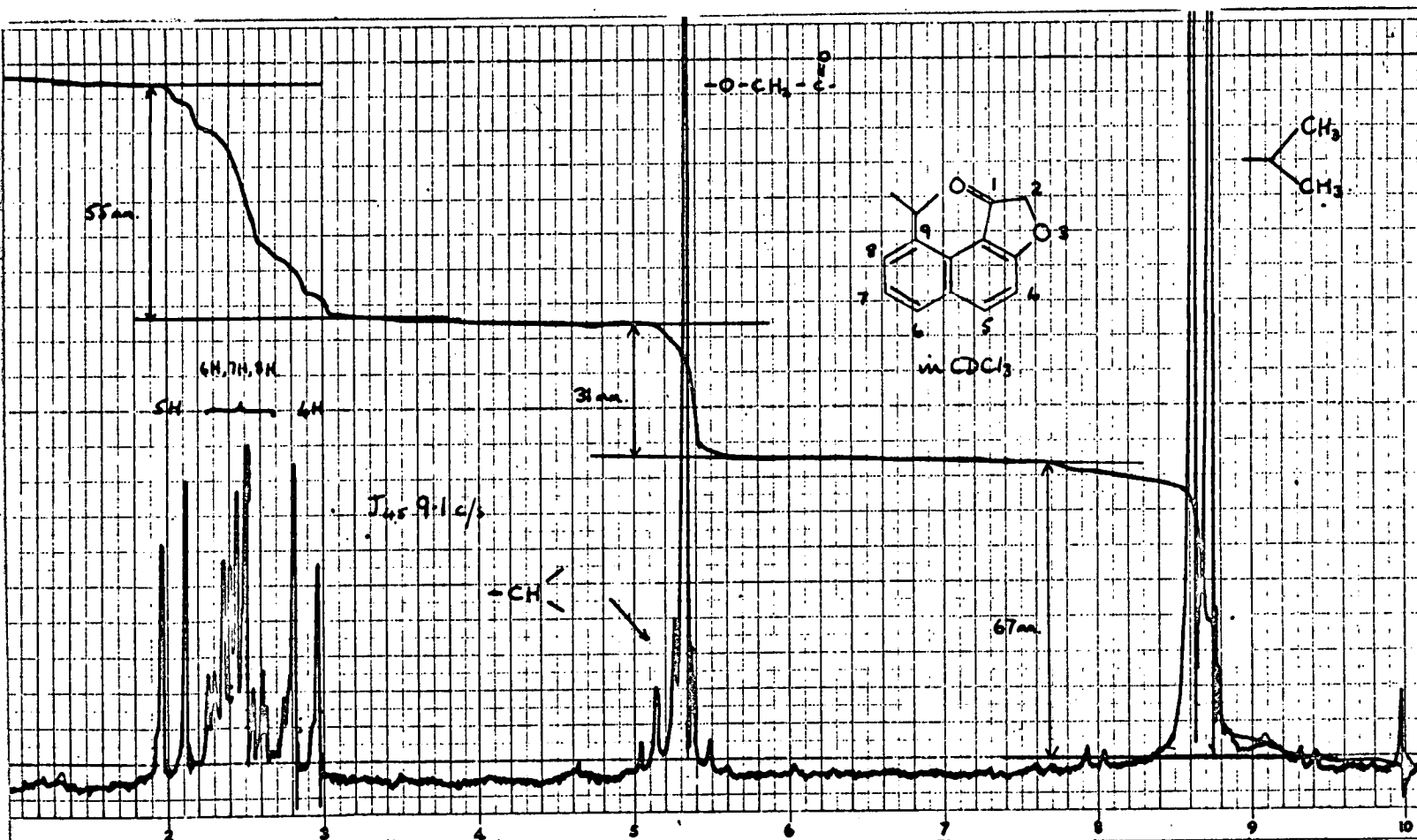
9-iso-Propylnaphtho [2,1-b] furan-1(2H)one

preferentially complexing with one or more methoxyl substituents rendering it inactive for acylation. The second product obtained, free from acid chloride and acid, was a mixture of two components as before, yet only 35 mg. was obtained from 1.46 g. of acid. No material was obtained on chromatography of this entire neutral product on silica gel and the experiment was abandoned. Since no more of the acid was available the cyclisation was not able to be repeated.

3) 2-Naphthyloxyacetyl chlorides
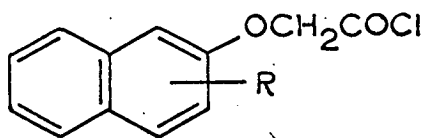
(5)

(a) R = H
(b) R = 7-OCH$_3$
(c) R = 8-CH$_3$
(d) R = 8-isoPr
(e) R = 8-Ph
(f) R = 1-Cl
(g) R = 1-CH$_3$

Treatment of the nuclear substituted 2-naphthyloxyacetyl chlorides (5b - 5e), inclusive, as well as the parent chloride (5a), with aluminium chloride in benzene under the usual conditions afforded high yields of the angular cyclic ketones (8, R various) with no trace of the linear isomers. The cyclisations of (5a, 5b and 5c), but not (5d and 5e), were accompanied by a small amount of solvent acylation to give the corresponding acetophenones, which were not isolated but inferred on account of low intensity CH$_2$ resonances near τ4.7 in the N.M.R. spectrum. (in CDCl$_3$). In all instances the proportion of solvent acylated

9-Methylnaphtho [2,1-b] furan-1(2H)one
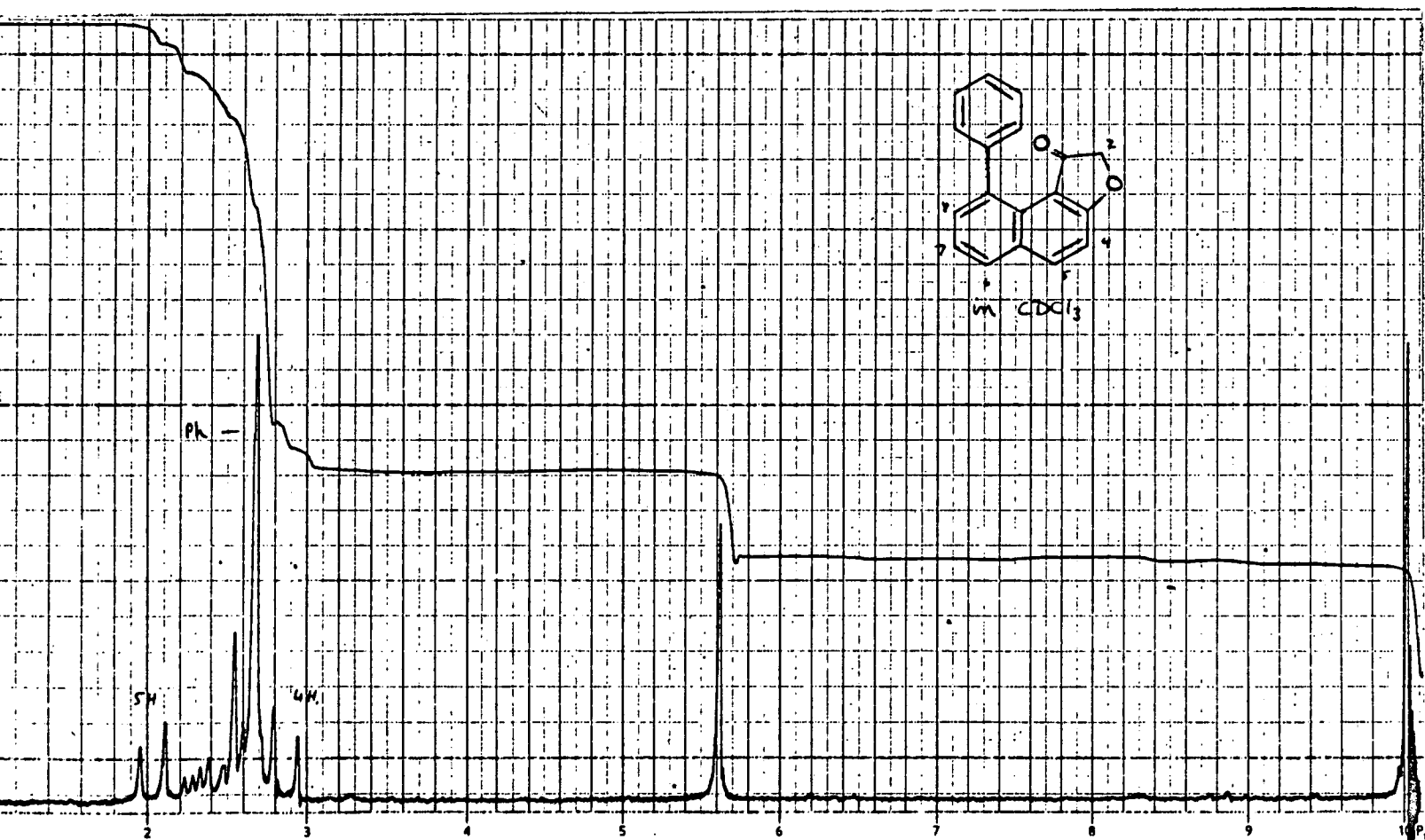
9-Phenylnaphtho [2,1-b] furan-1(2H)one

product was less than 10%.   The cyclic ketones were obtained

in a pure state by recrystallisation, generally only once, from

a suitable solvent and their structures verified by N.M.R.

spectroscopy.

That cyclisation to the angular naphthofuranone had occurred

was abundantly clear from the presence of two mutually coupled

ortho-split doublets in the spectra of the products from ring

closure of the unsubstituted and 8-substituted acid chlorides.

In these instances the doublet near $\tau 2.8$ was attributed to the

4H, and the downfield doublet near $\tau 2.0$ to the 5H on account of

its being both an α-proton and para with respect to the introduced

carbonyl function.   A notable feature of the unsubstituted

naphtho[2,1-b]furan-1(2H)one was the considerable downfield shift

of the proton attached to C_9 which absorbed some 35 c.p.s. below

the 5H at $\tau 1.30$, on account of its proximity to the carbonyl

group of the five-membered ring.

This latter feature was obvious also in the spectrum of

8-methoxynaphtho[2,1-b]furan-1(2H)one from cyclisation of (5b)

where, despite the conjugative +M effect of the neighbouring

methoxyl group, the 9H absorbed as the most downfield proton below

$\tau 2.0$.   The remainder of the spectrum was first order confirming

structure assignment.

Attempted cyclisation of 1-chloro-2-naphthyloxyacetyl

chloride (5f) gave only the intermolecular ketone (isolated in

65% yield) as the sole acylation product.   Competitive

decarbonylation had also occurred as was clear from the N.M.R.

spectrum of the crude product. Extraction of the crude material with N. sodium hydroxide provided a phenolic fraction on acidification identified spectroscopically as mostly 1-chloro-2-naphthol. Peaks near τ6.0 in the N.M.R. spectrum indicated the presence of benzylphenolic products but these were present only in very low concentration. The material neutral to the dilute alkaline wash consisted of diphenylmethane and the acetophenone; separation of these components was achieved by silica gel chromatography.

Spectroscopic examination of the crude product obtained from the interaction of 1-methyl-2-naphthyloxyacetyl chloride (5g) with aluminium chloride in benzene, showed the presence of a complex mixture where it was clear that decarbonylation had occurred to a very considerable extent and probably predominated over acylation. On account of the complexity of the mixture, the fact that little or no cyclic ketone appeared to be present and owing to initial separations with alkali failing to produce encouraging results, the experiment was discontinued.

4)   <u>2-(1-Naphthyloxy)isobutyryl chloride</u>
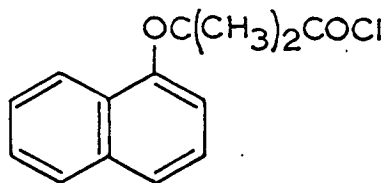
(142)

Cyclisation of 2-(1-naphthyloxy)isobutyryl chloride (142),

in CDCl₃
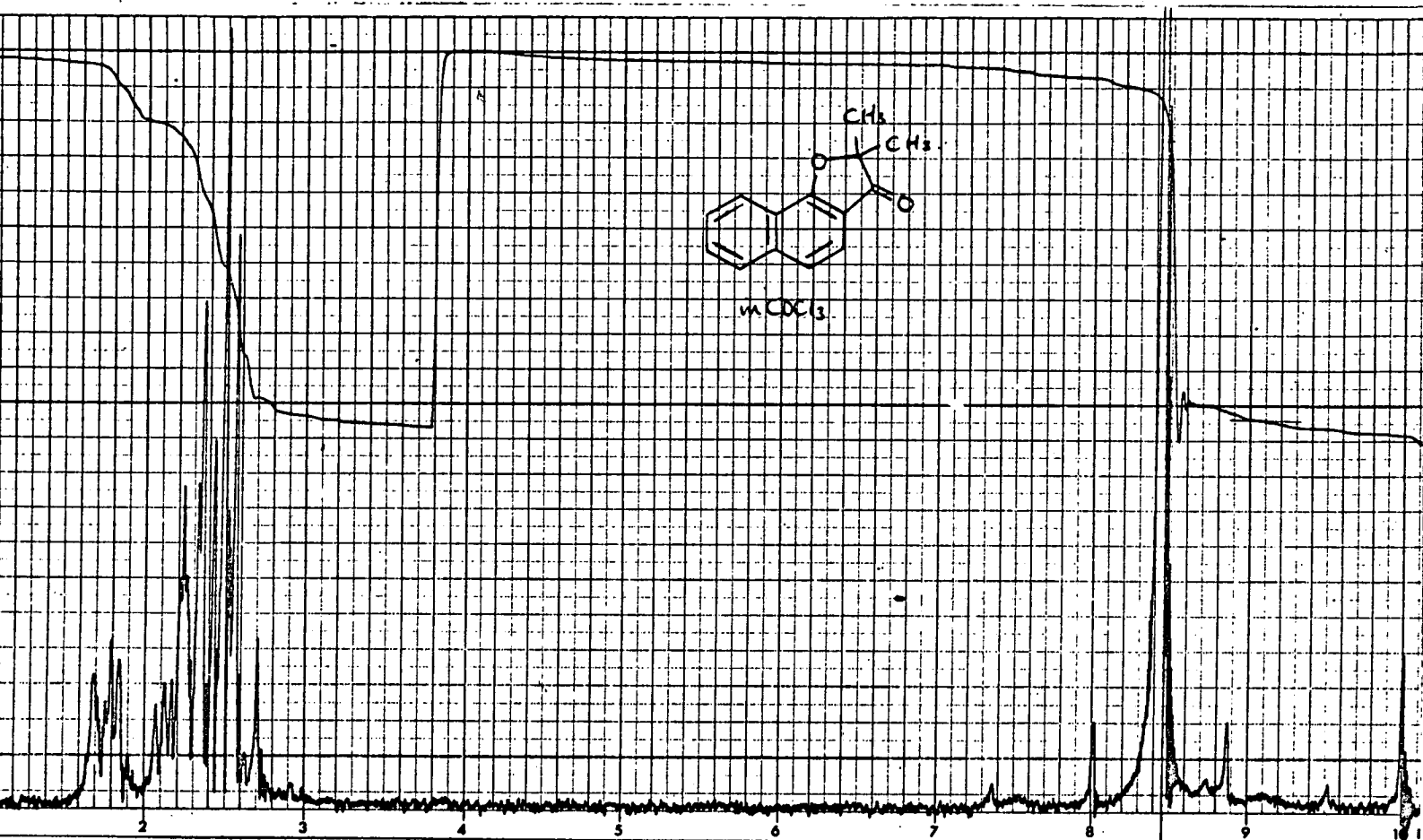
2,2-Dimethylnaphtho[1,2-b] furan-3(2H)one

the only side chain substituted halide investigated, proceeded smoothly to give a single component. The N.M.R. spectrum clearly showed this product by integration to be a ring closed material, identified on account of the absence of the naphthalene nucleus 2H and retention of the very much downfield 8H, as the angular ketone. Although this was the only acylation product of (142), a second material was obtained on chromatography of the filtrate used to recrystallise the major component. This small amount of material, which was eluted prior to the main band, was identified by mass spectrometry as a chloro- derivative of the cyclic ketone. Identification was based on the correct molecular weight for such a compound supplemented by a 3 : 1 isotopic ratio of the higher mass ions separated by two mass units quite characteristic of monochlorinated compounds. The N.M.R. spectrum indicated that the material was 5-chloro-2,2-dimethylnaphtho [1,2-b] furan-3(2H)one by virtue of a singlet at τ 2.84 (in CDCl$_3$) (4H). This material had clearly come from ring closure of the 4-chloro- substituted acid chloride, which in turn was prepared, apparently in less than 1% yield (from the yield of chlorinated ketone), as a by-product in the treatment of the naphthyloxyiso-butyric acid with 1.3 molar equivalents of thionyl chloride in benzene solution.

5) 1-Phenanthryloxyacetyl chloride
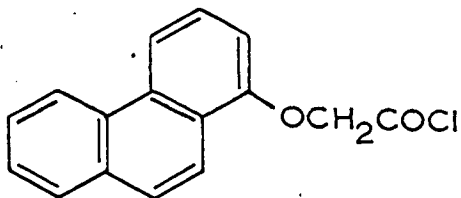
(143)

The crude cyclisation product from 1-phenanthryloxyacetyl chloride (143) was readily seen from N.M.R. spectroscopy to be a mixture of two CH_2 containing components on account of two singlets at $\tau 4.40$ and $\tau 4.91$ (in DMSO).   A high recovery of acid (70%) indicated a low conversion and it was found that for complete removal of the acid, warming the mixture in a large quantity of benzene with bicarbonate solution was required.   The I.R. spectrum (nujol mull) showed two, apparently carbonyl, absorptions at 1700 and 1760 cm.$^{-1}$.

Recrystallisation of the crude product from benzene gave a mixture highly enriched in the $\tau 4.9$ component – the major component – and a further recrystallisation afforded this material in a pure state.   It analysed excellently for $C_{16}H_{10}O_2$ as required for a ring closed product, although the carbonyl stretching frequency of 1760 cm.$^{-1}$ was higher than the expected value of ca. 1700 cm.$^{-1}$ which is observed for both benzo- and naphthofuranones.   Mass spectrometry confirmed the cyclic structure with a parent peak at $\frac{m}{e} = 234$.

The N.M.R. spectrum was critical in structure determination. Comparison of the aromatic region of the spectrum with the corresponding region in 1-phenanthrol, 1-phenanthryloxyacetic acid and its chloride strongly suggested that the ring closed product was the benzoxaphenalenone derivative (144) rather than the isomeric phenanthro [1,2-b] furan-3(2H)one (145).

(144)   (145)
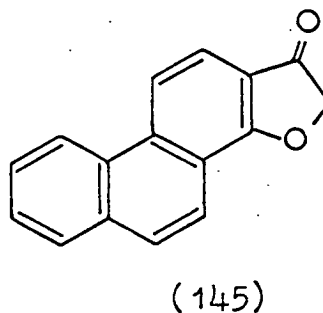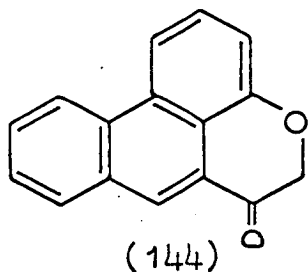
This assignment was based on the presence of an ortho-meta split quartet at $\tau 2.90$ which was the most upfield proton and thought to be the 11H in (144).   The corresponding protons at C_2 in 1-phenanthrol and its derivatives all absorbed furthest upfield as quartets near this chemical shift.   Pertinent data are tabulated below.

	τ 2H	solvent
1-phenanthrol	2.91	acetone
1-phenanthryloxyacetic acid	2.89	acetone
1-phenanthryloxyacetyl chloride	3.26	CS_2

A well established solvent effect accounts for the relatively higher value of the chemical shift observed for the chloride in carbon disulphide solution.

The 4H singlet required by (144) could not be definitely

attributed to a particular resonance, although lines of the expected intensity at τ2.10 and τ2.25 were evident.

The Mass Spectrum of the crude reaction mixture displayed no peak at m/e 312 which would correspond to the molecular ion-radical for the intermolecular product suspected to be the minor component.   The peak of highest mass was at m/e 280 corresponding to (P-32) for the acetophenone.   Loss of oxygen, however, does not seem to be likely.   The only neutral molecule with a molecular weight of 280 is the ethyl ester, however this could be clearly ruled out on the basis of the N.M.R. spectrum.   The nature of the minor component remains uncertain.

6) Methoxyphenoxyacetyl chlorides

(a) OCH_3 at C_2
(b) OCH_3 at C_3
(c) OCH_3 at C_4

(146)
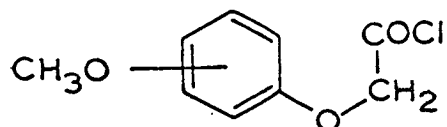
i)   Treatment of 3-methoxyphenoxyacetyl chloride (146b) with aluminium chloride in benzene in the usual manner afforded a mixture of three products.   The major product, 6-methoxybenzofuran-3(2H)one (147), was isolated in 58% yield by recrystallisation from ethanol, although present in over 90% yield in the crude product from integration of the N.M.R. spectrum. The two minor components were isolated by silica gel chromatography of the residue from the filtrate of the recrystallisation and identified as 2-phenoxy-3'-methoxyacetophenone (148) (3.7%) and 3-phenyl-6-methoxybenzofuran (149) in similar yield.
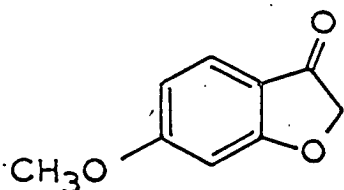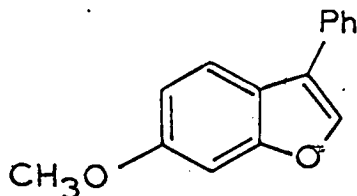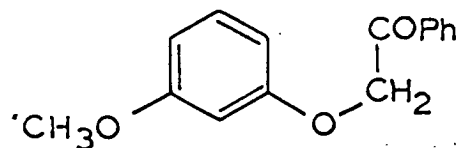
(147)   (149)   (148)

The benzofuran (149) was an unexpected product and its structure, apparent from the N.M.R. spectrum, was confirmed by the parent peak in the mass spectrum at $\frac{m}{e}$ 224.   It is a known compound having been synthesised by Baker et al. from (148) on

treatment with concentrated sulphuric acid, and a melting point of 43° C. is recorded.[84]   The material obtained in the present investigation, as a clear oil, resisted all attempts at recrystallisation, and even on chilling at -10° C. over a prolonged period it could not be induced to solidify.   That it was the same compound, however, was shown from an independent synthesis through a Grignard reaction with phenyl magnesium bromide on the cyclic ketone (147).   Dehydration occurred in situ.

The synthesis by Baker and his co-workers suggested a self-alkylation of the intermolecular ketone (148) in the formation of the benzofuran in the present investigation, rather than alkylation of the solvent by the complexed intramolecular ketone (147), although either is feasible.   Treatment of both (147) and (148) separately with 1 molar equivalent of aluminium chloride in an excess of dry benzene at reflux over 10 minutes confirmed that the acetophenone was the intermediate since it alone afforded the alkylated species.

ii) Acylation of 4-methoxyphenoxyacetyl chloride (146c) gave no detectable cyclic ketone, however solvent acylation to the acetophenone accounted for rather more than 50% of the material which had reacted.   The data collected are for reaction with 2.2 molar equivalents of aluminium chloride, otherwise reaction conditions are identical.   A synchronous experiment with 1.1 molar equivalents of catalyst led to 29% recovery of starting acid, whereas the recovery with twice this quantity of aluminium chloride was merely 6%.   The spectra of the crude products in

each case were similar.   It is assumed that complexing of the
aluminium chloride with the methoxyl group - cf. (6m) page 87 -
to some degree renders it less available for reaction as reflected
in the lower conversion to products.   A similar sluggish reaction
was observed on reaction of the isomeric (146a) with 1.1 molar
equivalents of catalyst as seen by the high recovery (68%) of
acid, vide infra.

As well as the intermolecular product, p-methoxyphenol (20%),
diphenylmethane (22%) and benzylphenolic material (21%) were also
isolated.   The procedure employed in the isolation of these
products involved, after initial extraction with a bicarbonate
solution to remove unreacted aryloxyacetic acid, extraction with
N. aqueous sodium hydroxide and with concentrated alcoholic
potassium hydroxide (from KOH pellets (35 g.) in methanol (75 ml.)
and water (25 ml.)).   The dilute alkaline wash, previously found
to be successful in obtaining the simple phenols in a high state
of purity from similar mixtures[4], afforded a mixture of phenol
and benzylphenolic material.   The strong alkaline wash, as well
as removing the remainder of the benzylphenol, also extracted a
small quantity of acetophenone.   The neutral material was
chromatographed on silica gel to obtain diphenylmethane and the
bulk of the acetophenone.   The isolation procedure was followed
closely by N.M.R. spectroscopy.

iii) 2-Methoxyphenoxyacetyl chloride (146a) on treatment with
1.1 moles of aluminium chloride in the usual manner afforded a
complex mixture as seen readily from the N.M.R. spectrum of the

crude product after complete removal of unreacted chloride as the
aryloxyacetic acid (68%).   N. sodium hydroxide extraction of the
crude product gave a phenolic fraction, mostly o-methoxyphenol
(5% by N.M.R. integration). Chromatography on silica gel of the
neutral material, without a strong alkali extraction, afforded in
order of elution with benzene diphenylmethane (5%), 2-benzyl-6-
methoxyphenol (4%), a mixture of benzylphenols (less than 1%) and
finally a fraction rich in the intermolecular ketone.   This final
fraction could not be separated into its components on further
chromatography but gave the acetophenone on recrystallisation from
ethanol in 9% isolated yield.   The minor components were not
positively identified.   It is possible that one of these products
was the diacylated species (150), on account of the presence of
two equally intense singlets at $\tau 4.63$ and $\tau 4.78$, one either side
of the acetophenone CH_2 absorption.
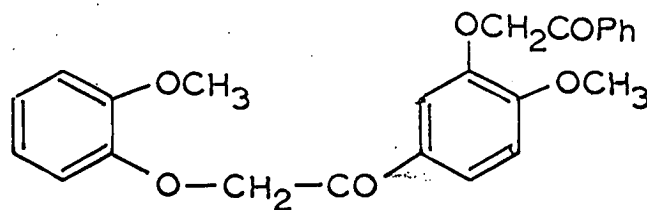
(150)

An analogue of (150) with similar spectral features was
isolated from the reaction of 3-methylphenoxyacetyl chloride
under similar conditions.[4]   A methylene absorption at $\tau 5.10$
of very low intensity in the final fraction mixture may arise from
the cyclic ketone.   This was the only evidence of the ring closed

product, but if correct in this assignment which at any rate is dubious, its proportion is less than 2%.

iv)   The rearrangement of the benzyl methoxyphenyl ethers (151, a-c) with aluminium chloride in benzene was also investigated and the major products shown to be diphenylmethane, the phenol and a mixture of benzylphenols where ortho isomers predominated in each case.

CH_3O—⬡—O—CH_2Ph

(151)
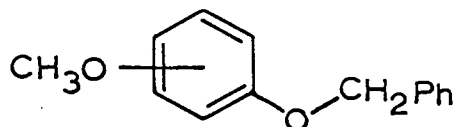
(a) OCH_3 at C_2

(b) OCH_3 at C_3

(c) OCH_3 at C_4

A discussion of the cyclisations and attempted cyclisations described in the preceding pages appears on page 128 et seq.

Attempted Cyclisations of Naphthyloxyacetic Acids

In an attempt to investigate the products of cyclisation of naphthyloxyacetic acids, as opposed to their chlorides, the use of sulphuric acid and polyphosphoric acid (PPA) were investigated.

Treatment of 1-naphthyloxyacetic acid with sulphuric acid gave only water-soluble products, presumably formed by sulphonation, despite a variation in acid concentration and reaction conditions. Its use as a condensing agent was abandoned in consequence of these preliminary investigations which were to some extent surprising in view of Hurd and Hayao's successful application of concentrated sulphuric acid to the ring closure of p-substituted phenoxypropionic acids.[85]

Polyphosphoric acid has been increasingly used as a condensing agent in ring closures of arylaliphatic acids and has been successfully applied to the syntheses of tricyclic oxygenated ketones. Thus Bell and Duewell prepared a series of 8-substituted 6,7-benzochromanones (153) by cyclisation of the corresponding nuclear substituted γ-(2-naphthyloxy)propionic acids (152).[86]
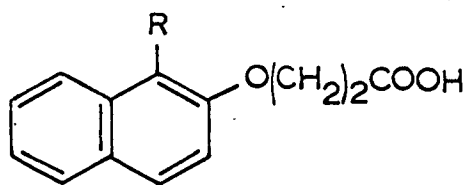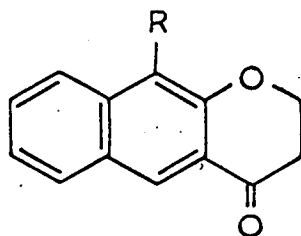
	average yield
R = CH₃	65%
R = OCH₃	70%
R = Br	12%
R = NO₂	5%

(152)   (153)

The conditions used for cyclisation by these investigators were essentially those previously applied by Loudon and Razdan[87] some years previously in chromanone syntheses, and required heating the acid with PPA at 100° C. for 30 minutes.

Reaction of 1-naphthyloxyacetic acid at such a temperature but for two hours with PPA afforded only 3% of the angular ketonic product, the remainder of the material being unreacted acid and recovered in the usual way.   Increasing the temperature to 120° C. and with a similar period of reaction gave a yield of 12.5% of the same ketone, as the sole product of reaction.   Heating at 130° C. or above, or increasing the time of reaction, afforded complex mixtures of products apparent by N.M.R. spectroscopic examination and no attempt was made to investigate these materials.

Cyclisation of 5-methoxy-, 4-chloro-, 2-chloro- and 4-nitro-1-naphthyloxyacetic acids were attempted at 110 - 120° C. over three hours.   Dark green or red colourations developed within a few minutes in all instances.   The angular ketones as the sole products were obtained in yields of 9% and 14% respectively in the first two cases, however only starting material was obtained from the 4-nitro- and 2-chloro- substituted acids.   Thus cyclisation when successful with PPA proceeds in an analogous fashion to ring closure of the chlorides with aluminium chloride.

Syntheses of Cyclic Ketones

The synthesis of naphtho[1,2-b] furan-3(2H)one (9, R = H) from the commercially available 1-hydroxy-2-naphthoic acid (31) and previously described by Anand and Venkataraman[11] was repeated.

It was shown conclusively, both spectroscopically and by mixed melting point, that the product ketone obtained in this way was identical to that obtained by cyclisation of 1-naphthyloxyacetyl chloride. It had previously only been demonstrated that the melting points (119° C.) were similar, although Ullmann[88] had reported the melting point of 91 - 92° C. in a synthesis from alkaline ring closure of 2-bromoacetyl-1-naphthyl acetate.

The ring closure in the unambiguous synthesis reported by Anand et al. proceeds through acid hydrolysis of the diazoketone (32) and the following mechanism is suggested :
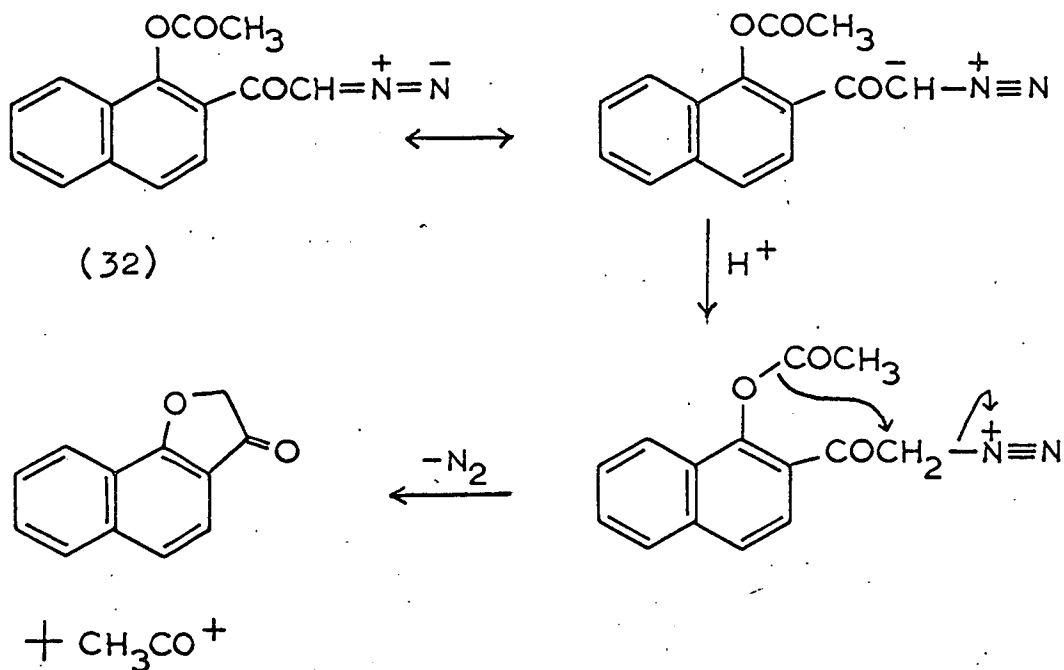
Both 5- and 6-methoxybenzofuran-3(2H)one were prepared by the literature method[14] already described in the Introduction (page 16). The former ketone was confirmed to be absent in the crude product from the reaction of 4-methoxyphenoxyacetyl chloride with aluminium chloride in benzene, and the latter was confirmed to be the major product on similar reaction of the 3-methoxy-substituted acid chloride.

6-Methoxy-1-oxaphenalen-3(2H)one (154) was found to be the minor product on acylation of 1,5-dimethoxynaphthalene with chloroacetyl chloride in carbon disulphide. The major component, and only other product observed in the N.M.R. spectrum of the crude product, was the ω-chloroacetophenone derivative (155).
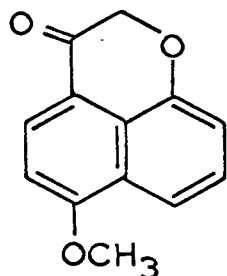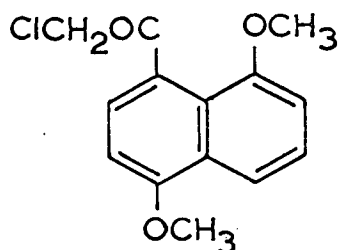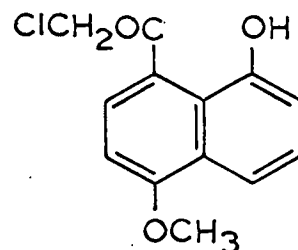
(154)   (155)   (156)

Acylation, as expected, had occurred exclusively para and peri with respect to the methoxyl groups, similar to the observed acetylation of the 1,5-dimethyl ether. Interesting, however, was that ether cleavage of the methoxyl group peri to the introduced substituent had occurred only to the extent of some 20%, and furthermore that ring closure had occurred in situ since none of the naphthol (156) was detected. Increasing the amount of

catalyst (aluminium chloride) to twice the theoretical amount, or lengthening the time of reaction, did not alter significantly the product ratio.   The low amount of peri demethylation is surprising in view of ortho ether cleavage occurring to over 85% in the chloroacetylation of both m- and p-dimethoxybenzene under similar conditions[14].   It seems to be likely that fission arises from relief of steric compression and would certainly be facilitated under the acidic conditions.   However, on steric grounds alone, peri demethylation might reasonably be expected to be greater than ortho cleavage since it is well established that substituents with a peri relationship are in much closer proximity, one with another, than similar substituents located ortho to each other.   Indeed such proximity effects are responsible for many of the unusual properties of naphthalene derivatives and are manifested too in many naphthalene reactions.[89] It is possible that with the naphthalene derivative described above the chloroacetyl substituent provides a considerable shielding of the peri methoxyl group in such a way that the aluminium chloride cannot complex readily with its ether oxygen and facilitate loss of the methyl group.

That cyclisation accompanies demethylation in the naphthalene system, but not in the benzene systems, may well be due to a more favourable geometry with the former and it cannot be overlooked that six- rather than five-membered ring formation ensues.
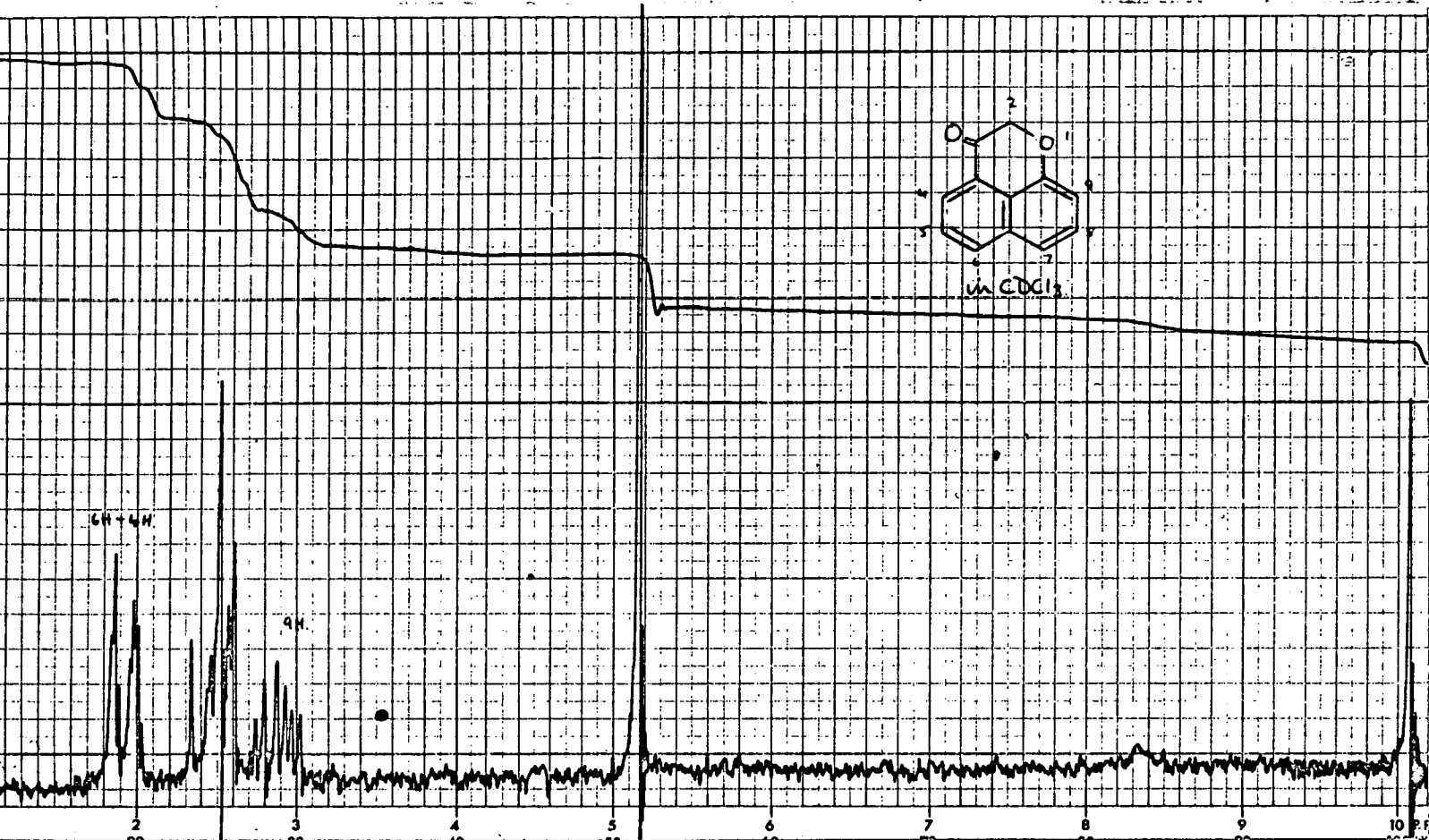
1-Oxaphenalen-3(2H)one
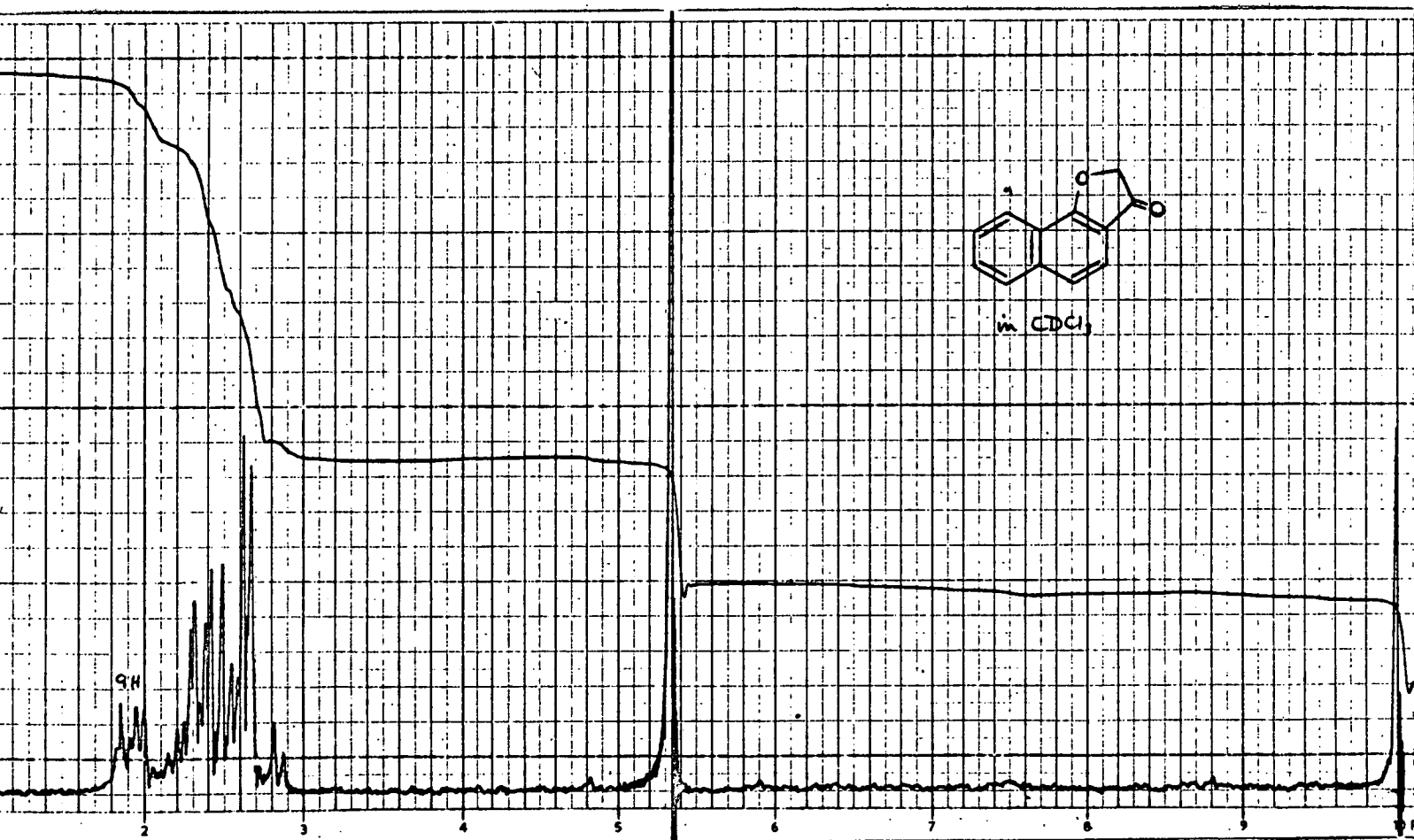
Naphtho[1,2-b]furan-3(2H)one

1-Oxaphenalen-3(2H)one (10, R = H), the six-membered ring peri condensed ketone which could arise from peri cyclisation of 1-naphthyloxyacetic acid, was prepared in a manner similar to that subsequently reported in the literature by Alderson and Livingstone,[16] and illustrated below.

(157)   (158)   (159)

(160)   (161)   (10, R = H)
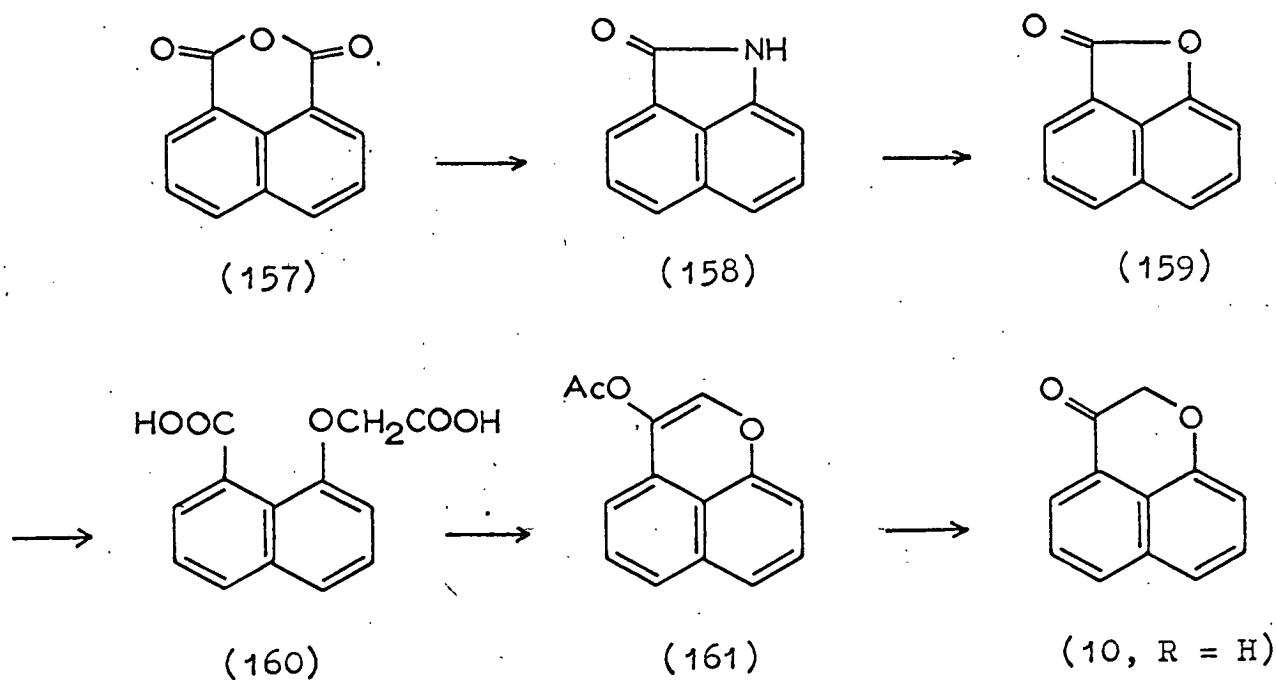
The starting material in the present synthesis was naphthalic anhydride (157) which was converted in nearly quantitative yield to the lactam of 1-amino-8-naphthoic acid (158) by a method similar to that employed by Birch et al.[90] This route involves initial condensation with hydroxylamine in pyridine to give N-hydroxynaphthalimide followed in situ by O-esterification with toluene-p-sulphonyl chloride and a Lossen-type rearrangement of the resultant ester with methanolic sodium hydroxide; decarboxylation and lactam formation in acid giving the final product. This route was found to be far superior than the

alternative procedures initially attempted through naphthalimide which require the use of hypochlorite[91] or chlorine.[92] A similar observation was made by Birch and his co-workers.

The lactam (158) was ring opened in alkaline solution, diazotised and heated with acid to yield the lactone of 8-hydroxy-1-naphthoic acid (159) in over 60% yield. Preparation of this lactone from 8-bromo-1-naphthoic acid by the method of Rule and Barnett[30] by replacement of the halogen on heating in alkaline solution with copper bronze was not able to be repeated. A yellow solid product of melting point 152 - 153° C. with no lactone carbonyl stretching frequency in the infra-red was obtained. This material was insoluble in common organic solvents and no N.M.R. spectrum was obtained. The product remains uncharacterised.

The lactone was converted into the diacid (160) with a vast excess of chloroacetic acid in alkaline solution. Acidification of the reaction mixture led to a salt being deposited from which the diacid was obtained by heating in strong acid solution. Recrystallisation from methanol gave material of melting point 254 - 256° C. which could not be raised by further recrystallisation. The I.R. and N.M.R. spectra were quite consistent with the material being 8-carboxy-1-naphthyloxyacetic acid for which O'Brien and Smith[3] record a melting point of 272 - 274° C. and Alderson and Livingstone[16] a value of 263 - 265° C.

In one recrystallisation of the diacid from methanol, presumably due to the presence of free acid, a monomethyl ester

was deposited (melting point 156 - 157° C.).   This was subsequently
identified as methyl 8-carboxy-1-naphthyloxyacetate (164) rather
than the isomeric 8-methoxycarbonyl-1-naphthyloxyacetic acid (165).
This was achieved by an unambiguous synthesis of (165) by the
scheme outlined below :
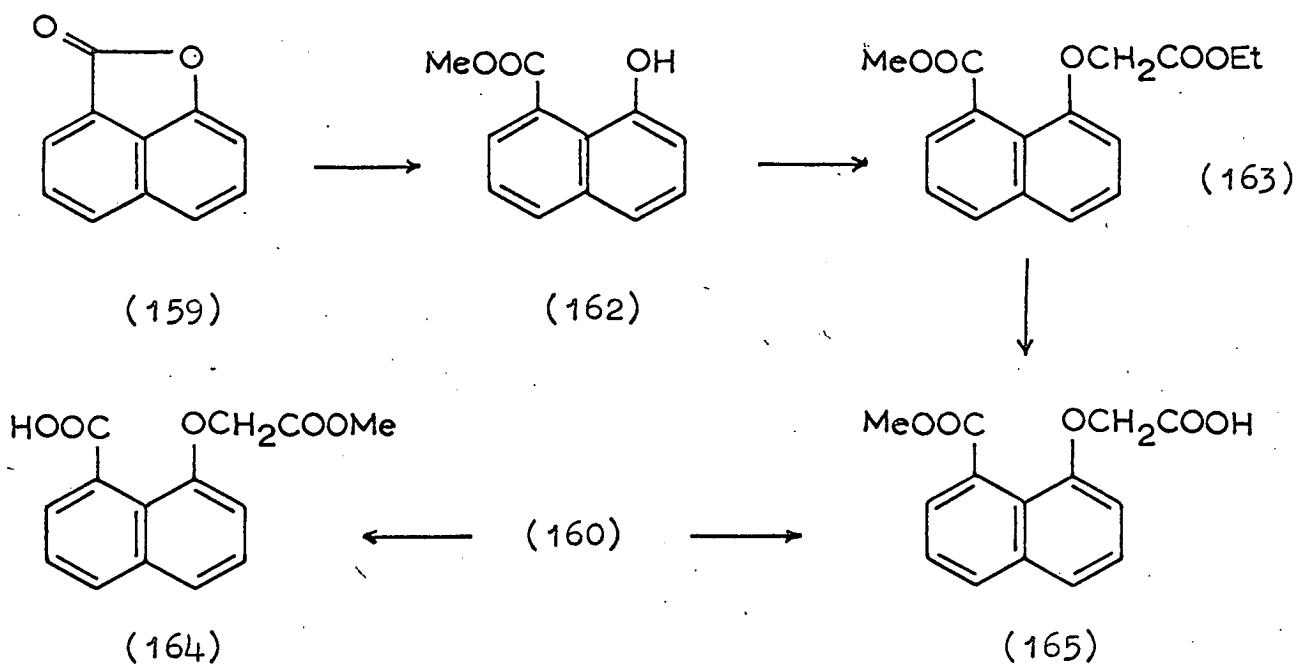
Although the product monoester in this synthesis was not
obtained in a pure state - it was contaminated by the diacid (160) -
the methyl resonance in the N.M.R. spectrum (in acetone) absorbed
at τ6.06.   This compared favourably with the methyl resonance in
the intermediate phenolic ester (162) at τ6.05 and contrasted
markedly with the shift of τ6.20 observed with the esterified
diacid suspected to be (164).   This result has since been
confirmed by Alderson and Livingstone who also claim (164) as the
product of esterification of (160).   Their evidence for the
assignment of structure was based on the isolation of some 7% of

the isomeric ester (165) on treatment of (162) with ethyl
bromoacetate and sodium methoxide over many hours and showing it
to be of different melting point to the esterification product.

Treatment of the di-potassium salt of (160) with potassium
acetate and acetic anhydride gave 3-acetoxy-1-oxaphenalene (161)
in 50% yield.   This type of ring closure is not novel but no
mechanism appears to have been postulated for the reaction.
The following is suggested :
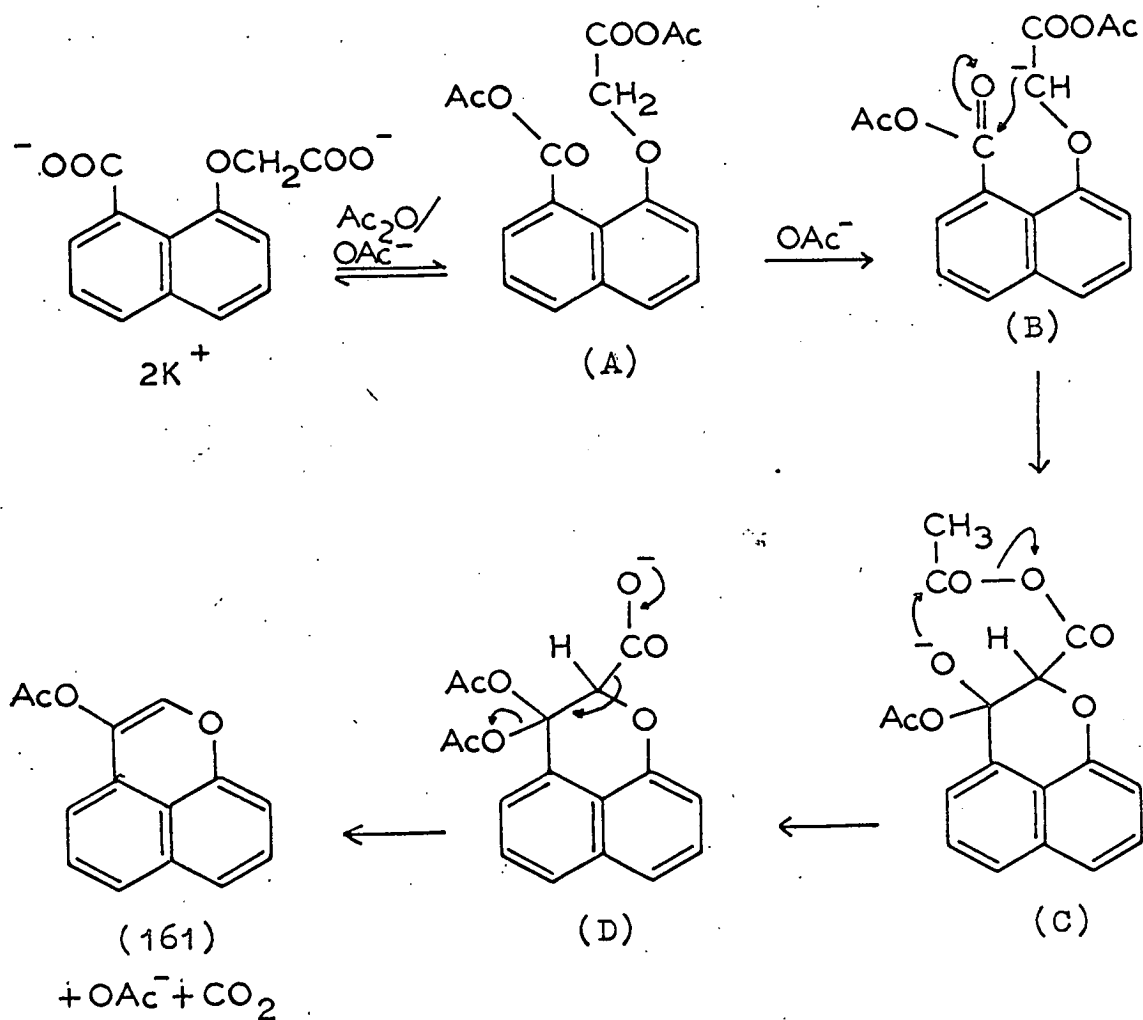
The initial stage in the reaction is almost certainly
formation of the mixed anhydride (A).   Acetate ion, being a

sufficiently strong base to remove a proton from the activated methylene of this species, would lead to the carbanion (B) which is then thought to add to the α-carbonyl at the peri position to give the species (C). Such a sequence of events is formally similar to current views concerning the initial mechanistic stages of the Perkin reaction for the preparation of $\alpha\beta$-unsaturated acids from aromatic aldehydes and aliphatic anhydrides under basic conditions. Formation of the enol acetate (161) from the ring closed species (C) may possibly occur through (D) which arises from acetyl migration to the alkoxide function. (D), which possesses a carboxylate anion and hence stabilised by resonance, would be favoured over its immediate precursor, and can then lose carbon dioxide and acetate ion to give the observed product. This seems the most feasible procedure for the loss of the superfluous side chains present in the intermediate (C).

Hydrolysis of the enol acetate was effected with lithium aluminium hydride in ether at room temperature. The N.M.R. spectrum of the crude product indicated a high yield of the oxaphenalenone which was obtained in a pure state by silica gel chromatography in 46% yield. The I.R. spectrum indicated that the product existed in the keto form with ν_{co} 1700 cm.$^{-1}$.

Previous attempts to hydrolyse the acetate in ethanol at 0° C. with 10% aqueous sodium hydroxide over five seconds and two seconds followed by immediate acidification led to only small amounts of the ketone being formed as seen from an examination of

the N.M.R. spectrum. In both instances the major product displayed a singlet at $\tau 4.2$, although this material could not be isolated either chromatographically on silica gel or alumina, or by recrystallisation. In the two second experiment the major component of the mixture was unreacted enol acetate. Nevertheless, since total removal of the acetate had occurred with a five second reaction time, its conversion to products is rapid. The component absorbing at $\tau 4.2$ may well be a dimer formed in the alkaline reaction mixture.

Alderson and Livingstone have since reported a 38% isolated yield of the ketone on hydrolysis of the enol acetate in methanol at -5° C. with 5% sodium hydroxide solution over 30 seconds. No other product is reported to be formed by these investigators.

Acetylation of Dimethoxynaphthalenes and Reversibility Considerations

The observation that 5-methoxy-1-naphthyloxyacetic acid cyclised with polyphosphoric acid, or with aluminium chloride on its chloride, to the angular ketone and not at all to the peri-condensed product seemed a very interesting result in view of the fact that the isoelectronic 1,5-dimethoxynaphthalene is reported to acetylate in nitrobenzene solution at the α-position. The acetylation in benzene was carried out and confirmed the above observation, although its validity could scarcely be doubted on account of the mass of data assimilated which indicates that α-naphthyl ethers acylate at the para position with acylating agents of many types and with a variety of catalysts.[94]

Nonetheless this excursion into the field of simple acetylation reactions revealed an interesting report by Buu-Hoï and Lavit[95] that 2,7-dimethoxynaphthalene (166) acetylates at the 3-position to give (167) and not at the 1-position, which would lead to (168), when catalysed by aluminium chloride in nitrobenzene solution.

(166)   (167)   (168)
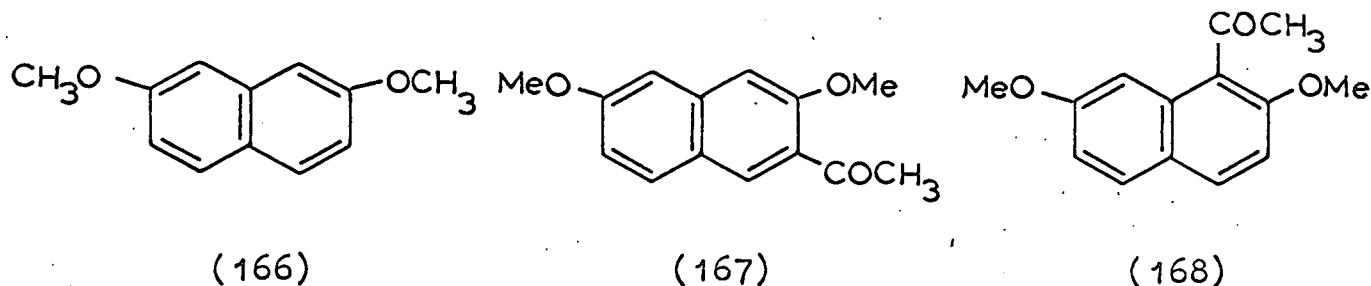
This seems not unreasonable since 2-methoxynaphthalene has been reported to acetylate at the 6-position in nitrobenzene reactions by a number of investigators, and a recent re-investigation of this latter acylation has shown by G.L.C. identification that the amphi- substituted ketone accounts for over 90% of ketonic products.[96] Since this analogy with 2-methoxynaphthalene appeared to be Buu-Hoi's main evidence in support of structure assignment to the product he obtained, it was decided to repeat the acetylation of 2,7-dimethoxynaphthalene.   There were two main reasons for doing this.   In the first place, 1-acetylation has been observed with 2-methoxynaphthalene in solvents other than nitrobenzene (e.g. 44% with carbon disulphide[96]) and secondly if β-acetylation does in fact occur with 2,7-dimethoxynaphthalene, then 7-methoxy-2-naphthyloxyacetic acid might well be expected to cyclise to the linear ketone on account of amphi-activation of the 3-position by the 7-methoxyl substituent.

The initial acetylation studied used benzene as solvent with a reaction time of 2.5 hours and the crude N.M.R. spectrum indicated high, indeed almost quantitative, acetylation. Recrystallisation of the product twice from petroleum ether (b.p. 60 - 80°), or from aqueous ethanol, gave a highly crystalline solid of sharp melting point (62.5 - 63° C.).   The N.M.R. spectrum (in $CDCl_3$) revealed that this material was the 1-substituted ketone (168).   This assignment of structure was based on an interpretation of the aromatic region of the spectrum which had the general appearance of two discrete groups of resonances.

The downfield lines, which integrated for two protons, appeared clearly as two overlapping ortho-split doublets at τ2.27 and τ2.38 with coupling constants of 9.0, and 8.7 c.p.s. respectively. The only structure consistent with this is 1-acetyl-2,7-dimethoxynaphthalene, where the protons concerned are the 4H and 5H. Furthermore these protons are both α-protons and their chemical shifts would be expected to be near this value. (cf. 2,7-dimethoxynaphthalene where the 4H and 5H are identical and absorbed (in $CDCl_3$) at τ2.40.) The three upfield protons all ortho to methoxyl groups, absorbed between τ2.7 and τ3.1, and could be ascribed to the 3H, 6H and 8H on account of the multiplicity observed. The 3H resonance had $J_{3,4}$ 9.0 c.p.s. and identified the 4H in the downfield region.

Comparison of the spectrum of the recrystallised material with the crude product revealed the presence of a second component (not the starting dimethyl ether) on account of a singlet at τ1.9. This was suspected at an early stage to be the 1H in the isomeric ketone, 2-acetyl-3,6-dimethoxynaphthalene (167) - the product claimed from the acetylation in nitrobenzene solution by Buu-Hoï. Repeating the reaction in nitrobenzene once more with a 2.5 hour reaction time at room temperature gave a similar crude product to that obtained with benzene on complete removal of solvent by steam distillation. The proportion of material absorbing at τ1.9, however, had increased slightly over the benzene run.

Performing the reaction yet again in nitrobenzene, but with a period of reaction of 14 hours to duplicate as nearly as possible the conditions reported by Buu-Hoï, gave yet again a

similar mixture although, significantly, the minor product, as
indicated by the τ 1.9 peak, had increased in amount.   The
acetyl CH_3- resonance (τ 7.4) in this instance displayed a
shoulder which appeared as a second line on expansion (line
separation 1 c.p.s.).   This observation added weight to the theory
that the second component was indeed the isomeric β-substituted
ketone (not a diacetylated species from the integration); but
more interesting was its increased proportion with longer time
of reaction.

Such an alteration in product distribution is indicative of
a reversible system and to test this theory two reactions were set
up, one in benzene and the other in nitrobenzene, where pure
1-acetyl-2,7-dimethoxynaphthalene was stirred in a dry atmosphere
with aluminium chloride (molar ratio 1 : 1.1) for 48 hours.   A
stream of dry hydrogen chloride was bubbled into these mixtures
for a few minutes at the beginning of the experiments and at
roughly eight hourly intervals during the course of the reactions.
The products obtained in both cases were mixtures, where the τ 1.9
peak was clearly visible.   A shortage of acetyl to methoxyl by
integration suggested that the acetylated products were present
to the extent of 72% (nitrobenzene) and 77% (benzene).   It was
assumed the remainder existed as non-acetylated dimethyl ether.
The aromatic region indicated the presence of 8% β-acylated
product and 69% recovered α-substituted starting material with
benzene.   The nitrobenzene run gave 21% and 51% respectively.

Attempts to separate the ketonic mixtures by column

chromatography on silica gel and alumina only afforded mixtures identical to the material applied, even on slow development and elution.   Distillation under reduced pressure afforded no enrichment of the minor product.   Gas chromatographic analysis using columns of Apiezon L (15%) on Celite and PegA (15%) on Celite at operating temperatures near 200° C. afforded no separation of the products.

The β-acetylated product was obtained in a nearly pure state by performing the acylation in nitrobenzene over several days. The course of the reaction was followed by withdrawing a small sample at suitable intervals, working up in the usual manner and analysing by N.M.R. spectroscopy.   To ensure that the samples withdrawn were representative of the whole, the reaction mixture was previously saturated with dry hydrogen chloride.   For reversibility in the system the presence of HCl is mandatory, although it also had the effect of providing a homogeneous solution in nitrobenzene.

After six days at room temperature the β-acetylated product predominated over the original α-substituted species.   The appearance of two sharp singlets at $\tau 6.3$ and $\tau 6.55$ of equal intensity after four days indicated the presence of a third (and possible a fourth) product species.   This product (or products) increased in proportion with time and although never isolated was thought to be a dimeric dypnone-like molecule.   Novak and Protiva,[97] in this connection, report the formation of a dypnone produced by self-condensation of 2-acetyl-6-methoxynaphthalene as a by-product

in the acetylation of 2-methoxynaphthalene in nitrobenzene.   It
is probable in this instance that the dypnone is that formed from
the less stericly hindered β-acetylated ether and this is
consistent with the experimental observation that it only appeared
when the β-ketone was present in reasonable quantity.

After eighteen days the reaction mixture was decomposed and
solvent removed by steam distillation.   The dark oil obtained was
extracted with a small amount of cold benzene, and on removal of
solvent, recrystallised from petroleum ether (b.p. 60 - 80°).   The
solid obtained was clearly a mixture from the N.M.R. spectrum
consisting of some 75% 2-acetyl-3,6-dimethoxynaphthalene, the
remainder being the 3-demethylated analogue (OH at τ-1.7,
COCH$_3$ at τ 7.30 and 1H at τ 1.82).   A further small amount of
material was obtained on concentration of the filtrate, which
consisted of over 90% of the dimethoxy ketone similarly
contaminated.

An attempt to prepare unambiguously 2-acetyl-3,6-dimethoxynaph-
thalene from 2,7-dimethoxynaphthalene was unsuccessful.
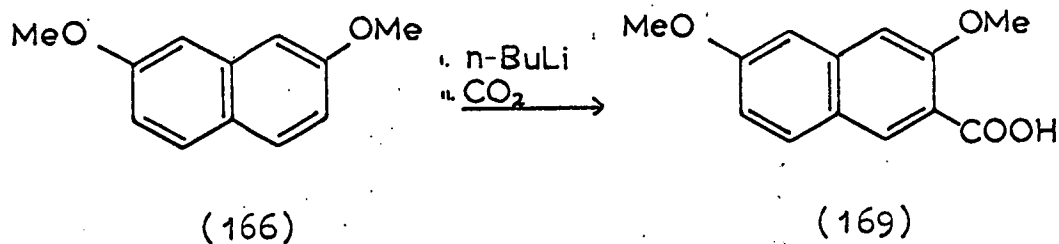
Although the acid (169) was prepared in 20% yield through

Figure 2. Partial N.M.R. Spectra of Monoacetyl Derivatives of
2,7-Dimethoxynaphthalene
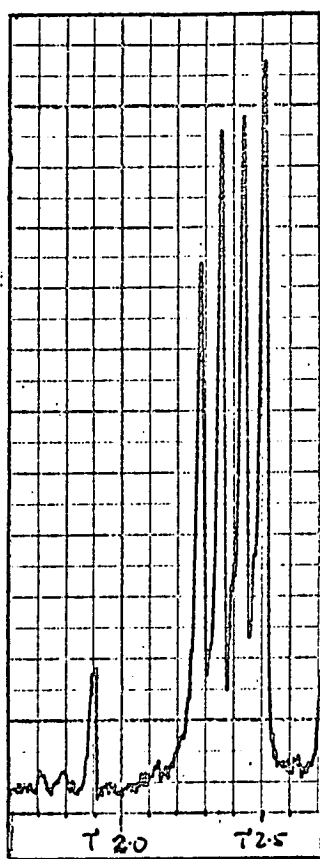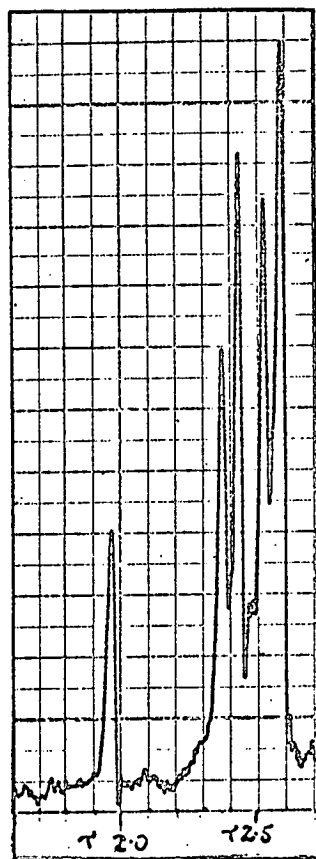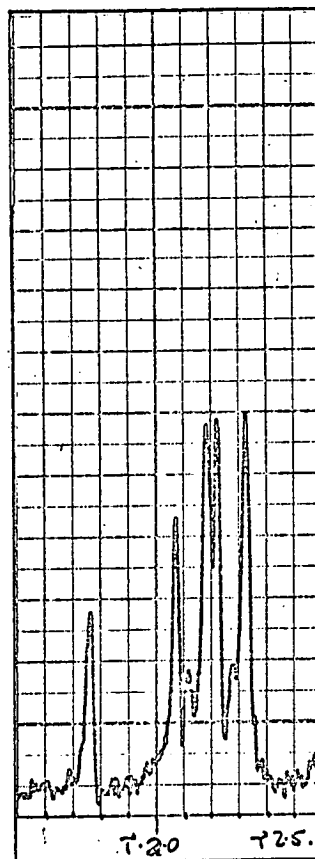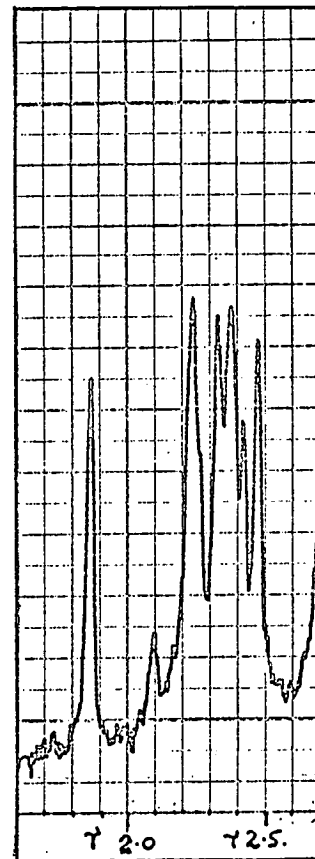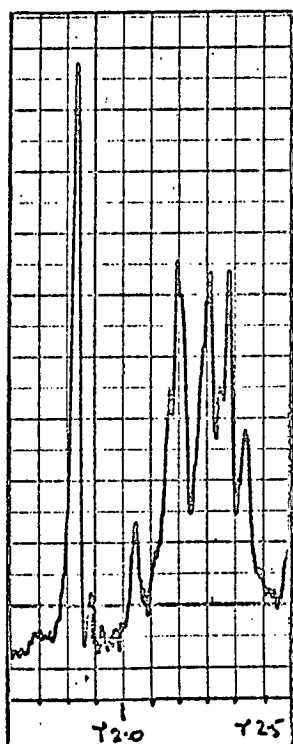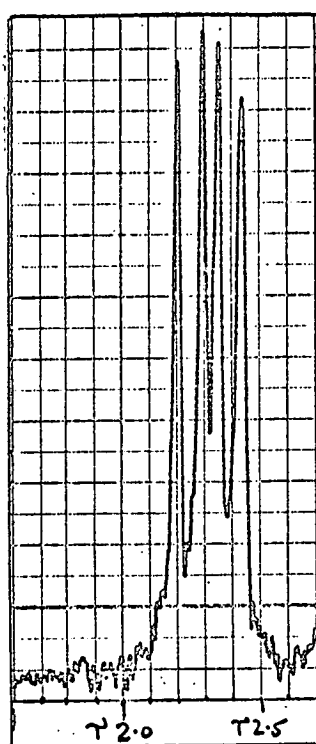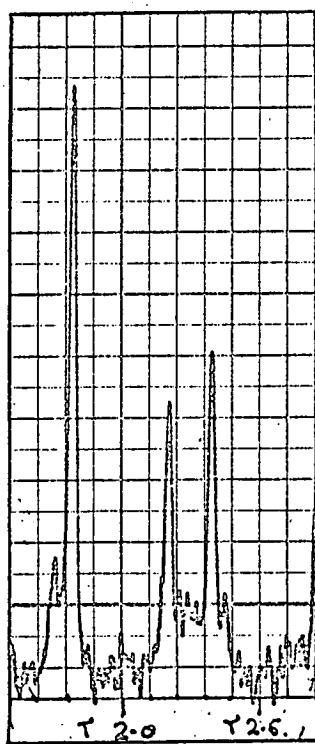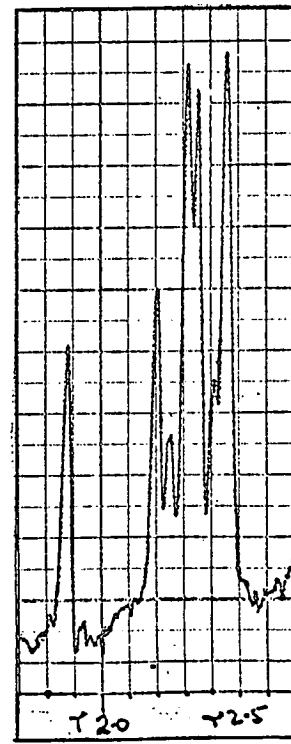
Data relating to Figure 2 :

Figure 2 on the facing page consists of a number of partial N.M.R. spectra (range   1.6 - ca. ·2.7) relating to products obtained in studies into the acetylation of 2,7-dimethoxynaphthalene.   The singlet below   2.0 in all spectra except (f) is attributed to the 1H in 2-acetyl-3,6-dimethoxynaphthalene.   The spectra clearly indicate that reversibility exists in the system.

Legend :

(a)   Product from 2.5 hour run in nitrobenzene at 25° C.

(b)   As (a) but over 14 hours.

(c)   As (a) but over 24 hours.

(d)   As (a) but over 48 hours.

(e)   As (a) but over 312 hours.

(f)   Pure 1-acetyl-2,7-dimethoxynaphthalene.

(g)   Nearly pure 2-acetyl-3,6-dimethoxynaphthalene.

(h)   Product obtained on treating pure 1-acetyl-2,7-
       dimethoxynaphthalene with aluminium chloride
       in nitrobenzene saturated with hydrogen chloride
       gas for 48 hours.

carbonation of the lithium derivative of (166) by the method of Gilman,[98] treatment of its chloride with dimethyl cadmium in benzene at reflux for 1.3 hours gave no detectable methyl ketone (167), even on repeating the reaction with a fresh batch of reagent. This approach was abandoned.

The Fries reaction of the acetate of 7-methoxy-2-naphthol was investigated in nitrobenzene solution and the crude products examined spectroscopically. With one molar equivalent of aluminium chloride at room temperature over 2 hours the product obtained was a mixture of 1-acetyl-2-hydroxy-7-methoxynaphthalene (82%) by rearrangement, and 7 methoxy-2-naphthol (18%). Repeating the reaction at 100 - 110° over one hour afforded in almost quantitative yield the 1-acetyl derivative together with a small amount (ca. 5%) of the isomeric 2-acetyl-3-hydroxy-6-methoxynaphthalene, identified by the characteristic τ1.9 singlet. The Fries rearrangement then had substituted the aromatic nucleus in the same manner as the short reaction time acetylation of the dimethoxynaphthalene and presumably the presence of the small amount of β-substituted product arises from reversibility in the system at increased temperature.

The concept of reversibility in Friedel-Crafts acylations is not a new one, having first been proposed by Gore in 1955.[99] Even so only a few systems have been demonstrated to display this phenomenon, although in fairness, it would appear from the literature that it has been rarely investigated.

The theory was originally put forward to account for apparently

abnormal acylations in polycyclic systems. It is held that
acylation is most likely to occur rapidly and predominantly at the
most reactive aromatic position. In instances where this position
is also hindered, resonance stabilisation would be expected to be
reduced and deacylation would ensue, followed by resynthesis at a
less hindered and, of course, less reactive position. This is
tantamount to saying that α-substitution in the system currently
being reported is under kinetic control and β-substitution under
thermodynamic control. The system may be represented in the
following manner :

Kinetic product   Thermodynamic product
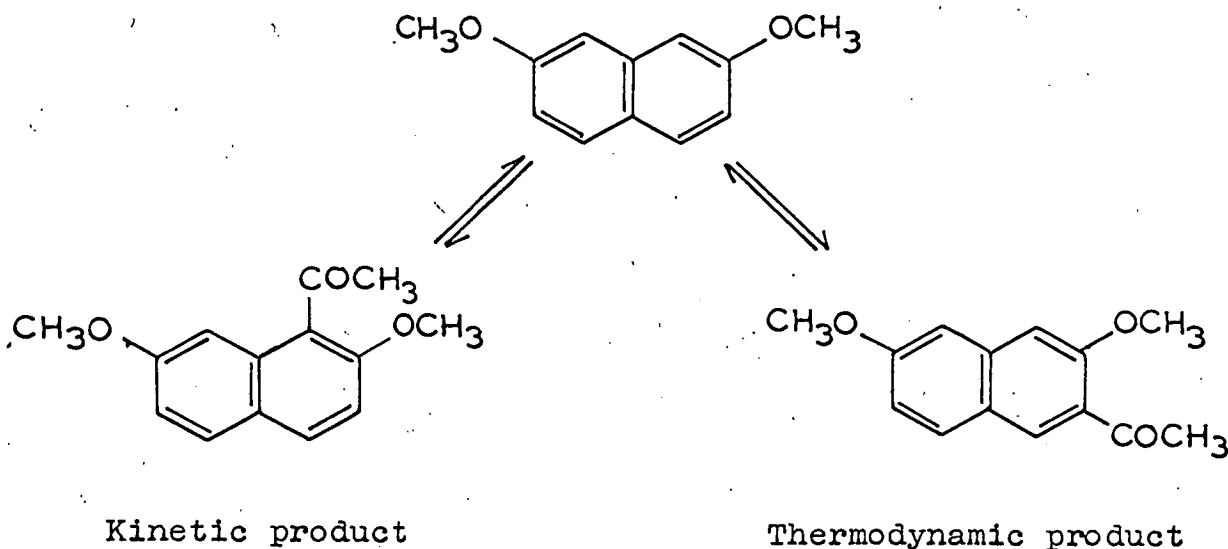
The sulphonation of naphthalene is a well established
example of this sort of reversible system.

Proof of the experimental importance of reversible acylation
has been given for the acetylation of 1-naphthol[100] and of
anthracene[101, 102, 103] and has also been demonstrated to
occur to a very slow and almost insignificant extent with

2-methoxynaphthalene.[96]   On the other hand, reversibility has been shown to be unimportant in inter alia the benzoylation of naphthalene[104] and anthracene[102] and in the acetylation of naphthalene[105] and 2-bromonaphthalene.[105]   This is indeed interesting since the theory was originally expounded with naphthalene itself as a typical example - clearly in the absence of supporting evidence.

The observation that reversibility is trivial in the acetylation of 2-methoxynaphthalene requires elaboration.   It appears that this system was only tested for reversibility with chloroform as solvent. The rearranged ketone, 6-acetyl-2-methoxynaphthalene, was obtained in 3% yield as indicated by G.L.C. analysis of the crude product mixture after much longer heating than the normal acetylation where the amphi- substituted ketone was obtained in 14% yield.   The only conclusion that can be drawn is that reversibility is of little significance with this particular solvent.   With nitrobenzene the yield of amphi- substituted ketone on normal acetylation was 43%, but, strangely, reversibility was not examined in this solvent.

It seems reasonable that the solubility of the ketone-aluminium chloride complex is an important factor for reversibility.   In instances where the initial product is precipitated rapidly from the reaction mixture as a largely insoluble complex with the catalyst, further reaction may be prevented or at best controlled by the finite solubility of the complex in the solvent employed. In this author's experience solubility is greater (generally complete) with nitrobenzene than with most other solvents,

e.g. benzene, chloroform, carbon disulphide, commonly used in acylations. That solubility does seem to be important is supported by the observation that rearrangement of (168) to (167) in the current study proceeded at a greater rate in nitrobenzene (homogeneous system) than in benzene (grossly heterogeneous throughout).

An examination of the acetylation of 2,7-dimethoxynaphthalene in other solvents such as carbon disulphide, ethylene dichloride or chloroform, might well be instructive. A study, too, of the reaction with various addition sequences might well be found to influence the proportion of products formed. In this latter connection the proportion of catalyst to acylating agent, the molar ratio (Q), may well be found to be an important factor. Since the above were not considered to be relevant to the main theme of the present investigation, these studies were not undertaken.

Another system worthy of further study is the acetylation of 2,3-dimethoxynaphthalene. Buu-Hoi and Lavit[106] report isolation of the 6-acetyl derivative in 66% yield with nitrobenzene as solvent. The position of substitution was not proven but based on analogy with 2-methoxynaphthalene, supported by comparison of melting points. The acetylation was undertaken in the present study with benzene as solvent over 2.5 hours, and the sole product obtained, purified by recrystallisation, shown by N.M.R. spectroscopy to be 6-acetyl-2,3-dimethoxynaphthalene on account of a first order analysis being possible.

Whether or not the 1-acetyl derivative rearranges under Friedel-Crafts conditions was not investigated.   It is certainly true that an acetyl substituent at the 1-position would be subjected to strong destabilising influences and would be expected to migrate by analogy with 1-acetyl-2,7-dimethoxynaphthalene.   It is also likely to be true that steric repulsions would be so great at the 1-position, on account of the two adjacent methoxyl groups, that the 1-acetyl derivative would not be at all favoured in an acetylation and that the product observed is both the kinetic and thermodynamic one.

Mass Spectra of Naphthofuranones and Related Compounds

A number of the tricyclic ketones prepared in the course of the present investigation were examined mass spectrometrically and the following data are recorded.

With the unsubstituted systems, naphtho[1,2-b]furan-3(2H)one, naphtho[2,1-b]furan-1(2H)one and 1-oxaphenalen-3(2H)one, a strong resemblance was observed in the initial fragmentation pattern. In all three cases the molecular ion-radical, also the base peak, is found at m/e 184^+, and the main pathway for breakdown of this ion involves loss of a radical of mass 29 (·CHO) to give the even electron species at m/e 155^+. Further fragmentation of this latter species occurs through expulsion of carbon monoxide to give the fragment of mass 127^+. That such a sequence occurs was verified in all cases by metastable ions at m/e 130.6 ($184^+ \rightarrow 155^+$) and m/e 104.1 ($155^+ \rightarrow 127^+$). An abundant peak at m/e 126^+ probably arises from loss of a hydrogen atom from the species at m/e 127^+.

In the absence of data relating to labelled compounds, it is not possible to say which carbon and oxygen are expelled first and hence no attempt is made to assign structures to the above fragments.

A table of the relative abundance of the higher mass ions appears on the following page, where all peaks with m/e >100 and of relative abundance >2% are recorded.

Relative Abundance of Higher Mass Ions as Percentage of Parent Peak

m/e	naphtho[1,2-b] furan-3(2H)one	naphtho[2,1-b] furan-1(2H)one	1-oxaphenalen- 3(2H)one
185	13	13	13
184	100	100	100
183	7	4	11
156	12	7	5
155	81	47	33
154	3.5	3.5	8
128	2.3	6	8
127	55	27	29
126	55	31	27

The subsequent breakdown of the aromatic nucleus appears to be complex, however, the most abundant ions (3.5 - 13% of the parent peak) are at m/e 77^+, 76^+, 75^+, 74^+, 64^+, 63^+, 51^+ and 50^+ and these appear in all spectra suggesting that mass spectrometric distinction between isomers would not only be difficult but in all probability impossible.

Similar fragmentations were observed with nuclear substituted ketones, although there was frequently a tendency towards breakdown of the substituent. Thus 8-methylnaphtho[1,2-b]furan-3(2H)one, as well as showing the characteristic fragments from fission in the ketone ring, also appears to breakdown by loss of a

methyl radical. The proportion fragmenting by this latter course, however, is small since the relative abundance of the $(P-15)^+$ species is only 3% and peaks corresponding to further breakdown are equally low in abundance.

6-Methoxynaphtho[1,2-b]furan-3(2H)one was observed to display two discrete fragmentation patterns confirmed by the presence of metastable ions and these may be represented in the following decomposition processes :

$$C_{13}H_{10}O_3^+ \xrightarrow{m^* = 159.9} C_{12}H_9O_2^+ \xrightarrow{m^* = 133.2} C_{11}H_9O^+$$

$$m/e=214^+ \qquad\qquad m/e=185^+ \qquad\qquad m/e=157^+$$

$$\downarrow m^* = 185.05$$

$$C_{12}H_7O_3^+ \xrightarrow{m^* = 146.9} C_{11}H_7O_2^+ \xrightarrow{m^* = 119.6} C_{10}H_6O^+$$

$$m/e=199^+ \qquad\qquad m/e=171^+ \qquad\qquad m/e=143^+$$

Thus the characteristic fragmentation occurring by loss of ·CHO and CO (upper line) competes with a process where initial breakdown is connected with the methoxyl function. In this second process, loss of a methyl radical followed by loss of CO occurs. Such a pattern is reminiscent of the initial fragmentation of 1,7-dimethoxynaphthalene reported by Barnes et al. where fragmentation of the α-methoxyl substituent predominates and occurs through a similar process.[114]

A similar dual decomposition pattern occurs with the isomeric

5-methoxynaphtho[1,2-b] furan-3(2H)one, however, reaction at the methoxyl group in this instance appears to predominate.

With 4-chloro- and 4-iodo-naphtho[1,2-b] furan-3(2H)one retention of the halogen with initial cleavage in the ketone ring is the most important pathway to breakdown.   With the iodo- substituted ketone an alternative process appears to be loss of the halogen as I· on account of a peak at m/e 183^+, which then seems to undergo the following transformations associated with the ketone ring :

$$183^+ \xrightarrow{\;m^* = 131.3\;} 155^+ + CO \quad \text{and} \quad 155^+ \xrightarrow{\;m^* = 104.1\;} 127^+ + CO$$
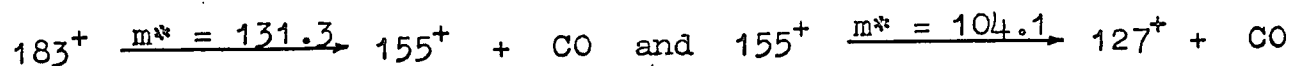
Surprisingly no similar pathway appears to occur with the chloro- substituted ketone.

Relative abundances of the higher mass ions of the substituted ketones appear on the following pages.

Relative Abundance of Higher Mass Ions as Percentage of Parent Peak

m/e	6-methoxynaphtho [1,2-b] furan -3(2H)one.	5-methoxynaphtho [1,2-b] furan -3(2H)one.	8-methylnaphtho [1,2-b] furan -3(2H)one.
215	13.5	13.5	
214	100	100	
200	3	9	
199	21	72	13
198			100
186	3.5	4	
185	9	2	
183			3.3
171	4.5	1.5	
170			9
169			43
157	3.2	2	
155			2
143	2.4	7	
142	1.5	1	10
141			40
140			16
139			27
127			2.5

Relative Abundance of Higher Mass Ions as Percentage of Parent Peak

m/e	4-iodonaphtho [1,2-b] furan-3(2H)one	4-chloronaphtho [1,2-b] furan-3(2H)one
311	27	
310	100	
282	10	
281	76	
254	2.5	
253	19	
252	2.5	
220		36
218		100
191		12.5
189		45
183	6	
163		3.5
162		6
161		11
160		12
155	39	
153	18	
127	45	

Discussion of Cyclisation Results

1-Naphthyloxyacetyl chlorides.

A striking difference in reactivity between 1-naphthylpropionic acids and their chlorides, and 1-naphthyloxyacetic acids and their chlorides to ring closure has been observed. With the former a distinct preference towards peri condensation prevails (see Introduction), whereas the oxyacetic acids have been shown in the present investigation to give rise to the angular ketones.

That angular cyclisation proceeds with 1-naphthyloxyacetic acid or its chloride is reasonably explained on the basis of activation of the adjacent β-position by electron release from the ether oxygen atom. The complete lack, however, of the peri condensed product in the ring closure of both the 5-methoxy-substituted acid with PPA, or its chloride with aluminium chloride, is particularly surprising in view of the aforementioned activation of the 2-position being offset in this instance by activation of the 8-position by the p-methoxyl substituent. In fact, p-substitution is generally favoured with aromatic ethers suggesting that activation of C_8 is likely to be greater than activation of C_2, particularly in this case since the positively charged oxyacetyl carbonium ion would be expected to withdraw electrons into the side chain rendering them less available for activation of C_2. A molecular-orbital approach was used in an attempt to explain these observations and pertinent data are provided below.

Hückel M.O. calculations of the total π-electron energy for the

Wheland intermediates (A - D), where ring closures at the 2- and
8- positions are concerned, using standard parameters for the
Coulomb and resonance integrals (α and β respectively) for carbon
and oxygen atoms and carbon-oxygen bonds, respectively, were
carried out.[10] It was assumed that

$$\alpha_o = \alpha_c + 2.0\beta$$

$$\beta_{c-o} = 0.7\beta_{c-c}$$
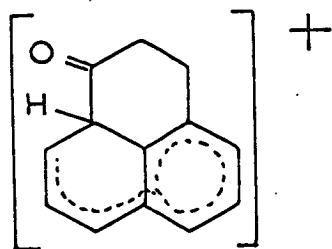
(A)
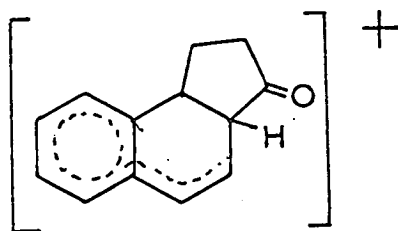
(B)
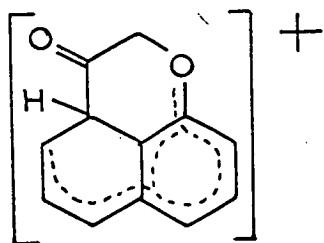
(C)
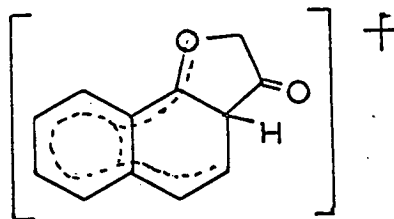
(D)

It was found that a significant difference ($>4\%$) in total
π-electron energy exists between the Wheland intermediates (A)
and (B), where the value for (A) is larger indicating that it,
which gives rise to the peri condensed product, ought to be
preferred. In these calculations it was assumed that C_1 is more
electronegative than the other carbon atoms on account of a slight

inductive effect towards the acylium ion.   Nonetheless a similar result holds if one assumes no electronic effect although the increased energy of the α- substituted intermediate over the β-substituted one is reduced to about 1.6%.[109]   The above predictions, of course, are in agreement with experimental observation.

With the Wheland intermediates (C) and (D) involved in ring closure of 1-naphthyloxyacetyl chlorides, an insignificant difference (i.e. < 0.1%) in localisation energies was calculated and all else being equal the angular and peri ketones ought to be equally favoured.   It is clear then that this approach is insufficient to account for the solely angular acylation observed and suggests that other factors, not taken into account in these calculations, are important.

Similar M.O. calculations when applied to the metastable intermediates (E) and (F) for cyclisation of 5-methoxy-1-naphthyloxyacetic acid indicated that the peri annellated species (E) was favoured on a π-electron energy basis over the corresponding angular structure (F) by some 2%.

(E)   (F)

These calculations take no account of the nature of the electrophilic reagent and can be equally applied to the acetylation and chloroacetylation of the isoelectronic 1,5-dimethoxynaphthalene with which they are in agreement with experimental observation, since in each case acylation occurs at the α-position.

In point of fact the calculations are more strictly applicable to the dimethoxynaphthalene since it was assumed that both substituents had exactly similar effects. No account was taken of a reduced electron donating effect of the positively charged oxyacetyl group in the reacting acid or for that matter the reduced conjugation of its oxygen atom due to an out of plane deformation demanded in the reacting state. Both of these effects provide additional increments favouring the peri structure (E).

Since the observed cyclisation on a localisation energy basis appears to be quite abnormal, this reinforces the aforementioned state-
:ment to the effect that some other factor or factors are of critical significance in these ring closures.

It is unlikely that ring size is the criterion which favours angular 5-membered ring formation over 6-membered peri condensation, since it can be readily demonstrated that the reactive acylium ion, neglecting nuclear deformations and deflections of the substituent, approaches to within 0.9 Å of C_8 and yet is not able to approach nearer to C_2 than 1.8 Å. This assumes a C-C bond length of 1.52 A, a C-O bond length of 1.21 A, a tetrahedradal carbon angle of 109.5°, a trigonal carbon angle of 120° and an angle subtended at oxygen of 121°. Carbon atom distances in the naphthalene skeleton are

assumed to be $C_1 - C_2$ 1.36 Å and $C_1 - C_8$ 2.4 to 2.5 Å, values which
have been accurately determined for naphthalene itself.[110]

Unfavourable interaction in the Wheland intermediates may
also be interpreted to favour peri annellation and essentially
these interactions are a manifestation of ring size. Thus it
can be readily demonstrated with molecular models that in the
Wheland transition state (A), a relatively flexible ketone ring
is formed which can assume conformation where eclipsing of the
alicyclic hydrogens is small and indeed a dihedral angle of
30 - 50° seems to be probable. On the other hand, the meta-
stable intermediate (B) is a more rigid structure and demands
considerable unfavourable eclipsing of hydrogens. An exactly
similar situation scarcely prevails with (C) and (D) from
1-naphthyloxyacetyl chlorides, although it is true that a
somewhat less unfavourable eclipsing of hydrogens with the ether
oxygen lone pairs is bound to occur, and as a result favour the
peri structure.

It is considered that the most reasonable explanation of
exclusive angular cyclisation of the 1-naphthyloxyacetyl chlorides
examined is due to the geometry of the molecule and is a direct
consequence of the peri-hydrogen atom. It has been shown by
dipole measurements, inter alia, that methyl α-naphthyl ethers
exist predominantly in the preferred conformation of the
substituent where the alkyl residue is orientated away from the
peri hydrogen and limited in libration by restrictions imposed
by resonance with the nucleus.[111]

The somewhat analogous, but even bulkier oxyacetyl residue in 1-naphthyloxyacetyl chlorides, would be expected to adopt a similar preferred conformation and on a time average basis to be more likely to attack C_2 than C_8.

Since cyclisation of 3-chloro-1-naphthyloxyacetyl chloride gives the ketone from condensation at C_2, it is clear that the -I effect of the halogen is insufficient to offset the conjugative (+E, +M) effects of the ether oxygen and that its steric effect is insufficient to disturb greatly the preferred conformation of the oxyacetyl group.

The greater steric effect of a 3-iodo substituent likewise does not suffice to promote peri-acylation or solvent attack. Since there was evidence of a second and third species present in low concentration in the product mixture from cyclisation of 3-iodo-1-naphthoxyacetyl chloride (see page 85), the above alternatives to angular ring closure cannot be completely ruled out;   however, there is no doubt that angular cyclisation predominates.

The failure to achieve cyclisation of the nitro- substituted acid chlorides studied with aluminium chloride in benzene is not unreasonable, and arises from net deactivation of the nucleus over benzene since the solvent acylated products were the only ones formed.   Failure to achieve cyclisation of 4-nitro-1-naphthyloxyacetyl chloride in an inert solvent - ethylene dichloride - at reflux, or with PPA on the acid clearly indicated a considerably deactivated nucleus, since in each case only the

acid was recovered from the reaction mixture.

2-Naphthyloxyacetyl chlorides.

Although molecular-orbital calculations were not applied
to the Wheland intermediates involved in ring closure of
2-naphthyl- substituted acids and their derivatives, resonance
theory suffices to account for the preferred angular cyclisation.

(G)   (H)   (J)
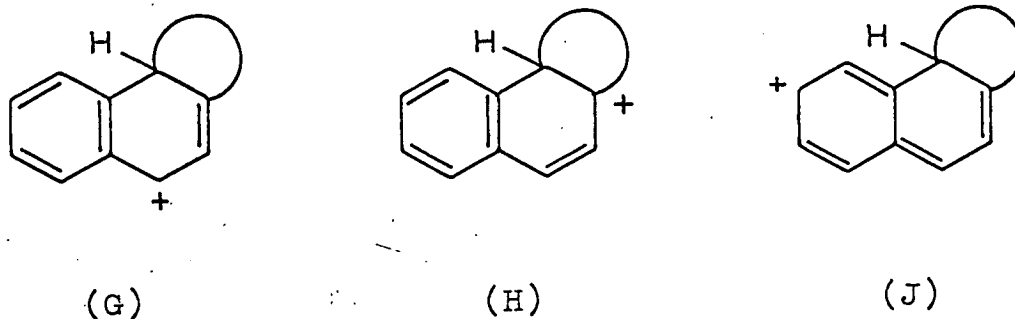
The charged species (G) and (H), which retain a benzenoid
ring, are considered to be the main contributing forms and
species such as (J), three in all, where the charge is delocalised
in the second ring are of considerably less importance.

With the linear metastable intermediate, according to
resonance theory, only (K) possesses a benzenoid ring and all
other canonical forms have quinoid forms such as (L)

(K)   (L)
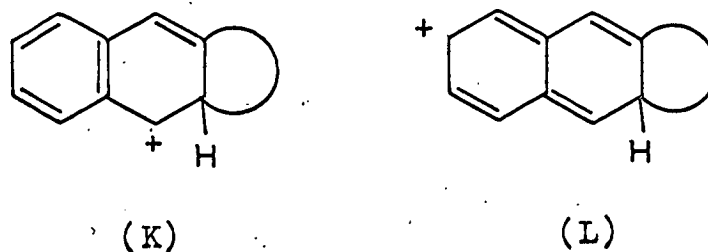
Since greater stabilisation arises from structures involving benzenoid residues, angular cyclisation is clearly favoured.

It appears that the activation at C_1 in 2-naphthyloxyacetyl chlorides is considerable - due of course to electron release from the ether oxygen attached to a C_2 - since these acid chlorides substituted at the 8-position with a methyl-, isopropyl-, or phenyl- substituent, and consequently providing an unfavourable steric effect to angular cyclisation, are not invoked to give rise to significant solvent attack or alternatively to linear ring closure. It is true that the solvent acylated species was observed in the cyclisation of 8-methyl-2-naphthyloxyacetyl chloride in 7% yield as indicated spectroscopically, however it is significant that none of the intermolecular acylation product was observed with the bulkier 8-phenyl- or 8-isopropyl-substituted acid chlorides. In this respect it is thought doubtful whether small proportions of intermolecular products ought to be heeded as important, despite constancy of solvent proportion. It is quite possible that a solubility or solvation effect governs the proportion of inter- to intra- molecular products formed and in accord with this explanation is the observation that all cyclisation mixtures were heterogeneous throughout the course of the reaction.

The low yields of intermolecular ketones obtained in the acylation of 3- and 4-nitro-1-naphthyloxyacetyl chlorides may be explained on this basis, where a slow rate of reaction is a

manifestation of heterogeneity and the rate determining step is acetophenone formation from the acylium ion. It is also possible and more likely, however, that the rate of acylium ion formation is the controlling factor in these reactions. In support of this latter view is that the observed yield of solvent acylated product from 4-nitro-1-naphthoxyacetyl chloride with benzene as solvent was nearly identical to the yield obtained under similar conditions with the more reactive anisole as solvent. Furthermore a nitro substituent which is electron withdrawing would be expected to decrease the basicity of the chlorocarbonyl group and this feature alone can account for a decrease in the rate of acylium ion formation.

The failure of both 1-methyl- and 1-chloro-2-naphthyloxyacetyl chlorides to ring close to the linear products may be interpreted in terms of deactivation of C_3 by an inductive electron attraction by the ether oxygen attached to C_2 in both cases and enhanced by a contribution from the chloro- substituent in the latter. For conjugative activation of C_3 by the ether oxygen only quinoid forms are possible, hence stabilisation of the intermediate by resonance is not favoured.

It is clear on account of observed decarbonylation products that the effect of both 1- substituents is not merely to block the angular cyclisation site but to assist in the unimolecular loss of carbon monoxide from the acylium ion. The observation that the methyl- substituted acid chloride gives rise to a considerable amount of decarbonylation products and that acylation

is of lesser importance is rationalised by the inductive effect
of the methyl group facilitating decarbonylation in the manner
depicted below :
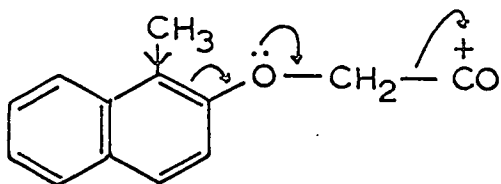
On account of the -I effect of the halogen in 1-chloro-2-
naphthyloxyacetyl chloride predominating over conjugative electron
release, the electrophilic character of the reactive acylium ion
is not reduced to such an extent, hence intermolecular acylation
predominates over decarbonylation.

A similar trend in product distributions was observed by
Palmer and McVie with 1-chloro- and 1-methylphenoxyacetyl
chlorides.[5]

The reversible Friedel-Crafts system encountered with
1-acetyl-2,7-dimethoxynaphthalene suggested the possibility of
linear cyclisation of 7-methoxy-2-naphthyloxyacetyl chloride by
analogy.   That only the angular ketone was obtained, which
showed no tendency to isomerise under conditions allowing for
reversibility, is reasonably explained in terms of the
destabilising α-acetyl function in the dimethyl ether derivative
being held rigidly in a 5-membered ring in the cyclic ketone
with a resultant net decrease in peri interaction and absence of
an ortho steric destabilising influence.

1-Phenanthryloxyacetyl chloride.

A similar resonance theory approach is able to account for peri acylation observed with 1-phenthryloxyacetic acid through its chloride.   The main contributing form to the transition state for 10- acylation is undoubtedly (M).   Other contributing forms of lesser significance where the positive charge is distributed over the residual unsaturated system, for convenience, are omitted.

Main contributing

forms for 10- and

2- acylation :
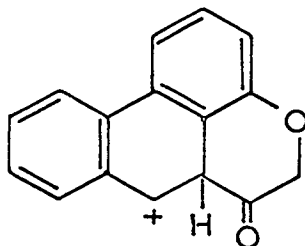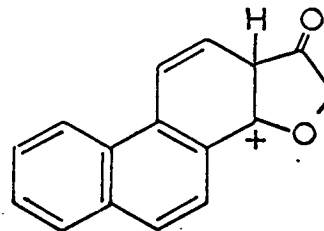
(M)   (N)

For acylation at the 2-position the principal contributing form is (N), which involves an intact naphthalene skeleton.   It may be possible for the oxygen atom to donate a lone pair, however for it to assist in charge delocalisation in this way, C   and O   are required to be in the same plane and with a strained five-membered ring this requirement is unlikely to be met.

It is a well established feature that with polycyclic hydrocarbons, substitution (and addition) reactions occur more readily in such a way as to isolate two fully benzenoid residues, as in (M), than to occur in the outermost ring of the system, as

as in (N). This can readily be seen from a consideration of the stabilisation energy lost in the reaction; the smaller the loss, the more favoured is the transformation. Thus (M) with two benzenoid residues retains a stabilisation energy of (2 x 36) = 72 Kcal. mole $^{-1}$. (N), however, to a first approximation, has a stabilisation energy of only 63 Kcal. mole $^{-1}$. This latter value assumes the product to have the stabilisation energy of naphthalene (61 Kcal. mole $^{-1}$) increased by the extra stabilisation of styrene over benzene (2 Kcal. mole $^{-1}$). Thus formation of (M) involves a smaller stabilisation energy loss and ought to be favoured.

Methoxyphenoxyacetyl chlorides.

As expected acylation of 3-methoxyphenoxyacetyl chloride gave a high yield of the cyclic ketone from acylation para to the methoxyl substituent, with none of the ortho substituted product. That no ortho acylation occurs is in general agreement with a vast number of acylations of anisole reported to give exclusive para substitution. The remainder of the material arose from intermolecular acylation and was either the acetophenone itself or its alkylation product, 6-methoxy-3-phenylbenzofuran, from condensation at the reactive 6-position of the aromatic nucleus. The percentage ratio of intramolecular to intermolecular products of 93 : 7 is a reasonable value, reflecting a moderate rate of formation of the intermolecular ketone.

In accord with the data collected by Palmer and McVie[5] in

their investigation into the interaction of 2- and 4- substituted
phenoxyacetyl chlorides with aluminium chloride in benzene,
substantial decarbonylation was observed with both 2- and 4-
methoxyphenoxyacetyl chlorides.   The results of these investi-
gators have been discussed briefly in the Introduction together
with the most probable mechanism for the formation of the
observed decarbonylation products which involves initial formation
of the aryl benzyl ether after unimolecular CO loss.

A good separation of products from the 4-methoxy- substituted
acid chloride reaction was possible with a high (95%) accounta-
bility of material using 2.2 molar equivalents of aluminium
chloride.   A comparison of the total acylation to alkylation
for this reaction as percentage yields compares surprisingly well
with that obtained by Palmer and McVie for the 4-halogeno-
analogues :

	4-OCH$_3$ isolated	4-Cl	4-Br	4-I
Total acylation (%)	49	53	54	46
Total alkylation (%)	43	44	44	46

These data for the 4-halogeno- reactions are calculated from
the N.M.R. spectra and are thought to be more reliable than the
isolated values on account of difficulties encountered in
separation.

It appears that the combined +M and -I effects of these
substituents are similar.   Electron donation by a substituent
facilitates decarbonylation on account of a reduction in the

electrophilic character of the acylium ion leading to a lower tendency towards acylation. The inductive effect (-I), on the other hand, would enhance acylation.

A low conversion to products with 2-methoxyphenoxyacetyl chloride and a poor separation into products renders the data collected slightly less reliable since these were based upon proportions calculated from N.M.R. spectra. Even so a similar comparison of the percentage ratio of total acylation to total alkylation is instructive:

	2-OCH$_3$	2-F	2-Cl	2-I
Total acylation (%)	11	84	80	74
Total alkylation (%)	13	12	11	21

The high proportion of acylation in the 2-halogeno- series, which decreases as the electronegativity decreases, suggests that the -I effect is important and promotes acylation at the expense of decarbonylation. However with the 2-methoxy-substituted acid chloride it would appear that the +M effect is more efficient and the net result is similar to the 4-methoxy-substituted isomer, although differing inasmuch as alkylation (decarbonylation) predominates.

From the product ratios of benzylphenol : diphenylmethane : phenol produced in the acid chloride experiments and comparison with the corresponding ratio from the benzyl ether rearrangement, a good degree of similarity was observed by Palmer and McVie, which led to their postulating the aryl benzyl ether as an

intermediate in decarbonylation. A large discrepancy is appareent
in the present investigation, as illustrated below :

	Ph$_2$CH$_2$ (%)	Phenol (%)	Benzylphenol (%)
2-OCH$_3$			
acid chloride reaction	5	5	8
benzyl ether reaction	59	53	39
4-OCH$_3$			
acid chloride reaction	22	20	21
benzyl ether reaction	71	73	27

The values quoted above for the acid chloride experiments
are as a percentage of total products.

Clearly the proportion of benzylphenolic material from
decarbonylation of the acid chlorides is higher than expected
from the benzyl ether rearrangements. This may be explained
in terms of a concentration effect, since in the decarbonylation
process the concentration of benzyl ether produced is always low
and conversion to particular products may be controlled by this
feature.

EXPERIMENTAL

GENERAL NOTES

1. Melting points were recorded with a Gallenkamp melting
    point apparatus (Model MF - 370) and are uncorrected.
    Boiling points are similarly uncorrected.

2. Microanalyses were by Weiler and Strauss Ltd., Oxford, by
    Andrew H. Baird Ltd., Edinburgh, and by Alfred
    Bernhardt, Elbach uber Engelskirchen, West Germany.

3. Infra-red spectra were recorded on a Unicam SP 200
    Spectrophotometer.

4. Nuclear magnetic resonance spectra were recorded on a
    Perkin-Elmer R.10 (60 Mc./sec.) spectrometer with
    tetramethylsilane as an internal standard, or
    alternatively at 100 Mc./sec. on a Varian Associates
    HA.100 spectrometer.   It may be assumed that data
    is given for spectra recorded at 60 Mc./sec. unless
    otherwise stated.

5. Mass spectra were recorded on an A.E.I. MS.902 double-
    focussing mass spectrometer.

6. Solutions were dried over a magnesium or sodium sulphate.

7. Dry benzene and ether refers to commercial solvent dried
    for at least 48 hours over freshly pressed sodium wire.

8. Chromatography was carried out on alumina (Type H, supplied
    by Peter Spence & Sons Ltd., Widnes) or on silica gel
    (MFC grade supplied by Hopkin & Williams Ltd., Essex.)

The Preparation of Phenols

Syntheses in the main were based on literature methods and in these instances only an outline is given. Spectral data for phenolic products are collected in Table 5, and for intermediates in the text.

1) 2-Chloro-1-naphthol and 4-chloro-1-naphthol [58, 107]

These were prepared in admixture from 1-naphthol (72 g., 0.5 mole), sulphuryl chloride (68 g., 0.5 mole) in chloroform (300 ml.) at 60° C. The product which deposited on cooling, on recrystallisation from chloroform afforded pure 4-chloro-1-naphthol (41 g., 46%)

m.p. 120 - 121° C. lit.[58] m.p. 121° C.

Steam distillation of the residue from the reaction mixture on prior removal of solvent gave enriched 2-chloro-1-naphthol. Preparation of the tosyl esters of this mixture and recrystallisation of the product twice from methanol gave the pure ester of 2-chloro-1-naphthol (m.p. 100 - 101° C.). Alkaline hydrolysis afforded pure 2-chloro-1-naphthol (12.6 g., 7%)

m.p. 63 - 65° C. lit.[58] m.p. 64 - 65° C.

2) 3-Nitro-1-naphthol

i) 6-Acetyl-1,2,3,4-tetrahydronaphthalene (104)[108]

Acetylation of commercial tetralin (340 g., 2.58 moles) with acetyl chloride (236 g., 3.0 moles) in carbon tetrachloride (1700 ml.) by the Perrier procedure afforded 6-acetyltetralin (441 g.) as a

crude red oil.   This material was not purified.   Yield   95%.

The I.R. spectrum (liquid film) had ν_{CO} 1680 cm.$^{-1}$.   The N.M.R. spectrum (in CCl_4) had CH_3 at τ7.63 (singlet),   alicyclic protons as two multiplets at τ7.3 (four protons at C_1 and C_4) and τ8.25 (four protons at C_2 and C_3).   ABX aromatic region with 8H at τ3.06 ($J_{7,8}$ 8.5 c.p.s.).

ii)   Methyl-5,6,7,8-tetrahydro-2-naphthyl ketoxime (105)[59]

This was prepared from 6-acetyltetralin (50 g. lots) in 90 - 95% yield.

m.p.   100 - 104° C.   lit.   m.p.   106° C.

The I.R. spectrum (nujol mull) had ν_{OH} at 3270 cm.$^{-1}$.   The N.M.R. spectrum (in $CDCl_3$) had CH_3 at τ7.73 (singlet), α-alicyclic protons at τ7.25 (multiplet) and β-alicyclics at τ8.2 (multiplet);   8H at τ3.0.

iii)   6-Acetamido-1,2,3,4-tetrahydronaphthalene (106)[59]

Beckmann rearrangement of the oxime (100g. lots) with polyphosphoric acid at 105° C. for 10 - 15 minutes gave 6-acetamidotetralin in 88 - 95% yield.

m.p.   104 - 105° C.   lit.   m.p.   104 - 106° C.

The I.R. spectrum (nujol mull) had ν_{CO} at 1655 cm.$^{-1}$ and ν_{NH} at 3300 cm.$^{-1}$.   The N.M.R. spectrum (in acetone) had NH at τ1.0 and ABX aromatic region with 8H at τ3.05 ($J_{7,8}$ ca. 7.5 c.p.s.) Remaining resonances obscured by solvent.

iv) 6-acetamido-1,2,3,4-tetrahydro-7-nitronaphthalene (107)[59]

The amide (106) (110 g.) was nitrated with nitric acid/acetic anhydride to give the purified 7-nitro derivative in 29% yield after recrystallisation of the product from ethanol.

m.p. 134 - 135° C.   lit. m.p. 133 - 135° C.

The N.M.R. spectrum (in $CDCl_3$) had CH_3 at $\tau 7.71$ (singlet) and characteristic alicyclic multiplets at $\tau 7.20$ and 8.20.   The aromatic region had two singlets at $\tau 1.54$ (8H) and $\tau 2.10$ (5H), with the NH at $\tau -0.27$.

v) 6-Amino-1,2,3,4-tetrahydro-7-nitronaphthalene (108)[59]

Acid hydrolysis of the amide gave a near quantitative conversion to the aminonitrotetralin (108).

m.p. 124 - 126° C.   lit. m.p. 127° C.

The N.M.R. spectrum (in $CDCl_3$) had aromatic singlets at $\tau 2.20$ (8H) and $\tau 3.50$ (5H), broad NH_2 at $\tau 4.1$ and discrete alicyclic multiplets at $\tau 7.3$ and 8.3.

vi) 1,2,3,4-Tetrahydro-6,7-dinitronaphthalene (109)[59]

The above amine (80 g.) when diazotised and the isolated diazonium salt treated with a cupro-cupri sulphate solution afforded 49.5 g. of a mixture of products from which the required dinitro- product (18.2 g.) was obtained by recrystallisation from methanol.   Yield 21%

m.p. 104 - 107° C.   lit. m.p. 107 - 108° C.

The N.M.R. spectrum (in $CDCl_3$) gave signals at $\tau 2.41$ (5H and 8H), $\tau 7.1$ (four protons) and $\tau 8.1$ (four protons).

vii) 2,3-Dinitronaphthalene (110)[59]

Aromatisation of (109) (17.5 g.) by bromination and thermal dehydrobromination of the adduct in situ led to 9.3 g. of 2,3-dinitronaphthalene.   Yield 54%

m.p. 173-174° C.   lit. m.p. 174° C.

The N.M.R. spectrum (in $CDCl_3$/acetone) had a singlet at τ1.58 (1H and 4H).   The four remaining aromatic protons absorbed between τ1.80 and 2.30 as an almost symmetrical multiplet.

viii) 1-Methoxy-3-nitronaphthalene (111)[60]

2,3-Dinitronaphthalene (7.0 g.) afforded 1-methoxy-3-nitronaphthalene (6.4 g.) as the sole product of reaction on warming at 40 - 50° C. with sodium methoxide (28 g.) in methanol (350 ml.).   Yield 98%.

m.p. 103 - 104° C.   lit. m.p. 103 - 104° C.

ix) 3-Nitro-1-naphthol (112)

The above methyl ether (2 g.) was mixed with hydriodic acid (S.Gr. 1.7) in glacial acetic acid (20 ml.) and heated under reflux for 10 hours.   The solution was cooled, diluted with water and the solid product collected.   The product was taken up in 10% sodium hydroxide solution, and the alkaline solution extracted several times with ether.   Acidification of the alkaline solution precipitated 3-nitro-1-naphthol which was filtered, washed with water and dried. Yield 1.5 g. (78%).

m.p. 167 - 168° C.   lit.[63] m.p.   169 - 170° C.

3) <u>5-Methoxy-1-naphthol</u>

1,5-Dihydroxynaphthalene (16 g., 0.1 mole) was warmed with a solution of potassium hydroxide pellets (8.4 g., 0.15 mole) in water (70 ml.) to give a solution, then quickly cooled and dimethyl sulphate (15 g., 0.12 mole) let in with stirring. The mixture was warmed at 50 - 60° C. for 30 minutes, cooled, made stongly alkaline, then filtered to remove a quantity of the dimethyl ether. Acidification of the filtrate afforded a crude product which was filtered at the pump and worked with water. Recrystallisation of this material twice from aqueous acetic acid gave 5-methoxy-1-naphthol (8.2 g.). Yield 43%

m.p. 139 - 140° C. lit. m.p. 140° C.

4) <u>7-Methyl-1-naphthol</u> <u>6-Methoxy-1-naphthol</u>
<u>7-Methoxy-1-naphthol</u> <u>5,6,7-Trimethoxy-1-naphthol</u>
<u>1-Phenanthrol</u>

The above phenols were prepared according to the method outlined on page 57. Literature methods were generally employed. Yields and physical data for intermediates are recorded in Tables 1 - 4

Table 1

Physical Data for Arylketopropionic acids Prepared by Succinoylation of Aromatic Substrates with $AlCl_3$.

Ketopropionic acid (119), R =	Yield %	m.p. (^{o}C.) obs. lit.		I.R. spec. ν_{co} (nujol)	N.M.R. Spectrum
4-CH$_3$	93-98	127-129	129[a]	1685	OH at 1.8; A$_2$X$_2$ aromatic region at 2.15 and 2.78 (J 8.5 c.p.s.); CH$_2$ (triplets) at 6.75 and 7.21; CH$_3$ at 7.62. (in CDCl$_3$)
4-OCH$_3$	74-80	146-147	146[b]	1665, 1697	A$_2$X$_2$ aromatic region at 1.98 and 2.90 (J 8.8 c.p.s.); OCH$_3$ at 6.10; CH$_2$ (triplet) at 6.72. (in DMSO)
2-OH-3,4-(OCH$_3$)$_2$	53	142-149	152[c]	1640, 1705	OH at -2.3 and 0.3; 5H at 3.46 and 6H at 2.42 (J$_{5,6}$ 8.6 c.p.s.); OCH$_3$ at 6.05 and 6.12; CH$_2$ (triplets) at 6.7 and 7.2. (in CDCl$_3$)

Notes: a. Reference 122   b. Reference 47   c. Reference 123

Table 2

Physical Data for Arylbutyric acids Prepared by Clemmensen Reduction (Martin's Modification [125])

Butyric acid (120), R =	Yield	m.p./b.p. (^{o}C.) obs.	lit.	I.R. spec. ν_{co} cm.$^{-1}$	N.M.R. Spectrum
4-CH$_3$	94	58-59	59[a]	1690 (nujol)	Singlets at -1.57 (OH), 3.00 (all aromatics) and 7.73 (CH$_3$); aliphatics at 7.2 - 8.3. (in CDCl$_3$)
4-OCH$_3$	78	168-180/ at 1.5mm. 59-61	61[b]	1705 (CS$_2$)	Singlets at -1.87 (OH) and 6.32 (OCH$_3$); 2H at 3.0 and 3H at 3.31; aliphatics at 7.2 - 8.2. (in CCl$_4$)
2-OH-3,4-(OCH$_3$)$_2$	65	99-102	103[b]	1705 (CS$_2$)	OCH$_3$ (singlets) at 6.10 and 6.17; 5H at 3.58 and 6H at 3.20; aliphatics at 7.2 - 8.3. (in CDCl$_3$)

Notes: a. Reference   122   b. Reference   47

Table 3

Physical Data for Substituted 1-Tetralones from Ring Closure of Arylbutyric acids

1-tetralone (121), R=	condensing agent	Yield %	m.p./b.p. (^{o}C.) obs.	lit.	I.R. spec. ν_{co} cm.$^{-1}$	N.M.R. spec.
7-CH$_3$	80% H$_2$SO$_4$ on acid	43	135-145/ at 12 mm. 30-33	35[b]	1687 (CS$_2$)	d
7-OCH$_3$	AlCl$_3$ on acid chloride: i in Cl$_2$C:CCl$_2$ ii in benzene	50 78	61-62	62[c]	1685 (CS$_2$)	e
5-OH-6,7-(OCH$_3$)$_2$	85% H$_2$SO$_4$ on acid	74	153-154	155[c]	1690 (nujol)	f

Notes: a.   Methylation in alkali with dimethyl sulphate afforded 5,6,7-trimethoxy-1-tetralone in 85% yield.

b.   Reference 122   c.   Reference 47

d.   8H at 2.39, 6H at 2.85, 5H at 3.04, CH$_3$ at 7.70. (in CS$_2$)

e.   8H at 2.70, 5H at 2.97, 6H at 3.19, OCH$_3$ at 6.30.(in CS$_2$)

f.   8H at 2.73, OCH$_3$ at 6.02 and 6.10, OH at 3.8.   (in CDCl$_3$)

Table 4

The Dehydrogenation of Tetralones to 1-Naphthols

Product phenol:	Conditions[a]	Yield %	m.p./b.p. ($^\circ$C.) obs.	lit.[ref]	Notes
7-Methyl-1-naphthol	Pd/C	56	105-108	111[124]	b
7-Methoxy-1-naphthol	Pd/C	62	160-165at 3.5 mm. 103-104	105[132]	c
5,6,7-tri-methoxy-1-naphthol	S	-	-	-	d
6-methoxy-1-naphthol	S	47	140-146at 0.6 mm. 84 - 85	85[133]	e
1-Phenanth-rol	Pd/C	34	151-154	155[134]	f

Notes

a. Catalytic dehydrogenations were performed with a 30%
    preparation of palladium on charcoal prepared from
    palladium chloride.   A catalyst to ketone ratio of
    1.0 g./0.1 mole was used and the mixture heated in a
    Woods metal bath at 300 - 320° C. (bath temperature)
    for 3 - 3.5 hours.   The product was extracted into
    alkali and purified by distillation if necessary.

Notes to Table 4 continued

Sulphur dehydrogenations were performed by heating the ketone with the required amount of sulphur for 40 – 45 minutes at 240 – 250° C. (bath temperature).

b. After recovery of 7-methyl-1-tetralone (21%) by distillation under reduced pressure, trituration of the residue with a small amount of acetone gave a solid product. Recrystallisation from acetone afforded long white needles of 7,7'-dimethylnaphtho[1,2-b:2',1'-d]furan.

   Yield   7%   m.p.   166 – 167° C.

   $C_{22}H_{16}O$ requires: C, 89.7; H, 5.5%   M. 296
            found   : C, 89.2; H, 5.7%   M. 296 (mass spectroscopy)

c. As in b. above, after recovery of the tetralone (24%) by distillation, recrystallisation of the residue from acetone afforded white needles of 7,7'-dimethoxynaphtho-[1,2-b:1',2'-d]furan.

   Yield   6%   m.p.   159 – 160° C.

   $C_{22}H_{16}O_3$ requires: C, 80.5; H, 4.9%   M. 328
            found   : C, 80.8; H, 5.7%   M. 328 (mass spectroscopy)

d. Dehydrogenation with sulphur afforded a mixture of the naphthol and thionaphthol (ca. 1 : 1 by N.M.R.). No identifiable product was obtained using Pd/C.

e. 6-Methoxy-1-tetralone was obtained commercially.

f. A sample of 3,4-dihydro-1(2H)phenanthrenone, synthesised from naphthalene in ca. 30% yield, was provided by Mr. D.S. Leitch, B.Sc.

5) 3-Chloro-1-naphthol and 3-iodo-1-naphthol

i) A pentachloroketonaphthalene (112?)[67]

Dry chlorine gas was bubbled through a solution of 1-naphthol (100 g.) in glacial acetic acid (350 ml.) at 10 - 15° C. for 6 hours and the mixture left at room temperature overnight. The following day a yellow crystalline precipitate was filtered off, washed with a small quantity of benzene and recrystallised from benzene to afford a pentachloroketo product as small white needles (76 g.). Yield 35%.

m.p. 154 - 156° C. lit. m.p. 156 - 157° C.

The N.M.R. spectrum (in acetone) had complex aromatic multiplets between $\tau 1.6$ and $\tau 2.4$ (four protons) and a sharp singlet at $\tau 3.82$ (one proton)

ii) 2,3,4-Trichloro-1-naphthol (113)[67]

2,3,4-Trichloro-1-naphthol (49 g.) was obtained from reduction of the pentachloroketo compound (75 g.) in acetic acid at 90° C. with an excess of sodium sulphite in aqueous solution. Yield 94%.

m.p. 157 - 158° C. lit. m.p. 159 - 160° C.

The I.R. spectrum (nujol mull) had ν_{OH} 3400 cm.$^{-1}$.

The N.M.R. spectrum (in CDCl$_3$) had OH at $\tau 3.8$ with the aromatic region as two groups of multiplets at $\tau 1.7 - 2.0$ (5H and 8H) and $\tau 2.2 - 2.55$ (6H and 7H).

iii) 3-Chloro-1-naphthol

2,3,4-Trichloro-1-naphthol (37.2 g.) in glacial acetic acid (300 ml.)

was heated at reflux with hydriodic acid, S.Gr. 1.7, (300 g.) for 2 hours, cooled and added to water (5 l.) containing sulphuric acid (10 ml.). The mixture was stirred for a few minutes and the solid which collected filtered at the pump and washed with a little water.

Distillation of the product (26.3 g.) through a short Vigreux under reduced pressure afforded two volatile fractions -

(a) b.p. 178 - 185° C./ 28 mm. Hg   (7.5 g.)

(b) b.p. 185 - 200° C./ 28 mm. Hg   (8.1 g.)

and a residue (9.4 g.) which was not distilled.

Redistillation of the first fraction, which was mostly the required product, afforded 3-chloro-1-naphthol (5.1 g.) which recrystallised from carbon tetrachloride as white needles.

Isolated yield 17%

m.p. 108 - 109° C.   lit.[66] m.p. 108° C. (see page 51)

iv) 3-Iodo-1-naphthol

The residue from the distillation in iii) above afforded pure 3-iodo-1-naphthol (8.8 g.) as long white needles on recrystallisation from carbon tetrachloride.

Isolated yield 17%

m.p. 132 - 133° C.   lit.[66] m.p. 133 - 134° C.

The N.M.R. spectrum of the crude reaction mixture indicated a ratio of 3-chloro- : 3-iodo- of ca. 1 : 1.

6) 1-Methyl-2-naphthol

2-Hydroxy-1-naphthaldehyde (17.2 g.) on Clemmensen reduction

with amalgamated zinc in strong aqueous acid at reflux over 8 hours
afforded 1-methyl-2-naphthol (6.3 g.) on recrystallisation of the
crude product from aqueous acetic acid and then from light petroleum
(b.p. 60 - 80°).   Yield 40% theory.

m.p. 108-110° C.   lit.[112] m.p.111·° C.

7) 1-Chloro-2-naphthol [113]

Sulphuryl chloride (13.5 g., 0.1 mole) was let in dropwise
into a solution of 2-naphthol (14.4 g., 0.1 mole) in carbon
disulphide (50 ml.) at 25 - 30° C. The mixture was maintained
at ca. 30° C. for 2 hours and the solvent removed under reduced
pressure. Recrystallisation of the crude product from aqueous
acetic acid gave pure 1-chloro-2-naphthol.

Yield 13·8 g.   77% theory
m.p. 68 - 69° C.   lit. m.p. 69° C.

8) 8-Phenyl-2-naphthol

i)   7-methoxy-1-phenyl-1,2,3,4-tetrahydro-1-naphthol

Freshly distilled bromobenzene (39 g., 0.25 mole) in dry
ether (30 ml.) was added slowly with stirring to magnesium turnings
(6.1 g., 0.25 mole) in dry ether (70 ml.) containing a crystal of
iodine at such a rate as to maintain gentle reflux. After the
final addition the mixture was refluxed for 15 minutes. 7-Methoxy-
1-tetralone (35.2 g., 0.2 mole) in dry ether (150 ml.) was let

in dropwise to the Grignard preparation maintaining gentle reflux throughout the addition. After a further 45 minutes heating the reaction was cooled and decomposed by addition to ice-cold dilute hydrochloric acid, mixed thoroughly for several minutes and the organic phase separated. The aqueous phase was extracted twice with small quantities of ether and the combined ether solutions washed with water, dried and solvent removed under diminished pressure to yield 49.9 g. of a yellow viscous oil.

The N.M.R. spectrum (in $CDCl_3$) indicated over 90% conversion to the carbinol together with unreacted tetralone.

The I.R. spectrum (liquid film) had ν_{OH} 3500 cm.$^{-1}$. The N.M.R. spectrum had singlets at $\tau 2.76$ (phenyl), $\tau 6.45$ (OCH_3) and $\tau 7.56$ (OH) with an ABX aromatic region where the 5H absorbs at $\tau 2.93$ ($J_{5,6}$ ca. 8.5 c.p.s.). The alicyclic protons absorbed as multiplets near $\tau 7.2$ (two protons) and $\tau 7.8 - 8.5$ (four protons).

ii)   7-methoxy-1-phenyl-3,4-dihydronaphthalene

Dehydration of the crude carbinol (49.7 g.) by refluxing for 1 hour in 1N hydrochloric acid (350 ml.) afforded the crude dihydronaphthalene (44.3 g.) as a yellow mobile oil on ether extraction of the cooled reaction mixture.

The N.M.R. spectrum (in $CDCl_3$) indicated complete conversion to the olefin. The phenyl group absorbed as a singlet at $\tau 2.73$, and the other aromatic protons as an ABX multiplet between $\tau 2.9$

and 3.5.   The vinyl proton triplet was at τ 3.97 and OCH$_3$ singlet at τ 6.46.

iii)   7-methoxy-1-phenylnaphthalene

The crude olefin (44.0 g.) was dehydrogenated by heating with 30% Pd/C (1.0 g.) at 300 - 320° C. (metal bath temperature) for 3 hours.   After cooling, the product was taken up in ether, filtered to remove the catalyst and extracted with 2N sodium hydroxide to remove any phenolic material.   After drying and removal of the solvent under reduced pressure, the crude 7-methoxy-1-phenylnaphthalene (36.3 g.) was obtained as a pale yellow oil.

The N.M.R. spectrum (in CDCl$_3$) showed total absence of vinyl protons and alicyclics and indicated the product to be in a high state of purity.   The spectrum had a degenerate aromatic region between τ 2.2 and 3.0 with only the phenyl group obvious as a singlet at τ 2.63.   OCH$_3$ absorbed at τ 6.41.

iv)   8-phenyl-2-naphthol

The preceding methyl ether (35 g.) was refluxed with hydriodic acid (S.G. 1.7, 270 ml.) in glacial acetic acid (270 ml.) for 7 hours.   After cooling, the dark red solution was diluted with water (500 ml.) and extracted with ether (3 x 200 ml.).   The combined ether extracts were extracted several times with 4N sodium hydroxide solution and these latter alkaline washes on

acidification afforded the crude naphthol as an oil which was isolated by ether extraction (23.2 g.). The product did not solidify nor was it able to be recrystallised. The N.M.R. spectrum, however, indicated the product to be in a high state of purity hence purification by distillation was not attempted.

Overall yield from 7-methoxy-1-tetralone   61%

9) 8-Methyl-2-naphthol

This was prepared in a similar manner to 8-phenyl-2-naphthol. Purification of 7-methoxy-1-methylnaphthalene was carried out by distillation and the fraction boiling at 142 - 160° C./15 mm. collected.   The overall yield of the naphthol from 7-methoxy-1-tetralone was 42%.

m.p. (crude) 60 - 65° C. lit.[136] m.p. 69 - 70° C.

10) 8-isoPropyl-2-naphthol

This was prepared as in 8) with putification of the olefin by distillation.   The fraction boiling at 90 - 112° C./0.8 mm. was dehydrogenated with Pd/C and the mixture obtained distilled under reduced pressure.   The fraction collected at 140 - 154° C./ 10 mm. was demethylated in the usual manner to afford the crude naphthol as an oil which partially solidified on standing.   The material could not be successfully recrystallised but was used as such.

Overall yield from 7-methoxy-1-tetralone   13%

11) 8-t-Butyl-2-naphthol

This was only prepared in admixture with 2-naphthol
(proportion 10% by N.M.R.) by the route given in 8). A
complex mixture of products was obtained in the initial Grignard
reaction and partial purification was achieved with the methyl
naphthyl ether by chromatography on silica gel.

The overall yield of the grossly impure naphthol was <2%
and no attempt was made to purify the product.

12) Attempted preparation of 4-methoxy-2-naphthol

a) 1-Methoxy-3-nitronaphthalene (2.5 g.) suspended in hot
ethanol (150 ml.) was treated dropwise over 15 minutes with sodium
dithionite (8.7 g.) in water (40 ml.). The mixture was refluxed
for 1.5 hours, filtered while hot to remove inorganic matter,
then added to water (500 ml.). The product which separated was
filtered, washed with a little water and dried. Recrystallisation
from petroleum ether (b.p. 60 - 80°) gave pure 4-methoxy-2-
naphthylamine (1.26 g., 50%).

m.p. 57 - 58° C. lit.[63] m.p. 57.5 - 58.5° C.

The I.R. spectrum (liquid film) had ν_{NH_2} at 3380 and 3450 cm.$^{-1}$.
The N.M.R. spectrum (in $CDCl_3$) had OCH_3 (singlet) at $\tau 6.25$, NH_2
at $\tau 6.33$, 2H at $\tau 3.90$, 4H at $\tau 3.57$ and 8H at $\tau 1.95$. $J_{2,4}$ 2.0 c.p.s.

The above amine (0.8 g.) was diazotised in dilute sulphuric
acid at 0° C. and the diazo solution let into 50% w/w sulphuric
acid and warmed to 60 - 70° C. for 10 minutes. After cooling

and diluting with water the aqueous reaction mixture was extracted several times with benzene and the organic layer washed with 2N sodium hydroxide. The alkaline extracts were acidified and re-extracted with benzene. Evaporation of the solvent afforded a solid product (0.45 g.). The N.M.R. spectrum had no OCH_3 resonance and lacked resolution suggesting the material isolated to be polymeric

b. Anhydrous potassium carbonate (28.0 g.) was added in portions to a mixture of 1,3-dihydroxynaphthalene (16 g.) in acetone (50 ml.). Dimethyl sulphate (16 g.) was then let in dropwise and the mixture heated at reflux for 2.5 hours. The acetone was distilled from the reaction mixture and the residue partitioned between benzene and 2N sodium hydroxide. Acidification of the alkaline layer afforded a crude product as a red oil (8.8 g.) isolated by extraction into benzene.

The N.M.R. spectrum indicated the oil to be a mixture of monomethylation products in the ratio of ca. 2 : 1. The product could not be induced to solidify on cooling or be recrystallised. Silica gel chromatography and distillation under reduced pressure afforded no separation or enrichment.

13) <u>Attempted preparation of 5,7-dimethoxynaphthalene</u>

The failure to repeat literature preparations at an early stage in synthesis, e.g. the partial reduction of 1,3-dinitro-naphthalene by the method of Rosenblatt et al.[63] (only the

diamine m.p. 92 - 94° C., lit.[63] m.p. 96° C. was obtained), the alkali fusion of 1-naphthylamine-5,7-disulphonic acid[82], and the reduction of 5,7-dinitrotetralin[81] are not recorded in detail.

a. Succinoylation of 1-acetamido-3,5-dimethoxybenzene (2 g.) in nitrobenzene (15 ml.) with aluminium chloride (1.4 g.) and succinic anhydride (0.5 g.) at 10 - 15° C. over 7 hours afforded after decomposition in the usual manner a phenolic material (0.5 g.) as the sole acidic product.   m.p. crude product 65 - 71° C.

The N.M.R. spectrum (in NaOD) indicated the product to be 1-hydroxy-6-methoxy-aceto-p-toluidine on account of a single aromatic resonance (2 protons) and three methyl singlets corresponding to $COCH_3$, OCH_3 and $Ar-CH_3$ at typical chemical shifts.

b. Nitration of 1-tetralone by the method of von Braun[135] with concentrated nitric acid at ca. -10° C. afforded as the major product the 7-nitro- derivative.   Increasing the temperature to 20° C. led to a vigorous reaction and the only product isolated on dilution with water was the oxidation product β-(2-carboxy-4-nitrophenyl)propionic acid identified spectroscopically.

Various nitrating mixtures of sulphuric and nitric acid at or near room temperature led to the same product being formed and no dinitro- derivative was able to be detected.

7-Nitro-1-tetralone had m.p. 71 - 72° C. (ethanol)

lit. m.p.   72° C.

The N.M.R. spectrum (in $CDCl_3$) had 8H at τ1.23, 6H at τ1.70 and 5H at τ2.51. $J_{5,6}$ 8.3 c.p.s. and $J_{6,8}$ 2.4 c.p.s.

β-(2-Carboxy-4-nitrophenyl)propionic acid had a m.p. 135° C. (aq.
acetic acid).

The N.M.R. spectrum (in acetone) had 3H at τ1.25, 5H at τ1.61
and 6H at τ2.25, and four aliphatic protons between τ6.3 and τ7.3.

Table 5

N.M.R. Spectral Data of Substituted 1- and 2-Naphthols

Naphthol	Proton chemical shifts in τ values									
	1H	2H	3H	4H	5H	6H	7H	8H	OH	CH$_3$
1-Naphthols										
2-Cl [a]	–	–	d	d	d	d	d	1.83	4.1	–
3-Cl [c]	–	3.11	–	d	d	d	d	1.80	1.1	–
4-Cl [b]	–	3.05	2.55	–	d	d	d	d	0.7	–
3-I [c]	–	2.83	–	2.29	d	d	d	1.82	1.5	–
2-NO$_2$ [b]	–	–	2.07	2.61	d	d	d	1.60	0.4	–
4-OCH$_3$ [b]	–	3.16	3.35	–	d	d	d	d	1.5	6.11
5-OCH$_3$ [b]	–	3.03	2.64*	2.14*	–	3.10	2.72*	2.27*	1.1	6.02
6-OCH$_3$ [a]	–	3.44	d	d	d	–	d	1.91	3.0	6.20
7-OCH$_3$ [a]	–	3.29	2.92	2.66	2.34	2.88	–	2.51	4.0	6.19
7-CH$_3$ [a]	–	3.31	d	d	2.32	d	–	2.07	4.3	7.55
5,6,7-(OMe)$_3$ [a]	–	3.25	2.86	2.38	–	–	–	2.67	2.5	ca. 6.0
2-Naphthols										
8-CH$_3$ [e]	d	–	3.00	2.37	d	d	d	d	4.4	7.80
8-isoPr [a]	d	–	2.92	d	d	d	d	d	4.1	–[f]
8-Ph [a]	d	–	3.03	d	d	d	d	d	4.2	–[g]

Notes to above Table on following page.

Notes relating to Table 5

a.   solvent $CDCl_3$

b.   solvent acetone

c.   solvent $CDCl_3$/acetone

d.   signifies degeneracy or obscurity of signal

e.   solvent CCl_4

f.   CH at $\tau6.59$ and CMe_2 at $\tau8.75$.

g.   Ph- at $\tau2.72$ (singlet)

*   signifies resonance clearly visible but assignment

     uncertain.

The Preparation of Aryloxyacetic Acids

1) General Procedure

The majority of the aryloxyacetic acids were prepared from the corresponding phenols according to the following manner:

An aqueous solution of the phenol, chloroacetic acid and sodium hydroxide pellets in the molar ratio of 1 : 1 : 2, was refluxed gently for three to five hours. Acidification with 2N hydrochloric acid of the cold solution afforded a crude product together with unreacted phenol. Purification of the carboxylic acid was generally achieved by partitioning the crude product between saturated sodium bicarbonate solution and an organic solvent (benzene or chloroform). Acidification of the separated bicarbonate solution deposited the aryloxyacetic acid in a high state of purity. A single recrystallisation from a suitable solvent invariably gave a spectroscopically pure material of sharp melting point. The unreacted phenol was able to be recovered from the organic layer.

The acids of Type I, II and III prepared in this way are collected in Table 6. Spectral data appear in Table 7.
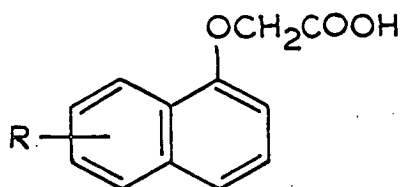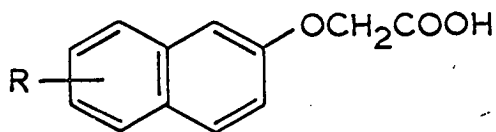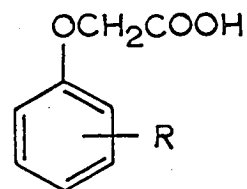
Type I   Type II   Type III

Table 6

Physical Constants of Aryloxyacetic Acids

Aryloxyacetic acid:	Yield %	Melting point (^{o}C.) and recrystallisation solvent		Microanalysis			
					%C	%H	%Hal	%N
Type I, R =							
H	59	192 – 193,[a]	ethanol				
3-Cl	63	168 – 169,	benzene	$C_{12}H_9ClO_3$,	req. ; 60.9	3.8	15.0
					found: 60.9	3.9	14.9
4-Cl	67	164 – 165,[b]	benzene				
3-I	61	179 – 180,	benzene	$C_{12}H_9IO_3$	req. : 43.9	2.8	38.4
					found: 44.0	2.8	38.7
4-OMe	67	161 – 162,	benzene	$C_{13}H_{12}O_4$	req. : 67.2	5.2	
					found: 67.3	4.7	
5-OMe	59	194 – 195,	benzene	$C_{13}H_{12}O_4$	req. : 67.2	5.2	
					found: 67.1	5.3	
6-OMe	64	185 – 186,	benzene	$C_{13}H_{12}O_4$	req. : 67.2	5.2	
					found: 67.6	6.0	
7-OMe	70	160 – 161,	benzene	$C_{13}H_{12}O_4$	req. : 67.2	5.2	
					found: 66.9	5.3	
7-Me	62	130 – 131, aq. ethanol		$C_{13}H_{12}O_3$	req. : 72.2	5.6	
					found: 77.2	7.0	
				$+1H_2O$	req. : 78.4	7.0	
5,6,7-OMe$_3$	57	135 – 136	benzene/ petrol	$C_{15}H_{16}O_6$	req. : 61.6	5.5	
					found: 62.1	5.5	

Table 6 Continued

Aryloxyacetic acid	Yield %	Melting point (°C.) and recrystallisation solvent		Microanalysis		%C	%H	%Hal	%N
Type I, R =									
3-NO$_2$	49	227 – 228,	aq.acetic acid	C$_{12}$H$_9$NO$_5$	req. :	58.3	3.7		5.7
					found:	59.1	3.9		5.9
Type II, R =									
H	69	155 – 156,[c]	water						
8-Ph	74	183 – 184,	benzene	C$_{18}$H$_{14}$O$_3$	req. :	77.7	5.1		
					found:	77.7	5.4		
8-Me	62	148 – 149,	benzene	C$_{13}$H$_{12}$O$_3$	req. :	72.2	5.6		
					found:	72.0	5.6		
8-isoPr	59	128 – 129,	benzene/ petrol	C$_{15}$H$_{16}$O$_3$	req. :	73.75	6.6		
					found:	73.4	6.8		
1-Cl	69	160 – 161,[d]	benzene						
1-Me	75	129 – 130,	benzene[h]	C$_{13}$H$_{12}$O$_3$	req. :	72.2	5.6		
					found:	77.9	6.7		
				+1H$_2$O	req. :	78.4	7.0		
Type III, R =									
2-OCH$_3$	62	119 – 120,[e]	water						
3-OCH$_3$	70	116 – 117,[f]	water						
4-OCH$_3$	72	110 – 111,[g]	water						
1-Phenanthryl- oxyacetic acid	58	191 – 193,	benzene	C$_{16}$H$_{12}$O$_3$	req. :	76.2	4.8		
					found:	75.9	4.8		

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Notes to Table 6

a. Lit.[1]   m.p.   193° C.

b. Lit.[126] m.p.   169° C.

c. Lit.[1]   m.p.   156° C.

d. Lit.[127] m.p.   156° C.

e. Lit.[128] m.p.   120 - 121°C.

f. Lit.[129] m.p.   118° C.

g. Lit.[130] m.p.   110 - 112° C.

h. Microanalysis sample recrystallised from water.

Table 7

N.M.R. Spectral Data of Naphthyloxyacetic acids in Table 6

Acid:	1H	2H	3H	4H	5H	6H	7H	8H	CH_2	CH_3
Type I, R=										
H [c]	–	3.10	d	d	2.12	d	d	1.72	5.10	–
3-Cl [a]	–	3.05	–	2.45	d	d	d	1.65	5.00	–
4-Cl [a]	–	3.17	2.57	–	d	d	d	d	5.11	–
3-I [a]	–	2.78	–	2.03	2.15	2.41*	2.47*	1.65	5.01	–
4-OCH_3 [a]	–	3.26	3.26	–	d	d	d	d	5.15	6.10
5-OCH_3 [c]	–	3.10*	2.57*	2.25*	–	3.04*	2.62*	2.18*	5.11	6.05
6-OCH_3 [a]	–	3.27	d	d	d	–	d	1.77	5.14	6.13
7-OCH_3 [c]	–	3.16	d	d	d	d	–	2.46	5.13	6.13
7-CH_3 [c]	–	3.15	d	d	2.25	d	–	1.96	5.17	d
5,6,7-$(OMe)_3$ [b]	–	3.33	2.77	2.29	–	–	–	2.57	5.18	ca. 6.0
3-NO_2 [c]	–	2.45	–	1.44	d	d	d	d	4.93	–
Type II, R =										
H [c]	d	–	d	d	d	d	d	d	5.20	–
8-Ph [c]	d	–	d	1.86	d	d	d	–	5.18	–[e]
8-Me [c]	d	–	d	2.13	d	d	d	–	5.14	d
8-isoPr [a]	d	–	2.80	2.19	d	d	d	–	5.20	–[f]
1-Cl [c]	–	–	2.66	2.09	d	d	d	d	4.98	–
1-Me [b]	–	–	2.90	2.34	d	d	d	d	5.27	7.42

Notes to above Table on following page.

Notes relating to Table 7

a. solvent acetone

b. solvent $CDCl_3$

c. solvent DMSO

d. signifies degeneracy or obscurity of signal

e. Ph- at $\tau 2.34$

f. CH at $\tau 6.34$ and CMe_2 at $\tau 8.62$

*   signifies resonance clearly visible but assignment
    uncertain.

2) 2-Chloro-1-naphthyloxyacetic acid

2-Chloro-1-naphthol (6.9 g., 0.04 moles) was added to a solution of methanol (50 ml.) containing dissolved sodium (0.9 g., 0.04 moles). Evaporation to dryness of the resulting mixture afforded the sodium salt which was added to dry benzene (20 ml.) containing ethyl bromoacetate (6.2 g., 0.04 moles) and boiled under reflux for 5 hours. After cooling, the reaction mixture was made up to about 200 ml. with benzene and washed several times with 2N sodium hydroxide. The organic layer after drying and removal of the solvent under reduced pressure afforded crude ethyl 2-chloro-1-naphthyloxyacetate (10.2 g.) as a dark viscous liquid.

The crude ester (10.0 g.) was heated under reflux with a mixture of 2N sodium hydroxide solution (50 ml.) and ethanol (50 ml.) for 30 minutes. After this time had elapsed the ethanol was removed by distillation in vacuo over a further 30 minutes. Acidification of the aqueous reaction mixture gave the crude acid (8.4 g.) which recrystallised from benzene to give pure 2-chloro-1-naphthyloxyacetic acid.

Yield 7.1 g.   75% theory.

m.p. 134 - 135.5° C.   Lit[3] 135° C.

Ethyl 2-chloro-1-naphthyloxyacetate had v_{co} 1750 cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) had absorptions at τ5.30 (CH_2 singlet), ethyl resonances at τ5.72 (quartet) and τ8.73 (triplet), degenerate aromatic at τ2.2 - 2.8 (5 protons) with 8H at τ1.70.

2-Chloro-1-naphthyloxyacetic acid had v_{co} 1725 cm.$^{-1}$ (nujol mull)

and in the N.M.R. spectrum (in DMSO) CH_2 singlet at $\tau 5.30$ and 8H at $\tau 1.68$.

3) <u>4-Nitro-1-naphthyloxyacetic acid</u>

Nitration of 1-naphthyloxyacetic acid (20 g.) in glacial acetic acid with nitric acid (S.G. 1.5) at less than 10° C. over 3 hours afforded the crude acid in nearly quantitative yield on pouring the reaction mixture on to ice cold water. The acid was purified by recrystallisation from dilute acetic acid.

<div style="text-align:center">

Yield   21.2 g.   85% theory

m.p. 212 - 213° C.   lit[4]   213° C.

</div>

The I.R. spectrum (nujol mull) had ν_{co} 1770 cm.$^{-1}$ and ν_{OH} 3200 cm.$^{-1}$. The N.M.R. spectrum (in DMSO) had inter alia CH_2 singlet at $\tau 4.90$.

4) <u>7-Methoxy-2-naphthyloxyacetic acid</u>

2,7-Dihydroxynaphthalene (32 g., 0.2 moles), chloroacetic acid (19 g., 0.2 moles) and sodium hydroxide pellets (24 g., 0.6 moles) in 250 ml. water were heated under reflux for 3 hours. After cooling, the precipitate which had deposited was collected at the pump, washed with water, then suspended in water and acidified with conc. hydrochloric acid. After stirring for several minutes the solid was filtered off, washed with water and recrystallised from dilute acetic acid to afford naphthalene-2,7-dioxyacetic acid (5.2 g., 9.5% theory)   m.p. 219 - 220° C.

Microanalysis: $C_{14}H_{12}O_6$ requires: C, 60.9;   H, 4.4%

found :   C, 60.5;   H, 4.5%

The filtrate from the above reaction mixture was acidified with 2N hydrochloric acid and the material deposited filtered off and washed with a little water.   This solid was stirred vigorously with aqueous sodium carbonate solution then filtered to remove unchanged diol.   Acidification of this second filtrate afforded the crude monoacid (22.4 g.) as a grey solid.   This solid was dissolved in excess 4N sodium hydroxide solution and stirred with dimethyl sulphate (25 g.) at 40 - 50° C. for 4 hours. After acidification the solid which deposited was collected and recrystallised twice from dilute acetic acid to afford 7-methoxy-2-naphthyloxyacetic acid.

Yield 9.7 g.   21% theory from diol

m.p. 161 - 162° C.

Microanalysis: $C_{13}H_{12}O_4$ requires: C, 67.2;   H, 5.2%

found: C, 67.1;   H, 5.1%

The I.R. spectrum (nujol mull) had ν_{co} 1715 cm.$^{-1}$.   The N.M.R. spectrum (in DMSO) had OCH_3 (singlet) at $\tau 6.15$, CH_2 (singlet) at $\tau 5.18$, 4H and 5H at $\tau 2.20$ with the remaining aromatic protons between $\tau 2.7$ and $\tau 3.1$.

The Preparation of 2-(1-naphthyloxy)isobutyric acid

1-Naphthol (50 g.) in acetone (500 ml.) with sodium hydroxide pellets (85 g.) was treated after about an hour's stirring with chloroform (50 g.) and the heterogeneous mixture refluxed for 8 hours. After removal of the solvent, the residue was taken up in 2N sodium hydroxide and extracted several times with chloroform. Acidification of the alkaline layer afforded 2-(1-naphthyloxy)isobutyric acid (75 g.) in a high state of purity.

m.p. 127 - 130° C.   Yield 94%

Recrystallisation from aqueous ethanol raised the melting point to 130 - 131° C.   lit[70] m.p. 130 - 131° C.

The I.R. spectrum (nujol mull) had ν_{co} 1700 cm.$^{-1}$.

The N.M.R. spectrum (in $CDCl_3$) had, inter alia, CMe_2 singlet at τ 8.30, 2H at τ 3.15 ($J_{2,3}$ 7.2 c.p.s., $J_{2,4}$ 2.3 c.p.s.), 8H at τ 1.76 (multiplet) and OH at τ -1.22.

The Preparation of Aryloxyacetyl Chlorides

Aryloxyacetyl Chlorides were in all cases prepared from the corresponding acids with thionyl chloride. Two methods were employed.

i) Deactivated aromatics

Aryloxyacetic acids with deactivating nuclear substituents (-E, -M groups) were refluxed in excess thionyl chloride for 90 minutes and the excess reagent removed by distillation under reduced pressure. Dry benzene (2 x 20 ml.) was distilled off the acyl chloride to ensure complete removal of thionyl chloride.

ii) All other acids

The aryloxyacetic acid and thionyl chloride, in a molar ratio of 1 : 1.3, were refluxed in dry benzene (25 - 50 ml.) for 45 - 60 minutes. The acid chloride was obtained by removal of solvent and excess reagent under reduced pressure.

In no instance was the acid chloride purified before further use, however its purity was always checked spectroscopically: single CH_2 resonance in the N.M.R. spectrum and ν_{co} 1800 ± 15 cm.$^{-1}$ in the I.R. spectrum.

The Interaction of Naphthyloxyacetyl Chlorides with Aluminium Chloride in Benzene

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

The acid chloride, previously prepared from the acid (one molar equivalent), in dry benzene (15 molar equivalents) was added dropwise over 20 - 30 minutes to a suspension of freshly powdered anhydrous aluminium chloride (1.1 molar equivalents) in dry benzene (15 molar equivalents) at 5 - 10° C. The mixture was stirred vigorously throughout the addition period, and then for a further 3 hours. Moisture was carefully excluded throughout the reaction and the temperature not allowed to rise above 10° C.

After reaction, the mixture was decomposed by pouring on to crushed ice and dilute hydrochloric acid and the mixture vigorously stirred for 30 - 60 minutes at room temperature. The benzene layer was separated from the acidic aqueous solution which was extracted twice with further quantities of benzene. The combined benzene extracts were washed several times with saturated sodium bicarbonate solution, washed with water, dried and the solvent removed under diminished pressure. Acidification of the bicarbonate extracts gave recovered acid (i.e. unreacted acid chloride which had been hydrolysed during the acid decomposition) which was identified in the usual manner. The crude product of the reaction (after removal of carboxylic acid) was examined by I.R. and N.M.R. spectroscopy to determine the

nature and range of products obtained. The N.M.R. spectrum also provided a quantitative measure of these products. Further experimental data are described in sections i) - iv).

i)   In fourteen of the twenty naphthyloxyacetyl chlorides treated in this manner fairly simple product mixtures or single compounds were obtained. These are listed in Table 8. Recrystallisation from a suitable solvent in these instances yielded the major component which was the cyclic ketone. In all cases (except 2-chloro-1-naphthyloxyacetyl chloride) the cyclisations were 'ambiguous' inasmuch as there were two available sites for cyclisation. From the crude N.M.R. spectra there was no evidence of mixtures of ring closed products; 1-naphthyloxyacetyl chlorides always giving 1,2 ring closure and 2-naphthyloxyacetyl chlorides cyclisation at the 1-position. Isolated yields of the cyclic ketones together with melting points and spectral data are collected in Table 9 and in the notes which follow it.

Table 8

Reaction of Naphthyloxyacetyl Chlorides involving Cyclisation.

Acid chloride	weight of acid used (g.)	recovered acid wt. (g.)	%	wt. and % composition of neutral product (N.M.R.) wt.(g.)	cyclic keto-ketone.	aceto-phenone.
(6), R =						
H	10.1	0.2	2	9.8	high	trace
2-Cl	2.4	0.2	8	2.0	85	15
3-Cl	1.77	trace	<2	1.58	q	0
4-Cl	2.37	trace	<2	2.03	q	0
4-OCH$_3$	2.90	0.2	7	2.60	q	0
5-OCH$_3$	2.32	0.3	13	1.89	85	15
7-OCH$_3$	1.90	0.1	5	1.73	85	15
7-CH$_3$	2.80	0.2	7	2.31	95	5
3-I	2.46	0.4	17	1.83	(a)	(a)
(5), R =						
H	3.33	0.3	9	2.50	96	4
7-OCH$_3$	2.32	0.2	9	2.10	89	11
8-CH$_3$	3.24	0.3	10	2.20	93	7
8-isoPr	0.81	trace	<2	0.68	q	0
8-Ph	2.78	trace	<2	2.49	q	0

Notes: q   signifies apparently single component

(a) on account of poor solubility, impossible to obtain

quantitative measure, but see page 85.

Table 9

Physical Data of Tricyclic Ketones

acid chloride	cyclic ketone	isolated yield %	m. p. ($^{\circ}$C.)	solvent for recrystall-isation	notes
(6), R =	(9), R =				
H	H	43	118-119	ethanol/petrol	a
3-Cl	4-Cl	85	191-192	ethanol	b
4-Cl	5-Cl	72	141-142	ethanol	c
3-I	4-I	31	204-206	benzene	d
4-OCH$_3$	5-OCH$_3$	63	140-141	ethanol	e
5-OCH$_3$	6-OCH$_3$	49	157-157.5	ethanol	f
7-OCH$_3$	8-OCH$_3$	62	163-164	ethanol	g
7-CH$_3$	8-CH$_3$	57	134-136	ethanol	h
(5), R =	(8), R =				
H	H	53	130.5-131	ethanol	i
7-OCH$_3$	8-OCH$_3$	56	154-155	ethanol	j
8-CH$_3$	9-CH$_3$	32	116-117	methanol	k
8-isoPr	9-isoPr	81	85-86	benzene/petrol	l
8-Ph	9-Ph	85	133-134	ethanol	m
(6),R=2-Cl	(10),R=9-Cl	68	142-143	ethanol	n

Notes to Table 9 on following pages.

Notes relating to Table 9.

a. Lit.[1] m.p. 119° C.

The I.R. spectrum (CS_2) had ν_{co} 1710 cm.$^{-1}$. The N.M.R.
spectrum (in $CDCl_3$) had CH_2 (singlet) at τ 5.26, 9H (multiplet)
at τ 1.82, 4H (doublet) at τ 2.48 and 5H (ortho/inter-ring
quartet) at τ 2.61. $J_{4,5}$ 8.6 c.p.s., $J_{5,9}$ 0.5 c.p.s.

b. $C_{12}H_7ClO_2$ requires: C, 65.9; H, 3.2; Cl, 16.2%

found: C, 65.7; H, 3.2; Cl, 15.1%

The I.R. spectrum (nujol mull) had ν_{co} 1702 cm.$^{-1}$. The N.M.R.
spectrum (in $CDCl_3$) had CH_2 (singlet) at τ 5.27, 9H (multiplet)
at τ 1.85, and 5H (singlet) at τ 2.57. 5H seen as doublet
on expansion with $J_{5,9}$ 0.8 c.p.s.

c. $C_{12}H_7ClO_2$ requires: C, 65.9; H, 3.2; Cl, 16.2%

found: C, 65.6; H, 3.2; Cl, 15.7%

The I.R. spectrum (CS_2) had ν_{co} 1716 cm.$^{-1}$. The N.M.R.
spectrum (in $CDCl_3$) had CH_2 (singlet) at τ 5.21, and
4H (singlet) at τ 2.43. 6H and 9H (α-protons of
naphthalene skeleton) were degenerate centered on τ 1.8;
7H and 8H also degenerate as an apparently symmetrical
eleven line multiplet centered on τ 2.53.

d. $C_{12}H_7IO_2$ requires: C, 46.5; H, 2.3; I, 40.9%

found: C, 46.6; H, 2.2; I, 40.9%

The I.R. spectrum (nujol mull) had ν_{co} 1698 cm.$^{-1}$. The
N.M.R. spectrum (at 100 Mc/sec. in DMSO as a very weak
solution) had CH_2 (singlet) at τ 5.04 and 5H (singlet)
at τ 1.85. 6H, 7H, 8H and 9H (complex multiplets) τ 1.6-2.4.

e. Lit.[13] m.p. 143° C.

The I.R. spectrum (CS$_2$) had ν_{co} 1714 cm.$^{-1}$. The N.M.R. spectrum (in CDCl$_3$) had CH$_2$ (singlet) at τ5.28 and OCH$_3$ (singlet) at τ6.08. Aromatic region had 4H (singlet) at τ3.34 and two almost symmetrical multiplets at τ1.85 (6H and 9H) and at τ2.39 (7H and 8H).

f. C$_{13}$H$_{10}$O$_3$ requires: C, 72.9; H, 4.7%

found: C, 72.9; H, 4.9%

The I.R. spectrum (CS$_2$) had ν_{co} 1715 cm.$^{-1}$. The N.M.R. spectrum (in CDCl$_3$) had CH$_2$ (singlet) at τ5.27 and OCH$_3$ (singlet) at τ6.04. Aromatic protons - 4H at τ2.56, 5H at τ2.06, 7H at τ3.01, 8H at τ2.56 and 9H at τ2.26. $J_{4,5}$ 8.7 c.p.s., $J_{7,8}$ 7.2 c.p.s., $J_{8,9}$ 8.4 c.p.s., $J_{7,9}$ 1.7 c.p.s. and $J_{5,9}$ 0.8 c.p.s.

g. C$_{13}$H$_{10}$O$_3$ requires: C, 72.9; H, 4.7%

found: C, 72.7; H, 4.5%

The I.R. spectrum (CS$_2$) had ν_{co} 1705 cm.$^{-1}$. The N.M.R. spectrum (in CDCl$_3$) had CH$_2$ (singlet) at τ5.30 and OCH$_3$ (singlet) at τ6.11. Aromatic protons - 6H at τ2.32, 7H at τ2.76, with 4H, 5H and 9H degenerate near τ2.70. $J_{6,7}$ 8.8 c.p.s., $J_{7,9}$ 3.2 c.p.s., and $J_{6,9}$ 1.0 c.p.s.

h. C$_{13}$H$_{10}$O$_2$ requires: C, 77.4; H, 5.4%

found: C, 76.9; H, 5.2%

The I.R. spectrum (CS$_2$) had ν_{co} 1705 cm.$^{-1}$. The N.M.R. spectrum (in CDCl$_3$) had CH$_2$ (singlet) at τ5.20 and CH$_3$ (singlet) at τ7.42. Aromatic protons - 9H at τ1.97,

6H at $\tau 2.17$ and 7H at $\tau 2.47$. The 4H and 5H resonances were near $\tau 2.5$, but could not be readily identified. $J_{6,7}$ 8.3 c.p.s. and $J_{7,9}$ 1.7 c.p.s.

i. Lit.[1] m.p. 131° C.

The I.R. spectrum (CS_2) had ν_{co} 1705 cm.$^{-1}$. The N.M.R. spectrum (in $CDCl_3$) had CH_2 (singlet) at $\tau 5.33$. Aromatic protons - 4H at $\tau 2.83$, 5H at $\tau 2.02$, 9H at $\tau 1.30$ with 6H, 7H and 8H as complex multiplets between $\tau 2.1$ and 2.6. $J_{4,5}$ 8.4 c.p.s.

j. $C_{13}H_{10}O_3$ requires: C, 72.9; H, 4.7%

found: C, 72.8; H, 4.8%

The I.R. spectrum (CS_2) had ν_{co} 1706 cm.$^{-1}$. The N.M.R. spectrum (in $CDCl_3$) had CH_2 (singlet) at $\tau 5.38$ and OCH_3 (singlet) at $\tau 6.09$. Aromatic protons - 4H at $\tau 3.04$, 5H at $\tau 2.40$, 6H at $\tau 2.16$, 7H at $\tau 3.01$ and 9H at $\tau 1.93$. $J_{4,5}$ and $J_{5,6}$ 8.9 c.p.s. and $J_{7,9}$ 2.7 c.p.s.

k. $C_{13}H_{10}O_2$ requires: C, 77.4; H, 5.4%

found: C, 77.4; H, 5.1%

The I.R. spectrum (CS_2) had ν_{co} 1700 cm.$^{-1}$. The N.M.R. spectrum (in $CDCl_3$) had CH_2 (singlet) at $\tau 5.35$ and CH_3 (singlet) at $\tau 7.02$. Aromatic protons - 4H at $\tau 2.86$, 5H at $\tau 2.03$ with 6H, 7H and 8H as complex multiplets at $\tau 2.3$ to 2.8. $J_{4,5}$ 8.4 c.p.s.

l. $C_{15}H_{14}O_2$ requires: C, 79.6; H, 6.2%

found: C, 79.5; H, 6.3%

The I.R. spectrum (nujol mull) had ν_{co} 1703 cm.$^{-1}$.

The N.M.R. spectrum (in $CDCl_3$) had CH_2 (singlet) at $\tau 5.35$, CMe_2 at $\tau 8.69$ and CH (multiplet) at $\tau 5.28$. Aromatic protons - 4H at $\tau 2.91$, 5H at $\tau 2.08$ with 6H, 7H and 8H as complex multiplets at $\tau 2.3$ to 2.7. $J_{4,5}$ 9.0 c.p.s.

m. $C_{18}H_{12}O_2$ requires: C, 83.1;   H, 4.7%

               found: C, 82.3;   H, 5.0%

The I.R. spectrum (nujol mull) had ν_{co} 1705 cm.$^{-1}$. The N.M.R. spectrum (in $CDCl_3$) had CH_2 (singlet) at $\tau 5.64$. Aromatic protons - 4H at $\tau 2.89$, 5H at $\tau 2.08$, Ph as an intense singlet at $\tau 2.70$ with remaining protons degenerate. $J_{4,5}$ 8.7 c.p.s.

n.   Lit.[3] m.p. 141 - 143° C.

The I.R. spectrum (CS_2) had ν_{co} 1703 cm.$^{-1}$. The N.M.R. spectrum (in $CDCl_3$) had CH_2 (singlet) at $\tau 5.02$. The aromatic region had 4H and 6H as degenerate multiplets between $\tau 1.8$ and 2.1, 5H at $\tau 2.46$ with 7H and 8H as a degenerate singlet at $\tau 2.58$.

$J_{4,5}$ 7.1 c.p.s., $J_{5,6}$ 8.7 c.p.s.

ii) Nitro- substituted 1-naphthyloxyacetyl chlorides

(a) The crude product obtained as described previously from reaction of 4-nitro-1-naphthyloxyacetyl chloride (from 4.9 g. of acid), contained considerable unreacted and unhydrolysed acid chloride which was successfully hydrolysed by stirring with 4N hydrochloric acid/benzene at 60 - 70° C. for several hours. The isolated crude product, free of the acid and its chloride, obtained as a yellow solid (1.0 g.) was identified by N.M.R. spectroscopy as 2-(4'-nitro-1-naphthyloxy)acetophenone which recrystallised from ethanol. The recovered acid amounted to 3.9 g. (80%).

Yield 1.0 g.   16% theory.

m.p. 172 - 173° C.

$C_{18}H_{13}NO_4$ requires: C, 70.35; H, 4.3; N, 4.6%

found: C, 70.9; H, 4.1; N, 4.5%

The I.R. spectrum (nujol mull) had ν_{co} 1680 cm.$^{-1}$ and the N.M.R. spectrum (in CDCl$_3$) had inter alia CH$_2$ (singlet) at τ 4.53.

Notes:

1. Repeating the above reaction in anisole (30 molar equivalents) with a similar quantity of the acid chloride etc. afforded 1.2 g. of a mixture of solvent acylated products. Yield 18%.

2. With ethylene dichloride as solvent at reflux no reaction occurred, only acid chloride and acid being recovered.

(b)   In attempting to hydrolyse unreacted acid chloride from reaction of 3-nitro-1-naphthyloxyacetyl chloride (from 1.5 g. of acid) ethanol, present in the chloroform used as solvent, produced a quantity of the ethyl ester.   Hydrolysis of the mixture (ester plus solvent acylated product) with hot 10% aqueous sodium hydroxide (15 ml.) and ethanol (10 ml.) over 1 hour afforded a mixture where the acetophenone appeared to have been decomposed.

N.M.R. spectral examination of the crude reaction product had indicated the product of acylation to be 2-(3'-nitro-1-naphthyloxy)acetophenone and the yield to be 15 to 20%.

Repeating the reaction with 0.5 g. of acid, but maintaining the temperature at 50 - 60° C., afforded a brown tar which was a complex mixture.   This experiment was abandoned.

iii)   1-Substituted 2-naphthyloxyacetyl chlorides.

(a)   Reaction of 1-chloro-2-naphthyloxyacetyl chloride (from 5.9 g. of acid) in the usual manner afforded 0.11 g. recovered acid (<2%) and 7.50 g. of crude product as a red oil. 1N sodium hydroxide extraction of 3.75 g. (one half) of the crude product gave 0.56 g. of a phenolic fraction on acidification of the alkaline washes.   The main component of this acidic material was identified spectroscopically to be 1-chloro-2-naphthol, contaminated by benzylphenolic material.   The products neutral to alkali (3.12 g.) when chromatographed on silica gel gave two bands ;

(a)   eluted with benzene :   0.34 g. diphenylmethane

(b)   eluted with benzene/chloroform (1 : 1) :
            1.85 g. ketonic product.

The ketonic product was identified spectroscopically as 2-(1'-chloro-2'-naphthyloxy)acetophenone which recrystallised from ethanol as white plates

$$m.p.\quad 107 - 108^{\circ}\ C.$$

$C_{18}H_{13}ClO_2$ requires: C, 72.85;   H, 4.4;   Cl, 11.95%

found: C, 72.8;   H, 4.7;   Cl, 11.8%

The I.R. spectrum (nujol mull) had ν_{co} 1695 cm.$^{-1}$ and the N.M.R. spectrum (in $CDCl_3$) had inter alia CH_2 at τ 5.01.

The following yields are given and based on actual isolation :

Recovered acid	2%
2-(1'-chloro-2-naphthyloxy)acetophenone	65%
Diphenylmethane	16%

(b)   Reaction of 1-methyl-2-naphthyloxyacetyl chloride (from 3.6 g. of acid) gave a complex mixture of products isolated as a red oil (4.0 g.).   Attempted separation with 1N sodium hydroxide allowed a separation into two fractions (a neutral and acidic one) each apparently containing six or seven components on spectroscopic examination.   On account of practical difficulties and extensive decarbonylation the experiment was abandoned.

iv)   Anomalous reactions.

(a)   Three separate reactions with 6-methoxy-1-naphthyloxy-acetyl chloride on a 1 g. scale or less afforded complex mixtures of products as tars and a low accountability of material. Results were non-reproducible hence the experiments were discontinued.

(b)   Reaction of 5,6,7-trimethoxy-1-naphthyloxyacetyl chloride (from 1.46 g. of acid) in the usual manner afforded a mixture of products where the acid chloride was the main component (ca.85% by N.M.R.).   The mixture was recycled with slightly more than twice the calculated amount of catalyst, otherwise carrying out the reaction and work up procedure as before.   The neutral product – the only material isolated – amounted to only 35 mg. obtained as a brown oil which gave no material of any quantity on silica gel chromatography.

The Cyclisation of 1-Phenanthryloxyacetyl Chloride

The cyclisation of the chloride (from 2.52 g. of acid) was carried out in the normal manner with benzene as solvent, to afford 0.68 g. of a solid product after complete removal of recovered acid (1.76 g., 70%).   Recrystallisation of the product twice from benzene afforded the major product (0.26 g.) in a pure state.   This was identified spectroscopically as benzo[f]-1-oxaphenalen-3(2H)one.

Yield 11%   m.p.   178 - 179° C.

$C_{16}H_{10}O_2$ requires: C, 82.0;   H, 4.3;   O, 13.7%

found: C, 82.0;   H, 4.2;   O, 13.7%

The I.R. spectrum (nujol mull) had ν_{co} 1760 cm.$^{-1}$.   The N.M.R. spectrum (in DMSO) had CH_2 (singlet) at τ5.07 with 11H at τ2.90 and remaining aromatic protons at τ1.1 - 2.7.

The minor component of the product mixture could not be isolated by chromatography on silica gel of the filtrate of the first recrystallisation.   It was not positively identified -

The Cyclisation of 2-(1-Naphthyloxy)isobutyryl Chloride

2-(1-Naphthyloxy)isobutyric acid (9.2 g.) was converted
into its chloride and reacted with aluminium chloride in benzene
in the usual manner.   Sodium bicarbonate extraction of the crude
product after hydrolysis gave no trace of recovered acid, and the
neutral product (8.6 g.) appeared to be a single component.
Recrystallisation from benzene/petroleum ether (b.p. 40 - 80°)
afforded 2,2-dimethylnaphtho [1,2-b] furan-3(2H)one (7.3 g.) as
almost colourless needles.

$$\text{Yield } 86\% \qquad \text{m.p.} \quad 56 - 57^\circ \text{ C.}$$

$C_{14}H_{12}O_2$ requires: C, 79.4; H, 5.75%

found: C, 79.0; H, 5.7%

The I.R. spectrum (CS$_2$) had ν_{co} 1702 cm.$^{-1}$.   The N.M.R.
spectrum (in CDCl$_3$) had CMe$_2$ (singlet) at τ 8.45, 9H at τ 1.73
and remaining aromatic protons at τ 2.1 - 2.9.

Silica gel chromatography of the residue from the filtrate
for recrystallisation (1.25 g.) afforded in order of elution with
benzene :

(a)   5-chloro-2,2-dimethylnaphtho [1,2-b] furan-3(2H)one (45 mg.)
with M = 246 (mass spec.), ν_{co} 1715 cm.$^{-1}$ (CS$_2$).   The
N.M.R. spectrum (in CDCl$_3$) had CMe$_2$ (singlet) at τ 8.43,
4H (singlet) at τ 2.83, 6H and 9H (multiplets) near
τ 1.7 and 7H and 8H (multiplets) τ 2.0 - 2.4.   Yield <1%.

(b)   Major product already isolated by recrystallisation (1.1 g.)
identified spectroscopically.   Total yield of cyclic
ketone 99%

The Cyclisations of 1-Naphthyloxyacetic Acids

1) With Sulphuric Acid

1-Naphthyloxyacetic acid (1 g.) in sulphuric acid* (20 ml.) afforded only water-soluble products on dilution of the reaction mixture and extraction into ether.

* (a) Concentrated sulphuric acid, room temperature for

8, 24 or 48 hours.

(b) 86% w/w sulphuric acid, room temperature for 24

hours, or at 100° C. for 1 hour

2) With Polyphosphoric Acid

1-Naphthyloxyacetic acid (1 g.) was added to PPA (25 g.) and the mixture maintained at 95 - 100° C. for two hours, with occasional stirring. The reaction mixture was diluted with water (200 ml.) and extracted several times with benzene. The combined organic extracts were washed several times with saturated sodium bicarbonate (to recover the acid - 93%), washed with water, dried and the solvent removed under reduced pressure to afford naphtho[1,2-b]furan-3(2H)one (28 mg., 3%) identified spectroscopically (N.M.R. and I.R.)

The yield was increased to 12.5% by increasing the temperature to 120° C. Further increase in temperature or altering the period of reaction to 20 hours gave complex mixtures of neutral products which were not investigated.

The reaction was carried out on a 1 g. scale at 110 - 120° C.
over 3 hours with four substituted 1-naphthyloxyacetic acids and
data are collected below. Product identification was by spectral
comparison with authentic samples.

Acid of (6), R=	Cyclic ketone (9), R=	% yield	% recovery of acid
5-OCH$_3$	6-OCH$_3$	9	81
2-Cl	nil		quantitative
4-Cl	5-Cl	14	71
4-NO$_2$	nil		quantitative

The Interaction of Methoxyphenoxyacetyl Chlorides with Aluminium Chloride in Benzene

1) 3-Methoxyphenoxyacetyl chloride

The chloride, prepared from 3-methoxyphenoxyacetic acid (6.07 g., 0.033 mole) in benzene with rather more than 1 molar equivalent of thionyl chloride, was taken up in dry benzene (20 ml.) and added over 20 minutes to a stirred suspension of anhydrous aluminium chloride (4.87 g., 0.037 mole) in dry benzene (20 ml.) maintained at 5 - 10° C. The mixture was then stirred in the cold for 3 hours.

After hydrolysis with ice and hydrochloric acid over 30 minutes in the usual manner, the organic layer was made up to 200 ml. by addition of benzene, separated from the aqueous acid and extracted several times with saturated sodium bicarbonate solution. Acidification of the bicarbonate extracts gave a trace of recovered acid (13 mg., 0.2%).

The benzene solution on removal of solvent afforded a yellow semi-solid product (5.6 g), the N.M.R. spectrum of which indicated the presence of three separate components (three OCH_3 signals). Recrystallisation from ethanol gave 3.5 g. (64%) of the major product, 6-methoxybenzofuran-3(2H)one. It was identified spectroscopically and had m.p. 93° C. (lit.[14] m.p. 93 - 93.5° C.). It showed no depression in melting point on admixture with an authentic sample.

The filtrate from the recrystallisation on removal of solvent

was taken up in benzene and shaken with methanolic potassium hydroxide solution several times until the alkaline washings displayed no colour. Removal of solvent gave 0.59 g. of material free from the cyclic ketone (absence of its CH_2 resonance in the N.M.R. spectrum). This material in the minimum amount of benzene was applied to a column of silica gel (60 g.) and afforded two bands on elution. Elution with benzene gave a clear oil (compound A) (0.280 g.) which could not be solidified, and chloroform/benzene (1 : 1 by volume) gave a pale yellow solid (0.303 g.) which on recrystallisation from ethanol had m.p. 83 - 85° C. Lit.[84] m.p. for 2-(m-methoxyphenoxy)acetophenone 85 - 86° C. Spectral data confirmed this assignment.

Compound A above was also prepared in two other ways and its identity shown to be 6-methoxy-3-phenylbenzofuran:

(a) Treatment of 6-methoxybenzofuran-3(2H)one (0.82 g.) in dry ether (30 ml.) under Grignard conditions with phenylmagnesium bromide, prepared from bromobenzene (0.8 g.) and magnesium (0.15 g.) in dry ether (20 ml.), afforded an oil (0.98 g.) after acid decomposition. Column chromatography on silica gel (20 g.) gave 0.63 g. of compound A on elution with benzene. Yield 56%.

(b) 2-(m-Methoxyphenoxy)acetophenone (200 mg.) in dry benzene (25 ml.) with finely divided anhydrous aluminium chloride (120 mg.) was heated at reflux for ten minutes. After decomposition with ice and dilute hydrochloric acid, the crude product (182 mg.) was chromatographed on silica gel, benzene eluting compound A (86 mg.)

(yield 50%) and chloroform eluting unchanged starting material (94 mg.)

An experiment similar to (b) directly above gave unchanged ketone when 6-methoxybenzofuran-3(2H)one was used in place of the intermolecular ketone. Hence the benzofuran clearly arises from intramolecular alkylation of the acetophenone in the cyclisation of the acyl chloride.

The following data is recorded in summary for the acylation reaction :

Recovered acid   0.2%

6-Methoxybenzofuran-3(2H)one :

Isolated yield 64% by recrystallisation of crude mixture.
% Composition 92 $\pm$ 2% by integration of crude N.M.R. spectrum.

2-(m-Methoxyphenoxy)acetophenone :

Isolated yield 3.7%. The I.R. spectrum (nujol mull) had ν_{co} 1690 cm.$^{-1}$. The N.M.R. spectrum (in CDCl$_3$) had CH$_2$ (singlet) at τ 4.80, OCH$_3$ (singlet) at τ 6.37 with aromatic region (eight protons) between τ 1.9 and 3.6.

6-Methoxy-3-phenylbenzofuran :

Isolated yield 3.7%. The N.M.R. spectrum (in CDCl$_3$) had OCH$_3$ (singlet) at τ 6.20 with complex aromatic region (ten protons) between τ 2.3 and 3.8 where only the 2H (singlet) was apparent at τ 2.35.

2) <u>4-Methoxyphenoxyacetyl chloride</u>.

4-Methoxyphenoxyacetyl chloride, prepared from 6.90 g.
(0.038 mole) of the acid with rather more than 1 equivalent of
thionyl chloride in benzene, was reacted with aluminium chloride
(11.0 g., 0.082 mole) in dry benzene (total volume 90 ml.) in
the usual manner. After decomposition and hydrolysis,
saturated sodium bicarbonate extraction led to recovery of the
acid (0.44 g., 6.4%), identified by I.R. spectroscopy. The
benzene solution was extracted with normal sodium hydroxide
solution (3 x 100 ml.) and then with methanolic potassium hydroxide
solution (3 x 100 ml.).

Acidification of the aqueous sodium hydroxide extracts gave
phenolic material (1.85 g.) shown by quantitative N.M.R.
spectroscopy to be a mixture of p-methoxyphenol (0.96 g.) and
benzylphenolic material (0.89 g.). The combined methanolic
potassium hydroxide extracts on acidification and extraction into
benzene gave a mixture (1.08 g.) subsequently identified from the
N.M.R. spectrum by integration as mostly 2-benzyl-4-methoxyphenol
(0.78 g.) and 2-(p-methoxyphenoxy)acetophenone (0.30 g.)

The neutral material (5.74 g.) from the organic layer on
removal of solvent was chromatographed in benzene on silica gel.
Benzene eluted diphenylmethane (1.38 g.), identified
spectroscopically, and chloform eluted the only other material
2-(p-methoxyphenoxy)acetophenone (4.30 g.)

The composition of the crude reaction mixture after hydrolysis

was as follows :

    Recovered acid   6.4%

    p-Methoxyphenol   20%

    2-Benzyl-4-methoxyphenol   21%

    Diphenylmethane   22% (isolated yield)

    2-(p-methoxyphenoxy)acetophenone 49% (isolated yield 44%)

    Material accounted for   95.4 $\pm$ 1%.

Notes:

1. 5-Methoxybenzofuran-3(2H)one was not detected in the work up procedure confirming its apparent absence in the crude reaction mixture by comparing the latter's N.M.R. spectrum with that of an authentic sample of the cyclic ketone.

2. The above data refers to an experiment where the acid chloride and aluminium chloride were in a molar ratio of 1 : 2.2. A previous experiment with a molar ratio of 1 : 1.1 under exactly similar conditions led to a much higher recovery of acid (29%). The crude reaction mixtures after removal of the unreacted acid chloride as the acid after hydrolysis were, however, similar in composition as inferred by comparison of their N.M.R. spectra.

3. 2-(p-Methoxyphenoxy)acetophenone :

        m.p. 65 - 67 $^{\circ}$C.   lit.[117] m.p. 67 $^{\circ}$C.

The I.R. spectrum (nujol mull) had ν_{co} 1690 cm.$^{-1}$. The N.M.R. spectrum (in $CDCl_3$) had CH_2 (singlet) at τ4.82 and

OCH_3 (singlet) at $\tau\,6.27$ with a singlet at $\tau\,3.16$ for the four protons in the disubstituted aromatic ring.

4.   2-Benzyl-4-methoxyphenol :

m.p. 75 – 77° C. (petroleum ether, b.p. 60 – 80°)

lit.[115] m.p. 77° C.

3)   <u>2-Methoxyphenoxyacetyl Chloride</u>

Interaction of the chloride, prepared from the acid (7.3 g., 0.04 mole), with aluminium chloride (5.9 g., 0.045 mole) in benzene (100 ml. total) afforded a mixture of products (2.5 g.) after complete removal of the aryloxyacetic acid (5.0 g., 68%).

1N Sodium hydroxide extraction of the product mixture afforded 0.61 g. of a phenolic fraction shown by quantitative evaluation of the N.M.R. spectrum to be a mixture of o-methoxy-phenol (0.26 g.) and benzylphenolic material (0.35 g.).   Silica gel chromatography of the neutral material afforded on elution with benzene, in order :

i)	diphenylmethane	0.34 g.
ii)	2-benzyl-6-methoxyphenol	0.30 g.
iii)	a mixture of benzylphenols	0.05 g.
iv)	a mixture	1.20 g.

The mixture from fraction iv) was not able to be separated into components on re-chromatography, but afforded 2-(o-methoxy-phenoxy)acetophenone (0.83 g.) on recrystallisation from ethanol.

From the data collected the proportion of products present
in the crude reaction mixture after hydrolysis is :

Recovered acid	68%
diphenylmethane	5%
o-methoxyphenol	5%
total benzylphenolic material	8%
2-(o-methoxyphenoxy)acetophenone	9%
materal unable to be accounted for	10%

Note:

2-(o-methoxyphenoxy)acetophenone :

m.p. 101 - 103° C.   lit.[116] m.p. 101° C.

The I.R. spectrum (nujol mull) had ν_{co} 1685 cm.$^{-1}$.

The N.M.R. spectrum had inter alia CH$_2$ (singlet)
at τ 4.70 and OCH$_3$ at τ 6.18.

The Preparation and Rearrangement with Aluminium Chloride of Aryl Benzyl Ethers

1) Preparation

The three isomeric benzyl monomethoxyphenyl ethers were prepared in the following manner :

The methoxyphenol (13.6 g., 0.11 moles) was added to an ethoxide solution prepared from finely cut sodium (2.5 g., 0.11 moles) in ethanol (100 ml.). Benzyl chloride (12.6 g., 0.1 mole) in ethanol (100 ml.) was added in one lot and the solution kept at room temperature overnight. The following day the mixture was concentrated by removal of most of the solvent by distillation and 2N sodium hydroxide solution added to the cooled residue. The neutral products were extracted into ether and the residue from the organic layer gave on distillation under reduced pressure, or on recrystallisation from petroleum ether (b.p. 60 - 80°) a pure sample of the aryl benzyl ether. N.M.R. spectral data, yields etc. are recorded in the following table.

Aryl benzyl ether (16), R =	m.p. or b.p. (°C.) obs. lit.	Yield[d] %	N.M.R.Spectrum ($CDCl_3$)		
			C_6H_5	CH_2	OCH_3
$2\text{-}OCH_3$	58- 59 62[a]	65	2.65	4.92	6.19
$3\text{-}OCH_3$	173-178/ at 12mm.Hg. [b]	73	2.78	5.17	6.43
$4\text{-}OCH_3$	68- 70 71[c]	81	2.67	5.03	6.31

Notes:

a. Reference 119

b. Oil with b.p. 120-125° C./0.2mm. recorded in reference 120

c. Reference 121

d. Yield after purification.

2) <u>Interaction of aryl benzyl ethers with aluminium chloride</u>
       <u>in benzene</u>

   i) Benzyl 4-methoxyphenyl ether

   To a stirred suspension of aluminium chloride (4.8 g., 0.037 moles) in dry benzene (40 ml.) at 5 - 10° C. was added a solution of benzyl p-methoxyphenyl ether (7.13 g., 0.033 moles) in benzene (40 ml.) over 30 minutes.   The reaction mixture was stirred at 5 - 10° C. for 2 hours, then hydrolysed by stirring with ice and dilute hydrochloric acid over 30 minutes.   The organic layer on separation and evaporation of solvent gave 9.0 g. crude product as a dark red oil, the N.M.R. spectrum of which showed total absence of starting benzyl ether.

   The crude product in benzene (200 ml.) was washed thoroughly with 1N sodium hydroxide solution (3 x 100 ml.) and then with methanolic potassium hydroxide solution (3 x 100 ml.).

   Acidification of the combined sodium hydroxide extracts gave a single product (3.03 g.) identified by I.R. and N.M.R. spectroscopy as p-methoxyphenol.

   The combined alcoholic potassium hydroxide washes on

acidification and extraction with benzene yielded 1.91 g. of an almost colourless oil which solidified readily on standing. The N.M.R. spectrum of this material was consistent with it being a benzylphenol and recrystallisation from petroleum ether (b.p. 60 - 80°) gave white needles of m.p. 76 - 77° C. Lit.[115] m.p. for 2-benzyl-4-methoxyphenol, 77° C.

The benzene layer, which had been exhaustively extracted with strong alkali, gave on evaporation of solvent a clear oil (3.99 g.), the N.M.R. and I.R. spectra of which were identical with an authentic sample of diphenylmethane.

ii) The above reaction conditions and product isolation procedures were extended to both o- and m-methoxyphenyl benzyl ether and the results obtained collected below

Aryl benzyl ether. (16), R =	Recovered ether %	Diphenylmethane %	Phenol %	Benzylphenol %
2-OCH$_3$	0	59	53	39[a]
3-OCH$_3$	0	57	56	41[b]
4-OCH$_3$	0	71	73	27[c]

Notes:

a. The proportion of benzylphenolic material allows for a small amount removed by the dilute alkaline wash (17% by wt. from the N.M.R. spectrum). Furthermore a mixture of benzylphenols

for 15 minutes after which time the excess lithium aluminium
hydride was decomposed by addition of ethyl acetate.   Water was
added and the organic phase separated and dried.   Evaporation of
the solvent under reduced pressure afforded a crude product which
was chromatographed on silica gel.   Benzene eluted 1-oxaphenalen-
3(2H)one which recrystallised from petroleum ether (b.p. 60 - 80°)
as small yellow plates (0.38 g.).   _ Yield 48%

m.p.   102.5 - 103° C.

$C_{12}H_8O_2$ requires :   C, 78.25 ;   H, 4.4 %

found   :   C, 78.0 ;   H, 4.5 %

The I.R. spectrum (CS_2) had ν_{co} 1700 cm.$^{-1}$.   The N.M.R.
spectrum (in $CDCl_3$) had, inter alia, CH_2 at τ 5.11 and 9H at
τ 2.90.

NOTE:

Hydrolysis in ethanol with 20% aqueous sodium hydroxide at
0° C. for 2-5 seconds afforded mixtures of products on acidification
and extraction into ether.   The above procedure was found to give
a better conversion to the ketone.

5)   6-Methoxy-1-oxaphenalen-3(2H)one.

1,5-Dimethoxynaphthalene (4.7 g., 0.025 mole) in carbon
disulphide (25 ml.) containing anhydrous aluminium chloride
(3.6 g., 0.027 mole) was treated dropwise with chloroacetyl
chloride (2.8 g., 0.025 mole) in carbon disulphide (10 ml.) over
15 minutes.   The mixture was refluxed overnight and the following

day the solvent was removed under reduced pressure. The semi-solid residue was broken up by addition of ice-cold dilute hydrochloric acid and benzene, and the organic layer separated, washed with water, and evaporated to afford a crude product (4.9 g.), as a brown viscous oil.

The N.M.R. spectrum indicated that the product was a mixture and recrystallisation twice from petroleum ether (b.p. 60 - 80°), in which the bulk of the material was insoluble when hot, afforded the minor component (0.65 g.) identified as 6-methoxy-1-oxaphenalen-3(2H)one.

$$\text{Yield} \quad 12\% \qquad \text{m.p.} \quad 72 - 73° \text{ C.}$$

$C_{13}H_{10}O_3$ requires: C, 72.9; H, 4.7%

found: C, 72.9; H, 4.9%

The I.R. spectrum (CS_2) had ν_{co} 1703 cm.$^{-1}$. The N.M.R. spectrum (in $CDCl_3$) had CH_2 (singlet) at τ 5.17 and OCH_3 (singlet) at τ 5.96. All aromatic protons were clearly visible: 4H at τ1.88, 5H at τ3.11, 7H at τ2.15, 8H at τ2.59 and 9H at τ2.91. $J_{4,5}$ 8.1 c.p.s., $J_{7,8}$ 8.2 c.p.s., $J_{8,9}$ 7.5 c.p.s. and $J_{7,9}$ 1.3 c.p.s.

Acetylation and Rearrangement Reactions

1) Acetylation of Dimethoxynaphthalenes in benzene

The dimethylether (9.4 g., 0.05 mole) in dry benzene (25 ml.) containing anhydrous aluminium chloride (7.3 g., 0.055 mole) was stirred at $<10°$ C. and acetyl chloride (3.9 g., 0.05 mole) in dry benzene (15 ml.) introduced dropwise over 15 minutes. The reaction mixture was stirred in the cold for 2.5 hours with the exclusion of moisture and then decomposed in the usual manner. The crude product was examined by N.M.R. spectroscopy and recrystallised, generally once, from petroleum ether (b.p. 60 - 80°) to provide the acetyl derivative in a pure state. The following data are collected in tabulated form :

Substituted dimethoxynaphthalene	Position[a] acetylated	% Yield after purification	m.p. (°C.) obs.	lit.(ref.)
1, 5	4	74	94-95	96[137]
2, 3	6	67	108-109	109[106]
1, 7	4	76	66-67.5	67[138]
2, 7	1	68	62-63	(b)

Notes:

(a) Only in the acetylation of 2,7-dimethoxynaphthalene was there evidence of a second acetylation product from comparison of the N.M.R. spectrum of the crude product with those of the purified material and starting material.

(b) Buu-Hoi and Lavit [95] record m.p. 65° C. for the product
of acetylation in nitrobenzene and indicate substit-
ution at the 3-position.

The following N.M.R. spectral data are recorded for the
acetyl derivatives :

4-Acetyl-1,5-dimethoxynaphthalene (in $CDCl_3$).

OCH_3 (singlets) at $\tau 6.00$ and 6.08; $COCH_3$ (singlet at
$\tau 7.57$; 2H at $\tau 3.21$; 3H at $\tau 2.78$, 6H at $\tau 3.08$,
7H at $\tau 2.57$ and 8H at $\tau 2.06$. $J_{2,3}$ 8.0 c.p.s.,
$J_{6,7}$ 7.3 c.p.s., $J_{7,8}$ 8.5 c.p.s. and $J_{6,8}$ 1.2 c.p.s.

6-Acetyl-2,3-dimethoxynaphthalene (in $CDCl_3$).

OCH_3 (singlets) superimposed at $\tau 6.28$; $COCH_3$ (singlet)
at $\tau 6.43$; 1H and 4H at $\tau 2.91$ and 2.99 (or vice versa),
5H at $\tau 1.80$, 7H at $\tau 2.15$ and 8H at $\tau 2.43$.
$J_{7,8}$ 8.4 c.p.s. and $J_{5,7}$ 1.4 c.p.s.

1-Acetyl-4,7-dimethoxynaphthalene (in CS_2).

OCH_3 (singlets) at $\tau 6.16$ and 6.25; $COCH_3$ (singlet) at
$\tau 7.55$; 2H at $\tau 2.42$, 3H at $\tau 3.55$, 5H at $\tau 2.66$, 7H at
$\tau 2.94$ and 7H at $\tau 1.15$. $J_{2,3}$ 8.2 c.p.s., $J_{7,8}$ 9.2 c.p.s.
and $J_{6,8}$ 2.7 c.p.s.

1-Acetyl-2,7-dimethoxynaphthalene (in $CDCl_3$).

OCH_3 (singlets) at $\tau 6.10$ and 6.15; $COCH_3$ (singlet) at
$\tau 7.37$; 3H at $\tau 2.95$, 4H at $\tau 2.27$, 5H at $\tau 2.38$,
6H at $\tau 2.97$ and 8H at $\tau 2.82$. $J_{3,4}$ 9.0 c.p.s.,
$J_{5,6}$ 8.7 c.p.s. and $J_{6,8}$ 2.4 c.p.s.

2) <u>Acetylation of 2,7-dimethoxynaphthalene in nitrobenzene</u>.

i) Acetylation of 2,7-dimethoxynaphthalene (2.7 g.) according to the method of Buu-Hoi[95] in nitrobenzene for 14 hours (final addition of catalyst) afforded a product on recrystallisation from petroleum ether (b.p. 60 - 80°) identical to that obtained from the 2.5 hour run in benzene. (The nitrobenzene was removed by steam distillation after decomposing the reaction mixture).

The N.M.R. spectrum of the crude product indicated that the 3-acetyl derivative was present to the extent of only ca. 15 - 20% of the ketonic products and that the major product was the 1-acetyl derivative.

ii) A similar experiment to i) above was set up and left at room temperature for several days. At suitable intervals a small sample was withdrawn and worked up in the usual manner and the product examined by N.M.R. spectroscopy, (see figure 2 - facing page 116A). After 18 days the reaction mixture was decomposed and worked up in the usual manner to afford a brown oil. This oil was extracted with a small amount of cold benzene and the benzene soluble residue on removal of the solvent recrystallised from petroleum ether (b.p. 60 - 80°). The crystalline solid obtained, on spectroscopic examination was seen to be a mixture of products and so too was a further quantity of solid material obtained on concentration of the filtrate.

The N.M.R. spectra (in $CDCl_3$) of these products indicated that the components were :

(a) 2-acetyl-3,6-dimethoxynaphthalene with OCH_3 (singlets) at τ6.04 and 6.10; $COCH_3$ (singlet) at τ7.35;   1H at τ1.87, and 8H at τ2.30. $J_{7,8}$ 9.8 c.p.s.

(b) 2-acetyl-3-hydroxy-6-methoxynaphthalene with $COCH_3$ (singlet) at τ7.30, 8H at τ1.80 and OH at τ-1.7.

3) <u>Fries rearrangement of 7-methoxy-2-naphthol acetate</u>

The acetate (2 g.), previously prepared from the naphthol with acetic anhydride/acetic acid, was added to a suspension of aluminium chloride (1.4 g.) in nitrobenzene (35 ml.) and the mixture stirred for 2 hours at room temperature.   After decomposing the reaction mixture, acidic products were extracted into 2N sodium hydroxide and obtained on acidification (1.8 g.). N.M.R. spectroscopic examination of the acidic material inferred a mixture of 1-acetyl-2-hydroxy-7-methoxynaphthalene (82%) and 7-methoxy-2-naphthol (18%).

Repeating the reaction at 100 - 110° C. over 1 hour gave a mixture (1.9 g.) of 1-acetyl-2-hydroxy-7-methoxynaphthalene ($>$95%) and 2-acetyl-3-hydroxy-6-methoxynaphthalene ($<$ 5%) from spectroscopic examination.

In neither experiment was product separation attempted.

4) Attempted synthesis of 2-acetyl-3,6-dimethoxynaphthalene

   i) Preparation of 3,6-dimethoxy-2-naphthoic acid.

   2,7-Dimethoxynaphthalene (18.8 g.) on treatment with
n-butyllithium in ether and carbonation according to the method
of Sunthankar and Gilman[98] gave 4.6 g. (20%) of 3,6-dimethoxy-2-
naphthoic acid on recrystallisation from benzene.

   m.p. 183 - 184° C.   lit. m.p. 185.5° C.

   The N.M.R. spectrum (in DMSO) had OCH_3 (singlets) at $\tau6.06$
and 6.11, 1H at $\tau1.76$, 4H at $\tau2.63$, 5H at $\tau2.70$, 7H at $\tau2.92$,
and 8H at $\tau2.13$. $J_{7,8}$ 9.0 c.p.s. and $J_{5,7}$ 2.5 c.p.s.

   ii) The above acid (3.3 g.) was converted into the acid chloride
by refluxing for several hours in excess thionyl chloride and
reacted in benzene with dimethylcadmium (four molecular proportions)
at reflux for 1.3 hours.   Decomposition of the reaction mixture
with ice/dilute sulphuric acid gave a quantity of solid (2.2 g.)
identified as the starting acid and an oil (1.2 g.).   Spectral
examination of the oil indicated it to be a complex mixture where
the expected product, 2-acetyl-3,6-dimethoxynaphthalene, appeared
to be absent.

   A similar mixture was obtained on re-cycling the recovered
acid, and the synthesis was abandoned.

5) Rearrangement of 1-acetyl-2,7-dimethoxynaphthalene

i) In benzene.

Pure 1-acetyl-2,7-dimethoxynaphthalene (2 g.) in dry benzene (15 ml.) was stirred with anhydrous aluminium chloride (1.5 g.) for 48 hours at room temperature. Immediately after setting up the experiment dry hydrogen chloride was bubbled into the reaction mixture for 2 - 3 minutes and again at roughly 8 hourly intervals. The mixture was worked up in the usual way and examined by N.M.R. spectroscopy.

The spectrum indicated that rearrangement had occurred to a small but significant extent. The proportion of acetylated material (from shortage of $COCH_3$ with respect to OCH_3 resonances) was 77% and the amount of rearranged product was 8%.

ii) In nitrobenzene.

The above experiment was repeated in nitrobenzene where a 72% acetylated product mixture was obtained and the amount of rearranged product was calculated to be 21%.

6) Attempted rearrangement of tricyclic ketones.

1-Oxaphenalen-3(2H)one and 8-methoxynaphtho[2,1-b]furan-1(2H)one were each examined for reversibility in benzene as in 5) above. In both cases a quantitative recovery of starting ketone was obtained.

The Interaction of Activated Aromatic Compounds with Thionyl Chloride

1) Reaction with 1,5-dimethoxynaphthalene

1,5-Dimethoxynaphthalene (1 g.) in thionyl chloride (5 ml.) was warmed gently to 30 - 35° C. whereupon an evolution of gas occurred. After 5 minutes the solution was poured on to water to decompose the thionyl chloride and the yellow solid which formed was broken up, filtered at the pump, washed several times with water, and dried. The product was identified as 4-chloro-1,5-dimethoxynaphthalene.

m.p.   116 - 118° C. (d)   lit.[118]   m.p.   122° C.

The mass spectrum gave M = 222 and clearly indicated the presence of chlorine. The N.M.R. spectrum (in DMSO) had OCH_3 (singlets) at $\tau 6.00$ and 6.04 with 2H and 6H at $\tau 2.85$, 3H at $\tau 1.74$, 7H at $\tau 2.50$ and 8H at $\tau 2.13$. $J_{2,3}$ 8.2 c.p.s., $J_{7,8}$ 8.2 c.p.s. and $J_{6,8}$ 1.6 c.p.s.

2) Reaction with 3-methoxyphenoxyacetic acid

3-Methoxyphenoxyacetic acid (2 g.) in excess thionyl chloride was heated at reflux over 2 hours and the excess reagent removed under diminished pressure. The N.M.R. spectrum of the crude product indicated a nearly 1 : 1 mixture of two components and net loss of one aromatic proton. The I.R. spectrum had ν_{co} 1805 cm.$^{-1}$

The esters of the mixture were prepared by refluxing the chlorides in ethanol for 1 hour and after removal of solvent the

product was chromatographed in benzene on silica gel.   No

separation was achieved and the experiment was abandoned.

A similar quantitative ring substitution occurred on refluxing
5-methoxy-1-naphthyloxyacetic acid in excess thionyl chloride.
Although the product was not investigated fully, it was apparent
from the N.M.R. spectrum, however, that an α-position had been
substituted.

BIBLIOGRAPHY

Bibliography

1. B.H. Ingham, H. Stephen and R. Timpe, J. Chem. Soc.,
    1931, 895.

2. N.M. Scollick, Ph. D. Thesis, University of Edinburgh, 1966.

3. S. O'Brien, and D.C.C. Smith, J. Chem. Soc., 1963, 2907.

4. G.J. McVie, Ph. D. Thesis, University of Edinburgh, 1967.

5. M.H. Palmer, and G.J. McVie, J. Chem. Soc.,(B), 1968, 745.

6. M.H. Palmer, and G.J. McVie, J. Chem. Soc.,(B), 1968, 742.

7. M.H. Palmer, and G.J. McVie, Tetrahedron Letters, 1966, 6405.

8. M.H. Palmer, and N.M. Scollick, accepted for publication

9. M.H. Palmer and G.J. McVie, J. Chem. Soc.,(B), 1968, 856.

10. M.H. Palmer, Unpublished work.

11. N. Anand, and K. Venkataraman, Proc. Indian Acad. Sci.,
    1948, 28, 160.

12. G. Haberland, and G. Kleinert, Ber., 1938, 71, 472.

13. C.J.P. Spruit, Rec. Trav. chim., 1948, 67, 285.

14. K. von Auwers, and P. Pohl, Ann., 1914, 405, 243.

15. P. Emmot, and R. Livingstone, J. Chem. Soc., 1958, 4629.

16. D. Alderson, and R. Livingstone, J. Chem. Soc., (C), 1967,
    1782.

17. J.N. Chatterjea, and K. Prasad, J. Indian Chem. Soc., 1960,
    37, 357.

18. R. Legros, and P. Cagniant, Compt. rend., 1960, 251, 553.

19. P.M.G. Bavin, Canadian J. Chem., 1960, 38, 1227.

20. R. Huisgen, and U. Rietz, Ber., 1957, 90, 2768.

21. R.D. Haworth, and G. Sheldrick, J. Chem. Soc., 1934, 1950.

22. H. Bendas, and C. Djerassi, J. Amer. Chem. Soc., 1956, 78, 2474.

23. A.L. Green, and D.H. Hey, J. Chem. Soc., 1954, 4306.

24. A.J.M. Wenham, and J.S. Whitehurst, J. Chem. Soc., 1956, 3857.

25. L.F. Fieser, and M.D. Gates, J. Amer. Chem. Soc., 1940, 62, 2335.

26. J.W. Cook, and C.L. Hewett, J. Chem. Soc., 1934, 365.

27. A.J.M. Wenham, and J.S. Whitehurst, J. Chem. Soc., 1957, 4037.

28. M.L. Drake, and W.C. McVey, J. Org. Chem., 1939, 4, 464.

29. R.C. Gilmore, Jr., and W.J. Horton, J. Amer. Chem. Soc., 1950, 72, 733.

30. G.A.R. Kon, and F.C.J. Ruzicka, J. Chem. Soc., 1936, 187.

31. G.A.R. Kon, and H.R. Soper, J. Chem. Soc., 1939, 790.

32. J. Lockett, and W.F. Short, J. Chem. Soc., 1939, 787.

33. R. Huisgen, and U. Rietz, Tetrahedron, 1958, 2, 271.

34. W.E. Truce, and G.A. Toren, J. Amer. Chem. Soc., 1954, 76, 695.

35. G.M. Oskengendler, and E.P. Gendrikov, Ukr. Khim. Zh., 1959, 25, 206; Chem. Abs., 1959, 53, 21928.

36. G.M. Oskengendler, and E.P. Gendrikov, U.S.S.R. Patent 110951; Chem. Abs. 1958, 52, 18469.

37. G. Leandri, Gazz. Chim. Ital., 1949, 79, 286.

38. K. Krollpfeiffer, and H. Schultze, Ber., 1923, 56, 1819.

39. E. Runne et al., 1930, U.S. Pat. 1,765,703.

40. M.S. Ahmad, and G. Baddeley, J. Chem. Soc., 1961, 2520.

41. J. Braun, O. Bayer, and L. Cassel, Ber., 1927, 60, 2602.

42. M.F. Ansell, and D.H. Hey, J. Chem. Soc., 1950, 2874.

43. M.H. Palmer, G.J. McVie, and D.S. Leitch, to be published.

44. L.F. Fieser, and C.K. Bradsher, J. Amer. Chem. Soc., 1936, 58, 1738.

45. W.P. Campbell, and D. Todd, J. Amer. Chem. Soc., 1942, 64, 928.

46. H. Hoyer, J. Prakt. Chem., 1934, 139, 94.

47. P.C. Mitter, and S. De, J. Indian Chem. Soc., 1939, 16, 35.

48. C.K. Ingold, and H.A. Piggott, J. Chem. Soc., 1923, 1469.

49. A. Rahman, A.T. Vazquez, and A.A. Khan, J. Org. Chem., 1963, 28, 3571.

50. M.S. Ahmed, and G. Baddeley, J. Chem. Soc., 1961, 2520.

51. D.D. Phillips, J. Amer. Chem. Soc., 1953, 75, 3223.

52. W.E. Bachmann, and W.S. Struve, J. Org. Chem., 1939, 4, 456.

53. D. Cook, Canadian J. Chem., 1959, 37, 48.

54. G.A. Olah, S.J. Kuhn, W.S. Tolgyesi, and E.B. Baker, J. Amer. Chem. Soc., 1962, 84, 2733.

55. P. Pfeiffer, Organische Molekulverbindungen, Ferdinand Enke, Stuttgart, 1927.

56. H. Meerwein, and H. Maier-Huser, J. Prakt. Chem., 1932, 51, 134.

57. R. Bolton, J. Chem. Soc., (B), 1968, 712 and 714.

58. R. Lesser, and G. Gad, Ber., 1923, 56, 963.

59. E.R. Ward , and T.M. Coulson, J. Chem. Soc., 1954, 4545.

60. D.C. Morrison, J. Org. Chem., 1962, 27[1], 296.

61. "Studies in Chemical Structure and Reactivity", J.H. Ridd (ed.), London, Methven, 1966.

62. A. Fischer, A.J. Read, and J. Vaughan, J. Chem. Soc., 1964, 3691.

63. D.H. Rosenblatt, M.M. Nachlas, and A.M. Seligman, J. Amer. Chem. Soc., 1958, 80, 2463.

64. J. Franzen, and K. Stauble, J. Prakt. Chem., 1921, 103, 352.

65. H.H. Hodgson, and R.L. Elliot, J. Chem. Soc., 1934, 1705.

66. A. Bryson, and R.W. Matthews, Aust. J. Chem., 1963, 16, 401.

67. T. Zincke, Ber., 1888, 21, 1027.

68. N.V. Hayes, and G.E.K. Branch, J. Amer. Chem. Soc., 1943, 65, 1555.

69. F.H. Lees, and F.H. Shedden, J. Chem. Soc., 1903, 83, 758.

70. G. Bargellini, Gazz. Chim. Ital., 1906, 36_2, 334.

71. C.W. Haigh, M.H. Palmer, and B. Semple, J. Chem. Soc., 1965, 6004.

72. H.S. Choguill and J.H. Ridd, J. Chem. Soc., 1961, 822.

73. J.B. Shoesmith, A.C. Hetherington, and R.H. Slater, J. Chem. Soc., 1924, 121, 1312 and 2278.

74. V. Gold, and M. Whittaker, J. Chem. Soc., 1951, 1184.

75. M. Orchin, L. Reggel, and R.A. Friedel, J. Amer. Chem. Soc., 1949, 71, 2743.

76. N.N. Woroshtzow, and V.A. Koptyug, Zhur. Obshchei Khim. (1958), 28, 2981.

77. J.E. Davies, F.E. King, and J.C. Roberts, Chem. and Ind., 1954, 1110.

78. J.E. Davies, F.E. King, and J.C. Roberts, J. Chem. Soc., 1955, 2782.

79. P.C. Mitter, and S. De, J. Indian Chem. Soc., 1939, 16, 35.

80. O. Brunner, and P. Hanke, Monatsh., 1954, 85, 88.

81. G. Schroeter, Ann., 1922, 426, 17.

82. "Naphthalene Compounds" p. 32 - 36. N. Donaldson, London, Edward Arnold, 1958.

83. R.D. Haworth, B.P. Moore, and P.L. Pauson, J. Chem. Soc., 1949, 3271.

84. W. Baker, A. Pollard, and R. Robinson, J. Chem. Soc., 1929, 1470.

85. C.D. Hurd, and S. Hayao, J. Amer. Chem. Soc., 1954, 76, 5065.

86. K.H. Bell, and H. Duewell, Aust. J. Chem., 1963, 16, 101.

87. J.D. Loudon, and R.K. Razden, J. Chem. Soc., 1954, 1470.

88. G. Ullmann, Ber., 1897, 30, 1466.

89. V. Balasubramaniyan, Chem. Rev., 1966, 66, 567.

90. A.J. Birch, M. Salahud-Din, and D.C.C. Smith, J. Chem. Soc., (C), 1966, 523.

91. F. Ullmann, and E. Cassirer, Ber., 1910, 43, 439.

92. A.P. Karishinin, and D.M. Kustol, J. Gen. Chem., (U.S.S.R.), 1959, 1898.

93. H.G. Rule, and A.J.G. Barnett, J. Chem. Soc., 1932, 2728.

94. "Friedel-Crafts and Related Reactions", (Vol. 3, Part 1), G.A. Olah (ed.), Interscience, 1964.

95. N.P. Buu-Hoi, and D. Lavit, J. Chem. Soc., 1956, 1743.

96. R.B. Girdler, P.H. Gore, and J.A. Hoskins, J. Chem. Soc., (C), 1966, 181.

97. L. Novak, and M. Protiva, Chem. listy, 1956, 50, 1610.

98. S.V. Sunthankar, and H. Gilman, J. Org. Chem., 1951, 16, 8.

99. P.H. Gore, Chem. Rev., 1955, 55, 229.

100. W. Borsche, P. Hofmann, and H. Kuhn, Ann., 1943, 554, 23.

101. P.H. Gore, J. Ord. Chem., 1957, 22, 135.

102. P.H. Gore, and J.A. Hoskins, J. Chem. Soc., 1964, 5666.

103. R.P. Linstead, Ann. Reports, 1937, 35, 254.

104. F.R. Jensen, J. Amer. Chem. Soc., 1957, 79, 1226.

105. R.B. Girdler, P.H. Gore, and J.A. Hoskins, J. Chem. Soc., (C), 1966, 518.

106. N.P. Buu-Hoi, and D. Lavit, J. Org. Chem. 1956, 21, 21.

107. H. Kast, Ber., 1911, 44, 1337.

108. D.T. Mowry, M. Renoll, and W.F. Huber, J. Amer. Chem. Soc.,
            1946, 68, 1105.

109. F.H. Burkitt, C.A. Coulson, and H.C. Longuet-Higgins,
            Trans. Faraday Soc., 1951, 47, 554.

110. D.W.T. Cruickshank, Acta Cryst., 1957, 10, 504.

111. K.B. Everard, and L.E. Sutton, J. Chem. Soc., 1949, 2312.

112. N.P. Buu-Hoi, and D. Lavit, J. Chem. Soc., 1955, 2776.

113. H.E. Armstrong, and E.C. Rossiter, Chem. News, 1889,
            59, 225.

114. C.S. Barnes, D.J. Collins, J.J. Hobbs, P.I. Mortimer, and
            W.H.F. Sasse, Aust. J. Chem.,
            1967, 20, 699.

115. W.F. Short, and M.L. Stewart, J. Chem. Soc., 1929, 553.

116. I. Lazennec, Bull. Soc. chim. France, 1909 4, 5, 501.

117. K.K. Thomas, and M.M. Bokadia, J. Indian Chem. Soc.,
            1966, 43, 713.

118. R.H. Thomson, J. Org. Chem., 1948, 12, 192.

119. L. Claisen, Ann., 1925, 442, 210.

120. K. Freudenberg, and J.M.A. de Lama, Ann., (1958), 612, 78.

121. J.C. Smith, J. Chem. Soc., 1931, 251.

122. E.B. Barnett, and F.G. Saunders, J. Chem. Soc., 1933, 434.

123. S. De in Chem. Abs., 1937, 31, 3896[9]

124. J.A. Corran, and W.B. Whalley, J. Chem. Soc., 1958, 4719.

125. E.L. Martin, J. Amer. Chem. Soc., 1936, 58, 1438.

126. J. Moszew, and T. Wachalewski, Roczniki Chem. 1960, 34, 1387.

127. L. Haskelberg, J. Org. Chem., 1947, 12, 426.

128. K. Auwers, and K. Haymann, Ber., 1894, 27, 2795.

129. A.W. Gilbody, W.H. Perkin, and J. Yates, J. Chem. Soc., 1901, 79, 1396.

130. C.F. Koelsch, J. Amer. Chem. Soc. 1931, 53, 304.

131. P.R. Wells, and E.R. Ward, Chem. and Ind., 1958, 36, 1172.

132. A.P. Lurie, G.H. Brown, J.R. Thistle, and A. Weissberger, J. Amer. Chem. Soc., 1961, 83, 5015.

133. R.J.W. Byrde, D.F. Downing, and D. Woodcock, Biochem. J., 1959, 72, 344.

134. L.F. Fieser, J. Amer. Chem. Soc., 1929, 51, 2460.

135. J. von Braun, Ann., 1927, 451, 1.

136. M. Tanaka, T. Kishi, and Y. Maruta, J. Antibiotics (Japan), 1959, Ser. B 12, 361 : through Chem. Abs. 1960, 54, 9856[d].

137. N.P. Buu-Hoi, and D. Lavit, J. Org. Chem., 1955, 20, 1191.

138. N.P. Buu-Hoi, and D. Lavit, J. Chem. Soc., 1956, 1743.

ABSTRACT OF THESIS.

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Title of Thesis ...... STUDIES IN CYCLISATION REACTIONS: THE PREPARATION OF TRICYCLIC ....
...... KETONES BY INTRAMOLECULAR ACYLATION. ....

The interaction of some twenty-four aryloxyacetyl chlorides and in particular 1- and 2-naphthyloxyacetyl chlorides, under Friedel-Crafts conditions with aluminium chloride in benzene has been investigated.

'Angular' cyclisation to the naphtho[1,2-b]furan-3(2H)one has been confirmed to be the dominant reaction of 1-naphthyloxyacetyl chloride and demonstrated to occur with seven nuclear substituted derivatives with electron releasing substituents, as well as with the side chain alkylated 2-(1-naphthyloxy)-isobutyryl chloride. Chlorides with -E, -M groups, however, acylate the solvent and peri ring closure has been confirmed to occur when the 2-position is blocked by halogen.

2-Naphthyloxyacetyl chloride cyclises to the 'angular' ketone, naphtho[2,1-b]furan-1(2H)one, and similar 2,1 ring closure has been shown to occur with 7- and 8-substituted derivatives, with no trace of the isomeric 'linear' ketones. 1- Substituted acid chlorides in this series do not undergo intramolecular acylation, but acylate the solvent and eliminate carbon monoxide to give rise to divers alkylation products.

1-Phenanthryloxyacetyl chloride has been shown to ring close to the 6-membered ring peri condensed ketone and not to the 5-membered ring product.

An attempt has been made to rationalise these results in terms of steric, electronic and conformational effects.

The present investigation has also included a study of the three isomeric monomethoxyphenoxyacetyl chlorides and it has been shown that while the substituent at the 3-position gives rise to exclusive acylation with cyclisation dominant, a methoxyl group in the 2- or 4- positions promotes extensive decarbonylation and these latter reactions are not accompanied by ring closure.

The acetylation of four dimethoxynaphthalenes in benzene has been examined and a reversible system demonstrated to operate in the acetylation of 2,7-dimethoxynaphthalene with aluminium chloride in benzene or nitrobenzene.

An improved synthesis of 3-iodo-1-naphthol, prepared in admixture with 3-chloro-1-naphthol, is reported together with a means of product separation.

Finally, the preparation of 1-oxaphenalen-2(2H)one and its 6-methoxy-derivative have been carried out. A synthesis of the former has since been independently recorded in the literature.

Use other side if necessary.