ORTHO — GROUP INTERACTIONS AND

A NOVEL NUCLEOPHILIC SUBSTITUTION.

A Thesis submitted to the University of Glasgow

for the Degree of Doctor of Philosophy

by

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July, 1963. D. M. S.

CONTENTS.

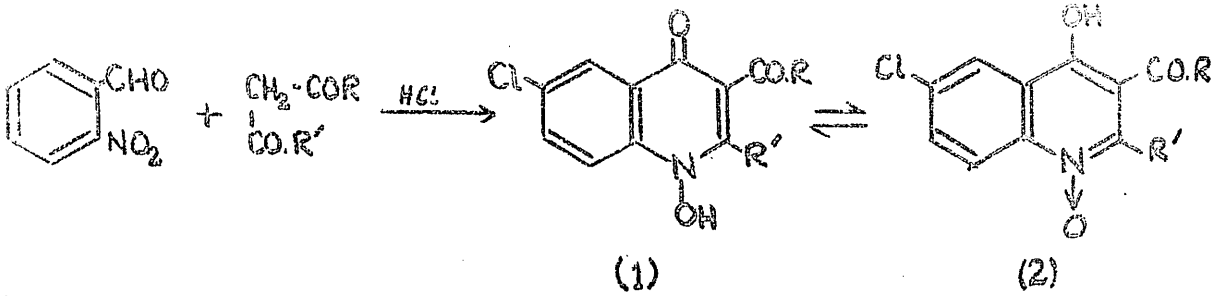
INTRODUCTION.

The synthesis of many benz-fused nitrogen heterocycles involves reduction of an aromatic nitro-compound containing an ortho-side-chain, and ring closure by condensation of the resulting amine with a suitable substituent in the side-chain. An increasingly large number of reactions is coming to light, however, in which the nitro-group appears to act as such with an ortho-side-chain, giving as a rule N-oxygenated heterocycles. Such reactions have been reviewed by Tennant [1], and have attracted a considerable amount of attention at Glasgow over the past few years [1-4].

Continuing the study of the mechanism of one such reaction, the author was led to examine the possibility of similar ortho-group interactions in substituted diaryl sulphoxides. The unusual and interesting problems which arose in the course of this investigation, and the novel reactions which were revealed, form the main subject of this thesis.

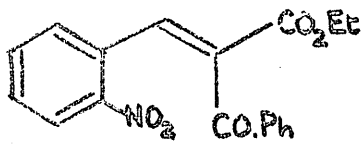
CHAPTER 1.

ORTHO - GROUP INTERACTIONS IN SUBSTITUTED NITROBENZENES.



(1) (2)

(1) : R = OEt, R′ = Me
(3) : R = R′ = Me
(4) : R = OEt, R′ = $CH_2.CO_2Et$
(7) : R = Ph, R′ = Me.



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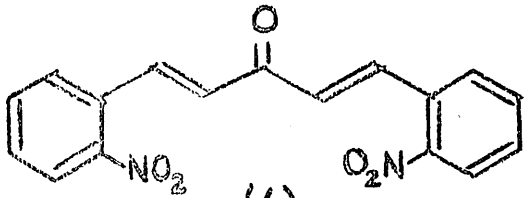

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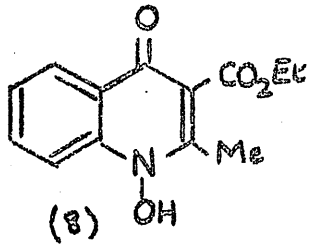

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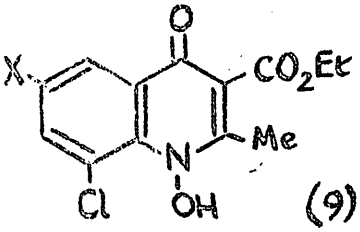

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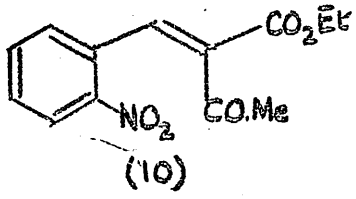

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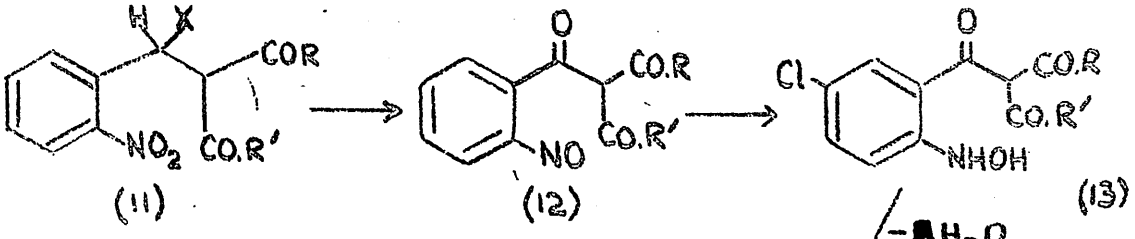

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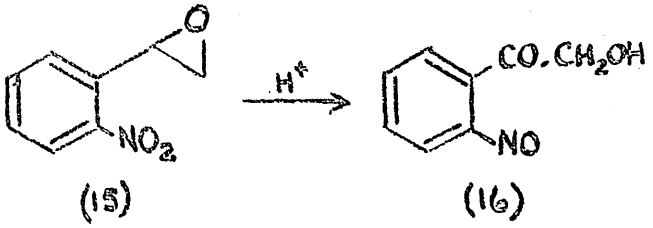

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CHAPTER 1

ORTHO-GROUP INTERACTIONS IN SUBSTITUTED NITROBENZENES.

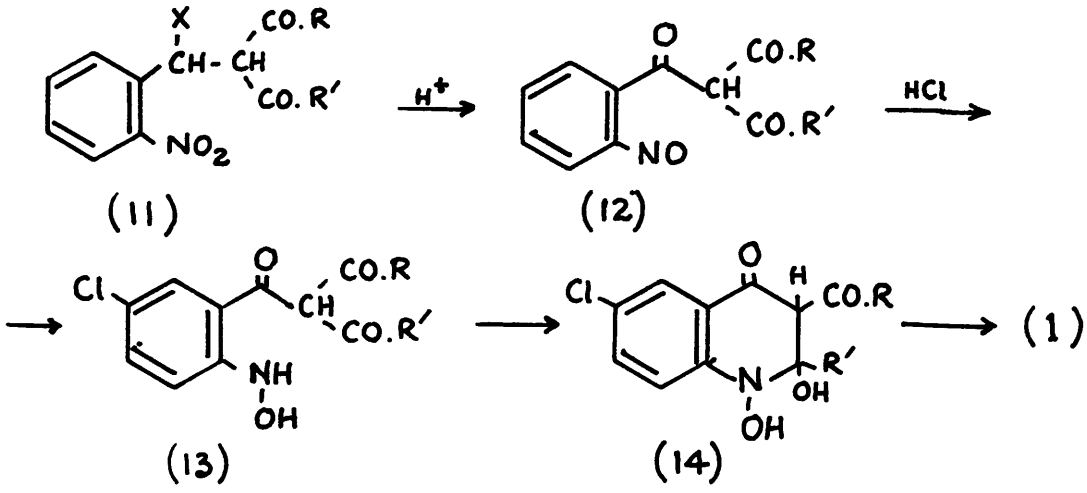
In the course of his research at Glasgow several years ago, Wellings [3] found that condensation of o-nitrobenzaldehyde with ethyl acetoacetate in presence of dry hydrogen chloride gave the 6-chloro-1-hydroxy-4-quinolone derivative (1), which is tautomeric with the 6-chloro-4-hydroxyquinoline-1-oxide (2). Similar reaction of o-nitrobenzaldehyde with acetylacetone and diethyl acetonedicarboxylate gave the corresponding products (3) and (4), but with ethyl benzoylacetate under the same conditions only the o-nitrobenzylidene derivative (5), and with acetone only the di-o-nitrobenzylidene derivative (6), appeared to be formed.

The novelty of these cyclisations, and the problems of establishing a satisfactory mechanism, prompted further inquiry. Tennant [1] showed that ethyl cyanoacetate and benzyl cyanide gave with o-nitrobenzaldehyde and hydrogen chloride only o-nitrobenzylidene derivatives, and drew attention to similar products already reported for reactions of o-nitrobenzaldehyde and dibenzyl ketone [5] and desoxybenzoin [6]. Cyclisation did occur, however, with benzoylacetone as the reactive methylene component in the condensation, and the product was assigned structure (7).

It was further shown by Tennant [1,4] that, when hydrogen bromide was used as condensing agent instead of hydrogen chloride,

halogen-free 1-hydroxy-4-quinolones were obtained: thus o-nitrobenzaldehyde and ethyl acetoacetate yielded (8). Cyclisation without entry of halogen was also observed with hydrogen chloride in presence of hydroquinone. 5-Chloro- and 5-bromo-2-nitrobenzaldehydes and ethyl acetoacetate gave with hydrogen chloride and hydrogen bromide the 6,8-dihalogeno-quinolone (9: X = Cl or Br) and the 6-halogeno-quinolone (1) or (1: Br for Cl) respectively.

The exact mechanism of the cyclisation is unknown, but in many cases o-nitrobenzylidene compounds are isolated together with the quinolone derivatives [4], and also give quinolones by renewed treatment with hydrogen halide: e.g. (10) → (1) with hydrogen chloride. It thus seems likely that o-nitrobenzylidene compounds, e.g. (10), or simply related compounds, e.g. (11: X = OH, Cl), are intermediates in the cyclisation. In the course of the reaction, reduction of the nitro-group and oxidation at the benzylic carbon atom of the side-chain take place. The mechanism proposed by Tennant [1] may be represented as follows:-



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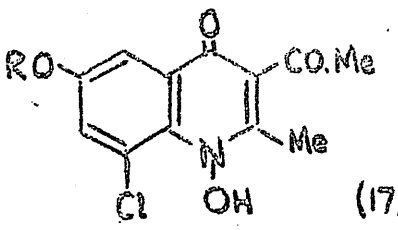

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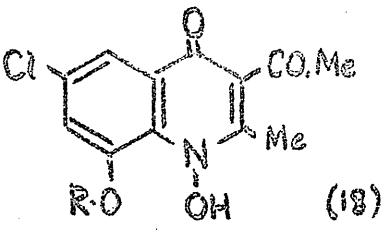

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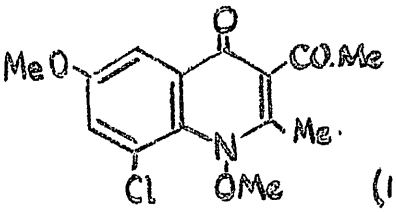

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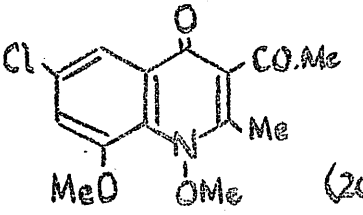

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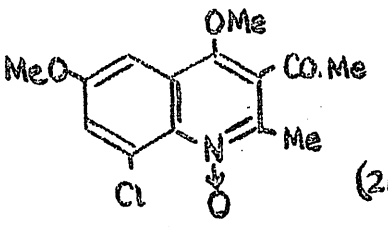

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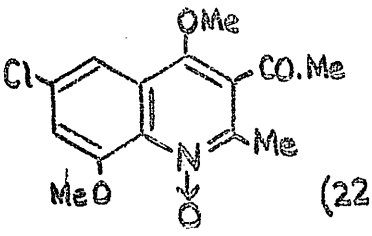

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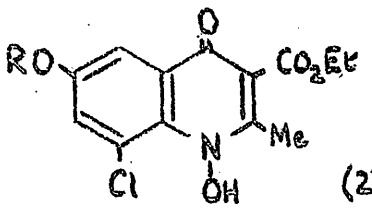

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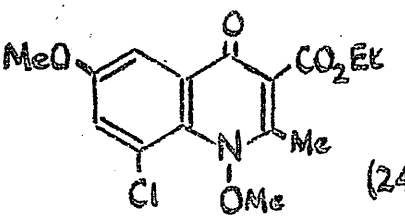

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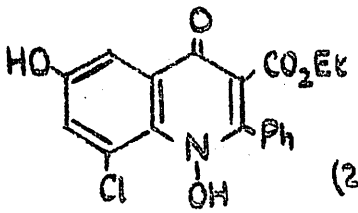

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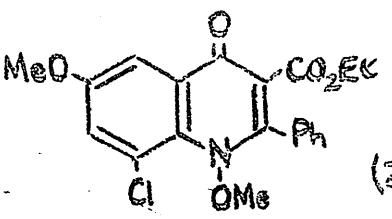

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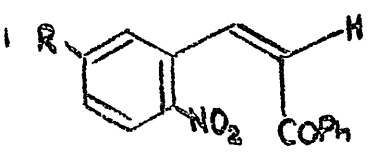
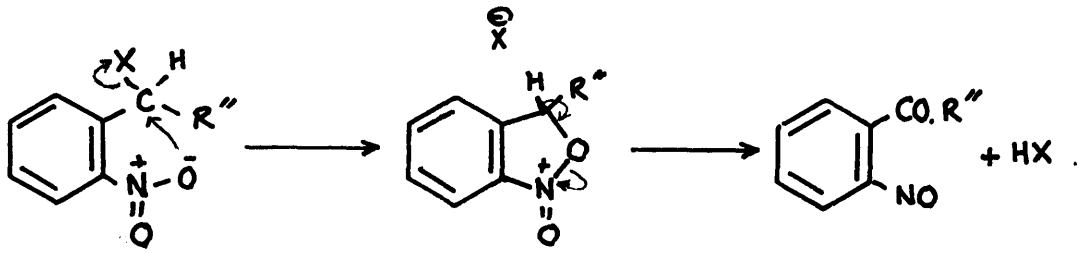


(27)

(or trans-).

An intramolecular oxidation-reduction of the type (11) ⟶ (12), although unusual, is not unknown: for instance, reaction of 2-(o-nitrophenyl)oxiran (15) with acid gives o-nitrosobenzoylcarbinol (16) [7]. Tennant has suggested that reduction of the nitrosoketone (12) to the hydroxylamine (13) is effected directly by hydrogen bromide, whereas this is possible with hydrogen chloride only through entry of chlorine into the aromatic ring, unless hydroquinone is present to provide alternative reducing power.

The oxygen transfer step (11)⟶(12) may conceivably proceed as shown below.



The author's first contribution to the study of this reaction concerned the effect of an electron-donating substituent ortho- or para- to the nitro-group in the nitrobenzaldehyde. It was expected that such electron-release towards the nitro-group would facilitate the reaction (11)⟶(12)⟶(13), and hence the cyclisation step.

5-Methoxy-2-nitrobenzaldehyde [8] reacted readily in ethereal solution with acetylacetone and dry hydrogen chloride, giving the 8-chloro-6-methoxyquinolone derivative (17: R = Me). The position of the chlorine was assigned by analogy with the reaction involving 5-chloro-2-nitrobenzaldehyde [1,4] (see p.4). Similar reaction of 3-methoxy-2-nitrobenzaldehyde [9] gave the 6-chloro-8-methoxy-isomer (18: R = Me). These quinolones gave a red-brown colour with ethanolic ferric chloride, and were converted, on warming with acetic anhydride, into N-acetates with characteristic [3,4] carbonyl absorption in the infra-red at ca. 1800 $cm.^{-1}$.

5-Hydroxy-2-nitrobenzaldehyde [10] reacted still more readily with acetylacetone and hydrogen chloride, the reaction being complete in 2 hours, compared with the 18-hour period normally required. The phenolic product (17: R = H) was unusual in that it was obtained as a stable hydrochloride, which liberated the free base only on treatment with aqueous sodium carbonate.

Owing to the low solubility of 3-hydroxy-2-nitrobenzaldehyde[11] in ether, no appreciable reaction with acetylacetone and hydrogen chloride occurred. Tetrahydrofuran, while a much better solvent, was unsuitable because of its tendency to react with hydrogen chloride, giving 4-chlorobutan-1-ol [12], but dimethylformamide gave no such side-reactions, and in this solvent 3-hydroxy-2-nitrobenzaldehyde and acetylacetone gave with hydrogen chloride the quinolone (18: R = H).

The simple relationship between the hydroxy- and methoxy-quinolones, e.g. between (17: R = H) and (17: R = Me), was verified by methylation. Treatment of the compounds (17: R = H) and (18: R = H), or their hydrochlorides, with diazomethane gave the dimethoxy-derivatives (19) and (20) respectively, compounds also obtained by methylation of (17: R = Me) and (18: R = Me). These dimethoxy-compounds were assigned the 1,6- and 1,8-dimethoxy-4-quinolone structures rather than the possible 4,6- and 4,8-dimethoxyquinoline-1-oxide structures (21) and (22), on the basis of their infra-red spectra, in which strong absorption at ca. 1620 $cm.^{-1}$ is consistent with a 4-quinolone structure [13], and also by analogy with the results of Ochiai and Hayashi [14], who showed that methylation of 1-hydroxy-4-quinolone ($\rightleftharpoons$ 4-hydroxy-quinoline-1-oxide) by diazomethane gave primarily 1-methoxy-4-quinolone.

In a parallel series, in which 5-methoxy- and 5-hydroxy-2-nitrobenzaldehydes were condensed with ethyl acetoacetate, the reaction involving the methoxy-aldehyde proceeded normally, affording the quinolone (23: R = Me). The corresponding hydroxy-quinolone (23: R = H) was obtained only as its hydrochloride; treatment of this compound with base caused a rapid decomposition from which no recognisable product could be isolated. Reaction of the hydrochloride with diazomethane, however, gave the

dimethoxy-derivative (24), identical with the methylation product of (23: R = Me).

The high reactivity of 5-hydroxy-2-nitrobenzaldehyde in the cyclisation reaction suggested that it might yield quinolone derivatives with a wider variety of reactive methylene compounds than o-nitrobenzaldehyde itself. The previous report [3] that o-nitrobenzaldehyde and ethyl benzoylacetate gave with hydrogen chloride only the o-nitrobenzylidene compound (5) was confirmed. When 5-hydroxy-2-nitrobenzaldehyde was used, however, an unstable hydrochloride resulted. It tended to decompose on recrystallisation, and yielded a very unstable base on treatment with alkali, but reaction with diazomethane gave a stable derivative, $C_{20}H_{18}ClNO_5$, with infra-red spectrum almost identical with that of (24). The formation of this compound, assigned the structure (26), was clear indication that cyclisation had occurred, giving initially the hydrochloride of (25).

This successful cyclisation, the first involving a benzoyl group in the side-chain, suggested that other aryl ketones might react with 5-hydroxy-2-nitrobenzaldehyde giving cyclised products; the case of acetophenone was investigated. It was known [15] that condensation of o-nitrobenzaldehyde and acetophenone in presence of hydrogen chloride gave only o-nitrobenzylideneacetophenone (27: R = H). When the 5-hydroxy-aldehyde was used, the corresponding product (27: R = OH) was isolated.

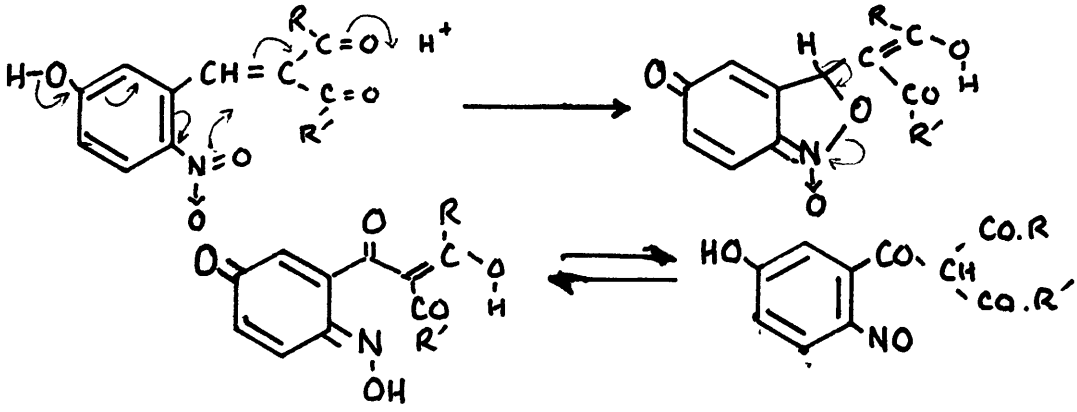
Previous findings [3] that reaction of o-nitrobenzaldehyde with acetone and hydrogen chloride gave only di-o-nitrobenzylideneacetone (6) were confirmed, and it was further shown that, in presence of an excess of acetone, the compound (6) was still the only isolated product. Cyclopentanone and cyclohexanone react similarly.

Two factors can be seen at this stage to contribute towards facilitating cyclisation of o-nitrobenzylidene compounds:-

(a) Strong electron-withdrawing influence in the side-chain.

(b) Ready accessibility of electrons to the nitrogen atom originally present in the nitro-group.

The first of these is provided by initial condensation of the nitrobenzaldehyde with a compound containing a highly reactive methylene group, and the second comes into play especially when the aldehyde contains an electron-donating substituent ortho- or para- to the nitro-group. The high reactivity of 5-hydroxy-2-nitrobenzaldehyde in the cyclisations may be accounted for by the following reaction path, in which the possible effect of the hydroxyl group in facilitating oxygen transfer is shown.

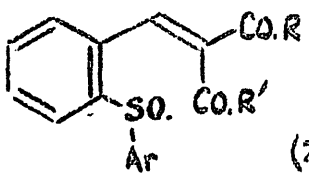


While the results described in this Chapter are undoubtedly relevant to considerations of the reaction mechanism, and while their significance might be increased by further experimentation along similar lines, it was decided at this stage to seek more fundamental information by a totally different approach. The unexpected and interesting problems which arose out of this approach are discussed in the following Chapters, and the investigation was thus set upon a new, and, as was soon apparent, a divergent course.

CHAPTER 2.

ORTHO - GROUP INTERACTIONS IN SUBSTITUTED DIARYL SULPHOXIDES.

FIGURE 3.



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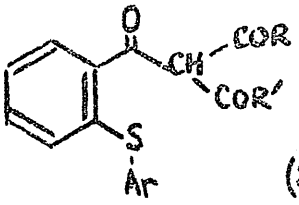

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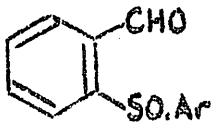

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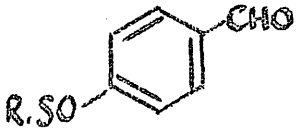

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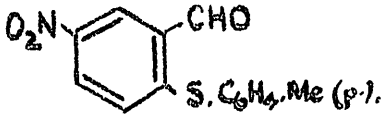

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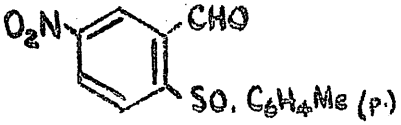

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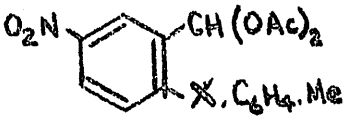

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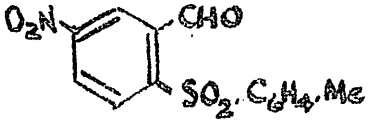

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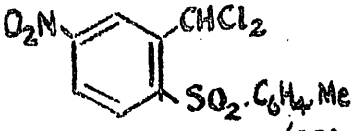

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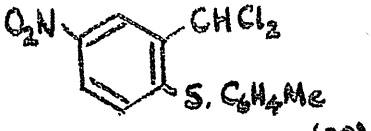

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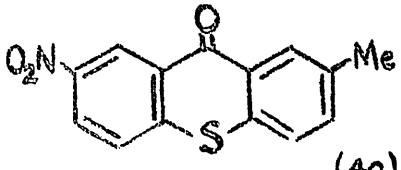

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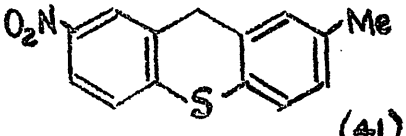

(41)

CHAPTER 2.

ORTHO-GROUP INTERACTIONS IN SUBSTITUTED DIARYL SULPHOXIDES.

The known facts about the cyclisation of certain o-nitrobenzylidene compounds to derivatives of 1-hydroxy-4-quinolone, e.g. (10) ⟶ (1), in presence of hydrogen halides are presented in Chapter 1. If the reaction proceeds by intramolecular oxidation-reduction as proposed (cf. p. 4)[1], intermediates of the nitroso-ketone type would probably be highly reactive and not easily isolated. In view of the scarcity of analogies in the literature for such an oxygen transfer, it was of interest to find a system closely related to that of an o-nitrobenzylidene compound in which the product of an oxygen transfer might be stable and isolable. o-Arylsulphinylbenzylidene compounds, e.g. (28), seemed likely analogues, and the possible product of oxygen transfer, (29), certainly ought to be much more stable than an o-nitroso-benzoyl compound such as (12).

A search of the literature revealed that sulphoxide-aldehydes such as (30) were unknown; indeed, the only known benzaldehydes substituted in any position by an alkyl- or aryl-sulphinyl group were the compounds (31: R = Et, Pr^n, Pr^i, Bu^n, Bu^i)[16]. They were obtained by controlled oxidation of the corresponding sulphide-aldehydes with hydrogen peroxide in acetic acid. Their chemical properties were not reported.

The ready accessibility of 5-nitro-2-(p-tolylthio)-benzaldehyde (32) [17] made the corresponding sulphoxide (33) the first synthetic objective. Although conditions were found under which controlled oxidation of the sulphide gave reasonably pure sulphoxide, this procedure was difficult to reproduce on a useful preparative scale, because of competing oxidation of the aldehyde. However, the sulphide-diacetate (34: X = S), formed by reaction of the aldehyde (32) with acetic anhydride and concentrated sulphuric acid, was oxidised by hydrogen peroxide in acetic acid, affording, under suitably chosen conditions, a good yield of either the sulphoxide (34: X = SO) or the sulphone (34: X = SO_2). These gave the aldehydes (33) and (35) respectively on mild acidic hydrolysis. A recent experiment by Mr. H. Clark [18] has shown that the sulphone-aldehyde (35) results also by reaction of 2-chloro-5-nitrobenz-aldehyde with sodium p-toluenesulphinate.

5-Nitro-2-p-tolylsulphinylbenzaldehyde (33) is a pale yellow crystalline solid of m.p. 178°. Significant maxima in its infra-red spectrum occur at 1680 (>C=O), 1525, 1340 (NO_2), 1075, 1050, 1030, 1010 $cm.^{-1}$ (S-O?). It forms an oxime and a 2,4-dinitro-phenylhydrazone, but attempted formation of the benzylidene diacetate (34: X = SO) by treatment with acetic anhydride and concentrated sulphuric acid failed, the aldehyde being recovered unchanged by the addition of the solution to cold water.

Unlike o-nitrobenzaldehyde, however, the sulphoxide-aldehyde (33) reacts with hydrogen chloride. When a solution of the aldehyde in dimethylformamide† was saturated with dry hydrogen chloride at room temperature and set aside overnight, a bright yellow solid crystallised out. It was identified as the sulphide-aldehyde (32), showing that reduction of the sulphoxide group had occurred. Addition of the yellow solution to ice-water gave a cream-coloured solid which, from its melting point and behaviour on a chromatoplate, was clearly a mixture. Fractional crystallisation from benzene-light petroleum gave a further crop of the sulphide-aldehyde (32) (total yield 40%) and a small amount of the original sulphoxide-aldehyde. Chromatography of the remainder on alumina gave a colourless compound, and more starting material (total recovery 12%).

The colourless compound contained nitrogen, sulphur, and chlorine, and its analysis corresponded to the formula $C_{14}H_{11}Cl_2NO_4S$. On the basis of this formula, it was produced in 29% yield. It crystallised in two forms: from ethanol or acetic acid, it formed thick needles, m.p. 142°, and from aqueous acetic acid or benzene-light petroleum, fine silky fibres, m.p. 138°. These two forms had slightly different infra-red spectra, but were

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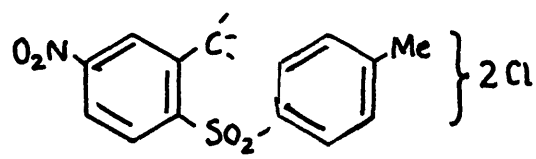
† The aldehyde (33) is sparingly soluble in ether.

interconvertible by recrystallisation from the appropriate solvent. The infra-red spectrum showed no carbonyl absorption, but maxima at 1530 and 1345 cm.$^{-1}$ indicated retention of the nitro-group, and those at 1320 and 1155 cm.$^{-1}$ suggested the presence of a sulphone group. (5-Nitro-2-p-tolylsulphonylbenzaldehyde (35) has $\nu_{max.}$ 1315, 1155 cm.$^{-1}$).

The dichloro-compound was insoluble in dilute alkali and acid. Neither of its chlorine atoms was present as a chloride ion, since its solution in acetonitrile gave no precipitate when mixed with a solution of silver nitrate in the same solvent. It was not oxidised by hydrogen peroxide in acetic acid at 100° , a further indication that the sulphur in the molecule was probably present as a sulphone group. It likewise resisted oxidation by alkaline potassium permanganate, but with sodium dichromate and aqueous acid it was oxidised to a carboxylic acid, $C_{14}H_9Cl_2NO_6S$, which was seen to result merely from the oxidation of one methyl group to carboxyl. On the assumption that no skeletal rearrangement of (33) had taken place, the partial structures (36) and (37) were written for the dichloro-compound and its oxidation product.



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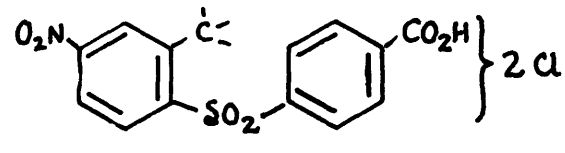

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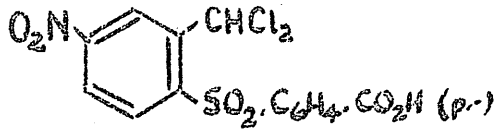

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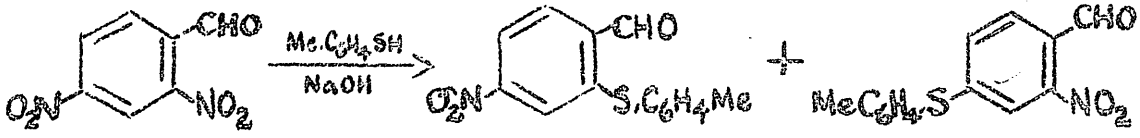

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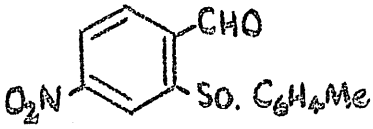

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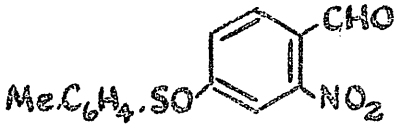

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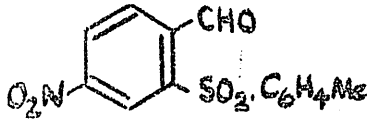

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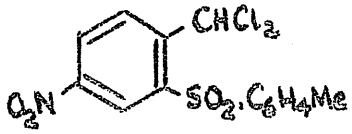

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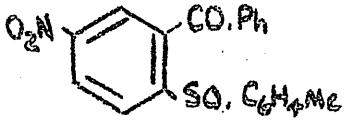

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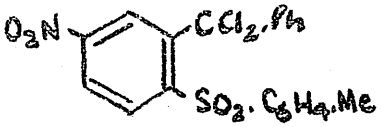

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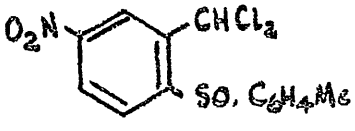


(51)

Only the chlorine atoms of the compound $C_{14}H_{11}Cl_2NO_4S$ remain to be located in the partial structure (36), possible positions being either in the side-chain or in the aromatic nuclei. All attempts to determine the correct positions of these chlorine atoms by hydrolysis failed; indeed, assignment of the correct structure to the dichloro-compound was complicated by experimental evidence which was apparently self-contradictory, and this is fully discussed in Chapter 3. The true structure of the compound is given in formula (38). Although the compound showed an abnormal resistance towards acid hydrolysis, the benzylidene chloride structure (38) was established beyond doubt on the following evidence:-

(a) The compound was formed in high yield by the action of phosphorus pentachloride on the sulphone-aldehyde (35), of which it is thus the corresponding dichloride.

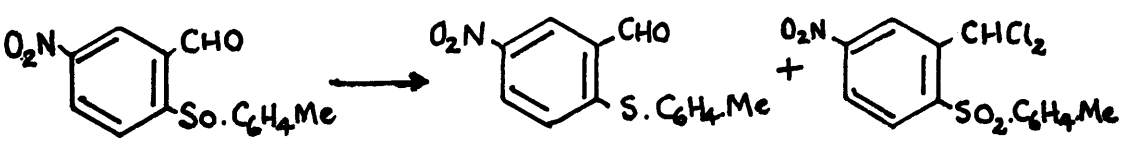
(b) The sulphide-dichloride (39), similarly obtained from the sulphide-aldehyde and and phosphorus pentachloride, behaved normally in regenerating the aldehyde (32) on acid hydrolysis. In concentrated sulphuric acid, as expected, further reaction occurred, giving a mixture of 2-methyl-7-nitrothioxanthone (40) and the corresponding thioxanthen (41) [17]. Oxidation of the sulphide-dichloride (39) with hydrogen peroxide in acetic acid at 100° gave the sulphone-dichloride (38).

(c) The sulphone-dichloride (38) reacted with piperidine giving an orange-yellow solid. When this crude material was warmed gently for a few minutes with concentrated hydrochloric acid, the sulphone-aldehyde (35) was precipitated. (The reaction of (38) with piperidine is discussed more fully in Chapter 3.)

The direct formation of the sulphone-dichloride from the sulphone-aldehyde (35), as in (a), and the ease with which the aldehyde is regenerated from the dichloride, as in (c), convincingly establish the structure of the dichloride as (38).

The sulphide- and sulphone-aldehydes (32) and (35) were unaffected by treatment with hydrogen chloride in dimethylformamide; however, reaction of the sulphide-aldehyde with dry chlorine in dimethylformamide afforded the sulphone-dichloride (38) together with the sulphone-aldehyde (35). The two products were obtained in almost equal amounts (41 and 44 per cent. respectively), and were separated by chromatography on alumina.

The overall result of the reaction



(33) (32) (38)

is that some of the sulphoxide molecules suffer reduction to

sulphide, while others undergo oxidation to sulphone, the latter process being accompanied by replacement of the carbonyl oxygen atom by two chlorine atoms. No analogous reactions appear to be already known, and so several sulphoxides related to 5-nitro-2-*p*-tolylsulphinylbenzaldehyde were prepared and their reaction with hydrogen chloride examined.

The mixture of 4-nitro-2-(*p*-tolylthio)benzaldehyde (43) and 2-nitro-4-(*p*-tolylthio)benzaldehyde (44), which results from the interaction of 2,4-dinitrobenzaldehyde and one equivalent of thio-*p*-cresol in alkali [17], was treated with acetic anhydride and concentrated sulphuric acid, and the diacetate mixture separated by fractional crystallisation from acetic acid. This separation was found to be much more convenient than the recommended [17] separation of the aldehyde isomers. The diacetates were identified by independent preparation from the appropriate pure aldehyde. Oxidation of the diacetates followed by hydrolysis gave the required sulphoxide-aldehydes (45) and (46).

The reaction of 4-nitro-2-*p*-tolylsulphinylbenzaldehyde (45) with hydrogen chloride proceeded in the same way as that of the 5-nitro-isomer (33), the sulphide-aldehyde (43) and the sulphone-dichloride (48) being formed. The reaction of this sulphide-aldehyde with chlorine was also similar to that observed in the 5-nitro-series, the sulphone-aldehyde (47) and its dichloride (48)

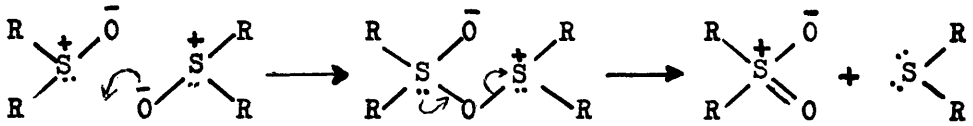
being identified as products. As expected, the dichloride also resulted by the action of phosphorus pentachloride on the sulphone-aldehyde. On the other hand, 2-nitro-4-p-tolylsulphinylbenzaldehyde (46), when treated with hydrogen chloride in dimethylformamide under the same conditions, was recovered unchanged in over 90 per cent. yield, and 5-nitro-2-p-tolylsulphinylbenzophenone (49), prepared by careful oxidation of the corresponding sulphide [17], gave under these conditions only the sulphide-ketone without any trace of the sulphone-dichloride (50).

MECHANISM.

The conversion of a sulphoxide-aldehyde by hydrogen chloride into the corresponding sulphide-aldehyde and sulphone-dichloride represents an oxidation-reduction of a most unusual type, in which halogenation accompanies the oxidation and not the reduction. It seems likely that the reaction involves interaction of the aldehyde and sulphoxide groups, since, when these groups are para- to each other, as in (46), no reaction occurs. Thus in considering the reaction mechanism, account must be taken of possible interactions of this type, together with the mechanism of oxidation-reduction, and the method of insertion of chlorine.

It was noted earlier (p. 14) that the yields of sulphide-aldehyde and sulphone-dichloride obtained in the 5-nitro-series, while not exactly equal, were of the same order of magnitude

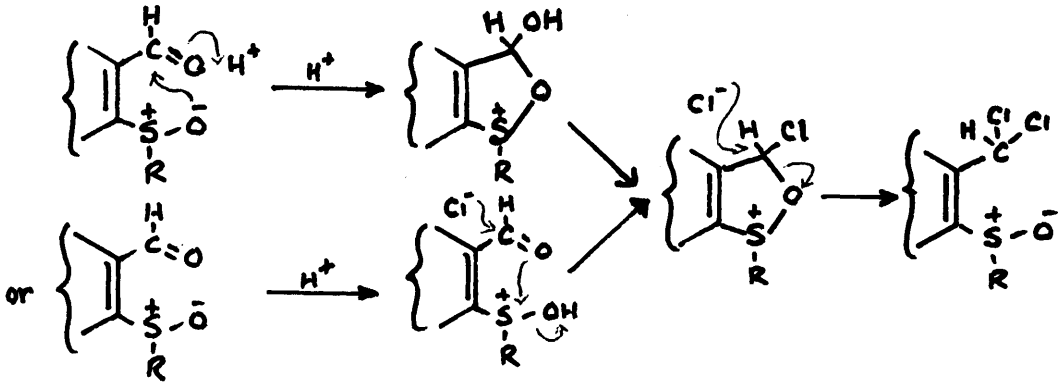
(in the molar ratio of approximately 4 : 3), and so a disproportionation type of mechanism was considered for the oxidation-reduction stage. Disproportionation reactions of sulphoxides are considered by Szmant [19] to occur in the following way:-



In the present case, however, it is difficult to see how a mechanism of this kind accounts for halogen insertion only in the sulphone fragment. Disproportionation of 5-nitro-2-p-tolylsulphinylbenzaldehyde (33) would presumably give a mixture of the corresponding sulphide (32) and sulphone (35). Both of these are known to be unaffected by hydrogen chloride in dimethylformamide, and yet the latter is not found as a product.

An interesting possibility of a disproportionation mechanism for the reaction (33) ⟶ (32) + (38) involved as intermediate the sulphoxide-dichloride (51). This on disproportionation would be expected to give the sulphide-dichloride (39) and the sulphone-dichloride (38). It was recalled that the former was readily hydrolysed to the aldehyde, while the latter was not. The formation of the dichloride (51) by the action of hydrogen chloride on the sulphoxide-aldehyde (33) was conceivable by the following

series of transformations:-



A synthesis of 5-nitro-2-p-tolylsulphinylbenzylidene chloride (51) by the action of phosphorus pentachloride on the sulphoxide-aldehyde (33) was not possible, the products of this reaction being the sulphide-dichloride (39) (yield 79%) and a small amount (3%) of the sulphone-dichloride (38). The sulphoxide-dichloride was, however, obtained in 59 per cent. yield by oxidation of the sulphide-dichloride (39) with hydrogen peroxide in acetic acid for 3 minutes at 100° . It reacted with hydrogen chloride in dimethylformamide, but only the sulphide-dichloride (yield 96%), was isolated; and the sulphide-dichloride, on renewed treatment with hydrogen chloride, was recovered unchanged.

The remaining possible type of disproportionation, involving oxygen exchange between one molecule of sulphoxide-aldehyde and one molecule of sulphoxide-dichloride, was quickly discounted. An equimolar mixture of the sulphoxide-aldehyde (33) and its dichloride (51) in dimethylformamide underwent no reaction when

treated with a little concentrated sulphuric acid, and with hydrogen chloride gave the same products as each component gave individually under the same conditions. No evidence of oxygen exchange was observed.

In view of these negative results, it thus seemed certain that the reaction occurred through the direct action of hydrogen chloride on the sulphoxide-aldehyde. Treatment of diphenyl sulphoxide with hydrogen chloride is known [20] to give rise to chlorodiphenylsulphonium chloride (52).

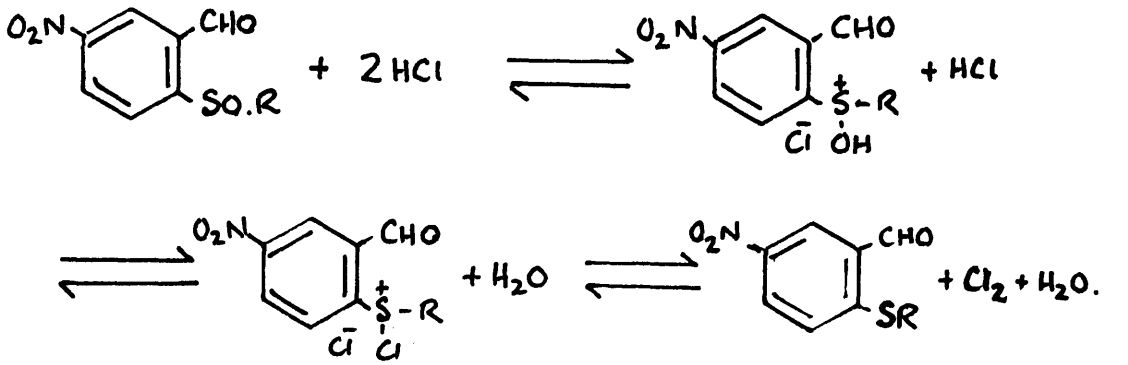
$$Ph_2\overset{+}{S}-\overset{-}{O} \underset{}{\overset{HCl}{\rightleftharpoons}} Ph_2\overset{+}{S}-OH \quad Cl^- \underset{H_2O}{\overset{HCl}{\rightleftharpoons}} Ph_2\overset{+}{S}-Cl \quad Cl^- \qquad (52)$$

The reaction is reversible, atmospheric moisture being sufficient to cause hydrolysis of the salt (52) to the sulphoxide. Chlorination of diphenyl sulphide also gives (52), but this reaction is reversible only on heating.

$$Ph_2S: \curvearrowright Cl-\overset{\curvearrowright}{Cl} \rightleftharpoons Ph_2\overset{+}{S}-Cl \quad Cl^-$$

These halides are not readily formed when a nitro-group is present,[21] presumably because the electron-attracting nitro-group will make it more difficult for the sulphur atom to bear a positive charge.

It seemed likely that, as a result of attack on the sulphoxide-aldehyde by hydrogen chloride, the following equilibria might be set up:-



Even if, in the last of these, between chlorosulphonium chloride and sulphide-aldehyde, the point of equilibrium might normally lie very much in favour of the former, the consumption of chlorine in some secondary reaction would be expected to drive the equilibrium towards the right and so permit isolation of the sulphide. To test this hypothesis, a solution of the sulphoxide-aldehyde (33) in dimethylformamide containing a little phenol was saturated with hydrogen chloride and set aside overnight; the sulphide-aldehyde was formed in very high yield, together with tiny amounts of chlorinated phenols. The sulphide-aldehyde was the only product isolated from the reaction of the sulphoxide-aldehyde with hydrogen chloride in benzene; it is not clear, however, whether benzene acts as a chlorine acceptor, since halogenated benzenes were not detected as products.

It was significant that formation of the sulphone-dichloride (38) did not occur to any appreciable extent when chlorine was removed (e.g. as chlorophenols) from the solution. There are two possible explanations for this. The chlorine may function as an

oxidising or halogenating agent, or both, in the dichloride formation. It may, however, assist dichloride production in a different way: if, as is possible, the sulphone-dichloride is formed *via* one of the intermediates in the above series of equilibria, a concentration of chlorine in the solution may be necessary to preserve an appreciable amount of that intermediate, and the displacement of the equilibria to the right through removal of chlorine would destroy the concentration of the intermediate, and with it any chance of dichloride formation.

Just as chlorine oxidises sulphides to sulphoxides, so it can oxidise sulphoxides to sulphones. It has already been noted (p. 17) that reaction of the sulphide-aldehyde (32) with chlorine gave the sulphone-dichloride (38), but that the sulphone-aldehyde (35) was also formed in significant amount. Treatment of the sulphoxide-aldehyde (33) with chlorine gave almost entirely the sulphone-aldehyde (35), and only a very small quantity of the dichloride (38). Oxidation of the sulphoxide-dichloride (51) to the sulphone (38) was effected by treatment with chlorine, but the yield was not quantitative, some unreacted sulphoxide being recovered.

In none of these experiments involving chlorine, however, were the conditions exactly comparable with those of the original reaction (33) $\longrightarrow$(32)+(38). In the latter, hydrogen chloride

was always present in excess, while in the former it was produced only by reduction of chlorine as the reaction proceeded.

The effect of hydrogen chloride on the reaction of the sulphide-aldehyde (32) with chlorine was therefore studied. When the aldehyde was allowed to react with chlorine in presence of pyridine or potassium carbonate, the yield of sulphone-aldehyde (35) was increased, and that of sulphone-dichloride (38) was diminished. On the other hand, when the solution of the sulphide-aldehyde was saturated simultaneously with chlorine and hydrogen chloride, the yield of dichloride was increased at the expense of sulphone-aldehyde.

The above results indicate that the sulphone-dichloride results through the joint action of chlorine and hydrogen chloride on the sulphide-aldehyde. p-Toluenesulphonic acid is not an effective substitute for hydrogen chloride. Hypochlorous acid oxidises (32) to (35) without formation of (38).

Unexpectedly, but also significantly, the sulphoxide-aldehyde (33), when treated simultaneously with chlorine and hydrogen chloride, gave the sulphone-aldehyde almost exclusively.

Results of the experiments described above are summarised in Tables 1 and 2.

TABLE 1.

Reactions of 5-Nitro-2-p-tolylsulphinylbenzaldehyde (33).

Expt. No.	Reagent(s)	Percentage yield of (32)	(33)	(35)	(38)	(39)
1.	HCl	40	12	-	29	-
2.	HCl, PhOH	88	-	-	-	-
3.	HCl, C_6H_6	80 +	-	-	-	-
4.	HCl, Cl_2	-	trace	83	2	-
5.	$Me.C_6H_4.SO_3H$, Cl_2	-	-	60 +	trace	-
6.	Cl_2	-	-	80	8	-
7.	PCl_5	-	-	-	3	79

Notes.

(a) A yield entered as "60 +" indicates a 60 per cent. yield of pure compound and a second crop of poorer quality.

(b) The entry "trace" denotes a small amount identified qualitatively by thin-layer chromatography but not isolated.

Experimental details are given on p. 72.

TABLE 2.

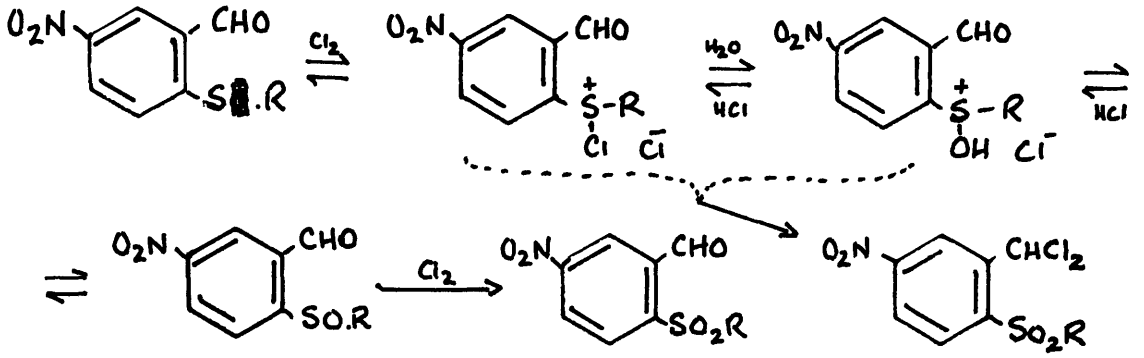
Reactions of 5-Nitro-2-(p-tolylthio)benzaldehyde(32).

Expt. No.	Reagent(s)	Percentage yield of (32)	(33)	(35)	(38)	(39)
1.	Cl_2	-	-	44	41	-
2.	Cl_2, K_2CO_3	-	-	71	trace	-
3.	Cl_2, C_5H_5N	-	-	59 +	trace	-
4.	Cl_2, $Me.C_6H_4.SO_3H$	-	-	68 +	trace	-
5.	Cl_2, HCl	-	-	12 +	60	-
6.	HOCl	-	-	77	-	-
7.	HCl	100	-	-	-	-

Notes. See Table 1 (p. 26).

Experimental details are given on p.73.

An approximate reaction scheme may be drawn up as follows:-



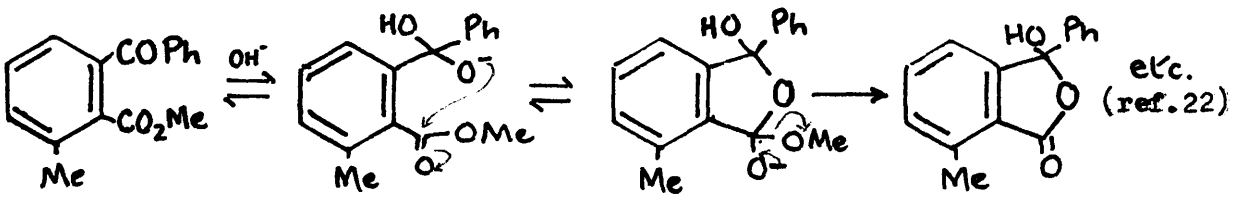
The sulphoxide-aldehyde (33) is oxidised so readily to the sulphone-aldehyde (35) by chlorine (even in presence of hydrogen chloride; cf. Table 1) that any sulphoxide-aldehyde formed in the reaction of the sulphide-aldehyde with chlorine would be expected to undergo further oxidation and appear in the final mixture of products as sulphone-aldehyde. If, then, as seems likely, the formation of sulphone-dichloride (38) represents a departure from the normal series of equilibria, this departure must occur <u>before</u> the sulphoxide stage is reached. Of the three preceding stages, the sulphide-aldehyde (32) itself is not entirely satisfactory as the point of deviation, since its reaction with chlorine, with or without hydrogen chloride, always leads to the formation of some sulphone-aldehyde, and it will be recalled that, in the reaction of sulphoxide-aldehyde with hydrogen chloride, the sulphone-aldehyde was not formed. The chlorosulphonium chloride seems the most likely intermediate, since the yield of sulphone-dichloride

is highest when the sulphide-aldehyde is treated with an excess of both chlorine and hydrogen chloride.

A plausible mechanism for the formation of the sulphone-dichloride (38) from the chlorosulphonium chloride is outlined below. Rearrangement of the salt in presence of hydrogen chloride could effect the required introduction of halogen at the aldehydic carbon.

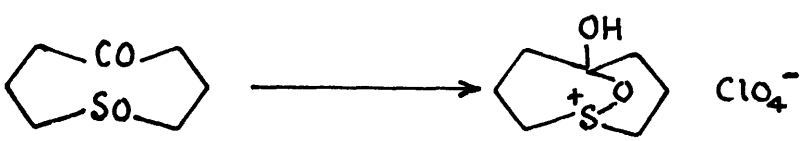
(53).

Such an interaction is broadly similar to that recently proposed [22,23] to account for the unexpectedly high rate of hydrolysis of o-aldehydo- and keto-benzoic esters, e.g.



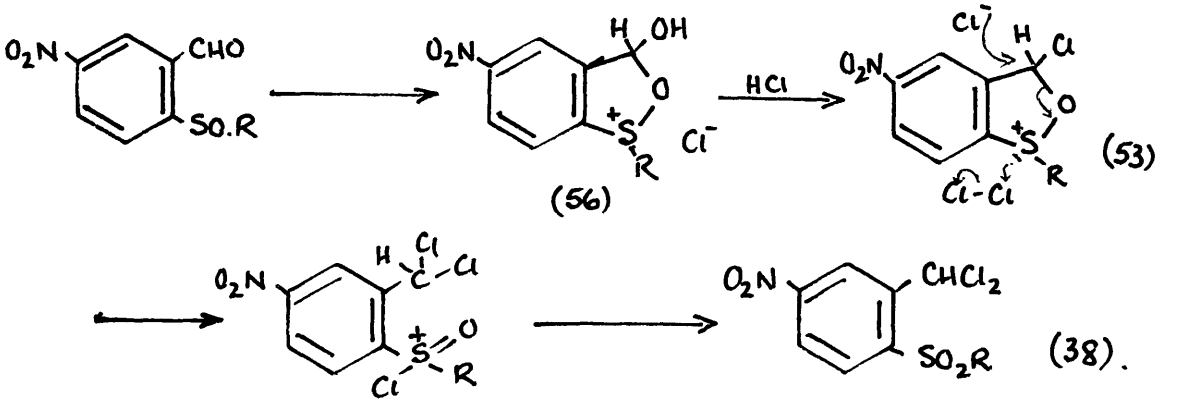
etc. (ref.22)

The same cyclic intermediate (53) might arise by a different reaction path. Leonard and Johnson [24] have shown that the sulphoxide-ketone (54) with perchloric acid gives the salt (55); on this basis, the sulphoxide-aldehyde with hydrogen chloride might give (56),



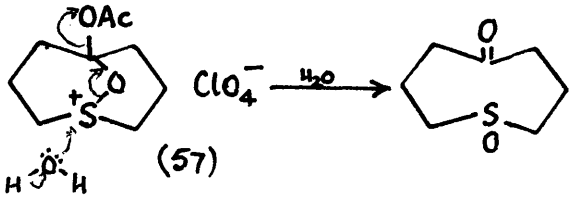
(54) (55)

which by further reaction would give (53). Transformation of this cyclic structure into the sulphone-dichloride (38) could take place as shown.

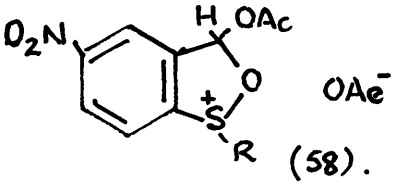


By this mechanism involving an ortho-interaction, the failure of 2-nitro-4-p-tolylsulphinylbenzaldehyde (46) to give the reaction is understandable. The failure of the benzophenone derivative (49) to give a sulphone-dichloride may be accounted for in terms of the diminished electrophilicity of the carbonyl carbon atom.

Analogy with the results of Leonard and Johnson may account for the observed failure of the sulphoxide-aldehyde (33) to give a diacetate with acetic anhydride and sulphuric acid. (The isomeric aldehyde (46), with the sulphoxide group in the para-position, readily forms a diacetate.) Leonard and Johnson found that their perchlorate salts formed acetates (e.g.(57)), which were hydrolysed in water, as shown below. The product of reaction of the sulphoxide-aldehyde with acetic anhydride and sulphuric acid may therefore be the unstable species (58).



(57)



(58).

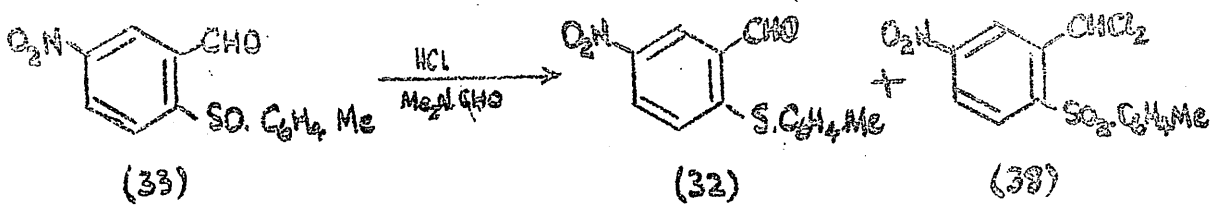
Although the mechanism outlined above for the reactions of the sulphoxide-aldehyde with hydrogen chloride and the sulphide-aldehyde with chlorine has not been confirmed, it is consistent with the experimental evidence at present available. It accounts also for one significant feature of these reactions not hitherto emphasised: that the only halogenated product obtained from either reaction was the sulphone-dichloride (38). The corresponding sulphide (39) and sulphoxide (51) were never detected, although their presence in quite small amounts would be expected to show on the chromatoplate examinations which were made. Thus if the formation of sulphone-dichloride represents a departure from a normal series of equilibria, it is always associated with an oxidation. The cyclic intermediate (53) is probably more easily oxidised than the chlorosulphonium chloride; certainly the lone pair of electrons on sulphur are more readily available for oxidation in the former, because of the diminished electron-attracting power in the aromatic nucleus.

This Chapter has sought to present some unusual features in the chemistry of o-arylsulphinylbenzaldehydes. It appears that abnormal behaviour of these aldehydes is to be expected in reactions with acidic reagents (hydrogen chloride, phosphorus pentachloride, and acetic anhydride - sulphuric acid, for instance), and that this abnormality may very well arise through interaction of the aldehyde group with the ortho-arylsulphinyl substituent.

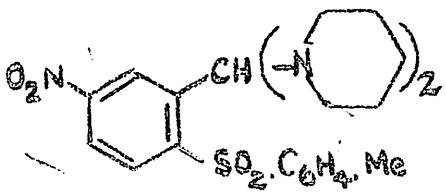
CHAPTER 3.

A NOVEL NUCLEOPHILIC SUBSTITUTION.

FIGURE 5.



(33) (32) (38)



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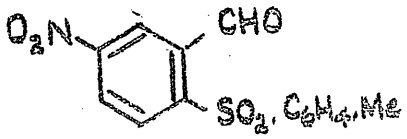

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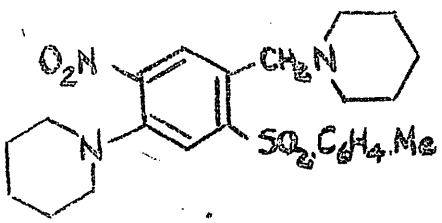

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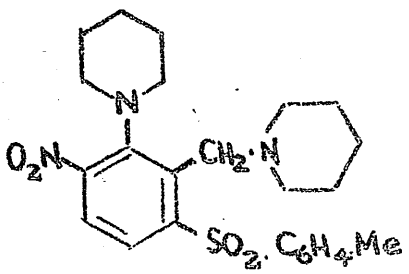

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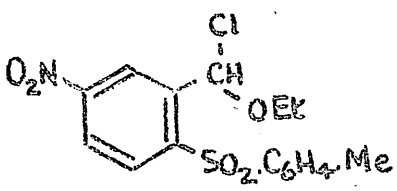

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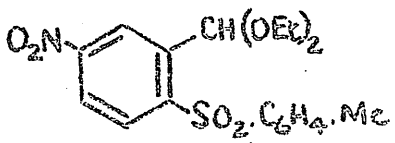
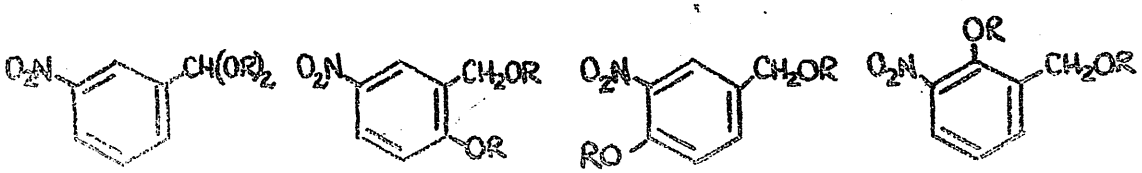


(63)



(64) (65) (66) (67)

(64)-(67) : R = Me, Et, Pr^n

CHAPTER 3.

A NOVEL NUCLEOPHILIC SUBSTITUTION.

It was shown in Chapter 2 that the reaction of 5-nitro-2-*p*-tolylsulphinylbenzaldehyde (33) with hydrogen chloride in dimethylformamide gave as products 5-nitro-2-(*p*-tolylthio)benzaldehyde (32) and 5-nitro-2-*p*-tolylsulphonylbenzylidene chloride (38), the structure of the latter being established by synthesis and conversion *via* the dipiperidino-derivative (59) into the sulphone-aldehyde (35). Earlier attempts to determine the positions of the two chloro-substituents through nucleophilic replacement had given results which, in the light of the structure (38) thus established, required further investigation.

Reaction of the sulphone-dichloride (38) with piperidine gave basic material which on hydrolysis yielded the aldehyde (35) and on crystallisation gave an orange dipiperidino-compound of m.p. 154°. The latter was expected to be the benzylidene dipiperidine (59), but such a structure did not account for its colour, since *m*-nitrobenzylidene dipiperidine is described by Dilthey and Stallmann [25] as almost colourless, and the presence of the *p*-tolylsulphonyl group should have little effect on the colour. When it was shown that the orange compound was stable towards hydrolysis by acid, the structure (59) was clearly unacceptable.

Re-examination of the crude reaction product showed it to be

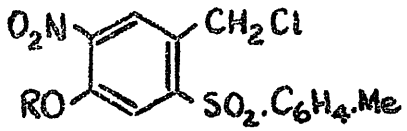
a mixture of two basic compounds. One of these was unstable, attempts to isolate it resulting in its decomposition to the sulphone-aldehyde (35); it is probably the benzylidene dipiperidine (59). The other was the orange base described above.

The orange dipiperidino-compound dissolved readily in concentrated hydrochloric acid, giving a colourless solution. Dilution of this solution with water caused a bright orange colour to develop, but the base was not precipitated until the solution was made alkaline. These observations suggest that, of the two basic nitrogen atoms in the molecule, one is very feebly basic, its hydrochloride being unstable in dilute acid, and the other strongly basic; the colour appears to be associated with the former, which is then probably situated ortho- to the nitro-group (o-nitrophenylpiperidine is red [26]). The other, strongly basic nitrogen could well be situated on the side-chain, since N-benzylpiperidine is expected to be a strong base. On this view, two structures, (60) and (61), are possible for the orange base. Of the two, (60) is the more likely, as entry of the piperidino-group into the aromatic nucleus would be expected to occur more readily at the less hindered position. Further support for the structure (60) was obtained by analogy with the series of reactions described below.

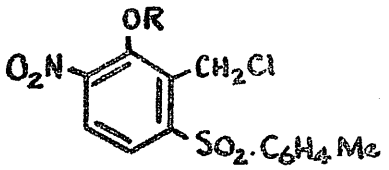
Reaction of 5-nitro-2-p-tolylsulphonylbenzylidene chloride

(38) with an excess of sodium carbonate in aqueous ethanol gave a compound, $C_{16}H_{16}ClNO_5S$, this formula corresponding to the replacement of one chlorine atom by an ethoxyl group. That only one halogen of a benzylidene halide should be replaced under these conditions was quite extraordinary. Benzylidene chloride undergoes hydrolysis to benzaldehyde under very mild alkaline conditions (e.g. by heating with a suspension of calcium carbonate in water [27a]), and yields acetals by reaction with sodium alkoxides[28]. The chloro-ethoxy-compound could not be the α-chloro-ether (62), since this should be even more reactive than the dichloride (38), and should thus afford the acetal (63) or the aldehyde (35), depending on the reaction conditions.

Renewed inquiry into the anomalous reaction showed that the compound $C_{16}H_{16}ClNO_5S$ was formed in approximately 70 per cent. yield when the sulphone-dichloride (38) was heated with either sodium carbonate in aqueous ethanol or one equivalent of sodium ethoxide in dry ethanol. In each case, the product crystallised from solution as the reaction proceeded. The methoxy-analogue, $C_{15}H_{14}ClNO_5S$, was obtained, although in slightly lower yield, by similar reaction of the dichloride with sodium methoxide in methanol. Treatment of the dichloride with sodium carbonate in aqueous methanol, however, gave a complex mixture of products, the nature of which is discussed later (p.42).



(68)



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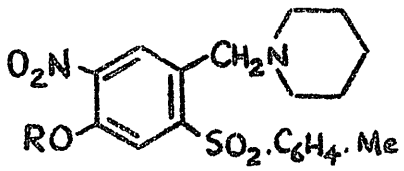

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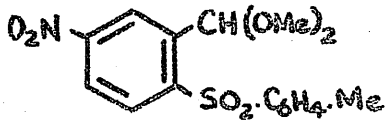

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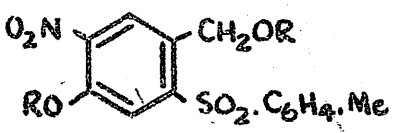

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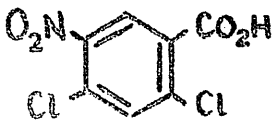

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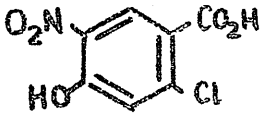


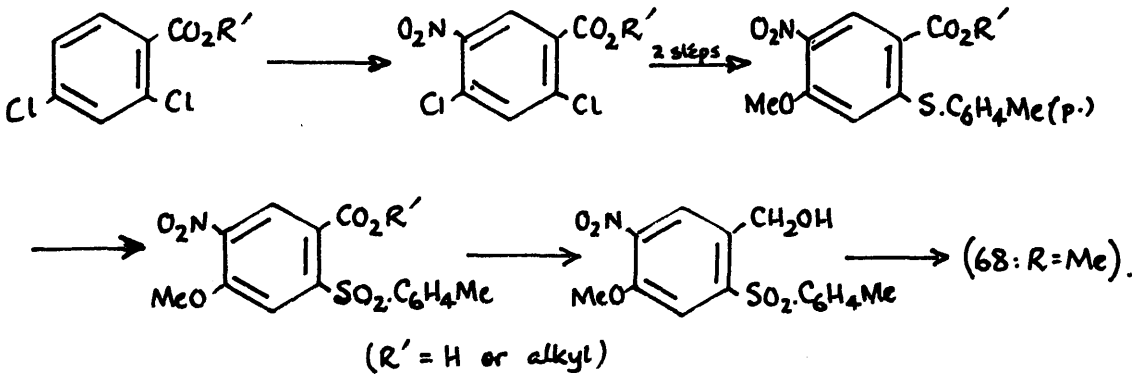
(74)

A search of the literature then disclosed that m-nitrobenzylidene chloride was found to undergo abnormal nucleophilic substitution when treated with a sodium alkoxide. Kliegl and Hölle[29] observed that such a reaction gave, in addition to the expected acetal (64), a mixture of products which were stable towards acid, and they identified these as the 2,5- and 4,3-alkoxynitrobenzyl alkyl ethers (65) and (66). Although the yield of these abnormal products was very small (about 10% in all), by comparison with the 70 per cent. yield of chloro-ethoxy-compound from the sulphone-dichloride, the strong similarity of the two reactions led to the proposal of 4-alkoxy-5-nitro-2-p-tolylsulphonylbenzyl chloride structures (68: R = Et and Me) for the chloro-ethoxy-compound and its methoxy-analogue. Again the 1,2,4,5-tetrasubstituted structure (68) was preferred to the possible 1,2,3,4-tetrasubstituted isomer (69) on steric grounds. It is to be noted that Kliegl and Hölle did not detect 2-alkoxy-3-nitro-isomers, (67), from their series of reactions.

The properties of the chloro-ethoxy-compound were consistent with the proposed structure (68: R = Et). Reaction with piperidine afforded a mono-piperidino-derivative, which was very pale yellow in colour and strongly basic as required for the N-benzylpiperidine (70: R = Et), and reaction with a further equivalent of sodium ethoxide gave an ethyl ether. The chloro-methoxy-compound similarly yielded a piperidino-derivative of comparable

colour and basicity, and a methyl ether, which was further shown to be non-identical with the acetal (71). The ethers were assigned the structures (72: R = Et, Me respectively) because their infra-red spectra closely resembled those of their chloro-alkoxy-precursors.

Confirmation of the proposed structures (68: R = Et, Me) was obtained by unambiguous synthesis of 4-methoxy-5-nitro-2-p-tolyl-sulphonylbenzyl chloride (68: R = Me). The route proposed was as follows:-



The preparation of 2,4-dichloro-5-nitrobenzoic acid (73) and its simple derivatives has been described in the literature [30,31]. The relative mobility of the two chloro-substituents under nucleophilic attack is important in considering the two-stage conversion of the dichloronitro-acid derivative into the corresponding 4-methoxy-2-p-tolylthio-compound. Since, in 2,4-dihalonitrobenzenes, the halogen in the 2-position is the more mobile [32], and since the carboxylate group is known [33] to be para-activating

and ortho-deactivating for replacement of nuclear halogen, it was expected that the 4-chloro-substituent in 2,4-dichloro-5-nitrobenzoic acid would be preferentially replaced by nucleophiles. Villiger's observation [30] that reaction of this acid with an excess of aqueous sodium hydroxide gives only the 2-chloro-4-hydroxy-acid (74) is in agreement with this prediction. The ortho-deactivation of the carboxylate group, caused by electrostatic repulsion of the attacking anion,[33], might tend to hinder easy replacement of the second chlorine atom by thio-p-cresoxide, and so, to avoid possible complications here, it was decided to attempt the substitution reactionson the methyl ester rather than on the free acid (73).

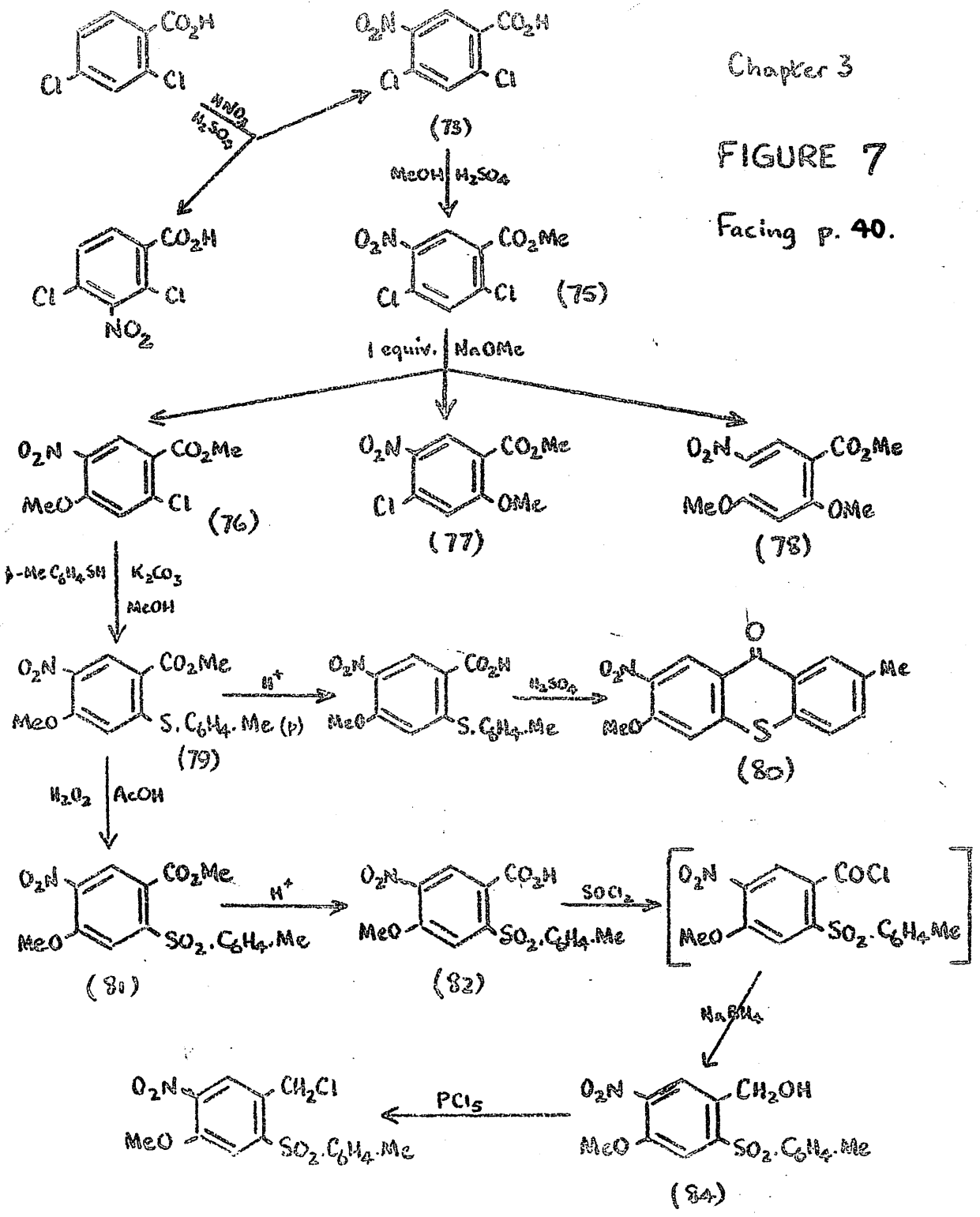
Oxidation of the p-tolylthio-group to p-tolylsulphonyl was not expected to present any problems, but the next stage, selective reduction of a benzoic acid derivative to the benzyl alcohol in presence of nitro- and arylsulphonyl groups, required careful consideration. Although lithium aluminium hydride normally reduces nitro-compounds (to azobenzenes) [34b] and sometimes reduces sulphones [34d], Felkin[35] has shown that ethyl p-nitrobenzoate may be reduced to p-nitrobenzyl alcohol by adding the calculated amount of lithium aluminium hydride to the ester, and his method has been used to effect several selective reductions of nitrobenzoic esters.[34c]. It was hoped that such a reduction might be successful here; in any case, however, it was expected that the required

Synthesis of 4-Methoxy-5-nitro-2-p-tolylsulphonylbenzyl chloride.

Chapter 3

FIGURE 7

Facing p. 40.



alcohol would result from reduction of the acid chloride by sodium borohydride, a reagent which does not normally reduce esters [34a] or nitro-compounds [34c]. The final stage, conversion of the alcohol into the chloride, was expected to be straightforward.

Nitration of 2,4-dichlorobenzoic acid gave a mixture of the 3- and 5-nitro-acids. These were separated, as recommended by Goldstein and Schaaf [31], by fractional crystallisation of their sodium salts from water, although the salt of the 5-nitro-acid was rather more soluble than these authors indicate. The 5-nitro-acid was converted into its methyl ester by heating it with methanol and concentrated sulphuric acid; Goldstein and Schaaf obtained the ester *via* the acid chloride.

The reaction of methyl 2,4-dichloro-5-nitrobenzoate (75) with one equivalent of sodium methoxide in dry methanol afforded a product $C_9H_8ClNO_5$, m.p. 133°, in 63 per cent. yield. This compound was considered to be the required methyl 2-chloro-4-methoxy-5-nitrobenzoate (76), by virtue of its hydrolysis in aqueous alkali to an acid of m.p. 226-228° (2-chloro-4-methoxy-5-nitrobenzoic acid has m.p. 235° [36]), and its non-identity with the known [37] 4-chloro-2-methoxy-5-nitrobenzoic ester (77) (m.p. 107.5°, m.p. of corresponding acid 160° [37]). The reaction mother-liquors gave on concentration a mixture, from which by

chromatography small amounts of the ester (77) and methyl 2,4-dimethoxy-5-nitrobenzoate (78) were isolated.

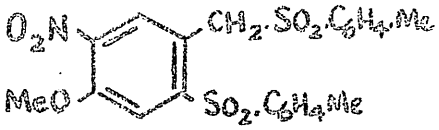
In view of the extremely rapid hydrolysis of the chloro-methoxy-ester (76) in aqueous alkali (the reaction was complete in 10 minutes), anhydrous conditions were clearly desirable for the reaction of the ester with a salt of thio-p-cresol. When equimolar proportions of the ester (76) and thio-p-cresol were heated together in dry methanol containing a suspension of potassium carbonate, the sulphide-ester (79) was produced in good yield. Confirmation of the structure (79) was obtained by acid hydrolysis of the ester to the corresponding benzoic acid (under alkaline conditions, partial replacement of the p-tolyl-thio-group occurred), and cyclodehydration of the acid in hot concentrated sulphuric acid [17] to 3-methoxy-7-methyl-2-nitro-thioxanthone (80), which was identified by its analysis, its insolubility in alkali and in most of the common organic solvents, and its infra-red spectrum ($\nu_{max.}$ 1630 cm.$^{-1}$).

Oxidation of the sulphide-ester to the corresponding sulphone (81) with hydrogen peroxide in hot acetic acid proceeded almost quantitatively. An attempt to effect selective reduction of (81) to the alcohol (83) with the calculated amount of lithium aluminium hydride [35] (cf. p.39) was unsuccessful, an extremely complex mixture being obtained. Accordingly, the sulphone-ester

was hydrolysed and the resulting acid (82) converted into its acid chloride. Reduction of the crude acid chloride with sodium borohydride in dioxan (the procedure recommended by Chaikin and Brown [39]) gave the required alcohol (83) in 70 per cent. yield. Reaction of the alcohol with phosphorus pentachloride gave 4-methoxy-5-nitro-2-p-tolylsulphonylbenzyl chloride (68: R = Me), identical with the abnormal substitution product of the sulphone-dichloride (38).

Reaction of 5-nitro-2-p-tolylsulphonylbenzylidene chloride (38) with other nucleophiles gave results much less well-defined than those described above. Hot aqueous sodium hydroxide caused resinification. With potassium cyanide in aqueous dimethylformamide decomposition to a black solid occurred even at room temperature. Sodium p-toluenesulphinate did not react at all. By interaction of the dichloride and the sodium salt of thio-p-cresol, a mixture was obtained, the nature of which has yet to be determined.

The mixture (see p.36) obtained by reaction of the sulphone-dichloride (38) with sodium carbonate in aqueous methanol was shown by thin-layer chromatography to contain at least five compounds. Chromatography of the mixture on silica gel showed one of the components to be the expected methoxybenzyl chloride (68: R = Me), but the yield was only 17 per cent., compared with 68 per cent. for the corresponding ethoxy-compound. The only



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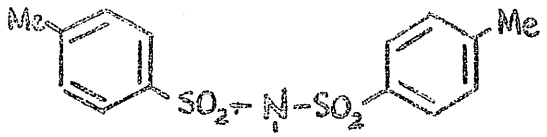

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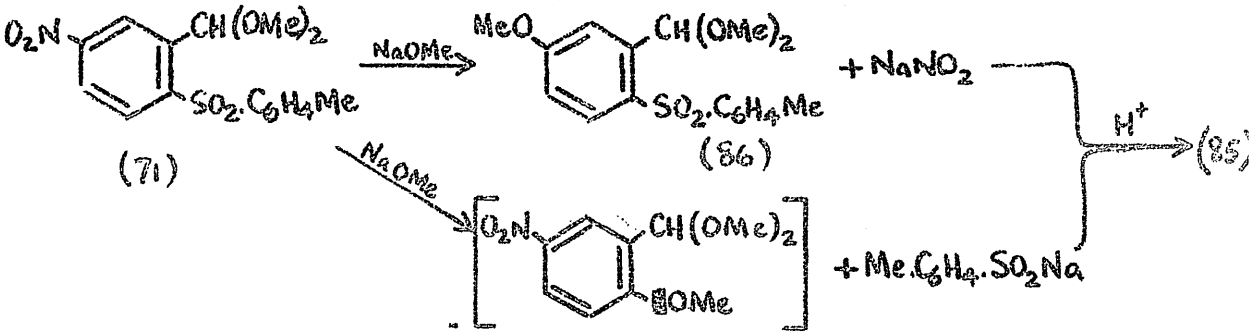
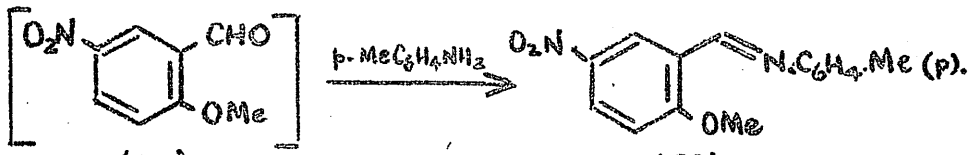
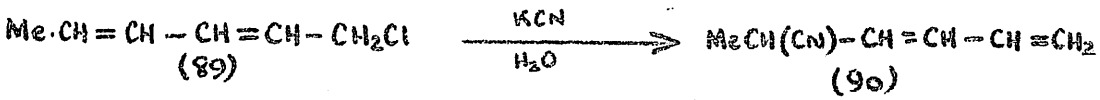


(71) (86) (85)

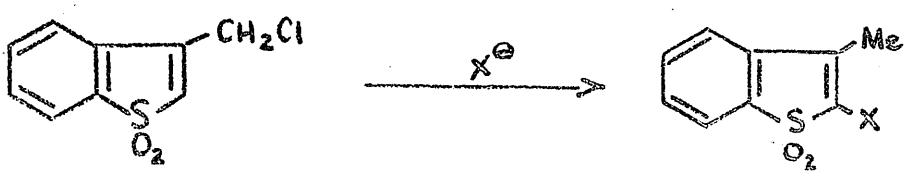


(87) (88).

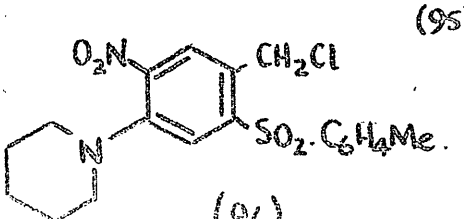


(89) (90)

(91) (92): X = CN (93): X = OMe



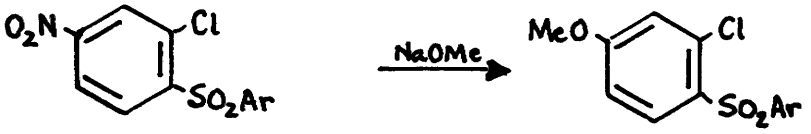
(94) (95) (X = OMe, SPh)



(96)

by-product identified was 4-methoxy-5-nitro-2-p-tolylsulphonylbenzyl p-tolyl sulphone (84), which, as was independently shown, results from the interaction of the benzyl chloride (68: R = Me) and sodium p-toluenesulphinate. The abnormal substitution leading to the formation of (68: R = Me) was therefore concurrent with another causing displacement of the p-tolylsulphonyl group. Mobility of such a substituent was not unexpected, since both the nitro- and arylsulphonyl groups are known [40] to be mobile in derivatives of o- and p-nitrodiphenyl sulphone.

For instance,



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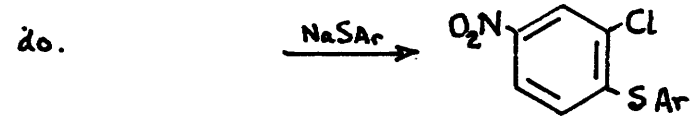
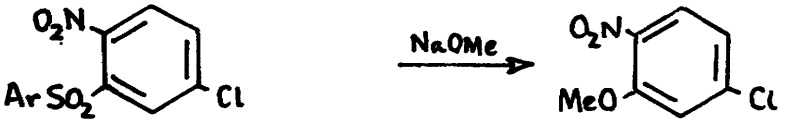


(ref. 41)



(ref. 42)

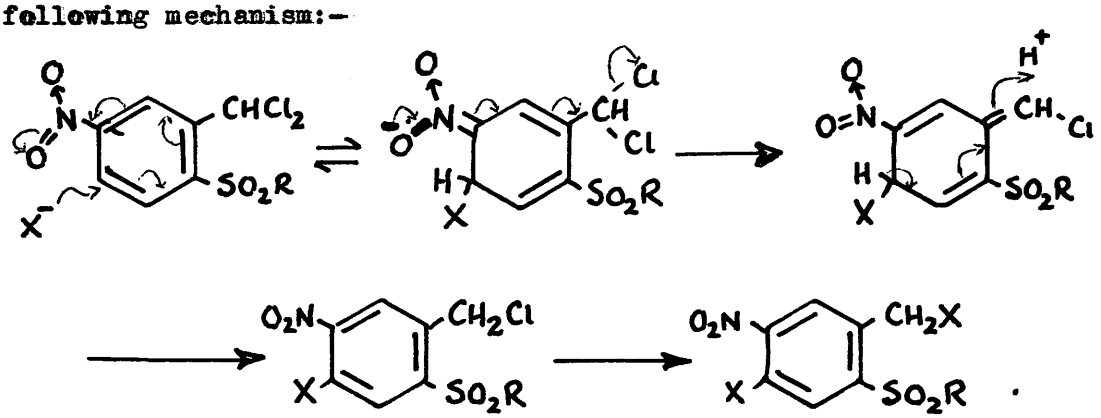
When the acetal (71) was treated with one equivalent of sodium methoxide in methanol, the abnormal reaction such as was observed for the dichloride (38) did not occur. Since the methoxyl groups in the side-chain are much inferior as leaving groups to the chlorine atoms of (38), the methoxide ions can now effect replacement of the nuclear substituents. When the ether-insoluble

portion of the crude reaction product was dissolved in water and the solution acidified, an acidic compound was precipitated; it was identified as di-p-toluenesulphonylhydroxylamine (85) [43], a product formed by combination of nitrous and p-toluenesulphinic acids, and thus indicative of partial replacement of both the nitro- and p-tolylsulphonyl groups.

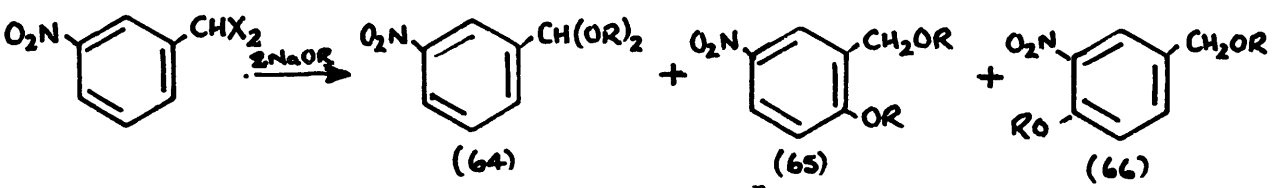
The methoxy-acetal (86), resulting from replacement of the nitro-group, was obtained, together with a gum, by evaporation of the solvent from the ether-soluble fraction. Acid hydrolysis of the gum gave a mixture containing 5-nitro-2-p-tolylsulphonyl-benzaldehyde (35) (from hydrolysis of unreacted acetal) and 2-methoxy-5-nitrobenzaldehyde (87)[44,45], the latter being identified as its p-toluidine Schiff base [45].

DISCUSSION.

The abnormal reaction of 5-nitro-2-p-tolylsulphonylbenzylidene chloride with nucleophiles is satisfactorily represented by the following mechanism:-

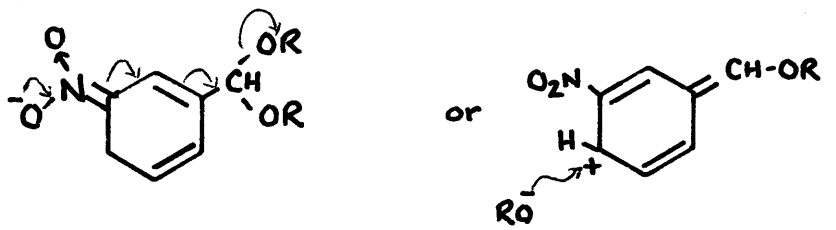


It is therefore a novel and interesting type of nucleophilic aromatic substitution, in which attack by the nucleophile takes place at a position remote from that occupied by the leaving group. Although some S_N2' reactions in the aliphatic (e.g. (89) ⟶ (90) [46]) and heterocyclic (e.g. (91) ⟶ (92) [47] and (93) [48], and (94) ⟶ (95) [49]) fields, are of the same general type, only one truly analogous reaction in a benzenoid system was found in the literature: Kliegl and Hölle's report [29] of the abnormal substitution of m-nitrobenzylidene halides, reference to which has already been made (p.37).



(X = Cl, Br; R = Me, Et, Pr^n.)

Kliegl and Hölle's work has been overlooked in current surveys of nucleophilic aromatic substitution. There seems little doubt that their reaction is an analogue of the two-stage substitution of the sulphone-dichloride, (i.e. (38) ⟶ (68) ⟶ (72)), and that the mechanism does not involve prior formation and subsequent rearrangement of the acetal (64) via either of the intermediates shown below.



The part played by the nitro-group in these abnormal reactions is shown in the proposed mechanism on p.44. That it is a significant part may be seen from the fact that abnormal substitutions of this type are unknown in the case of benzylidene chloride itself or of its o- and p-nitro-derivatives. The effect of the p-tolylsulphonyl group on the course of substitution of the sulphone-dichloride (38) must now be considered.

Comparison of Kliegl and Hölle's results with those described in this Chapter shows a very marked difference in the proportion of abnormal product formed in each case. The yield of abnormal products (65) and (66) obtained by Kliegl and Hölle was always small (10 - 20%), but increased with alkoxides in the order MeO^- < EtO^- < Pr^nO^-, and was more than doubled when m-nitrobenzylidene bromide was used instead of the chloride. On the other hand, the yield of alkoxynitrobenzyl chlorides (68) from the sulphone-dichloride (38) was high (60 - 70%); here also the yield increased on changing from methoxide to ethoxide. The large difference in yields must be accounted for by the presence of the p-tolyl-sulphonyl group.

The effect of the p-tolylsulphonyl group on the course of substitution is probably twofold. Being a bulky group, it will hinder the approach of reagents to the halogen-bearing carbon atom, and so retard the normal reaction sequence. Electrostatic repulsion

of an attacking anion by the negative sulphone oxygens need not be invoked, since the rate of hydrolysis of benzylidene chlorides is independent of the concentration of alkali present [50]. Being an electron-attracting group, the p-tolylsulphonyl group will contribute increased electrophilicity to the aromatic nucleus, and so promote nucleophilic attack there.

The remarkably high yield of the ethoxybenzyl chloride (68: R = Et) from the reaction of the sulphone-dichloride (38) with an excess of sodium carbonate in aqueous ethanol deserves further comment. The expected hydrolysis product, the sulphone-aldehyde, was not detected. It is known, however, that the rate of hydrolysis of benzylidene chlorides in aqueous base is greatly diminished when a nitro-substituent is present [51], and the blocking effect of the p-tolylsulphonyl group will also operate against normal hydrolysis. The survival of the ethoxy-benzyl chloride is surprising, and may perhaps be accounted for by a combination of steric effects and the insolubility of the compound in the reaction medium. Such insolubility is not a characteristic of the corresponding methoxy-compound (68: R = Me), and significantly it is obtained from (38) and aqueous methanolic sodium carbonate in only 17 per cent. yield.

Steric hindrance round the halogen-bearing carbon atom may account for the enhanced yield of abnormal products obtained by

Kliegl and Hölle when m-nitrobenzylidene bromide was used instead of the chloride. A steric effect may also be responsible for the increasing amounts of abnormal products in the series MeO^-, EtO^-, Pr^nO^-, but it is perhaps combined with increase in the nucleophilic character of the reagents, and this may not be exerted equally at the aromatic and aliphatic centres, if the rate of solvolysis of benzylidene chlorides is independent of the concentration of anionic nucleophiles.

It seems most probable that the reaction of the dichloride (38) with piperidine, giving N-(5-nitro-4-piperidino-2-p-tolylsulphonylbenzyl)piperidine (60) proceeds by a two-step mechanism of similar type, although the intermediate piperidinobenzyl chloride (96) was never isolated. Treatment of the dichloride (38) with exactly two equivalents of piperidine resulted in a 50 per cent. recovery of the former, and so it must be inferred that the second replacement occurs significantly more rapidly than the first. Certainly the abnormal reaction appears to involve separation of charges in some intermediate, such as (97), since the yield of (60) increases at the expense of the normal product (35) in solvents of increasing polarity (see Table 3). It is noteworthy, however, that with piperidine a normal reaction product is always found, whereas with alkoxides this is never isolated. This provides a point of contrast between these nucleophilic substitutions and those of the S_N2' type, for which neutral reagents are usually

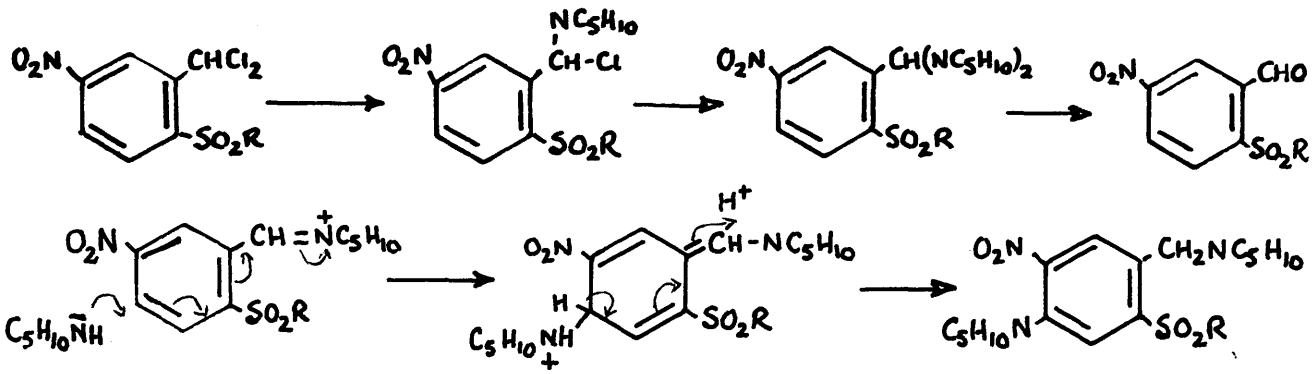
TABLE 3.

Reaction of 5-Nitro-2-p-tolylsulphonylbenzylidene Chloride with Piperidine.

Solvent	Percentage yield of Normal product (35)	Abnormal product (60)
Benzene	43	30
Piperidine	33	43
Dimethylformamide	29	46

more effective than anions.

The possibility that reaction of the dichloride (38) with piperidine may proceed by a different course cannot be ruled out at present. A possible scheme involving an enamine intermediate is shown below.



Further investigations are in progress with a view to determining the exact course followed. Extensions of the present work now

under consideration include the study of parallel reactions in heteroaromatic compounds.

The abnormal nucleophilic substitution of 3-nitrobenzylidene halides, described by Kliegl and Hölle, showed how the effect of the nitro-group in activating the ortho- and para- positions was strong enough to introduce an abnormal reaction course in competition with the normal easy replacement of the reactive halogen atoms in the side-chain. The experiments on the sulphone-dichloride (38) are even more striking: in addition to providing a mechanism for Kliegl and Hölle's reaction, they show how the additional effect of one substituent may alter the situation to such an extent that the normal replacement is almost entirely superseded by the abnormal. This abnormal substitution is another novel reaction encountered in the course of a different investigation, in a field which continues to present interesting problems.

EXPERIMENTAL

EXPERIMENTAL.

Melting points were determined on a Kofler hot-stage apparatus. Infra-red spectra were measured for Nujol mulls on a Perkin-Elmer Infracord spectrophotometer. Chromatographic alumina was standardised according to Brockmann's procedure. Light petroleum used for crystallisation was the fraction of b.p. 60-80°, unless stated otherwise.

CHAPTER 1.

5-Hydroxy-2-nitrobenzaldehyde.- Nitration of m-hydroxybenzaldehyde was carried out in cold benzene solution, as recommended by Hornig [10]. The crude nitration product was washed with hot benzene and recrystallised from water, giving 5-hydroxy-2-nitrobenzaldehyde, m.p. 168-169° (literature value 167-168°) in 33% yield. Methylation with dimethyl sulphate and sodium hydroxide [8] gave 5-methoxy-2-nitrobenzaldehyde, m.p. 81-82° (lit. 83°).

3-Methoxy-2-nitrobenzaldehyde. - Nitration of m-methoxybenzaldehyde according to the procedure of Hodgson and Beard [9] gave 3-methoxy-2-nitrobenzaldehyde, m.p. 98-100° (from benzene; lit. 102°.).

3-Hydroxy-2-nitrobenzaldehyde. - This results from nitration of m-hydroxybenzaldehyde in very small amount (at most ca. 10%)[52], and the method of Ek and Witkop [11] was therefore used. 3-Hydroxy-2-nitrotoluene was prepared [53] by sulphonation of m-cresol, nitration of the resulting disulphonic acid, and steam distillation of the nitration product. Acetylation with acetic anhydride and aqueous sodium hydroxide at 0°, [27b], and oxidation of the acetate with chromium trioxide in acetic anhydride gave 3-acetoxy-2-nitrobenzylidene diacetate, acid hydrolysis of which afforded 3-hydroxy-2-nitrobenzaldehyde, m.p. 152-153° (from ethanol; literature value 157°).

3-Acetyl-8-chloro-1,4-dihydro-1-hydroxy-6-methoxy-2-methyl-4-oxoquinoline (17: R = Me). - A solution of 5-methoxy-2-nitrobenzaldehyde (1 g.) and acetylacetone (0.55 g.) in the minimum volume of dry ether (ca. 40 ml.) was saturated at room temperature with dry hydrogen chloride, cooling being provided by a bath of cold water. The solution was set aside overnight and the crystalline product (the hydrochloride of (17: R = Me)) collected. Recrystallisation from ethanol furnished the free base, (17: R Me), m.p. 221° (decomp.), $\nu_{max.}$ 2500 (broad), 1690 $cm.^{-1}$ (Found: C, 55.4; H, 4.1; N, 5.2. $C_{13}H_{12}ClNO_4$ requires C, 55.4; H, 4.3; N, 5.0%). It reacted (a) with ferric chloride in ethanol, giving a red-brown solution, (b) with acetic anhydride at 100°, giving the 1-acetoxy-

derivative, m.p. 154° (from ethanol), $\nu_{max.}$ 1800, 1680 cm.$^{-1}$ (Found: C, 55·4; H, 4·2. $C_{15}H_{14}ClNO_5$ requires C, 55·7; H, 4·4%), and (c) with dimethyl sulphate and aqueous sodium hydroxide at 20° or with a solution of diazomethane in ether, giving the 1-methoxy-derivative, (19), m.p. 173° (from methanol), $\nu_{max.}$ 1680, 1620 cm.$^{-1}$ (Found: C, 56·7; H, 4·6; N, 4·6. $C_{14}H_{14}ClNO_4$ requires C, 56·9; H, 4·8; N, 4·7%).

3-Acetyl-6-chloro-1,4-dihydro-1-hydroxy-8-methoxy-2-methyl-4-oxoquinoline (18: R = Me), m.p. 198° (from ethanol), was similarly obtained from 3-methoxy-2-nitrobenzaldehyde and acetylacetone. (Found: C, 55·5; H, 4·2; N, 4·9. $C_{13}H_{12}ClNO_4$ requires C, 55·4; H, 4·3; N, 5·0%). It also gave a red-brown colour with ferric chloride in ethanol. The 1-acetoxy-derivative had m.p. 137° (from ethanol), $\nu_{max.}$ 1800, 1680 cm.$^{-1}$ (Found: C, 55·85; H, 4·4; N, 4·6. $C_{15}H_{14}ClNO_5$ requires C, 55·7; H, 4·4; N, 4·3%), and the 1-methoxy-derivative (20) had m.p. 167° (from methanol), $\nu_{max.}$ 1680, 1620 cm.$^{-1}$ (Found: C, 57·1; H, 5·0; N, 5·0. $C_{14}H_{14}ClNO_4$ requires C, 56·9; H, 4·8; N, 4·7%).

3-Acetyl-8-chloro-1,4-dihydro-1,6-dihydroxy-2-methyl-4-oxoquinoline (17: R = H). – When a solution of 5-hydroxy-2-nitrobenzaldehyde (1 g.) and acetylacetone (0·6 g.) in dry ether (ca. 40 ml.) was saturated with dry hydrogen chloride, crystallisation

of the hydrochloride of (17: R = H) began almost immediately. It was collected after 18 hr. (although a second experiment showed that reaction was complete in 2 hr.). Recrystallised from ethanol, it had m.p. 173° (decomp.), $\nu_{max.}$ 2450, 1630 cm.$^{-1}$ (Found: C, 47·6; H, 4·0; N, 4·4. $C_{12}H_{11}Cl_2NO_4$ requires C, 47·4; H, 3·65; N, 4·6%). It dissolved in dilute sodium carbonate, giving a bright yellow solution, which, on careful neutralisation with acetic acid, became green and then blue-violet. Dilution with water precipitated the free base, m.p. 183° (decomp.) (from ethanol), $\nu_{max.}$ 3500, 3350, 2700 (m), 1650 cm.$^{-1}$. (Found: C, 54·0; H, 3·8; N, 5·15. $C_{12}H_{10}ClNO_4$ requires C, 53·9; H, 3·8; N, 5·2%).

Treatment of the hydrochloride with a solution of diazomethane in ether gave the 1,6-dimethoxy-derivative, identical (mixed m.p., infra-red spectrum) with the methylation product (19) of the quinolone (17: R = Me).

3-Acetyl-6-chloro-1,4-dihydro-1,8-dihydroxy-2-methyl-4-oxoquinoline (18: R = H). — A solution of 3-hydroxy-2-nitrobenzaldehyde (1 g.) and acetylacetone (0·6 g.) in dimethylformamide (3 ml.) was saturated with dry hydrogen chloride and the solution set aside. Crystallisation began after about 1 hr.. Addition to water (50 ml.) after 18 hr. gave a yellow solid; this was filtered off, washed with water, and crystallised from acetic acid, affording the quinolone (18: R = H), m.p. 187° (decomp.)

(Found; C, 54·2; H, 3·9; N, 5·2. $C_{12}H_{10}ClNO_4$ requires C, 53·9; H, 3·8; N, 5·2%). It gave a dark green colour with ferric chloride in ethanol, and was converted, by reaction with diazomethane, into the dimethoxy-derivative (20), m.p. and mixed m.p. 167°.

Ethyl 8-chloro-1,4-dihydro-1-hydroxy-6-methoxy-2-methyl-4-oxoquinoline-3-carboxylate (23: R = Me), was obtained from the reaction of 5-methoxy-2-nitrobenzaldehyde, ethyl acetoacetate, and hydrogen chloride in ethereal solution. It had m.p. 207° (decomp.) (from ethanol), $\nu_{max.}$ 1720 cm.$^{-1}$ (Found: C, 54·0; H, 4·7; N, 4·6. $C_{14}H_{14}ClNO_5$ requires C, 53·8; H, 4·5; N, 4·5%). It gave a red-brown colour with ethanolic ferric chloride solution. The 1-acetoxy-derivative had m.p. 138° (decomp.) (from ethanol), $\nu_{max.}$ 1800, 1720 cm.$^{-1}$ (Found: C, 54·1; H, 4·6; N, 3·9. $C_{16}H_{16}ClNO_6$ requires C, 54·3; H, 4·6; N, 4·0%), and the 1-methoxy-derivative (24) had m.p. 145° (from ethanol), $\nu_{max.}$ 1720, 1610 cm.$^{-1}$ (Found: C, 55·2; H, 5·1; N, 4·3. $C_{15}H_{16}ClNO_5$ requires C, 55·3; H, 4·95; N, 4·3%).

Ethyl 8-chloro-1,4-dihydro-1,6-dihydroxy-2-methyl-4-oxoquinoline-3-carboxylate (23: R = H), was obtained as its hydrochloride, m.p. 177° (from ethanol), by the action of dry hydrogen chloride on a solution of 5-hydroxy-2-nitrobenzaldehyde (1 g.) and ethyl acetoacetate (0.78 g.) in dry ether (ca. 40 ml.).

(Found: C, 46·6; H, 3·55; N, 4·5. $C_{13}H_{13}Cl_2NO_5$ requires C, 46·7; H, 3·9; N, 4·2%). It dissolved in aqueous sodium carbonate, giving a bright yellow solution, which, on standing or on neutralisation with acetic acid, developed a violet colour. By dilution of the neutralised solution with water, only a tiny amount of colourless solid was precipitated, and this decomposed on attempted crystallisation, giving a violet solution. The violet colour changed back to yellow on renewed treatment with sodium carbonate solution.

Reaction of the hydrochloride with a solution of diazomethane in ether gave the dimethoxy-derivative (24), m.p. and mixed m.p. 145°.

Ethyl 8-chloro-1,4-dihydro-1,6-dihydroxy-4-oxo-2-phenyl-quinoline-3-carboxylate, (25), was formed as its hydrochloride, m.p. 211–214° (decomp.) by the action of hydrogen chloride on a solution of 5-hydroxy-2-nitrobenzaldehyde (1 g.) and ethyl benzoylacetate (1·15 g.) in dry dimethylformamide (3 ml.). The hydrochloride was partly decomposed by recrystallisation from dimethylformamide; analytical data did not correspond to the hydrochloride or the free base. Reaction of the crude hydrochloride with diazomethane gave the 1,6-dimethoxy-derivative (26), m.p. 165° (from ethanol), $\nu_{max.}$ 1725, 1620 cm.$^{-1}$. (Found: C, 62·2; H, 4·9; N, 3·7. $C_{20}H_{18}ClNO_5$ requires C, 61·9;

H, 4·7; N, 3·6%).

The free base (25) was obtained by treatment of the hydrochloride with aqueous sodium carbonate and then neutralising the yellow solution with acetic acid, but it decomposed readily on attempted crystallisation.

5-Hydroxy-2-nitrobenzylideneacetophenone (27: R = OH). - A solution of 5-hydroxy-2-nitrobenzaldehyde (1 g.) and acetophenone (0·72 g.) in dimethylformamide (3 ml.) was saturated with dry hydrogen chloride and set aside overnight. The dark red solution was added to ice-water and the crude solid product extracted with ether. The extract was clarified by filtration through charcoal, and phenolic material removed by washing with dilute sodium hydroxide solution. Acidification of the alkaline extract gave 5-hydroxy-2-nitrobenzylideneacetophenone (0·7 g.), m.p. 187° (from methanol), (Found: C, 66·7; H, 4·2; N, 5·0. $C_{15}H_{11}NO_4$ requires C, 66·9; H, 4·1; N, 5·2%).

Condensations of o-Nitrobenzaldehyde with Monoketones. - Reaction of o-nitrobenzaldehyde with acetone (ca. 1·5 equivalents) in ethereal hydrogen chloride gave di-o-nitrobenzylideneacetone (6), m.p. 172° (from acetic acid), $\nu_{max.}$ 1670 cm.$^{-1}$ (Found: C, 62·7; H, 3·9; N, 8·5. Calc. for $C_{17}H_{12}N_2O_5$: C, 63·0; H, 3·7; N, 8·6%). Pfeiffer and Segall [54] record m.p. 170·5 - 171°.

2,5-Di-o-nitrobenzylidenecyclopentanone was similarly obtained from o-nitrobenzaldehyde and cyclopentanone. It had m.p. 172° (from ethanol), and $\nu_{max.}$ 1690 cm.$^{-1}$ (Found: C, 65·4; H, 4·2; N, 8·0. Calc. for $C_{19}H_{14}N_2O_5$: C, 65·1; H, 4.0; N, 8·0%). Wallach [55] records m.p. 170·5°.

2,6-Di-o-nitrobenzylidenecyclohexanone had m.p. 147° (from ethanol) and $\nu_{max.}$ 1670 cm.$^{-1}$. (Found: C, 66·2; H, 4·6; N, 7·6. Calc. for $C_{20}H_{16}N_2O_5$: C, 65·9; H, 4·4; N, 7·7%). Wallach [55] records m.p. 142° and Sparatore [56] m.p. 140-142°.

EXPERIMENTAL:

CHAPTER 2.

5-Nitro-2-(p-tolylthio)benzaldehyde (32), m.p. 156° (from acetic acid), was obtained in 94% yield by reaction of 2-chloro-5-nitrobenzaldehyde with the sodium salt of thio-p-cresol in aqueous ethanol [17].

5-Nitro-2-(p-tolylthio)benzylidene Diacetate (34: X= S). - Concentrated sulphuric acid (0·5 ml.) was added to a suspension of the sulphide-aldehyde (32) (20 g.) in acetic anhydride (150 ml.) and the mixture shaken at room temperature until the aldehyde dissolved. The solution was set aside for 2 hr., during which time some of the product crystallised. Addition to cold water (1·5 l.) caused crystallisation of the remainder. The diacetate (24·3 g., 88%) had m.p. 117° (from acetic acid) and $\nu_{max.}$ 1750 cm.$^{-1}$ (Found: C, 57·7; H, 4·3; N, 3·9. $C_{18}H_{17}NO_6S$ requires C, 57·6; H, 4·6; N, 3·7%).

5-Nitro-2-p-tolylsulphonylbenzylidene Diacetate (34: X= SO_2).- A solution of 5-nitro-2-(p-tolylthio)benzylidene diacetate (7 g.) in warm acetic acid (80 ml.) was treated with 30 per cent. hydrogen peroxide solution (60 ml.). The solution, the yellow colour of which rapidly disappeared, was heated at 100° for 45 min., cooled, and added to cold water (600 ml.). The precipitated

sulphone was filtered off, washed with water, dried, and crystallised from acetic acid. It had m.p. 150° (Found: C, 53·0; H, 4·35; N, 3·65. $C_{18}H_{17}NO_8S$ requires C, 53·1; H, 4·2; N, 3·4%). Yield 5·3 g. (70%).

5-Nitro-2-p-tolylsulphinylbenzylidene Diacetate (34: X = SO). - A solution of 5-nitro-2-(p-tolylthio)benzylidene diacetate (30 g.) in acetic acid (900 ml.) was treated at room temperature with portions of 30 per cent. hydrogen peroxide solution (total volume 120 ml.), and the yellow solution set aside at room temperature, with occasional shaking. After 24 hr., the solution, now colourless, was added to ice-water, (3 l.) and the precipitate collected, washed with water, and dried. The sulphoxide-diacetate had m.p. 114° (from methanol) (Found: C, 55·1; H, 4·5; N, 3·5. $C_{18}H_{17}NO_7S$ requires C, 55·2; H, 4·4; N, 3·6%). The diacetate crystallised from benzene-light petroleum with inclusion of benzene (Found: C, 58·4; H, 5·0; N, 3·6. $C_{18}H_{17}NO_7S.\ \frac{1}{2}C_6H_6$ requires C, 58·6; H, 4·7; N, 3·3%). This compound had m.p. 93-95°. Yield 80% .

5-Nitro-2-p-tolylsulphonylbenzaldehyde (35). - The sulphone-diacetate (34: X = SO_2) (5 g.), 6N sulphuric acid (100 ml.), and acetic acid (80 ml.) were heated together under reflux for 30 min.. The aldehyde (35) crystallised from the cooled solution. It had m.p. 144° (from acetic acid), $\nu_{max.}$ 1680 (>C=O), 1530, 1345 (NO_2), 1315, 1155 cm.$^{-1}$ (SO_2). (Found: C, 55·1; H, 3·8; N, 4·7. $C_{14}H_{11}NO_5S$

requires C, 55·1; H, 3·6; N, 4·6%). Yield 3·4 g. (91%).

5-Nitro-2-p-tolylsulphinylbenzaldehyde (33). – Hydrolysis of the sulphoxide-diacetate (34: X = SO) as described for the sulphone (preceding paragraph), and dilution of the resulting solution with water, gave the sulphoxide-aldehyde (33) in 90% yield. It had m.p. 178° (from benzene), $\nu_{max.}$ 1680 (>C=O), 1525, 1340 (NO_2), 1075, 1050, 1030, 1010 $cm.^{-1}$ (SO ?) (Found: C, 58·2; H, 4·1; N, 4·8. $C_{14}H_{11}NO_4S$ requires C, 58·1; H, 3·8; N, 4·8%). It formed an oxime, m.p. 156° (from ethanol ; with melting and re-solidification at ca. 80°) (Found: C, 55·2; H, 4·0; N, 9·0. $C_{14}H_{12}N_2O_4S$ requires C, 55·25; H, 4·0; N, 9·2%), and an orange 2,4-dinitrophenylhydrazone, m.p. 280° (from dimethylformamide – ethanol) (Found: C, 51·1; H, 3·9; N, 16·1 . $C_{20}H_{15}N_5O_7S$. $Me_2N.CHO$ requires C, 50·9; H, 4·1; N, 15·5%).

Reaction of 5-Nitro-2-p-tolylsulphinylbenzaldehyde with Hydrogen Chloride. – A solution of the sulphoxide-aldehyde (33) (1·16 g.) in dimethylformamide (18 ml.) was saturated at room temperature with dry hydrogen chloride, and the yellow solution set aside overnight. The yellow solid which crystallised during this period was separated by decanting off the supernatant liquid, and was identified (mixed m.p., infra-red spectrum) as 5-nitro-2-(p-tolylthio)benzaldehyde (32). Yield 0·13 g.

Addition of the dimethylformamide mother-liquor to ice-water caused precipitation of a cream-coloured solid, m.p. 110-116°, which was shown by thin-layer chromatography to be a mixture of three compounds. Fractional crystallisation of this solid from benzene-light petroleum gave a further crop of the sulphide-aldehyde (32) (0·31 g.; total yield 0·44 g., 40%), and a small amount (0·04 g.) of unreacted sulphoxide-aldehyde. The remainder of the mixture was chromatographed on alumina (Grade I); elution with benzene containing a trace of ether gave a colourless compound (0·41 g.), m.p. 142° (from ethanol), identified as 5-nitro-2-p-tolylsulphonylbenzylidene chloride (38) by comparison with an authentic sample (see below). Yield 29%. Elution with methanol afforded further sulphoxide - aldehyde (0·10 g.; total recovery 12%).

5-Nitro-2-(p-tolylthio)benzylidene Chloride. (39). - A mixture of 5-nitro-2-(p-tolylthio)benzaldehyde (32) (10 g.) and phosphorus pentachloride (20 g.) was heated under reflux for 5 min., cooled, and the semi-solid mass treated with crushed ice and then with water. The oily product was extracted with benzene, and the extract washed with sodium bicarbonate solution and then with water, dried ($MgSO_4$) and evaporated. The crude sulphide-dichloride (39), an oil, was purified by filtration of a solution in benzene through a column of alumina (Grade I).

Evaporation of the benzene afforded the dichloride (7·8 g., 65%) as a cream-coloured solid, m.p. 75° (from light petroleum). (Found: C, 51·1; H, 3·3; N, 4.4. $C_{14}H_{11}Cl_2NO_2S$ requires C, 51·2; H, 3·4; N, 4·3%).

When the sulphide-dichloride (39) was hydrolysed by heating with aqueous sulphuric acid and acetic acid for 3 hr., the aldehyde (32) was regenerated. When cold concentrated sulphuric acid was used, hydrogen chloride was liberated, and the resulting dark red solution gave, by addition to water, a mixture of 2-methyl-7-nitrothioxanthone (40) and 2-methyl-7-nitrothioxanthen (41), separated by fractional crystallisation [17] and identified by comparison with authentic samples [17].

5-Nitro-2-p-tolylsulphonylbenzylidene Chloride (38). - (a) 5-Nitro-2-p-tolylsulphonylbenzaldehyde (35) (1 g.) and phosphorus pentachloride (2 g.) were heated together under reflux for 5 min., cooled, and the resulting solid treated with crushed ice, then with water. The crude solid dichloride was dissolved in benzene, and the washed ($NaHCO_3$, H_2O) and dried ($MgSO_4$) solution chromatographed on alumina (Grade I). (b) A solution of 5-nitro-2-(p-tolylthio)benzylidene chloride (0·1 g.) in acetic acid (2 ml.) was treated with 30 per cent. hydrogen peroxide solution (1 ml.), and the mixture heated for 1 hr. at 100°, cooled, and added to water. The sulphone-dichloride (38)

obtained in each case (yield 82 and 68 per cent. respectively) had m.p. 142° (from ethanol or acetic acid) (Found: C, 46.95; H, 3.3%) or m.p. 138° (from aqueous acetic acid or benzene–light petroleum) (Found: C, 46.55; H, 3.15; N, 4.1. $C_{14}H_{11}Cl_2NO_4S$ requires C, 46.7; H, 3.1; N, 3.9%).

Reaction of 5-Nitro-2-(p-tolylthio)benzaldehyde (32) with Chlorine. – A solution of the sulphide-aldehyde (32) (1 g.) in dimethylformamide (15 ml.) was saturated with dry chlorine at room temperature, and set aside overnight. Addition to ice-water caused precipitation of a colourless solid. This was filtered off, dissolved in benzene, and the washed ($NaHCO_3$, H_2O) and dried ($MgSO_4$) solution chromatographed on alumina (Grade I). Elution with 10% ether–benzene gave the sulphone-dichloride (38), (0.54 g., 41%), and with pure ether gave the sulphone-aldehyde (35) (0.49 g., 44%).

Reactions of 5-Nitro-2-p-tolylsulphonylbenzylidene Chloride.

(a) Oxidation. A solution of sodium dichromate (0.4 g.) in water (1 ml.) and concentrated sulphuric acid (0.5 ml.) was added to a solution of 5-nitro-2-p-tolylsulphonylbenzylidene chloride (38) (0.1 g.) in acetic acid (3 ml.), and the mixture heated under reflux for 2 hr., cooled, and poured into water. 5-Nitro-2-p-carboxyphenylsulphonylbenzylidene chloride (42)

was precipitated. It had m.p. 250° (from acetic acid) (Found: C, 43·2; H, 2·3; N, 3·8; Cl, 18·2. $C_{14}H_9Cl_2NO_6S$ requires C, 43·1; H, 2·3; N, 3·6; Cl, 18·2%). Yield 69%. The sulphone-dichloride (38) was not oxidised by hydrogen peroxide in acetic acid at 100°, or by a boiling aqueous solution of potassium permanganate and sodium carbonate.

(b) Attempted Hydrolysis. The sulphone-dichloride (38) was recovered unchanged from attempted acid hydrolysis, as follows:-

(i) A solution of the dichloride in concentrated sulphuric acid was set aside overnight, and was then poured on to crushed ice.

(ii) A solution of the dichloride (0·1 g.) in a mixture of acetic acid (2·5 ml.), water(1 ml.), and concentrated sulphuric acid (0·5 ml.) was heated under reflux for 10 hr., cooled, and added to water.

(c) With Piperidine. The dichloride (0·3 g.) and piperidine (3 ml.) were heated together for 5 min., cooled, and the semi-solid mass treated with crushed ice. The orange product was dissolved in concentrated hydrochloric acid (colourless solution), and on gentle warming, the sulphone-aldehyde (35), m.p. and mixed m.p. 140-142°, was precipitated.

4-Nitro-2-(p-tolylthio)- and 2-Nitro-4-(p-tolylthio)-benzylidene Diacetates. - 2,4-Dinitrobenzaldehyde was treated with thio-p-cresol and sodium hydroxide in aqueous ethanol

according to the procedure of Loudon et al.[17], giving a mixture of 4-nitro-2-(p-tolylthio)- (43) and 2-nitro-4-(p-tolylthio)-benzaldehydes(44). A portion of this mixture (1·36 g.) was suspended in acetic anhydride (10 ml.), and concentrated sulphuric acid (0·03 ml.) was added. The suspension was shaken until the aldehyde had dissolved, and the brick-red solution set aside for 3 hr., by which time some crystals had formed. The acetic anhydride was removed by stirring with water (100 ml.), and the yellow solid filtered off and crystallised from acetic acid, affording 4-nitro-2-(p-tolylthio)benzylidene diacetate, (1·11 g.), as yellow prisms, m.p. 129° (Found: C, 57.55; H, 4·7%). A second crop of crystals (0·30 g.) from the acetic acid mother-liquor was of a much lighter colour, and a third crop (0·28 g.) was obtained by diluting the solution with water. This compound, 2-nitro-4-(p-tolylthio)-benzylidene diacetate, crystallised from ethanol in fine cream-coloured needles, m.p.104° (Found: C, 57·4; H, 4·6; N, 3·9. $C_{18}H_{17}NO_6S$ requires C, 57·6; H, 4·6; N, 3·7%).

Identification of these diacetates was accomplished by preparation from the corresponding pure aldehydes (43) and (44) by the process described on p. 60 for the 5-nitro-2-(p-tolylthio)-isomer (34: X = S).

4-Nitro-2-p-tolylsulphinylbenzylidene diacetate, was formed in 68% yield by oxidation of the corresponding sulphide with

hydrogen peroxide in acetic acid under the conditions described on p. 61 for the 5-nitro-isomer. It crystallised from methanol in two forms: rapid cooling of the saturated solution gave needles, m.p. 144-148°; when cooling was slow, the diacetate was obtained as tiny hard prisms, m.p. 140° (Found: C, 55·1; H, 4·5; N, 3·75. $C_{18}H_{17}NO_7S$ requires C, 55·2; H, 4·4; N, 3·6%).

4-Nitro-2-p-tolylsulphinylbenzaldehyde (45). - Hydrolysis of the sulphoxide-diacetate, as described for the 5-nitro-series on pp. 61-62, gave the aldehyde as bright yellow plates, m.p. 211° (from benzene-light petroleum) in 92% yield. (Found: C, 58·4; H, 3·9; N, 5·0. $C_{14}H_{11}NO_4S$ requires C, 58·1; H, 3·8; N, 4·8%).

2-Nitro-4-p-tolylsulphinylbenzylidene diacetate had m.p. 143° (from methanol) (Found: C, 55·0; H, 4·6; N, 3·7. $C_{18}H_{17}NO_7S$ requires C, 55·2; H, 4·4; N, 3·6%), and 2-nitro-4-p-tolylsulphinylbenzaldehyde (46) had m.p. 137° (from benzene-light petroleum) (Found: C, 57·8; H, 3·8; N, 5·0. $C_{14}H_{11}NO_4S$ requires C, 58·1; H, 3·8; N, 4·8%).

4-Nitro-2-p-tolylsulphonylbenzylidene diacetate was prepared by oxidation of the corresponding sulphide as described on p. 60 for the 5-nitro-isomer. It had m.p. 165° (from acetic acid) (Found: C, 53·1; H, 4·25. $C_{18}H_{17}NO_8S$ requires C, 53·1; H, 4·2%).

4-Nitro-2-p-tolylsulphonylbenzaldehyde (47) had m.p. 181° (from acetic acid) (Found: C, 55·1; H, 3·8. $C_{14}H_{11}NO_5S$ requires C, 55·1; H, 3·6%).

4-Nitro-2-p-tolylsulphonylbenzylidene Chloride (48). - A mixture of the sulphone-aldehyde (47) (0·2 g.) and phosphorus pentachloride (0.4 g.) was heated under reflux for 5 min., and the product isolated in the same way as the isomeric compound (38) (see p. 64). The sulphone-dichloride (48) (0·20 g., 85%) had m.p. 145° (from ethanol). (Found: C, 46·9; H, 3·25; N, 4·1. $C_{14}H_{11}Cl_2NO_4S$ requires C, 46·7; H, 3·1; N, 3·9%).

Reaction of 4-Nitro-2-p-tolylsulphinylbenzaldehyde (45) with Hydrogen Chloride. - A solution of the aldehyde (0·5 g.) in dimethylformamide (10 ml.) was saturated with dry hydrogen chloride and set aside overnight. The yellow semi-solid mass was stirred with crushed ice, cold water was added, and the yellow solid filtered off, washed, and dried. Crystallisation from acetic acid gave the sulphide-aldehyde (43) (0·16 g., 34%), m.p. and mixed m.p. 147°. The acetic acid mother-liquor was evaporated, and the residue crystallised from benzene-light petroleum, giving the sulphone-dichloride (48), (0.14 g., 23%), m.p. and mixed m.p. 144-145°.

Reaction of 4-Nitro-2-(p-tolylthio)benzaldehyde (43) with

Chlorine. - Under the conditions described for the 5-nitro-isomer on p. 65, a mixture of sulphone-aldehyde (47) and sulphone-dichloride (48) was obtained.

5-Nitro-2-p-tolylsulphinylbenzophenone (49). - To a solution of 5-nitro-2-(p-tolylthio)benzophenone [17] (4 g.) in acetic acid (80 ml.) at 100° was added 30 per cent. hydrogen peroxide solution (16 ml.), and the solution heated at 100° for 4 min., cooled, and poured on to crushed ice. The precipitated sulphoxide (49) was filtered off, washed, dried, and crystallised from ethanol containing a little acetic acid. It had m.p. 154° (Found: C, 65·9; H, 4·3; N, 4·0. $C_{20}H_{15}NO_4S$ requires C, 65·7; H, 4·1; N, 3·8%). Yield 3·66 g. (88%).

Reaction of 5-Nitro-2-p-tolylsulphinylbenzophenone with Hydrogen Chloride. - This reaction, carried out in the usual way (cf. p. 62) on the sulphoxide-ketone (0·5 g.) in dimethylformamide (10 ml.), gave the sulphide-ketone (0·40 g., 88%). A little unchanged sulphoxide was recovered. The products were purified by chromatography on silica gel; elution with benzene gave the sulphide, and with methanol the sulphoxide.

Reaction of 5-Nitro-2-p-tolylsulphinylbenzaldehyde (33) with Phosphorus Pentachloride. - The aldehyde (0·5 g.) and phosphorus pentachloride (1 g.) were mixed. Heat was evolved,

as a vigorous reaction set in; when, after a few minutes, this subsided, a clear yellow liquid remained. It was boiled for 5 min., then cooled, and treated with crushed ice and water. The yellow oil was extracted with benzene, and the extract washed ($NaHCO_3$, H_2O), dried ($MgSO_4$), and evaporated. Crystallisation took place when the oil was chilled and triturated with methanol; the product (0·34 g.) was identified, by comparison with an authentic sample, as 5-nitro-2-(p-tolylthio)benzylidene chloride (39). The methanol was evaporated, and the residue was dissolved in a 3 : 1 benzene–light petroleum mixture and chromatographed on alumina (Grade I). A further quantity of sulphide-dichloride (39) (0·10 g.) was obtained by elution with the same 3 : 1 mixture (total yield 79%). Elution with benzene containing a little ether gave the sulphone-dichloride (38) (0·02 g., 3%).

5-Nitro-2-p-tolylsulphinylbenzylidene Chloride (51). – To a solution of 5-nitro-2-(p-tolylthio)benzylidene chloride (39) (4 g.) in acetic acid (80 ml.) at 100° was added 30 per cent. hydrogen peroxide solution (16 ml.), and the resulting solution heated at 100° for 3 min., then cooled and added to crushed ice. The colourless solid was filtered off, washed with water, dried in vacuo, and crystallised from light petroleum (b.p. 100–120°). The sulphoxide-dichloride (51) (2·47 g., 59%) had m.p. 163–166° (
(Found: C, 48·6; H, 3·1; N, 4·2. $C_{14}H_{11}Cl_2NO_3S$ requires C, 48·85;

H, 3·2; N, 4·1%). The melting point depends on the rate of heating of the sample; slow heating gave a value of 157-166°.

Reaction of the sulphoxide-dichloride (51) with hydrogen chloride in dimethylformamide gave the sulphide-dichloride (39) in 96% yield, and with chlorine in dimethylformamide, the sulphone-dichloride (38) was produced in 67% yield.

Reactions listed in Tables 1 and 2 (pp. 26-27). -These reactions were carried out in dimethylformamide (except for No. 3 in Table 1), according to the method described on p. 62 and p.65. Products were separated, if necessary, by chromatography, and crystallised from the appropriate solvents. The variations in the starting materials are set out below.

Table 1.

1. Hydrogen chloride. See p. 62.
2. Hydrogen chloride and phenol. Aldehyde (145 mg.) and phenol (47 mg., 1 equivalent) in 2 ml. solvent.
3. Hydrogen chloride and benzene. Aldehyde (145 mg.) dissolved in benzene (8 ml.)
4. Hydrogen chloride and chlorine. Aldehyde (500 mg.) in 8 ml. solvent was saturated with a mixture of approximately equal (v/v) amounts of hydrogen chloride and chlorine.
5. p-Toluenesulphonic acid and chlorine. Aldehyde (300 mg.) and acid (300 mg.) in 4 ml. solvent.

6. Chlorine. Aldehyde (1 g.) in 15 ml. solvent.

7. Phosphorus pentachloride. See p. 80.

Table 2.

1. Chlorine. See p.65.

2. Chlorine and potassium carbonate. Aldehyde (500 mg.) in 8 ml. solvent containing in suspension AnalaR potassium carbonate (1 g.)

3. Chlorine and pyridine. Aldehyde (500 mg.) in dimethylformamide (8 ml.) and pyridine (1 ml.)

4. Chlorine and p-toluenesulphonic acid. As in Table 1, No. 5.

5. Chlorine and hydrogen chloride. As in Table 1, No. 4.

6. Hypochlorous acid. See below.

7. Hydrogen chloride. Aldehyde (300 mg.) in 4 ml. solvent.

Reaction of 5-Nitro-2-(o-tolylthio)benzaldehyde with Hypochlorous Acid. — A solution of the sulphide-aldehyde (0.3 g.) in dimethylformamide (5 ml.) and water (0.5 ml.) was treated with a solution of N-chlorosuccinimide (0.3 g.; ca. 2 equivalents) in dimethylformamide (1 ml.). A mixture of concentrated sulphuric acid (0.2 ml.), water (0.2 ml.), and dimethylformamide (1 ml.) was added, and the mixture shaken until the initially formed yellow precipitate re-dissolved. The solution quickly became colourless; after 18 hr., it was poured into ice-water. The colourless product

was washed with sodium carbonate solution (to remove succinimide), and then with water, and crystallised from acetic acid, giving the sulphone-aldehyde (35), (0·26 g., 77%), m.p. and mixed m.p. 140–142°.

EXPERIMENTAL:

CHAPTER 3.

Reaction of 5-Nitro-2-p-tolylsulphonylbenzylidene Chloride (38) with Piperidine. - The dichloride (38) (0·3 g.) was heated with piperidine (3 ml.) at 100° for 5 min., cooled, and the semi-solid mass added to crushed ice. The orange-yellow product was filtered off and washed with water.

(a) The solid was dissolved in concentrated hydrochloric acid (colourless solution). When the solution was gently heated for a few minutes, 5-nitro-2-p-tolylsulphonylbenzaldehyde (35), m.p. and mixed m.p. 140-142°, was precipitated. The acid solution, when made strongly alkaline, yielded N-(5-nitro-4-piperidino-2-p-tolylsulphonylbenzyl)-piperidine (60). On crystallisation from light petroleum containing a little benzene, it had m.p. 154° (Found: C, 63·1; H, 6·8; N, 8·8. $C_{24}H_{31}N_3O_4S$ requires C, 63·0; H, 6·8; N, 9·2%).

(b) A solution of the crude reaction product in benzene was chromatographed on silica gel. Elution with benzene gave the sulphone-aldehyde (35) (85 mg., 33%) and with 10% ether-benzene the orange dipiperidino-compound (60) (165 mg., 43%).

4-Ethoxy-5-nitro-2-p-tolylsulphonylbenzyl Chloride (68: R = Et). - (a) 5-Nitro-2-p-tolylsulphonylbenzylidene chloride (38) (0.36 g.) was suspended in a solution of sodium ethoxide

(from sodium, 0·023 g.) in dry ethanol (5 ml.), and the mixture heated under reflux for 1 hr. . (b) The dichloride (38) (0·5 g.), AnalaR sodium carbonate (0·5 g.), ethanol (40 ml.), and water (10 ml.) were heated together under reflux for 1½ hr. .

In each case the product crystallised out as the reaction proceeded, and was filtered off from the cooled solution. It was washed with hot water, dried *in vacuo*, and recrystallised from benzene–light petroleum. The chloride (68: R = Et) had m.p. 194°. (Found: C, 52·2; H, 4·3; N, 4·0. $C_{16}H_{16}ClNO_5S$ requires C, 52·0; H, 4·4; N, 3·9%). Yields: (a) 70%, (b) 68%.

4-Ethoxy-5-nitro-2-p-tolylsulphonylbenzyl ethyl ether (72: R = Et), m.p. 116° (from ethanol), was formed by interaction of the chloride (68: R Et) and 1 equivalent of sodium ethoxide in ethanol; a solution of the reagents was boiled for 30 min. and concentrated *in vacuo*, and the ether purified by chromatography of a benzene solution on alumina. (Found : C, 56·75; H, 5·6; N, 3·7. $C_{18}H_{21}NO_6S$ requires C, 57·0; H, 5·6; N, 3·7%).

N-(4-Ethoxy-5-nitro-2-p-tolylsulphonylbenzyl)-piperidine (70: R = Et), produced when the chloride (68: R Et) (0·1 g.) and piperidine (1 ml.) were heated together at 100° for 5 min., had m.p. 136° (from ethanol). (Found: C, 60·4; H, 6·4; N, 6·7. $C_{21}H_{26}N_2O_5S$ requires C, 60·3; H, 6·3; N, 6·7%).

4-Methoxy-5-nitro-2-p-tolylsulphonylbenzyl chloride (68: R = Me), m.p. 160° (from acetic acid – methanol), was formed in 58% yield by the interaction of the dichloride (38) and 1 equivalent of sodium methoxide in methanol under the conditions described on p. 75 for the 4-ethoxy-analogue. (Found: C, 50.7; H, 4.0; N, 4.1. $C_{15}H_{14}ClNO_5S$ requires C, 50.6; H, 4.0; N, 3.9%). The derived benzyl methyl ether (72: R = Me) had m.p. 104° (from methanol) (Found: C, 54.4; H, 5.05; N, 4.0. $C_{16}H_{17}NO_6S$ requires C, 54.7; H, 4.9; N, 4.0%), and the N-benzylpiperidine (70: R = Me) had m.p. 134° (from methanol) (Found: C, 59.2; H, 5.9; N, 7.0. $C_{20}H_{24}N_2O_5S$ requires C, 59.4; H, 6.0; N, 6.9%).

The reaction of the dichloride (38) with sodium carbonate in aqueous methanol gave a mixture of products; this was chromatographed in benzene on silica gel. Elution with benzene gave the chloride (68: R = Me) in 17% yield. A solid obtained by elution with 10% ether–benzene was identified (mixed m.p., infra-red spectrum) as 4-methoxy-5-nitro-2-p-tolylsulphonylbenzyl p-tolyl sulphone (84) (see below).

Methyl 2,4-Dichloro-5-nitrobenzoate (75). – A solution of 2,4-dichloro-5-nitrobenzoic acid [31] (25 g.) in methanol (125 ml.) and concentrated sulphuric acid (12.5 ml.) was heated under reflux for 5 hr., and then concentrated until it became turbid. The methyl ester, which crystallised from the cooled solution, had m.p. 62° (from methanol). (literature [31] value 62°). Yield 23.4 g.

Methyl 2-Chloro-4-methoxy-5-nitrobenzoate (76). – A solution of sodium methoxide (from sodium, 1.85 g.) in dry methanol (50 ml.) was added to a warm solution of methyl 2,4-dichloro-5-nitrobenzoate (75) (20 g.) in dry methanol (250 ml.), and the mixture heated under reflux for 1 hr., then concentrated to ca. 200 ml., and cooled. The crystalline product was collected, washed with hot water, dried *in vacuo*, and recrystallised from methanol, giving the required chloro-methoxy-ester (76) (12.4 g., 63%), m.p. 135° (Found: C, 43.9; H, 3.4. $C_9H_8ClNO_5$ requires C, 44.0; H, 3.3%). The mother-liquors were combined and concentrated, affording a solid of m.p. 60–78°, a portion of which was chromatographed in benzene on alumina (Grade I). A fraction eluted with benzene and repeatedly crystallised from methanol gave methyl 4-chloro-2-methoxy-5-nitrobenzoate (77), m.p. 103° (Found: C, 43.9; H, 2.9%). Goldstein and Schaaf [37] record m.p. 107.5°. Elution with 25% benzene–ether gave methyl 2,4-dimethoxy-5-nitrobenzoate (78), m.p. 149° (from methanol). (Found: C, 49.8; H, 4.85. Calc. for $C_{10}H_{11}NO_6$: C, 49.8; H, 4.6%). Goldstein and Jaquet [38] record m.p. 150°.

Methyl 4-Methoxy-5-nitro-2-(p-tolylthio)benzoate (79). – To a warm solution of methyl 2-chloro-4-methoxy-5-nitrobenzoate (76) (12.3 g.) and thio-p-cresol (6.2 g.) in dry methanol (200 ml.) was added AnalaR potassium carbonate (3.5 g.), and the mixture heated under reflux for 2 hr., and filtered hot. The pale yellow

solid was washed with hot water, and recrystallised from acetic acid. The sulphide-ester (79) had m.p. 213° (Found: C, 57·5; H, 4·5; N, 4·3. $C_{16}H_{15}NO_5S$ requires C, 57.65; H, 4·5; N, 4·2%). Unreacted chloro-methoxy-ester (76) (3·0 g.) crystallised from the cooled filtrate. It was treated with the appropriate amounts of thio-p-cresol and potassium carbonate, so giving more of the sulphide-ester (79), the total yield of which was 12·7 g. (76%).

4-Methoxy-5-nitro-2-(p-tolylthio)benzoic Acid, m.p. 263° (from acetic acid), was obtained when the ester (79) (0·5 g.) was heated with acetic acid (20 ml.), water (10 ml.), and concentrated sulphuric acid (10 ml.) for 5 hr., and the cooled solution poured into water. (Found: C, 56·5; H, 3·9; N, 4·4. $C_{15}H_{13}NO_5S$ requires C, 56·4; H, 4·1; N, 4·4%). It was cyclodehydrated to 3-methoxy-7-methyl-2-nitrothioxanthone (80) by heating with concentrated sulphuric acid for 15 min. at 100° and pouring the resulting dark red solution on to crushed ice. The thioxanthone had m.p. 293° (from dimethylformamide), $\nu_{max.}$ 1630 cm.$^{-1}$. (Found: C, 59·9; H, 3·75; N, 4·7. $C_{15}H_{11}NO_4S$ requires C, 59·8; H, 3·7; N, 4·65%).

Methyl 4-Methoxy-5-nitro-2-p-tolylsulphonylbenzoate (81). — A solution of the sulphide-ester (79) (10 g.) in acetic acid (300 ml.) at 100° was treated with 30 per cent. hydrogen peroxide solution (100 ml.), and the solution heated at 100° for 30 min.

cooled, and added to ice-water. The sulphone-ester (81) so obtained (9.64 g., 88%) had m.p. 165° (from acetic acid). (Found: C, 52.85; H, 4.3; N, 4.1. $C_{16}H_{15}NO_7S$ requires C, 52.6; H, 4.1; N, 3.8%).

4-Methoxy-5-nitro-2-p-tolylsulphonylbenzoic Acid (82). - A solution of the sulphone-ester (81) (8 g.) in acetic acid (200 ml.) water (70 ml.), and concentrated sulphuric acid (80 ml.) was heated under reflux for 4 hr., cooled, and added to water. The precipitated acid, crystallised from aqueous acetic acid, had m.p. 242°. (Found: C, 51.2; H, 3.9; N, 4.2. $C_{15}H_{13}NO_7S$ requires C, 51.3; H, 3.7; N, 4.0%). Yield 7.4 g. (96%).

4-Methoxy-5-nitro-2-p-tolylsulphonylbenzyl Alcohol (83). - Thionyl chloride (15 ml.) was added to a suspension of 4-methoxy-5-nitro-2-p-tolylsulphonylbenzoic acid (82) (1 g.) in benzene (20 ml.), and the mixture heated under reflux until the acid had dissolved and evolution of fumes had ceased (ca. 1½ hr.). Evaporation of the solution *in vacuo* gave the acid chloride as a colourless crystalline solid. Residual thionyl chloride was removed by distillation with benzene.

A solution of the acid chloride in AnalaR dioxan (30 ml.) was added dropwise to a stirred suspension of sodium borohydride (1 g.) in AnalaR dioxan (25 ml.). The reaction mixture was then stirred for a further 30 min. at room temperature, heated under reflux for 1 hr., cooled, and poured into ice-water.

Crystallisation of the solid product from methanol gave the alcohol (83) (0.68 g., 70%), m.p. 157°. (Found: C, 53·25; H, 4·5; N, 4·2. $C_{15}H_{15}NO_6S$ requires C, 53·4; H, 4·5; N, 4·15%).

A mixture of the alcohol (0·2 g.) and phosphorus pentachloride (1 g.) was heated (violent reaction!) until a clear melt was obtained. This was allowed to stand for 10 min. at 100°, and was then cooled and added to ice-water. The solid product was extracted with benzene, and the extract washed, dried, and evaporated, giving 4-methoxy-5-nitro-2-p-tolylsulphonylbenzyl chloride (68: R = Me), m.p. and mixed m.p. 156-158°. Yield 59%.

4-Methoxy-5-nitro-2-p-tolylsulphonylbenzyl p-tolyl sulphone (84) was formed when a solution of the chloride (68: R = Me) (0.18 g.) and sodium p-toluenesulphinate (0·15 g.) in dimethylformamide (2·5 ml.) and water (0.5 ml.) was heated at 100° for 2 hr. . The solution was diluted with water (1 ml.), and cooled. The bis-sulphone (84) crystallised out. It had m.p. 166° (from methanol). (Found: C, 55·3; H, 4·3; N, 3·0. $C_{22}H_{21}NO_7S_2$ requires C, 55·6; H, 4·45; N, 2·95%). Yield 0.21 g. (85%).

α,α-Dimethoxy-5-nitro-2-p-tolylsulphonyltoluene (71). - A suspension of 5-nitro-2-p-tolylsulphonylbenzaldehyde (35) (1 g.) in methanol (2 ml.) was treated with concentrated sulphuric acid (0.3 ml.) . After a few minutes, the suspension became sticky,

and it was rubbed with a glass rod; a crystalline solid gradually separated. This was washed with sodium carbonate solution and then with water, dried, and recrystallised from methanol. The acetal so obtained (0.70 g.) had m.p. 107°. (Found: C, 54.8; H, 4.7; N, 4.4. $C_{16}H_{17}NO_6S$ requires C, 54.7; H, 4.9; N, 4.0%).

Reaction of the Acetal (71) with Sodium Methoxide. - A solution of the acetal (0.35 g.) and sodium methoxide (from sodium, 0.023 g.) in dry methanol (4 ml.) was heated under reflux for 2 hr.; the methanol was evaporated, and the residue extracted with ether. The ether-insoluble solid was dissolved in water, and acidified. The colourless precipitate was collected and identified as di-p-toluenesulphonylhydroxylamine (85), m.p. 120-122°(decomp.) (from methanol) (Found: C, 49.25; H, 4.2. Calc. for $C_{14}H_{15}NO_5S_2$: C, 49.3; H, 4.4%). The mixed m.p. with an authentic sample [43] (m.p. 120-124°: lit. m.p. 125° (decomp.)) was undepressed, and the two samples had identical infra-red spectra.

Evaporation of the ether extract at room temperature gave a mixture of colourless crystals and a yellow gum. The former, washed free from gum with a little ether, were recrystallised from methanol, giving 5,α,α-trimethoxy-2-p-tolylsulphonyltoluene (86), m.p. 105°. (Found: C, 60.2; H, 5.9. $C_{17}H_{20}O_5S$ requires C, 60.7; H, 6.0%).

The gum was hydrolysed by boiling with 6N sulphuric acid (3 ml.) and acetic acid (2 ml.) for 1 hr., and the products

isolated by addition to water and extraction with ether. The washed ($NaHCO_3$, H_2O) and dried ($MgSO_4$) extract afforded on evaporation a mixture, one component of which was sparingly soluble in ether. It was identified (m.p., infra-red spectrum) as 5-nitro-2-p-tolylsulphonylbenzaldehyde (35). The ether-soluble portion was extracted with boiling water, and a low-melting solid crystallised from the cooled extract. Its infra-red spectrum was almost identical with that of 2-methoxy-5-nitrobenzaldehyde [44,45] (87). It was converted, by heating for a few minutes with a solution of p-toluidine in ethanol, into N-(2-methoxy-5-nitrobenzylideme)-p-toluidine (88) [45], m.p. and mixed m.p. 163-165° (from ethanol).

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14. [illegible]

15. [illegible]

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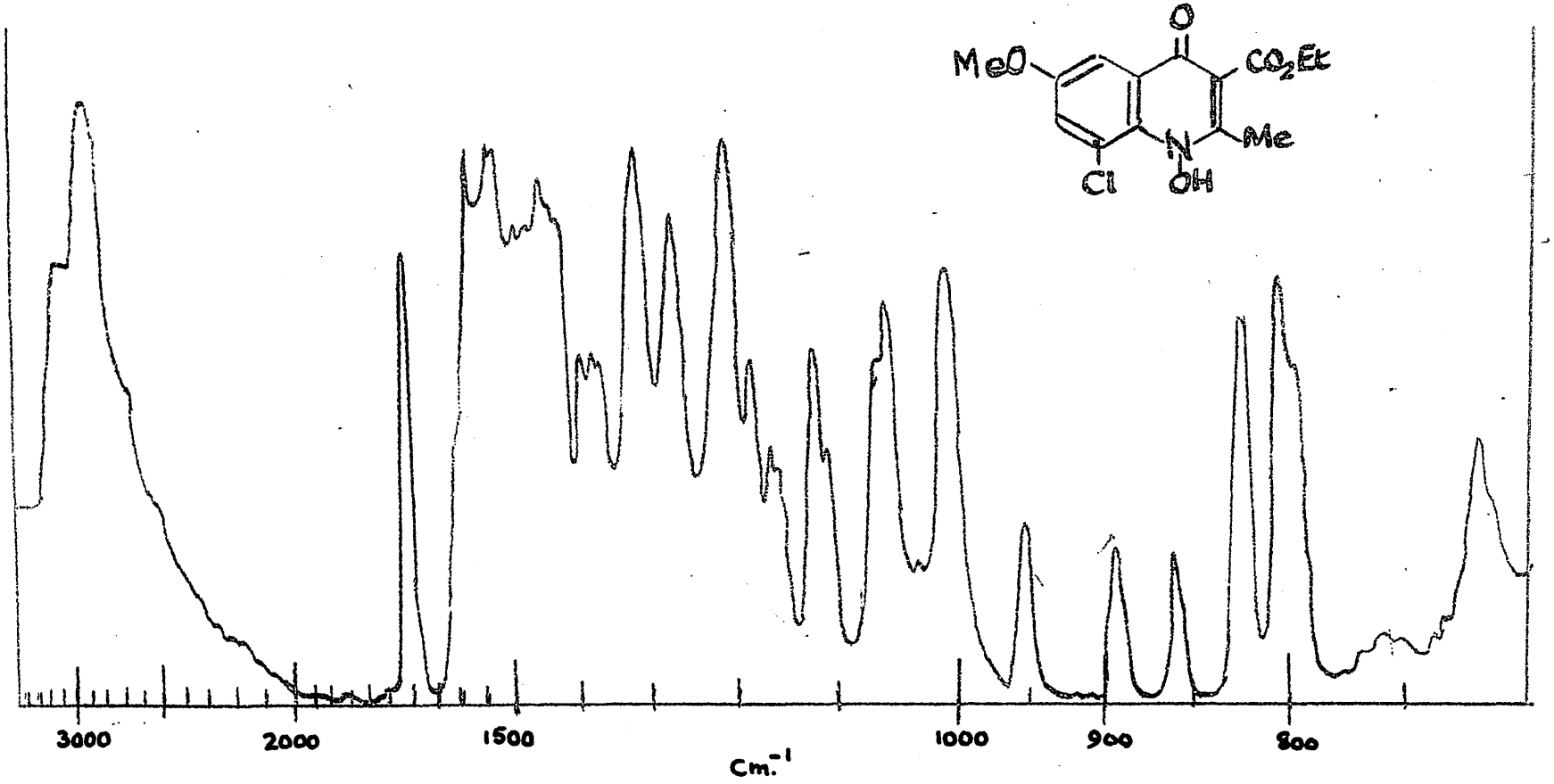
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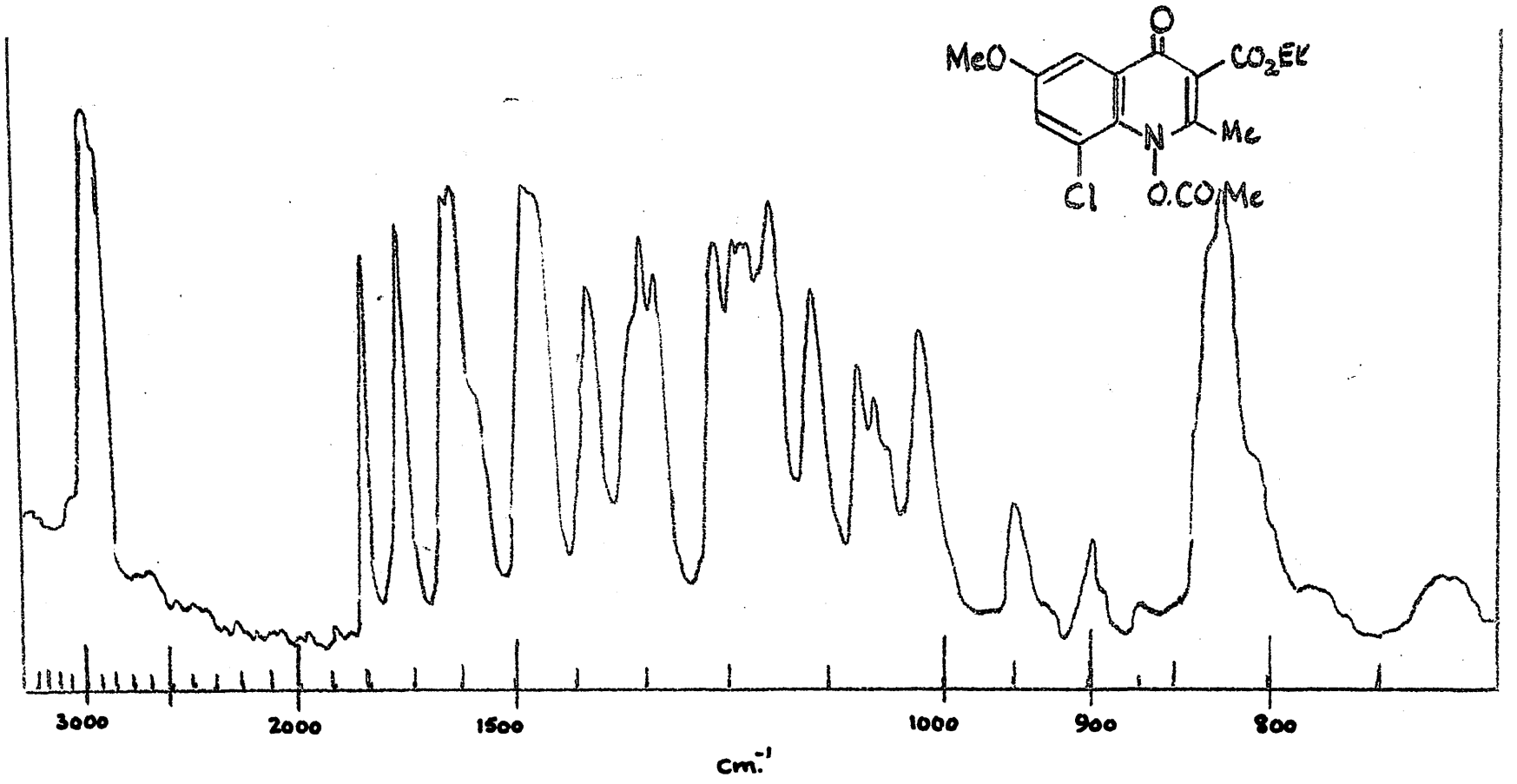
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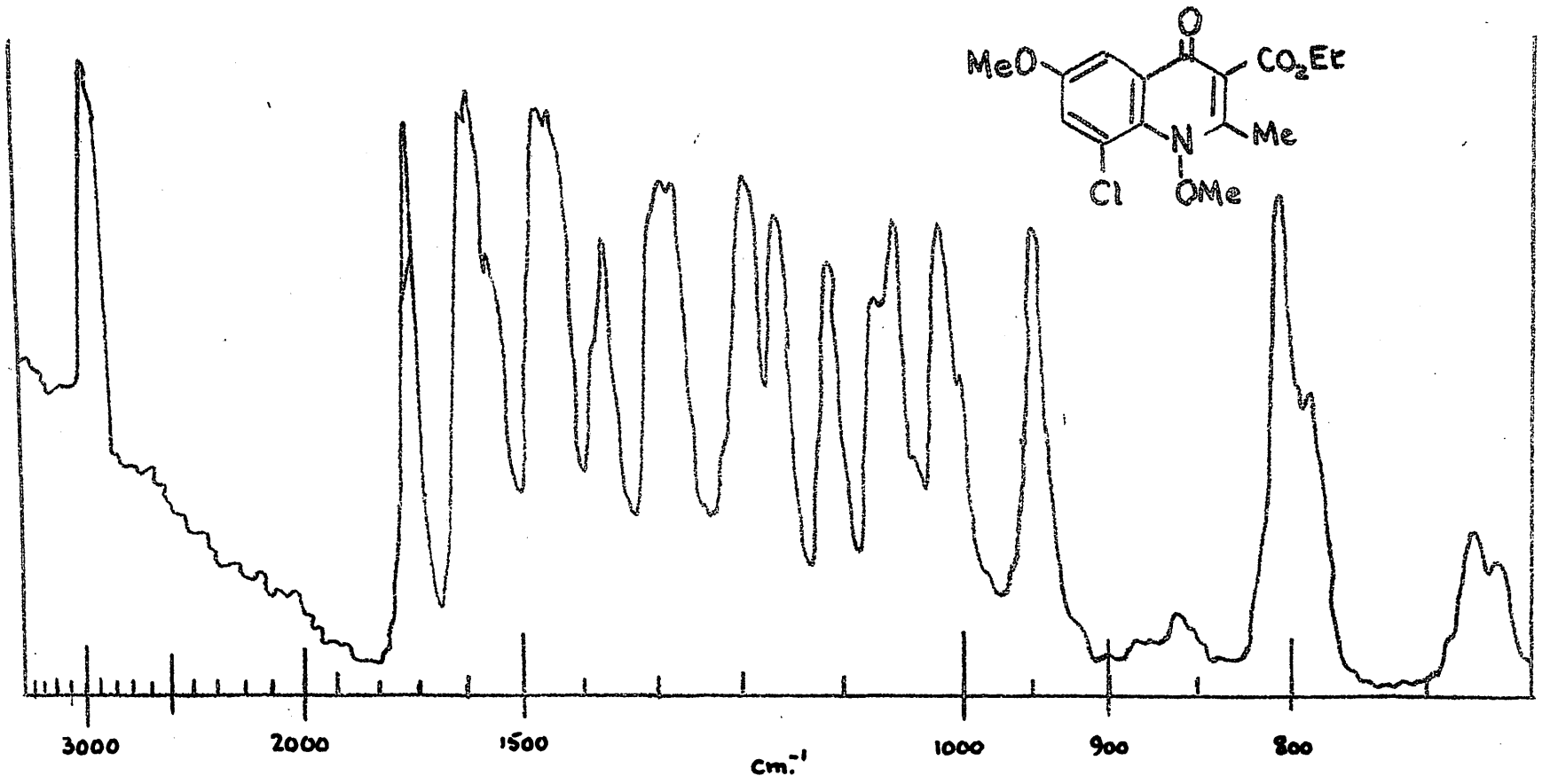
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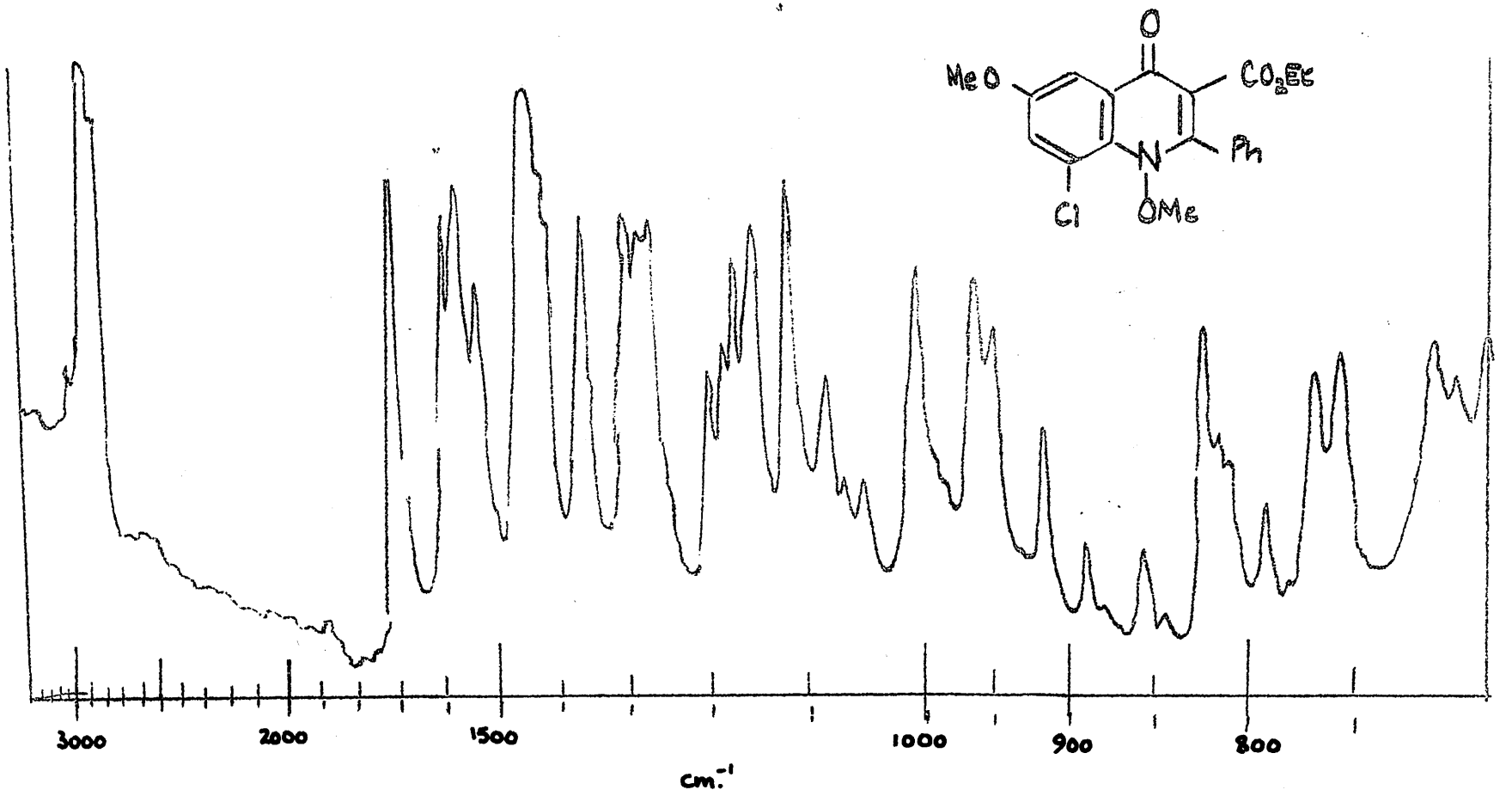
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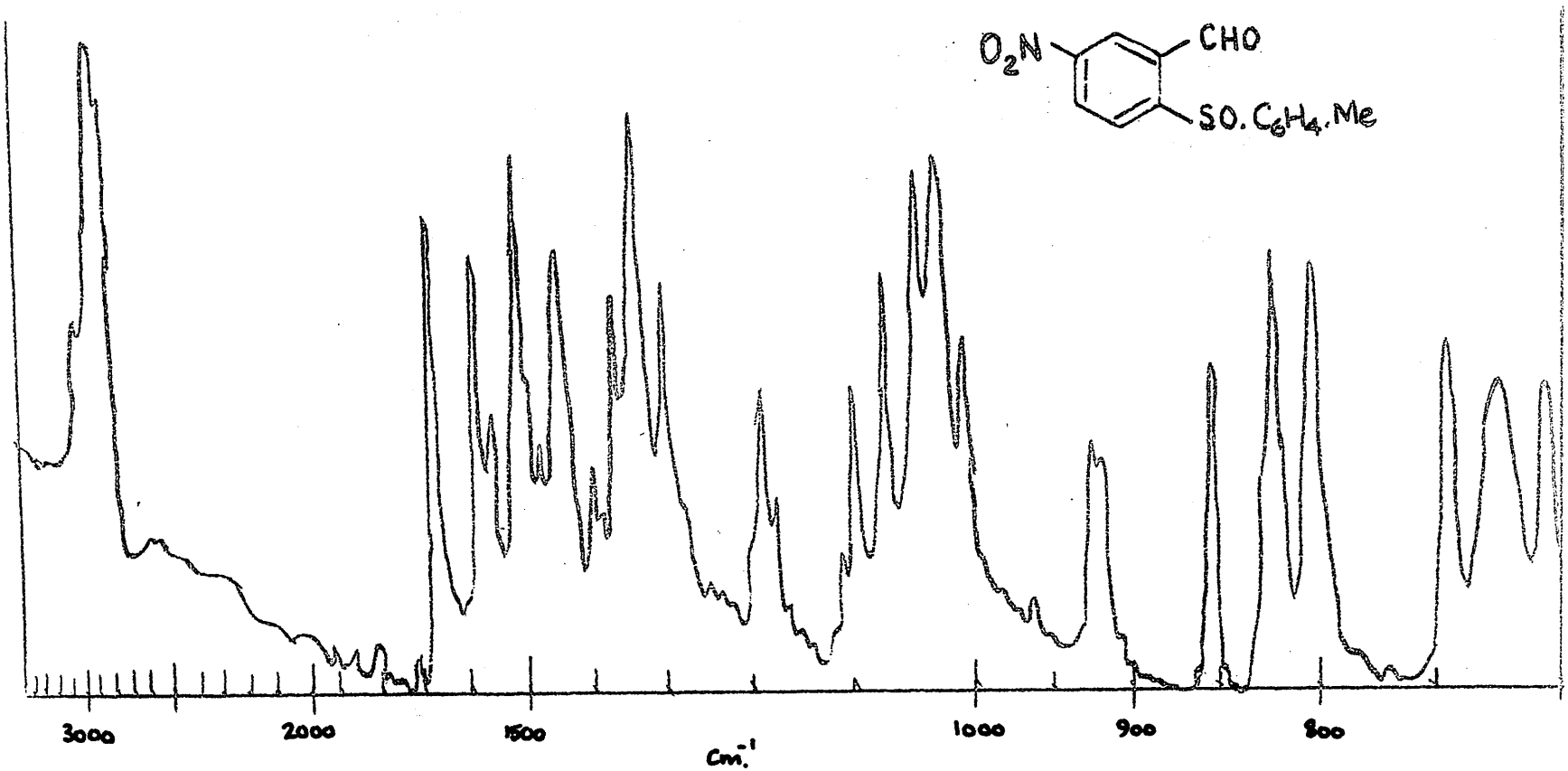
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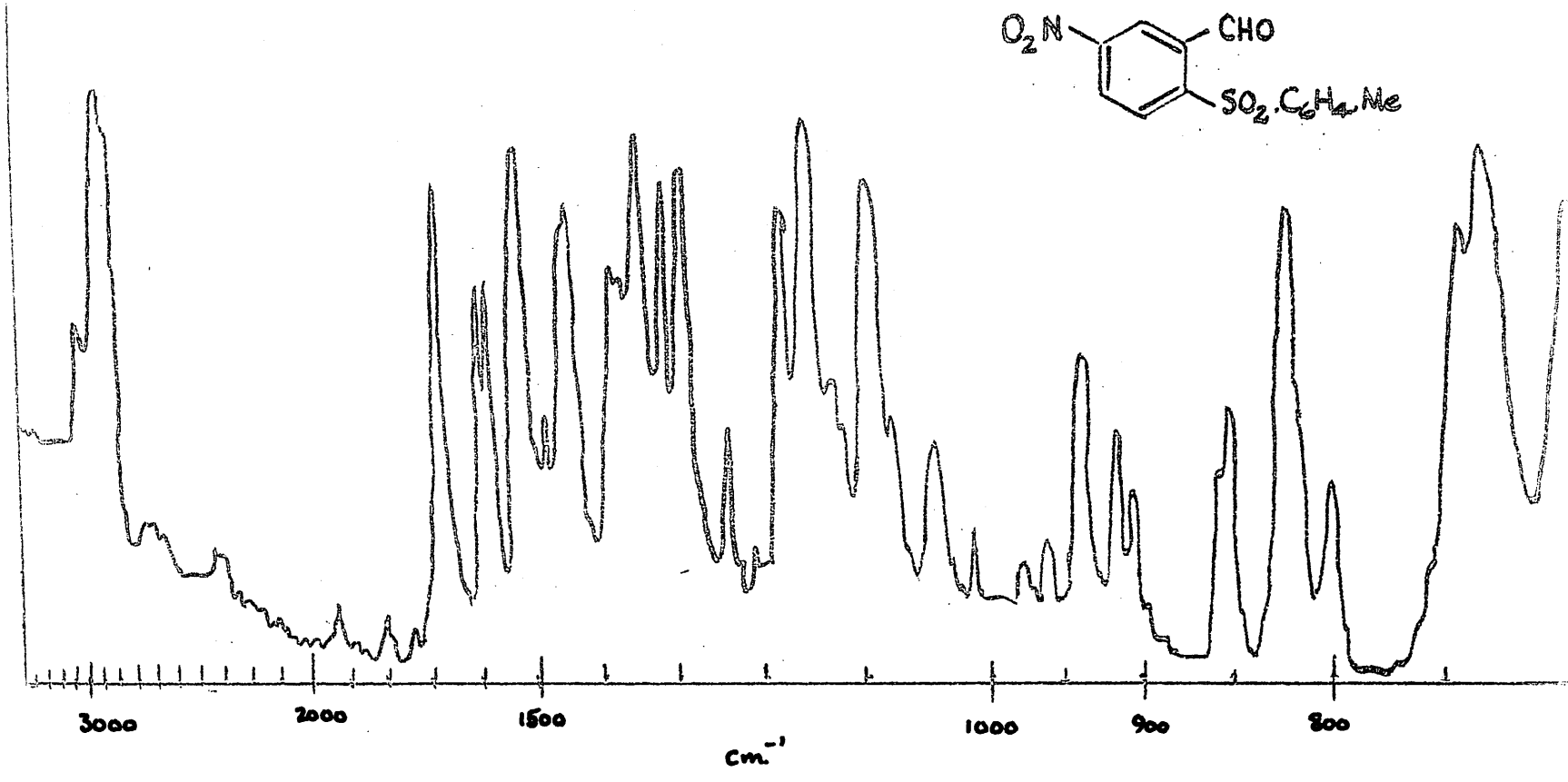
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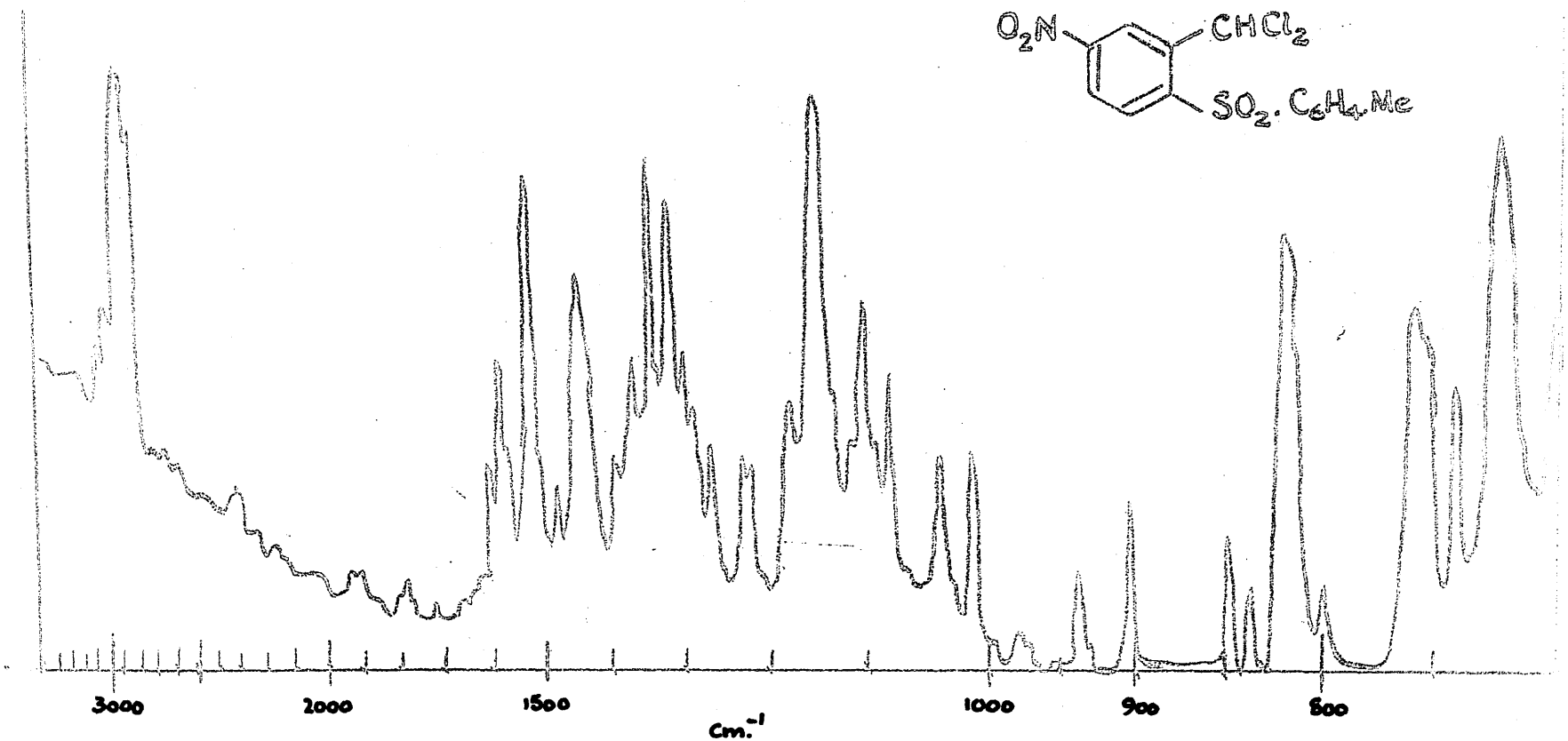
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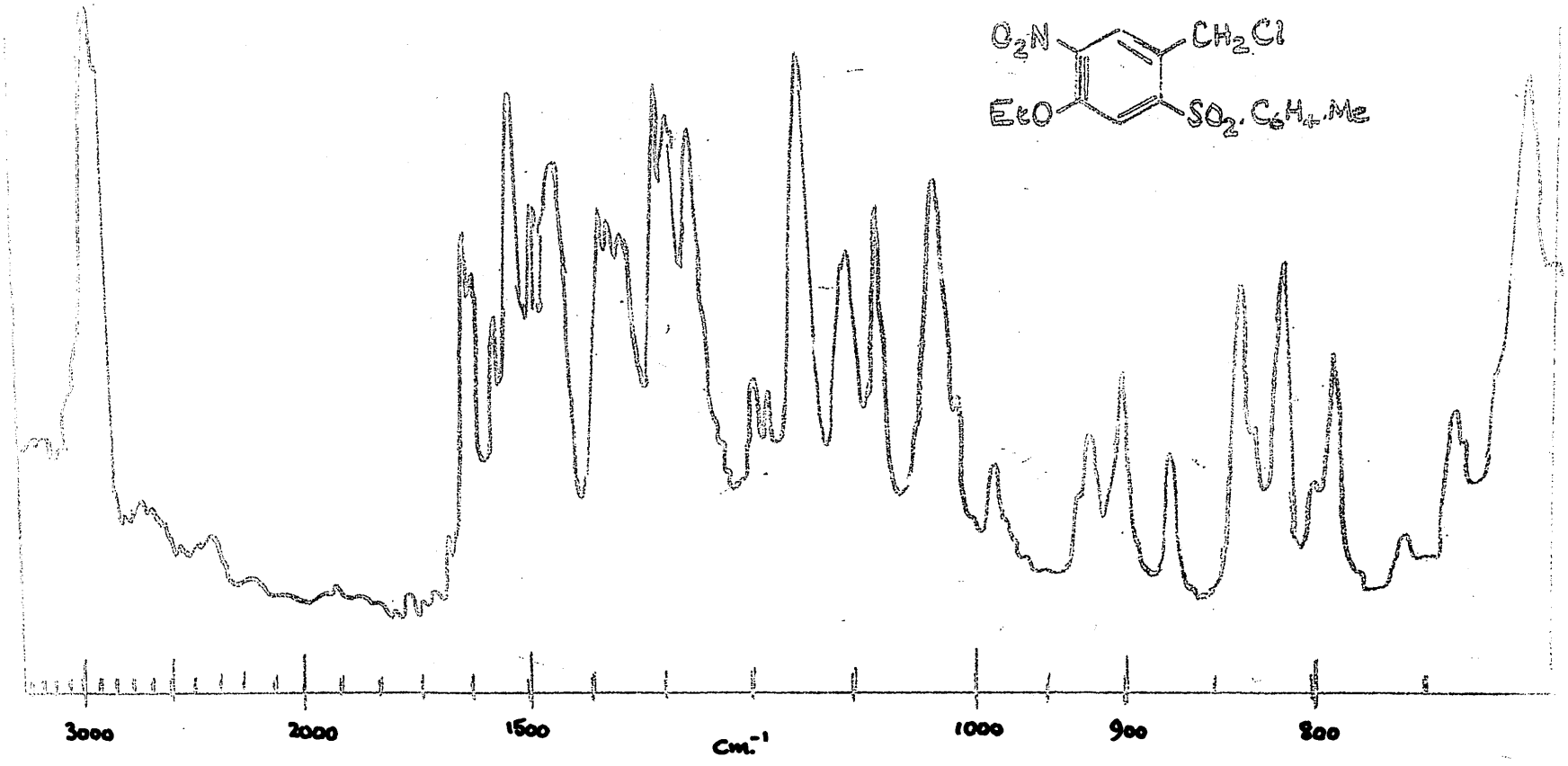
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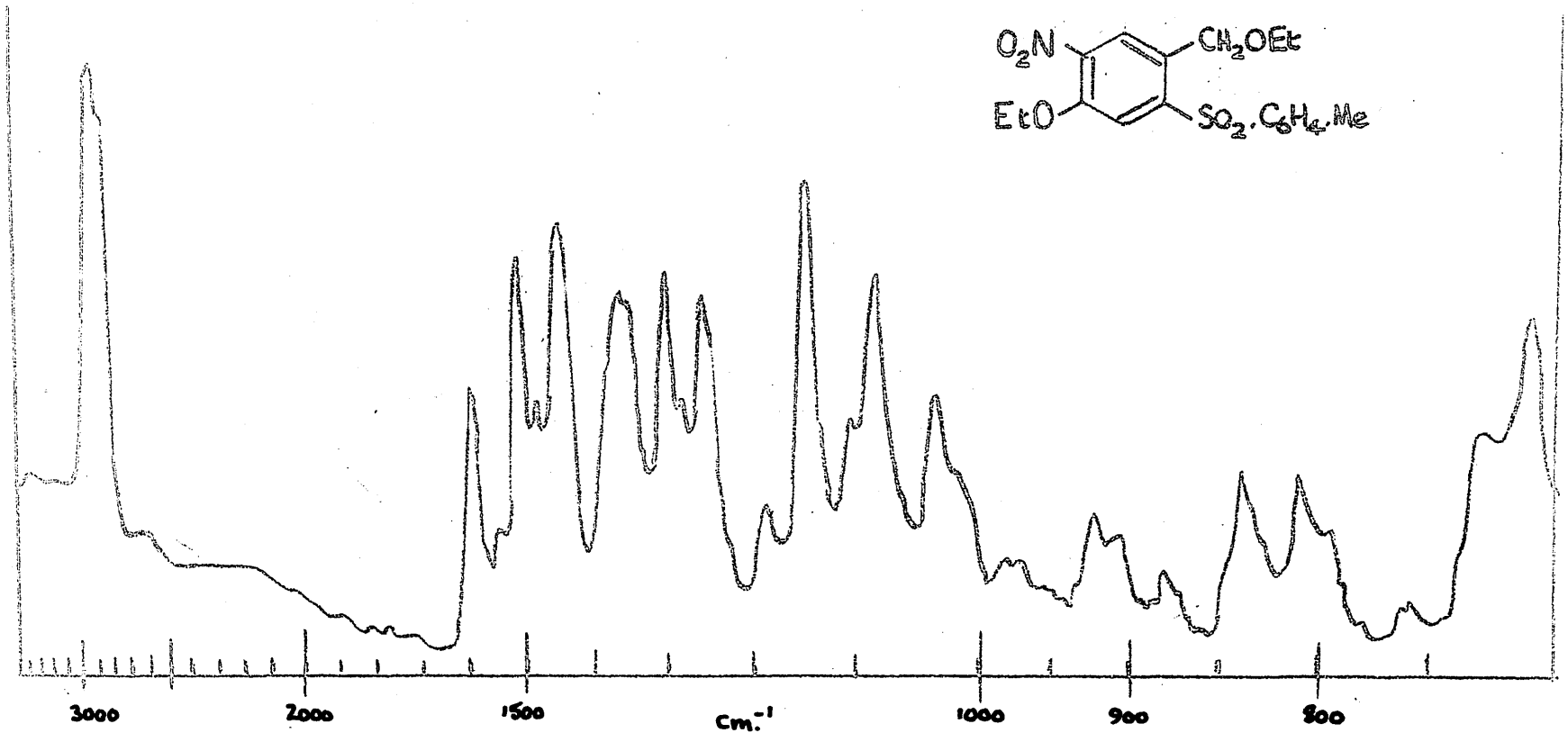
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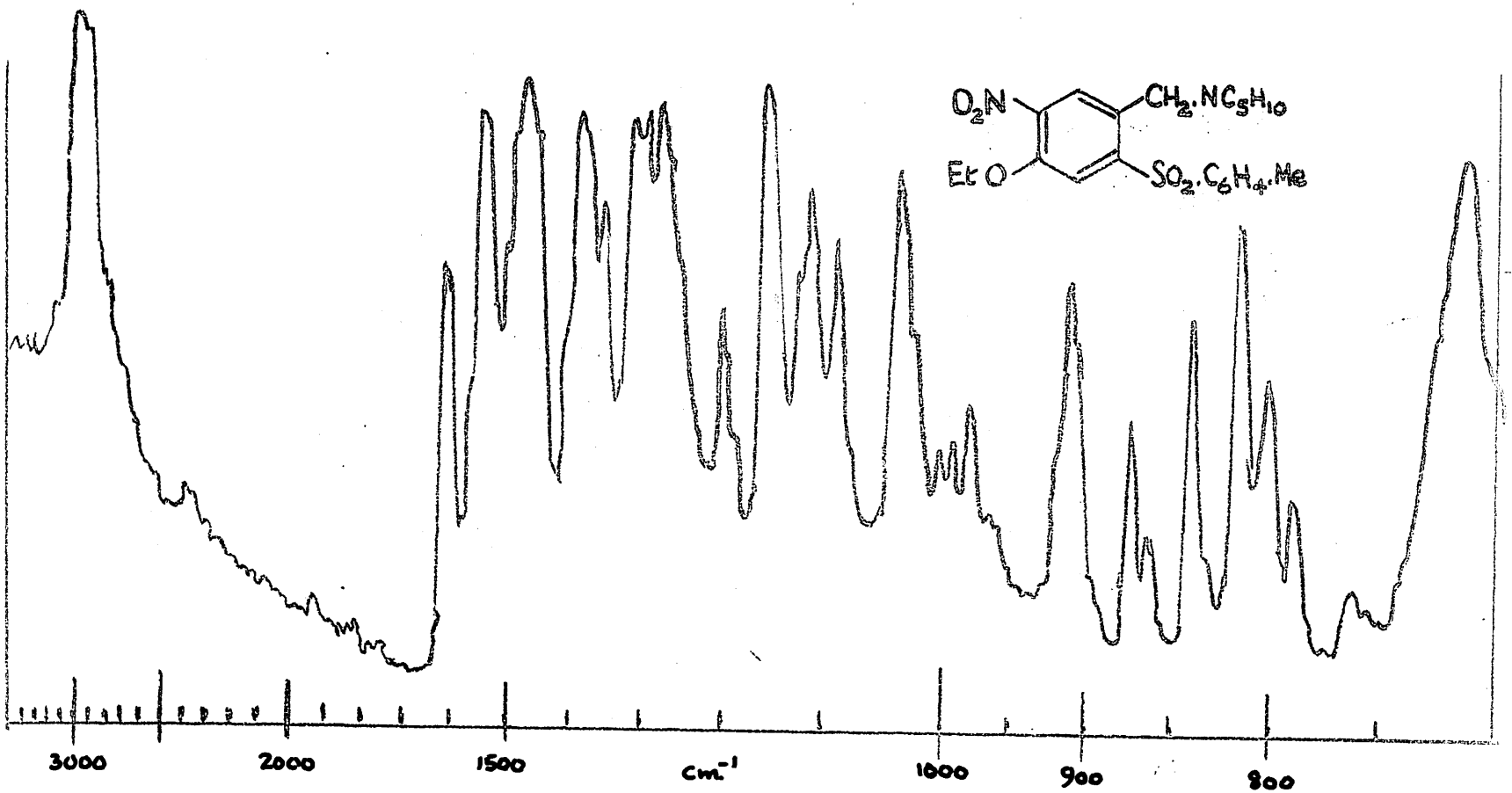
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