THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

ENTITLED

"SUBSTITUENT INTERACTION IN ORTHO-SUBSTITUTED NITRO-BENZENES"

Submitted to the UNIVERSITY OF GLASGOW

by GEORGE TENNANT B.Sc.

MAY 1961

ACKNOWLEDGEMENTS

The writer would like to express his sincere thanks to Dr.J.D.Loudon whose encouragement and kindly advice have been unfailing during the three years' research which this thesis represents.

Thanks are due to Mr.J.M.L.Cameron and Staff for their advice and for the accurate analytical data.

The writer is also greatly indebted to the Department of Scientific and Industrial Research for providing a three-year maintenance allowance.

CONTENTS

INTRODUCTION

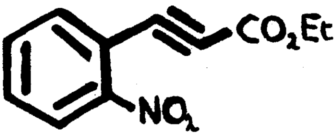
Since the writer's field of study was a broad one, widely if vaguely recognised, but never systematically examined and in some of its known reaches scarcely even touched, it involved a considerable amount of literature research. In this way much was accumulated that is immediately connected with the experimental work in this thesis and much more that is less closely related. Relevant material of the latter type has been assembled in Chapter I; that of the former type is dispersed in the subsequent chapters which contain an account of the writer's own experiments. Throughout, the reactions are classified broadly, according to the pH of the environment in which they occur. At present while the reaction mechanisms are unknown, or purely speculative, a more closely knit assembly is not possible.

It is standard practice in heterocyclic syntheses to make a nitro group, after reduction, the source of the aza atom in the heterocycle. As will appear, however, from the evidence of the ensuing papers, there is good reason to believe that the nitro group as such can react with a suitable side-chain in ortho-nitrobenzene derivatives. The nature of the interaction may be simple condensation, or, variously effected, oxidation-reduction. The immediate products may be unstable, and undergo further reaction, so that it is often difficult to be sure either of the steps involved, or of the order in which they occur. It is particularly unfortunate that many of the transformations are effected in ethanolic alkali, a reagent which has strong reducing properties which may be exerted on the nitro group itself or on intermediates derived from it by intramolecular change. Oxidation-reduction processes have also been observed to occur between groups in para-substituted nitrobenzenes; these, however, are not discussed in this thesis.

DISCUSSION

CHAPTER I

A REVIEW OF SUBSTITUENT INTERACTIONS IN ORTHO-SUBSTITUTED NITRO BENZENES



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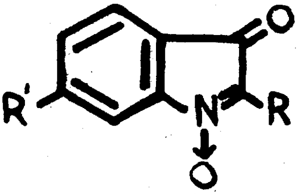

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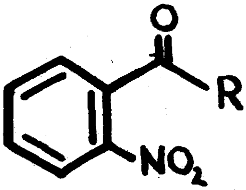

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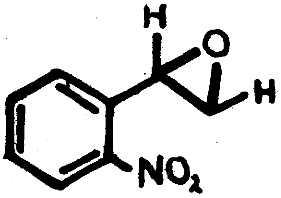

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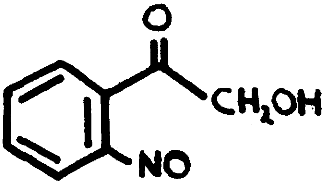

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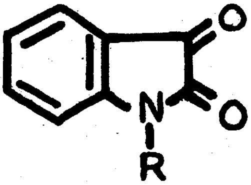

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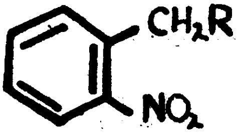

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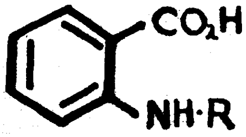

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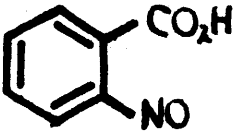

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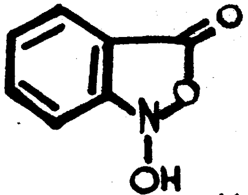

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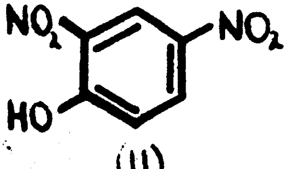

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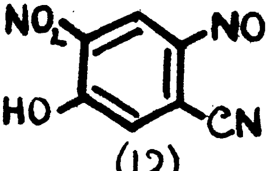

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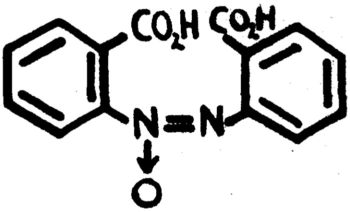

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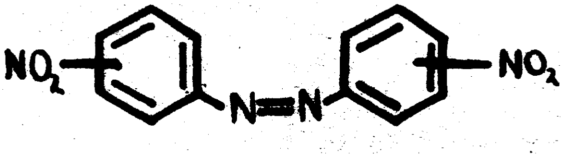

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CHAPTER I

A Review of Substituent Interactions in Ortho-Substituted Nitro-Benzenes

For the purposes of classification the various types of reactions have been grouped under one or other of the headings given below, according to the type of medium in which they occur.

ACID-CATALYSED INTERACTIONS

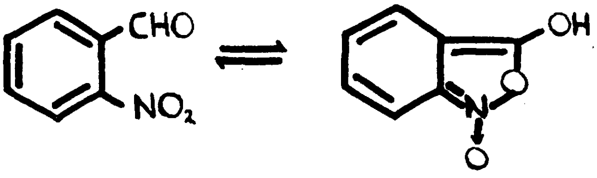
Reactions involving acid catalysed interaction between an ortho-nitro group and a side-chain are comparatively rare. Several examples of this type of reaction will be discussed in Chapter IV, and this present section is confined to a description of the few other examples reported in the literature.

Possibly the first example of this type of interaction was that described by Baeyer[1], who, during his classic researches on indigo, found that ethyl o-nitrophenylpropiolate (1) was converted by cold concentrated sulphuric acid to ethyl isatogen-2-carboxylate ((2), $R = CO_2Et$, $R' = H$). Needham and Perkin[2] noted that under the same conditions ethyl o-nitrobenzoylacetate ((3), $R = CH_2CO_2Et$) was merely hydrolysed to o-nitrobenzoylacetic acid ((3), R = CH_2COOH). This suggests that ethyl o-nitrobenzoylacetate is not an intermediate in the reaction.

Baeyer[3] later obtained diisatogen (17) by the treatment of di-o-nitrophenylacetylene (18) with mineral acid.

Arndt[4,5] found that treatment of o-nitrophenylethylene-oxide (4) with acid gives o-nitrosobenzoylcarbinol (5), an example of acid catalysed oxygen transfer from the nitro group to the side-chain. A similar type of reaction involving interaction with cyclisation, was discovered by Arndt et al.[6] who obtained 1-hydroxyisatin ((6), R = OH) by treating o-nitrobenzoyldiazomethane ((3), R = CHN_2) with mineral acid.

Tanasescu and coworkers[7] explained the acid-catalysed interaction of nitro groups with side-chains, in the particular case of o-nitrobenzaldehyde (cf. Chapter IV) by the so-called ring chain tautomerism of this compound in acid media -



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In support of this hypothesis Tanasescu claimed that

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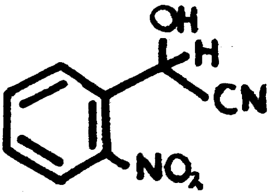

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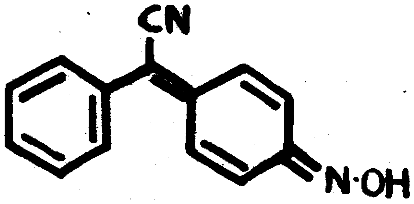

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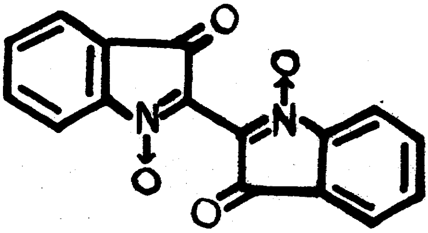

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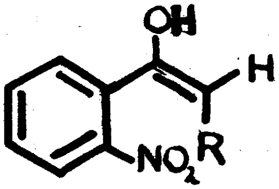

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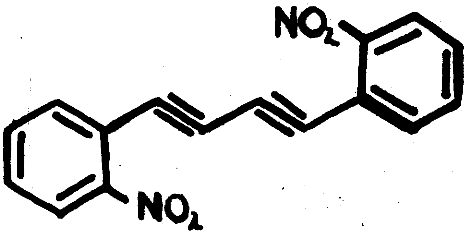

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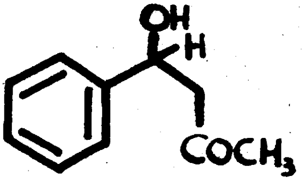

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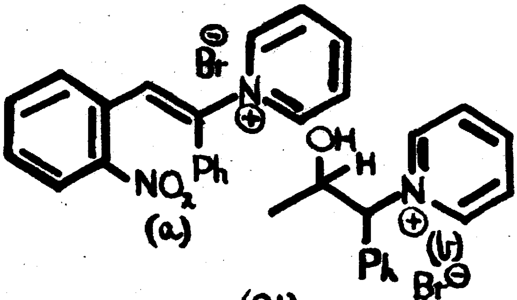

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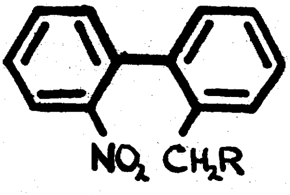

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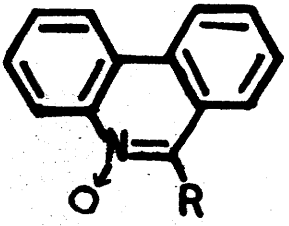

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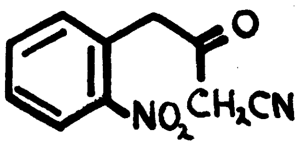

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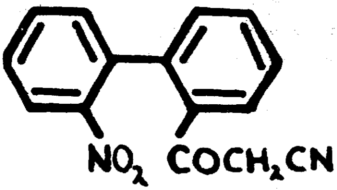

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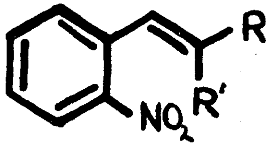

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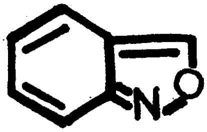

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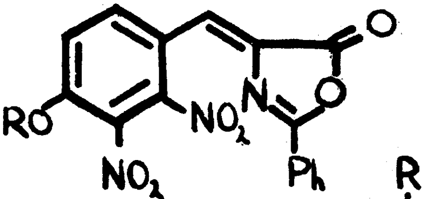

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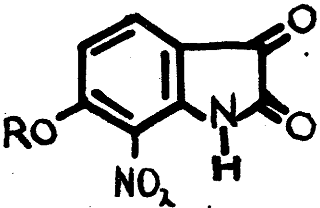

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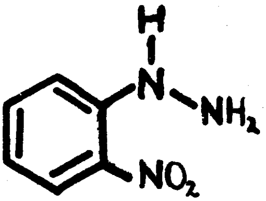

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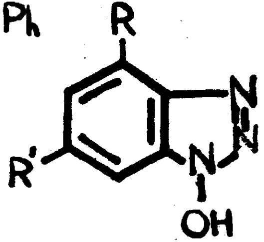

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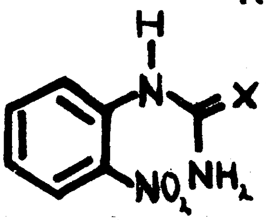

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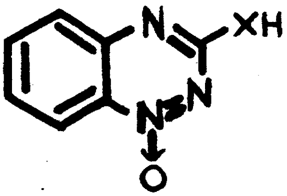

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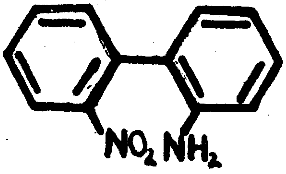

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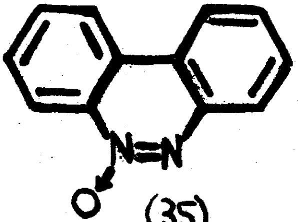

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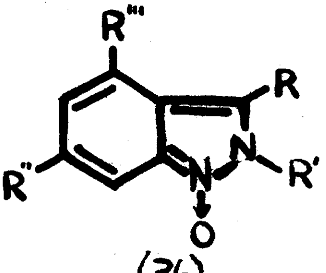

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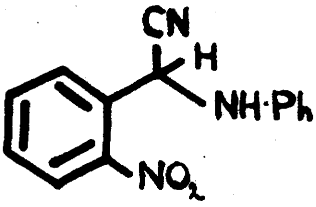

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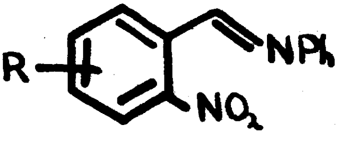

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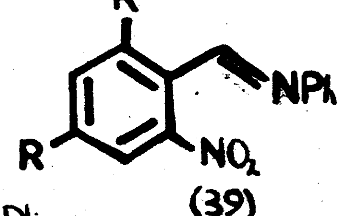

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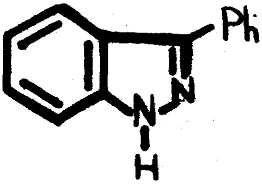

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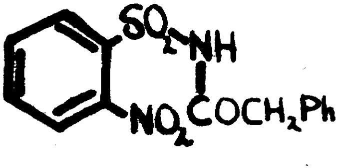

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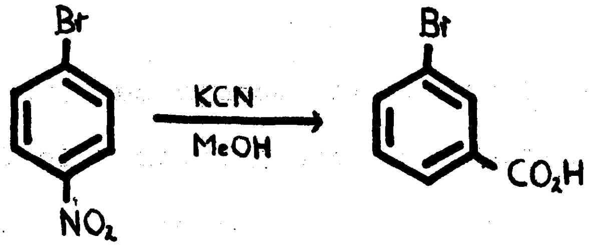
o-nitrobenzaldehyde gives the Zerewitinoff test for active hydrogen, an observation which could be taken as evidence for the presence of the species (B). Gilman and Fothergill[8] however, pointed out that nitro compounds in general interfere with the Zerewitinoff test, nitrobenzene itself giving a positive test for active hydrogen.

Another reaction possibly involving condensation of a nitro group with an ortho side-chain in an acid medium is the reported conversion of o-nitrophenyl acetic acid ((7), R = COOH) to N-acetylanthranilic acid ((8), R = $COCH_3$) in acetic anhydride[9].

BASE-CATALYSED INTERACTIONS

Of the nitro group side-chain interactions outlined in this review, those catalysed by base are the most common. Reactions in which a nitro group condenses with an ortho side-chain in presence of base are widely distributed throughout the literature and aromatic nitro compounds, in general, are notorious for their anomalous behaviour in basic media.

Von Richter[10] found that treatment of p-nitrobromobenzene (A) with aqueous ethanolic potassium cyanide gave m-bromobenzoic acid (B) in which a nitro group was lacking -



(A) (B)

This was the first example of a cine substitution and a good example of nucleophilic substitution at an aromatic nucleus. Bunnett and coworkers[11] have reviewed the Von Richter reaction and in a later publication, Bunnett[12] formulated a mechanism for this reaction involving a cyclic intermediate of the type (10) presumably formed by nucleophilic attack ortho to the nitro group in the nitrobenzene derivative by cyanide ion and subsequent cyclisation. Compound (10) is the ring tautomer of o-nitrosobenzoic acid (9) which if Bunnett's mechanism is correct, should be an intermediate in the reaction. In support of this Cullen and Ecuyer[13] recently reported the isolation of mixed azo- and azoxy-benzene derivatives and indazoles as by-products of the reaction. These products could be explained if nitrosobenzene derivatives were formed at some stage, a process which Borsche and Locatelli[14] have demonstrated in the conversion of the nitrobenzene derivative (11) to the nitrosobenzonitrile derivative (12) in aqueous ethanolic potassium cyanide. Lobry de Bruyn and others[15] made an intensive study of the behaviour of aromatic nitro compounds in aqueous and aqueous ethanolic base, and in every case displacement of a nitro group is effected. The ease with which this particular type of base-catalysed displacement reaction occurs has been demonstrated by Izzo[16] who described a particular case of this displacement in aqueous ethanolic sodium carbonate.

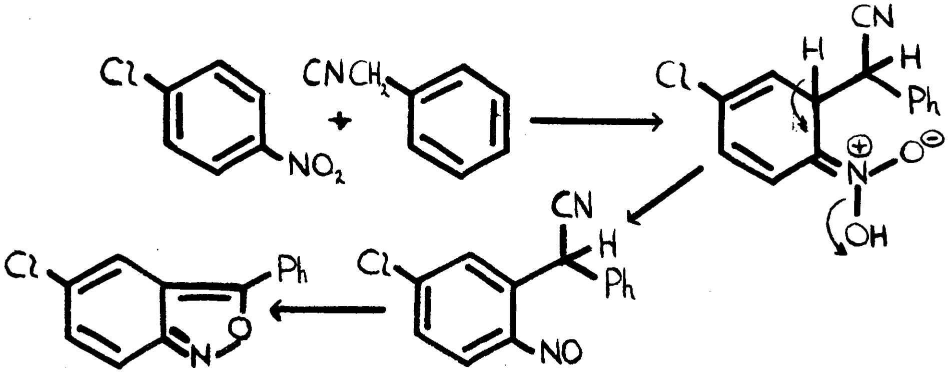
Base-catalysed nucleophilic displacement of a nitro group by an ortho side-chain with formation of a new cyclic system is also well known[17].

As well as causing displacement of the nitro group, aqueous ethanolic potassium cyanide can bring about a type of internal oxidation-reduction process between the nitro group and a suitable ortho side-chain. Thus Homolka[18] obtained o-azoxybenzenedicarboxylic acid (13) by the action of aqueous ethanolic potassium cyanide on o-nitrobenzaldehyde, presumably by way of o-nitrosobenzoic acid (9). Later, Lobry de Bruyn[19] obtained the corresponding dinitroazobenzene derivatives (14) by treatment of the dinitrobenzene derivatives under the same conditions. Robinson[20] reported a reaction of a similar type.

Heller[21] has actually demonstrated the formation of o-nitrosobenzoic acid (9) by the action of alcoholic ammonia solution on o-nitromandelonitrile (15) while Ekecrantz and

Ahlquist[22] isolated o-nitrosobenzoic acid along with the azoxybenzene derivative (13) in the reaction originally studied by Homolka[18]. o-Nitrosobenzoic acid has also been prepared by treating o-nitrobenzaldehyde with a mixture of ammonium acetate and ethanolic potassium cyanide[23].

Recently Davis and coworkers[24] described the nucleophilic substitution of nitrobenzene by benzyl cyanide in presence of methanolic potassium hydroxide, the product being the oximino derivative (16). This reaction has been developed into a new synthesis of anthranils illustrated in the following sequence[25] -



The reactions discussed above are of interest in demonstrating some ways in which nitrobenzenes can react in basic media and possibly the most interesting cases of nitro group reactions in such media involve condensation of the nitro group with an ortho side-chain.

Baeyer[26] obtained isatin ((6), R = H) by the action of dilute alkali on o-nitrophenylpropiolic acid ((1), CO_2H for CO_2Et) possibly via isatogen 2-carboxylic acid[27] ((2), R = CO_2H, R' = H). Forrer[28] reported the same result independently. A possible first step in this reaction might be hydration of the triple bond to give the enol form ((19), R = CO_2H) of the ketone ((3), R = CH_2CO_2H). This ketone could then cyclise to give the isatogen which is converted by hydrolysis to isatin. Baeyer and Drewson[29] in the same year obtained indigo by the action of dilute alkali on a mixture of acetone and o-nitrobenzaldehyde, and isolated the aldol (20) as an intermediate in the reaction.

Krohnke[30,31] has described a new synthesis of isatogens, involving base-catalysed cyclisation of the pyridinium salt (21)(a) using pyridine and diethylamine or sodium carbonate as the base, the product being in this case 2-phenyl isatogen ((2), R = Ph, R' = H). 5-Nitro-2-phenyl isatogen is obtained by the reaction of tolane with dinitrogen-tetroxide[32] and 2-phenylisatogen by the condensation of sodium phenylacetate with o-nitrobenzaldehyde in presence of acetic anhydride[33].

Where an isatogen, isatin or indigo is formed, base-catalysed cyclisation occurs with formation of a carbon-nitrogen bond, and other examples of this type of condensation are discussed in Chapter III. Muth *et al.*[34,35] have studied the base-catalysed condensation of nitro groups with reactive methylene groups in various derivatives of diphenyl (22). The products are phenanthridine-1-oxides (23). An interesting feature of this reaction is that in (22) when R = CN, CO_2Me, $CONH_2$, or COPh, the condensation proceeds smoothly, but when R = Br, OH, CO_2H or Ph no reaction occurs. This emphasises the requirement, for successful condensation, of activation of the methylene group. Muth <u>et al</u>. also found that cyclisation failed with 4-(2-nitrophenyl)-3-butano nitrile (24) and with 2-(2'-nitrophenyl)-benzoylacetonitrile (25), so that methylene reactivity is not the only requisite.

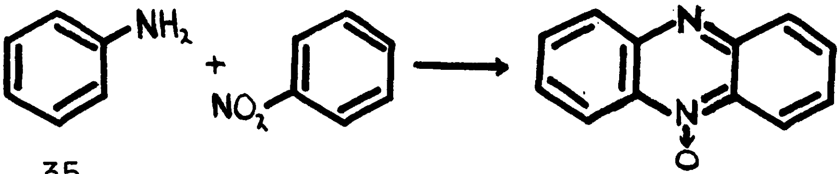
Another reaction probably proceeding by condensation of a nitro group with a methylene group in a side-chain is the formation of N-benzoylanthranilic acid ((8), R = COPh) from <u>α</u>-phenyl-<u>o</u>-nitrocinnamonitrile((26), R = Ph, R' = CN) in warm aqueous ethanolic potassium hydroxide[36]. The conversion of <u>o</u>-nitrotoluene to anthranilic acid ((8), R = H) in alkali may also proceed via intermediates formed by cyclisation of the nitro group with the ortho-methyl group. Scholl[37] has claimed, from a study of the mechanism of this reaction that anthranil (27) is an intermediate, a conclusion also reached by Lock[38], Schukina[39] and by Seibert[40].

Burton and Stoves[41] showed that treatment of the 2-nitrophenylketoisoxazole (28) with sodium hydroxide gives a good yield of the isatin derivative (29), and though the mechanism of this reaction is not known, it is possible that it proceeds by a cyclodehydration involving the nitro group and the ortho side-chain.

As well as condensation between a nitro group and a methylene group, reactions are known involving condensation of the nitro group with an amino or substituted amino group in the side-chain. The amino group may be present as a true amine or as an amide or urea derivative. In this case cyclisation leads to the formation of a new nitrogen-nitrogen bond.

Nietzki and Braunschweg[42] and independently Zincke and Schwartz[43] found that treatment of o-nitrophenylhydrazine (30) with aqueous alkali gave 1-benztriazole ((31), $R = R' =$ H) while Arndt *et al.*[44,45] have obtained triazine-1-oxides of the type ((33), X = O, S, or NH) by base-catalysed cyclisation of o-nitrophenylurea derivatives ((32), X = O, S, NH). Wolff *et al.*[46] used this reaction to prepare a series of 3-hydroxybenztriazine-1-oxides ((33), X = O). Borsche[47] has also reported the synthesis of the triazole ((31), R = Me, R = NO_2) by treatment of 3:5-dinitro-o-cresolmethylether with hydrazine hydrate.

A further variation of this reaction, namely base-catalysed condensation of a nitro group with an amino group of a nitro group with an amino group was discovered by Wohl[48] who obtained phenazine-1-oxide by the condensation of nitrobenzene with aniline in presence of alkali -

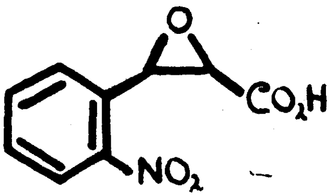


Muth et al.[35] showed that a similar intramolecular condensation occurs with 2-nitro-2'-amino diphenyl (34) to give benzocinnoline-1-oxide (35).

Treatment of o-nitromandelonitrile (15) with aniline in presence of sodium acetate gives a good yield of 2-phenyl-3-cyanoindazole-1-oxide[49] ((36), R = CN, R' = Ph, R'' = R''' = H) and Reissert and Lemmer[50] obtained the same compound, independently, by base-catalysed cyclisation of o-nitrophenylanilinoacetonitrile (37). Behr[51] converted o-nitrobenzylidene anilines of the type (38), in good yield, to the corresponding 3-cyano-2-phenyl indazole-1-oxide (e.g. (36)) by treatment with aqueous ethanolic potassium cyanide, while Secareanu and Lupas[52] found that 2:4:6-trinitrobenzylidene aniline ((39), R = R' = NO_2) was smoothly converted to 3-hydroxy-4:6-dinitro-2-phenyl indazole-1-oxide ((36), R = OH, R' = Ph, R'' = R''' = NO_2) by aqueous ethanolic sodium carbonate. The same authors[53] obtained a mixture of the indazole ((36), R = OH, R' = Ph, R'' = NO_2, R''' = H, N-H for N-O) and its 1-oxide

CHAPTER I

FLOWSHEET (4)



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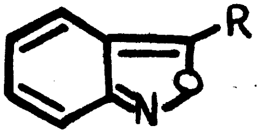

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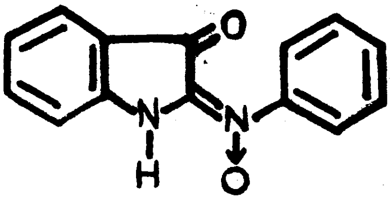

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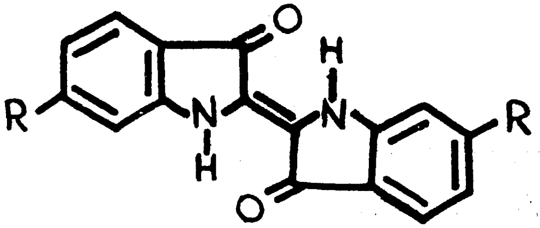

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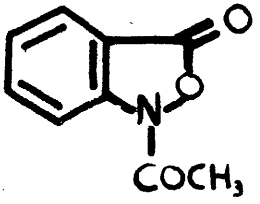

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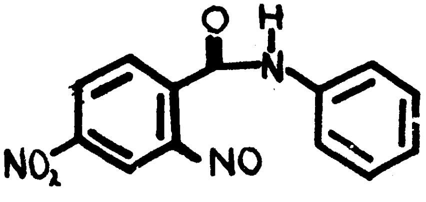

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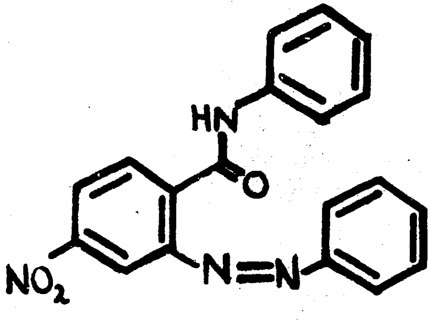

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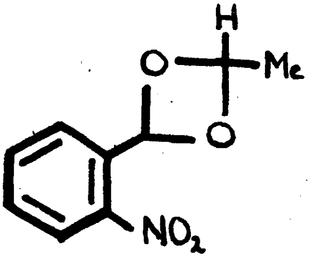

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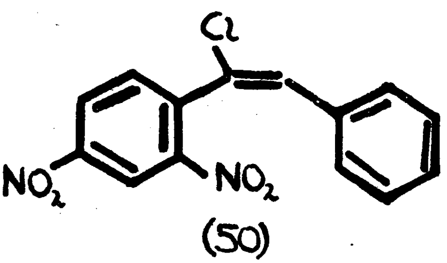


(50)

by similar treatment of 2:4-dinitrobenzylidene aniline ((39), $R' = H$, $R = NO_2$), the indazole presumably being formed by reduction of the oxide in the basic medium. The failure of o-nitrobenzylidene aniline ((39), $R' = R = H$) itself to cyclise under comparable conditions is surprising[53]. Secareanu and Lupas have also applied this reaction to the synthesis of the 2-N-tolyl derivatives[54] ((36), $R = OH$, $R' = p\text{-}C_6H_4(Me)$, $R'' = R''' = NO_2$). An interesting extension of this reaction was reported by Tanasescu and Tanasescu[55] who obtained 2-dimethylaminophenyl-3-hydroxy indazole-1-oxide ((36), $R = OH$, $R' = p\text{-}C_6H_4(NMe_2)$, $R'' = R''' = NO_2$) by treating ethyl-o-nitrophenyl acetate ((7), $R = CO_2Et$) with p-nitrosodimethylaniline in presence of bases such as sodium carbonate, or pyridine in alcohol. A reaction possibly related to these syntheses of indazoles is that described by Naito et al.[56] who obtained 3-phenyl indazole (40) by rearrangement of the sulphonamide derivative (41) in alkali.

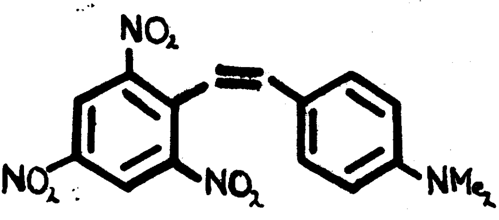
REACTIONS OCCURRING IN NEUTRAL MEDIA

Only two examples of this type of reaction have been discovered from a search of the literature.

o-Nitrophenylglycidic acid (42) when warmed with water, or steam-distilled gives anthroxanic aldehyde ((43),

CHAPTER I

FLOWSHEET (5)



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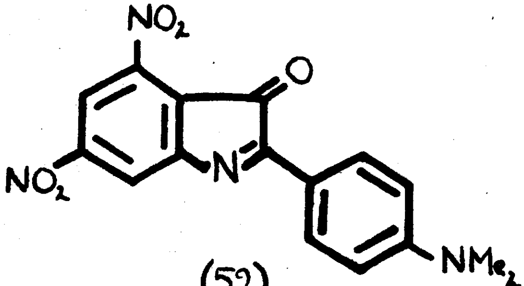

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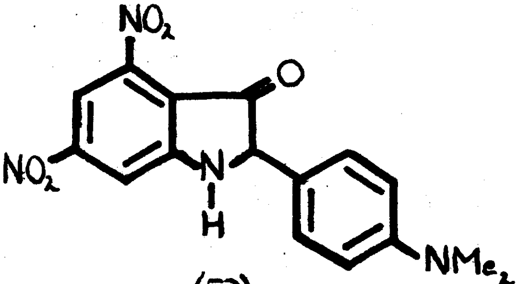

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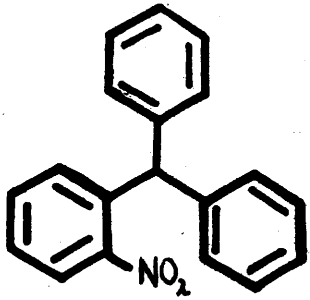

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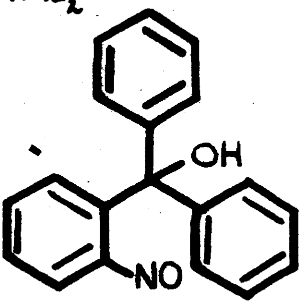

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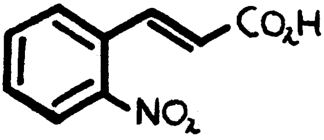

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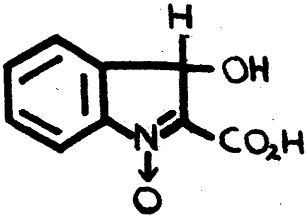

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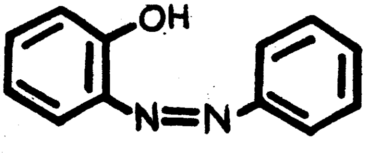

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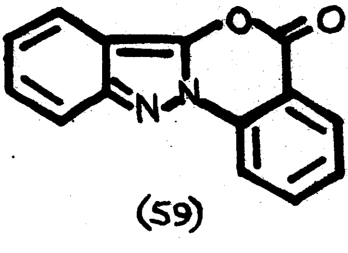


(59)

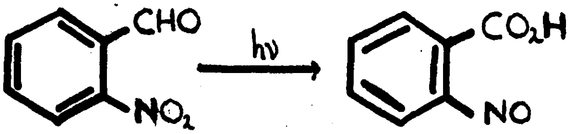
R = CHO)[57] and though the mechanism of this reaction is not known it is possible that either an oxygen transfer or a cyclodehydration mechanism is involved.

Allessandri[58] studied the reaction of o-nitrophenylacetylene ((17, H for CO_2Et) with nitrosobenzene and from a complex mixture of products, managed to isolate diisatogen (17), 1-hydroxyisatin ((6), R = OH) and the isatin derivative (44). Again, though the mechanism of this complex reaction is not clear, the structure of the products would indicate nitro group, side-chain interaction at some stage.

PHOTOCHEMICALLY INDUCED INTERACTIONS

In view of the present interest in organic reactions induced by irradiation, photochemical reactions involving nitro group side-chain interaction are of some importance, especially since one of the first photochemical reactions studied involved a mechanism of this type[59,62]. Both sunlight and artificial light have been used to bring about this particular type of reaction[59,60] and in at least one case a quantitative treatment is described[60].

Engler and Dorant[61] found that benzylidene derivatives of o-nitroacetophenone ((3), R = CH=CH.Ph) were transformed, by an oxidation-reduction process on exposure to sunlight in an inert solvent, to indigo derivatives (e.g. (45)). Shortly after this discovery Ciamician and Silber[62] and independently Lobry de Bruyn[63] reported the rearrangement of o-nitrobenzaldehyde to o-nitrosobenzoic acid (9) in ethanol in presence of sunlight -



This rearrangement also occurred when benzene was used as solvent and under the same conditions m- and p-nitrobenzaldehyde were unchanged.

This reaction obviously involves an oxygen transfer between the nitro and aldehyde groups.

When paraldehyde was used as solvent in the photochemical rearrangement of o-nitrobenzaldehyde, the product was not o-nitrosobenzoic acid but 1-acetylbenzisoxazolone (46)[59,62].

Sachs and Kempff[64] showed that o-nitrobenzylidene aniline ((38), R = H) underwent a similar type of photochemical rearrangement in benzene, the product being o-nitrosobenzanilide ((9), CONHPh for COOH) and Sachs and Sichel[65] extended this reaction to include the corresponding 2:4-dinitrobenzylidene anilines ((39), $R' = H$), the product in this case being 2-nitroso-4-nitrobenzanilide (47). In the latter reaction, the azobenzene derivative (48) was obtained as a by-product. Sachs and Sichel[66] have recorded further experiments on the photochemistry of the *o*-nitrobenzylidene anilines.

The photochemistry of *o*-nitromandelonitrile (15) and of *o*-nitrobenzyl alcohol ((15), H for CN) has also been studied[67], and Bamberger[68] showed that in the latter case the product was *o*-nitrosobenzaldehyde ((9), CHO for COOH). The glycol ester of *o*-nitrosobenzoic acid ((9),$OCO-(CH_2)_2OH$ for COOH) is obtained by the photochemical rearrangement of *o*-nitrobenzaldehyde ethylene acetal (49)[69] and the related photochemical reactions of the *o*-nitrobenzylidene acetals have been studied by Tanasescu and coworkers[70].

One of the most important cases of photochemical rearrangement in *o*-nitrobenzene derivatives is the conversion of certain *o*-nitrostilbene and tolane derivatives in pyridine, in presence of sunlight to the corresponding isatogen ((2), R = Ph). Since these compounds are not otherwise readily synthesised, this reaction has real practical value. 2:4-Dinitro-u-chlorostilbene (50) rearranges on irradition by sunlight in pyridine to 6-nitro-2-phenyl isatogen ((2), $R = Ph$, $R' = NO_2$)[71]. Pfeiffer[72] has given an excellent review of the scope of this reaction while Ruggli and coworkers[73] used the reaction to synthesise a large number of isatogen derivatives (cf. also ref.[74]).

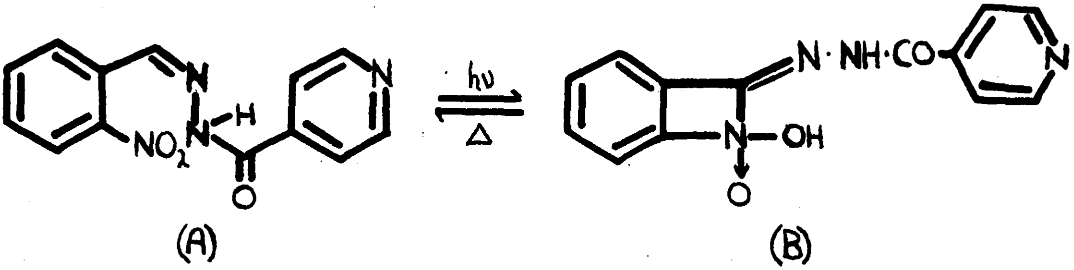
Recently Krohnke[75] described a new synthesis of isatogens involving rearrangement of the pyridinium ethanol salt (21)(b) to 2-phenyl isatogen ((2), $R = Ph$, $R' = H$) on irradiation with ultra-violet light in pyridine. Krohnke has formulated a mechanism for this rearrangement and in a later paper[31] he uses a similar reaction to synthesise 2-vinyl and 2-styryl isatogen ((2), R = vinyl or styryl, $R' = H$). Splitter and Calvin[76] in a very interesting paper showed that irradiation of $4'$-dimethylamino-2:4:6-trinitrostilbene (51) gives rise to a mixture of products from which the corresponding isatogen, indolenone (52) indoxyl (53) and anthranil (43) derivatives can be isolated as well as *p*-dimethylaminobenzaldehyde. The effect of substituents in the aromatic nuclei of the *o*-nitro stilbenes was also examined and a possible mechanism proposed.

2-Nitrophenylmethanes of the type (54) are reported to isomerise on exposure to sunlight to the corresponding 2-nitrosotriphenylmethylcarbinol derivative (55)[77]. Tanasescu[78] also claims that *o*-nitrocinnamic acid (56) rearranges in presence of sunlight to 3-hydroxy indoline-2-carboxylic acid-1-oxide (57). The same author has studied the photochemical behaviour of the aldol ((20), *m*-$C_6H_4.CO(NO_2)$-

for Me.CO-).

A related reaction is the photochemical rearrangement of azoxybenzene ((13), H for CO_2H) to o-hydroxyazobenzene (58)[80]. Bamberger described a similar type of reaction during his researches on o:o'-azoxybenzaldehyde ((13), CHO for CO_2H). This compound on irradiation rearranges and cyclises to give the indazole derivative (59)[81]. The mechanism of this reaction has been discussed by Bamberger and others[82].

A photochemical conversion of the type (A) $\rightleftharpoons$ (B) has recently been reported[83] -



(B) is readily converted back again to (A) on heating. The validity of the structure assigned to (B) is doubtful.

The photochemistry of a large number of o-nitrobenzylidene derivatives was studied by Ried and Wilk[84] who have made some interesting suggestions regarding the mechanisms involved.

CHAPTER II

A NOVEL SYNTHESIS OF A 2-AMINOQUINOLINE-1-OXIDE

CHAPTER II

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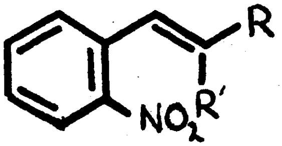

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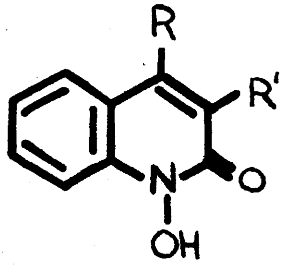

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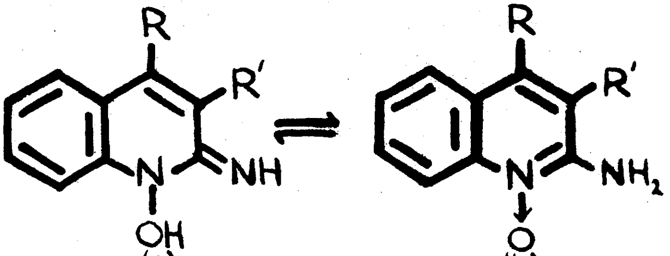
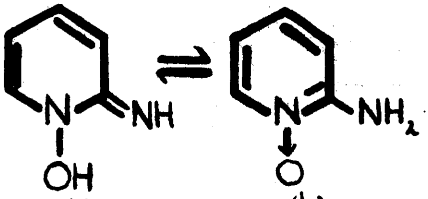


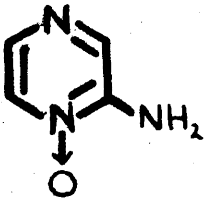
(a) (b)

(62)



(a) (b)

(63)



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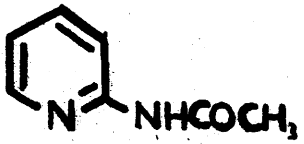

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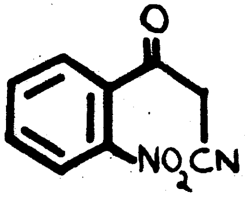

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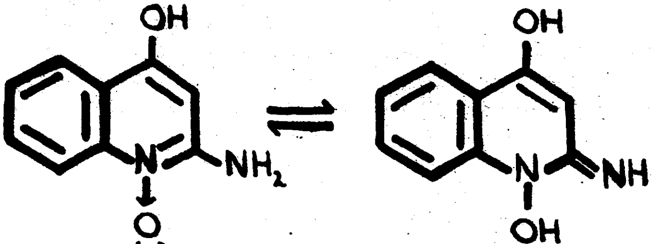


(a) (b)

(67)

CHAPTER II

A Novel Synthesis of a 2-Amino-quinoline-1-oxide.

The interaction of *α*-phenyl-*o*-nitrocinnamonitrile ((60), $R = Ph$, $R' = CN$) with aqueous ethanolic potassium cyanide and ammonium chloride was said by Brand and Loehr[85] to yield a product of molecular formula $C_{17}H_{13}N_3O$. Beyond this characterisation of the product they gave no evidence of its structure. In this department Wellings[86] had shown that ethanolic potassium cyanide converted the diester ((60), $R = R' = CO_2Et$) into the cyclic hydroxamic acid ((61), $R = CN$, $R' = CO_2Et$) and analogy with this reaction suggested that Brand and Loehr's product might well have the molecular formula $C_{16}H_{11}N_3O$ corresponding to the 2-aminoquinoline-1-oxide structure ((62), (a) or (b), $R = CN$, $R' = Ph$).

2-Aminoquinoline-1-oxides belong to a class of compounds which has been little investigated. As far as can be ascertained the only synthetic routes to these compounds, involve either oxidation of a quinoline derivative or reductive cyclisation of an *o*-nitrobenzene derivative. 2-Aminoquinoline-3-carboxyamide-1-oxide ((62), $R = H$, $R' = CONH_2$) and 2-aminoquinoline-3-carboxylic acid 1-oxide ((62), $R = H$, $R' = COOH$) were obtained by Heller and Wunderlich[87] by zinc and acetic acid reduction of *o*-nitrobenzylidenecyanoacetamide ((60), R = CN, R$'$ = $CONH_2$) and α-cyano-2-nitrocinnamic acid ((60), R = CN, R$'$ = COOH) respectively. Unfortunately these workers assigned the wrong structures to the products and recently Taylor and Kalenda[88] and Tyler[89] have proved conclusively that they are in fact simple derivatives of 2-aminoquinoline-1-oxide.

Catalytic reduction of α-phenyl-o-nitrocinnamonitrile ((60), R = CN, R$'$ = Ph) and of ethyl α-cyano-o-nitrocinnamate ((60), R = CN, R$'$ = CO_2Et)[90] gives 2-amino-3-phenylquinoline-1-oxide ((62), R = H, R$'$ = Ph) and ethyl 2-amino-quinoline-3-carboxylate-1-oxide ((62), R = H, R$'$ = CO_2Et), the reduction stopping at the N-oxide stage. This method of reductive cyclisation should be compared with the zinc and acetic acid method which normally leads to the quinoline itself or at least to mixtures of the quinoline and quinoline-1-oxide.

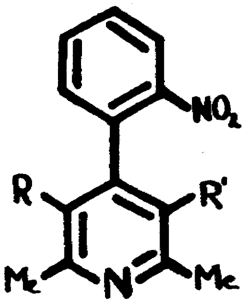
Though few syntheses of the 2-aminoquinoline-1-oxide system are recorded, the corresponding pyridine analogue, 2-aminopyridine-1-oxide ((63)) has been prepared by several methods. Because of controversy as to the fine structure of this molecule, it has received more attention than its benzo-derivative, 2-aminoquinoline-1-oxide but in general the facts elucidated for the pyridine derivative apply with some reservations to the quinoline derivative.

Newbold and Spring[91] described the first synthesis of 2-aminopyridine-1-oxide in 1949. Their method involved the preparation of 2-picolinamide-1-oxide ((63), $CONH_2$ for NH_2) followed by conversion of this compound to the free amine with alkaline hypobromite. These authors were also the first to draw attention to the deep blue colour which 2-aminopyridine-1-oxide imparts to alcoholic ferric chloride solution, though similar colours had already been observed with 2-aminoquinoline-1-oxides in contact with this reagent[87,88,89]. 2-Aminopyrazine-1-oxides e.g. (64) also give blue colours with alcoholic ferric chloride solution[92]. This colour is a fairly reliable diagnostic feature of 2-aminopyridine and quinoline-1-oxides in general, and the colour range blue-green to blue which these compounds exhibit contrasts with the deep red colour developed by the cyclic hydroxamic acids (e.g. (61))[93].

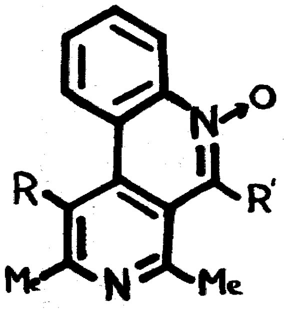
2-Aminopyridine-1-oxide has also been prepared by oxidation of 2-acetamidopyridine (65) with a peracid to give 2-acetamidopyridine-1-oxide ((63), $NHCOCH_3$ for NH_2) - (a method not applicable to the free amine) - followed by hydrolysis to the free amine[94]. A variation of this method developed by Katritzky involves the reaction of 2-aminopyridine ((65), NH_2 for NHAc) with ethyl chloroformate to give the 2-ethoxycarbonylamino derivative[95]. This derivative

CHAPTER II

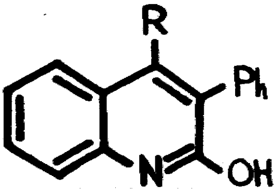
FLOWSHEET (2)



(68)



(69)



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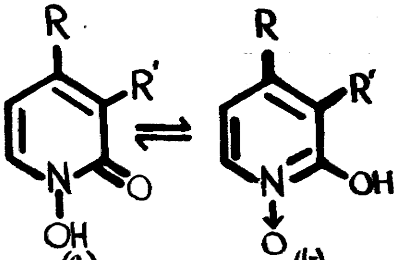
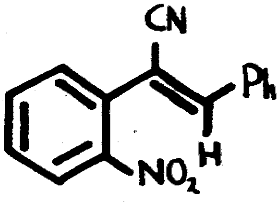


(a) (71) (b)



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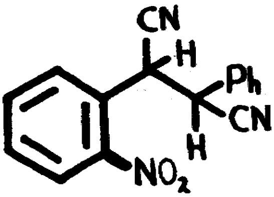
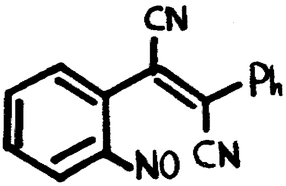


(73)



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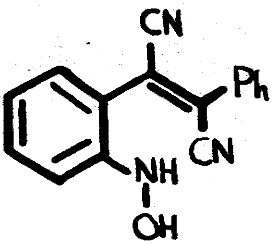


(75)

is oxidised by hydrogen peroxide in excellent yield to the urethane derivative of 2-aminopyridine-1-oxide (i.e. (63), $NHCO_2Et$ for NH_2) which on hydrolysis gives 2-aminopyridine-1-oxide in higher yield than in any of the previous syntheses[96]. It is noteworthy that the 2-urethane derivative ((63), $NHCO_2Et$ for NH_2) gives a deep red colour with alcoholic ferric chloride solution.

Arndt[97] claims that reduction of 2-nitrobenzoylacetonitrile (66) with zinc and ammonium chloride gives a product to which he has assigned the 2-amino-4-hydroxyquinoline-1-oxide structure ((67) (a) or (b)). This is interesting in view of the fact that Ames, Franklin and Grey[98] failed to synthesise this compound.

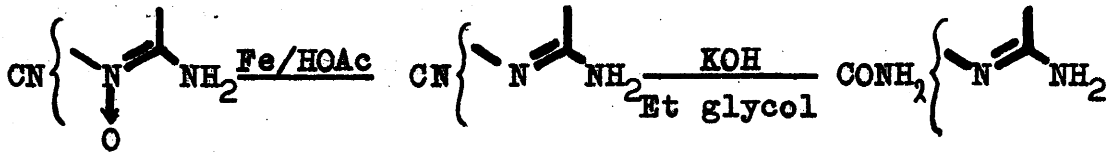
Reduction of 2:6-dimethyl-4-o-nitrophenylpyridine derivatives ((68), $R = H, R' = CN$, or $R = R' = CN$) with zinc and ethanol gives the corresponding 10-aminodiazaphenanthrene-9-oxides ((69), $R = H$ or CN, $R' = NH_2$)[99].

Brand and Loehr's Compound

Repetition of the conditions used by Brand and Loehr[85], namely, refluxing α-phenyl-o-nitrocinnamonitrile ((60), $R = Ph, R' = CN$) with excess aqueous ethanolic potassium cyanide solution in presence of ammonium chloride and a few drops of piperidine afforded at the end of 15 hrs. a brown amorphous solid insoluble in the alkaline reaction mixture.

Purification of this product by several crystallisations from ethanol gave deep yellow needles. The compound was basic, forming a colourless, rather unstable hydrochloride, readily decomposed to the free base by dissolution in water. The most significant feature of the base, however, was the deep blue-green colour which it gave in alcoholic ferric chloride solution. Analysis corresponded to the molecular formula $C_{16}H_{11}N_3O$. The infra-red spectrum revealed the presence of a primary amino group (3400 cm.$^{-1}$, 3200 cm.$^{-1}$) in keeping with the compound's basic properties, and an intact cyano group (2200 cm.$^{-1}$). Bands attributable to carbonyl groups were absent. Acetylation of the base gave a monoacetyl derivative shown by its infra-red spectrum to be a secondary amide (3300 cm.$^{-1}$, 1670 cm.$^{-1}$, 1550 cm.$^{-1}$). The peak at 1800 cm.$^{-1}$ characteristic of a cyclic N-acetoxy group[86] was lacking. The monoacetyl derivative gave only a weak red colour with alcoholic ferric chloride solution.

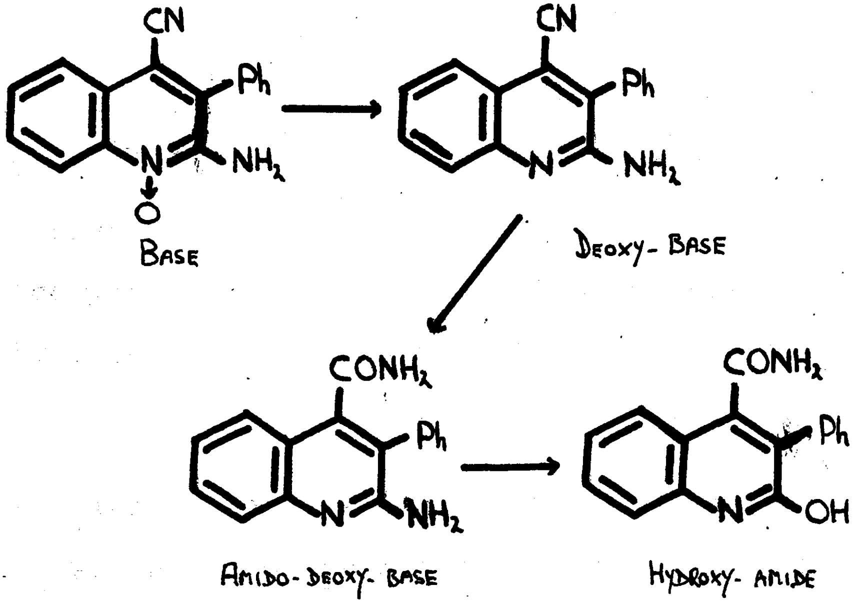
Reduction of the base with iron and acetic acid afforded a deoxy derivative corresponding to the molecular formula $C_{16}H_{11}N_3$. This reduction product gave no colour with alcoholic ferric chloride but retained the basic properties of the base, dissolving readily in mineral acid and forming a monoacetyl derivative having bands in the infrared spectrum corresponding to a secondary amide. The infrared spectrum of the deoxy base itself, showed peaks corresponding to a primary amino group and to a free cyano group. The monoacetyl deoxy base was identical in melting point, mixed melting point and infra-red spectrum with the product of hydrogenation of the monoacetyl base. The foregoing evidence indicated the presence of the 2-amino-N-oxide group in the molecule based on the reaction sequence -



base   deoxy base   amido deoxy base

Hydrolysis of the cyano group in the deoxy base proved difficult. Using forcing conditions, however, namely refluxing for a short period in 90% ethylene glycol with potassium hydroxide, hydrolysis to a primary amide was effected. The presence of an intact primary amino group in the amido deoxy base was again substantiated by the compound's basic properties and by its infra-red spectrum.

Finally, diazotisation and hydrolysis of the amido deoxy base gave a hydroxy amide which was shown to be identical in every respect with the known compound, 2-hydroxy-3-phenylquinoline-4-carboxyamide ((70), R = CONH$_2$)[100]. Synthesis of 2-hydroxy-3-phenylquinoline-4-carboxylic acid ((70), R = COOH) was accomplished by condensing the sodium salt of phenylacetic acid with isatin. The carboxylic acid was then readily converted to the acid chloride ((70), R = COCl) in refluxing thionyl chloride and reaction of this acid chloride with gaseous ammonia in chloroform gave a good yield of the amide ((70), R = CONH$_2$). On the basis of the above experimental evidence the base is formulated as 2-amino-4-cyano-3-phenylquinoline-1-oxide ((62), R = CN, R$'$ = Ph) and the degradation sequence can be set down as follows -



The blue-green colour developed by the base in contact with alcoholic ferric chloride solution is in agreement with its 2-aminoquinoline-1-oxide structure. It might be expected that acetylation of the base ((62), R = CN, R' = Ph) would lead to an N-acetoxy rather than an N-acetylamino derivative as observed. This would then agree with the acetylation characteristics of the cyclic hydroxamic acids (61)[86]. However, Katritzky[96] has shown that acylation of 2-aminopyridine-1-oxide ((63), (a) or (b)) which like 2-aminoquinoline-1-oxide is a tautomeric system, always leads to the formation of the more stable N-acyl derivative, though he has demonstrated the initial formation of a labile N-acyloxy derivative which rapidly rearranges to the N-acyl compound.

The present writer has shown that 2-amino-3-phenylquinoline-1-oxide ((62), R = H, R' = Ph)[90] also forms an N-acyl rather than an N-acetoxy derivative in acetic anhydride. This compound ((62), R = H, R' = Ph) gives a deep blue-green colour with alcoholic ferric chloride solution and as in the case of 2-acetylamino-4-cyano-3-phenylquinoline-1-oxide, its acetyl derivative gives only a weak red colour with this reagent.

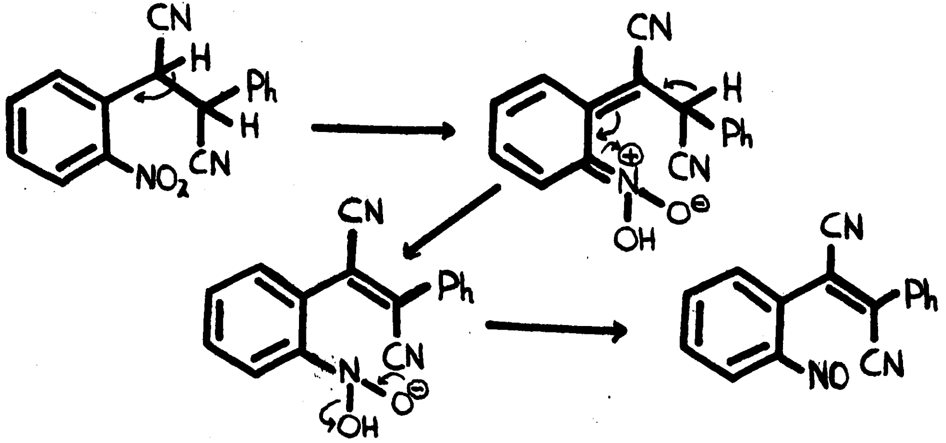
2-Amino-3-phenyl-4-cyanoquinoline-1-oxide ((62), R = CN, R' = Ph) was also prepared by warming $\underline{\alpha}$-phenyl-$\underline{o}$-

nitrocinnamonitrile ((60), R = CN, R' = Ph) with 50% aqueous potassium cyanide solution in ethanol for a few minutes on the steam bath. Similar treatment of *α*(*o*-nitrophenyl) cinnamonitrile (72) also gives a comparable yield of the base. This implies that the adduct (73) formed by addition of hydrogen cyanide to the double bond in either *α*-phenyl-*o*-nitrocinnamonitrile ((60), R = CN, R' = Ph) or *α*-(*o*-nitrophenyl)cinnamonitrile (72) is an intermediate in the reaction.

The Mechanism of the Reaction.

Any attempt to formulate mechanisms for the above and related[86] reactions can at this stage be based only on conjecture, but it is possible to indicate a plausible mechanism which would fit the experimental results.

As mentioned above, there is strong evidence that the adduct (73) is an intermediate in the reaction. In this molecule a saturated side-chain is situated ortho to a nitro group. Furthermore both available protons in the side-chain will be activated by the presence of the two cyano groups. From a consideration of some of the base-catalysed reactions discussed in Chapter I, it is clear that the adduct is "set up" for a dehydration process between the side-chain and nitro group transmitted through the nitro-benzene ring. This dehydration could be imagined as giving the nitroso compound (74) by the steps -



The nitro group in the original molecule has now been replaced by a nitroso group - a group which must be much more vulnerable to reduction in the basic reaction medium. Since aqueous ethanolic potassium cyanide can in certain cases[101,102] behave as a reducing agent, the reduction of the nitroso compount (74) to the hydroxylamine (75) is a possible step in the mechanism. The hydroxylamine could then cyclise to give the product, 2-amino-3-phenyl-4-cyanoquinoline-1-oxide. These considerations would of course, also apply with slight modifications to the reaction reported by Wellings[86].

This mechanism would explain why a quinoline and <u>not</u> a 3:4-dihydroquinoline derivative is obtained in the reaction, since if direct reduction of the nitro group was taking place, cyclisation of the hydroxylamine formed should lead to a 3:4-dihydro derivative (provided any dehydrogenating properties of the reaction mixture can be ignored).

CHAPTER [illegible]

THE SYNTHESIS OF 1-HYDROXY INDOLE DERIVATIVES

CHAPTER III

NEW SYNTHESES OF 1-HYDROXY INDOLE DERIVATIVES

CHAPTER III

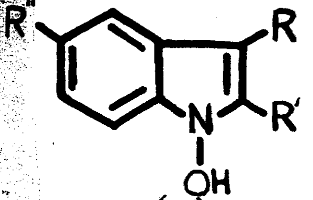
FLOWSHEET (1)

CHAPTER III

NEW SYNTHESES OF 1-HYDROXY INDOLE DERIVATIVES

CHAPTER III

FLOWSHEET (1)



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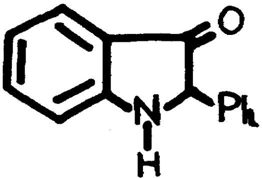

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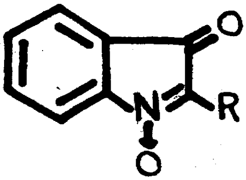

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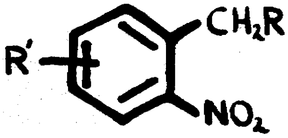

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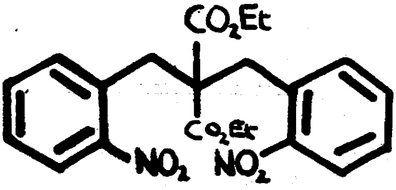

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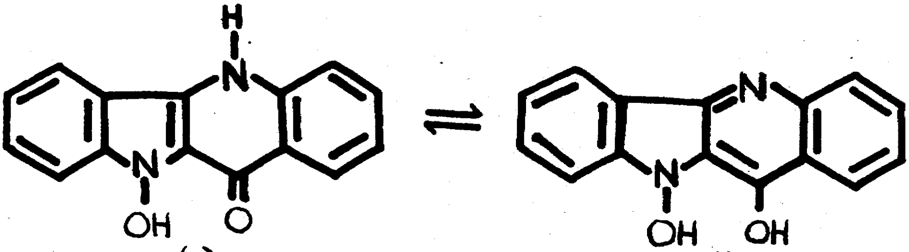
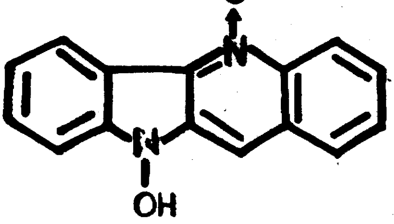


(a)

(81)

(b)



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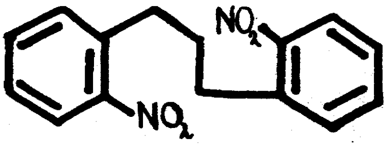


(83)

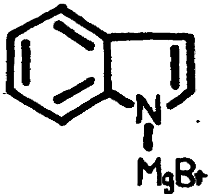
CHAPTER III

New Syntheses of 1-Hydroxy Indole Derivatives

Of the many indole derivatives reported in the literature, 1-hydroxy indoles are among the rarest. Fischer and Hutz[103] were the first to prepare a true 1-hydroxy indole. They obtained 1-hydroxy-2-phenyl indole ((76), R = H, R' = Ph, R'' = H) in good yield by cyclodehydration of α-benzoin oxime in concentrated sulphuric acid. Unfortunately Fischer[103,104] and later Wren[105] assigned the 2-phenylindoxyl structure (77) to this product. That the compound was in fact 1-hydroxy-2-phenyl indole was proved by Angeli[106,107] who showed that the nitroso derivative of Fischer's compound was identical with the oxime obtained from 2-phenyl isatogen ((78), R = Ph). Angeli and Angelico[107] were the first to demonstrate the presence of a readily acylatable hydroxyl group in these indole derivatives. The synthesis of 1-hydroxy indole-2-carboxylic acid ((76), R = H, R' = COOH, R''=H) was reported shortly afterwards by Reissert[108] who obtained the compound by base-catalysed cyclisation of o-nitrobenzylmalonic acid ((79), R = $CH(COOH)_2$, R' = H). It is noteworthy, in view of more recent work[86] that the diester ((79), R = $CH(CO_2Et)_2$ R' = H) appears to be hydrolysed before it undergoes cyclodehydration to the indole ((76), R = H, R' = COOH, R'' = H). 1-Hydroxy indole-2-carboxylic acid has also been prepared by

CHAPTER III

FLOWSHEET (2)



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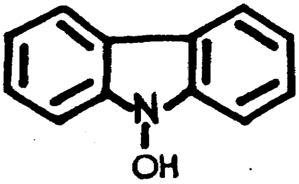

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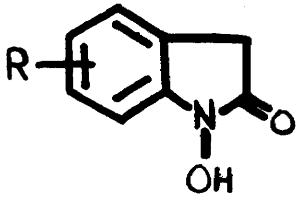
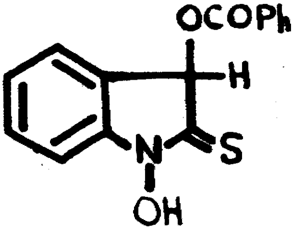


(86)



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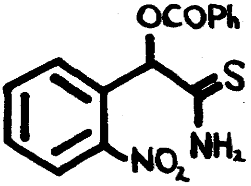

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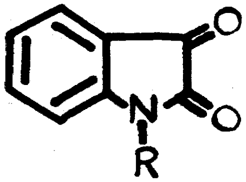

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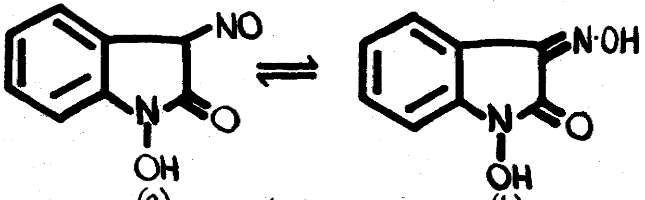
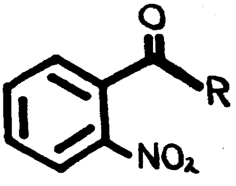


(a) (90) (b)



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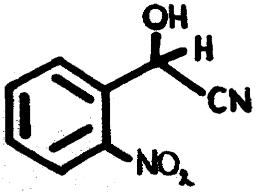


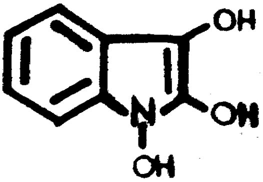
(92)

reduction of o-nitrophenyl pyruvic acid ((79), R = COCOOH, R' = H) with sodium amalgam[109]. Gabriel and coworkers[110] obtained a mixture of 1-hydroxy indole-2-carboxylic acid ((76), R = H, R' = COOH, R'' = H) and its ethyl ester ((76), R = H, R' = CO_2Et, R'' = H) by cyclisation of ethyl o-nitrobenzylacetoacetate ((79), R = $CH(CO_2Et)\ COCH_3$, R' = H) in dilute alkali, a reaction closely related to that reported by Reissert[108]. Fichter and Boehringer[111] described a similar type of cyclisation in ethyl bis-o-nitrobenzylmalonate (80), a compound previously studied by Rudin[112]. They assigned a dihydroxyquindoline type of structure (81) to the product of this reaction but it is possible that the true structure of this molecule, is more correctly formulated as (82). $\omega:\omega'$-(2:2'-Dinitrodiphenyl)propane (83) is a proposed intermediate in the reaction but cyclisation of such a compound under the conditions used is not likely.

Ingraffia[113] reported the preparation of 1-hydroxy indole ((76), R = R' = R'' = H) itself, by oxidation of 1-indolyl magnesium bromide (84) with hydrogen peroxide but Witkop[114] obtained a C-hydroxy derivative rather than an N-hydroxy derivative by the similar oxidation of the carbazole Grignard reagent, though it is possible that 1-hydroxy-carbazole (85) is initially formed. 1-Hydroxy indole-3-acetic acid ((76), R = CH_2CO_2H, R' = R'' = H) is the main

CHAPTER III

FLOWSHEET (3)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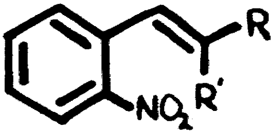
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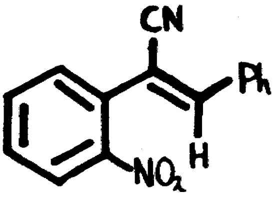
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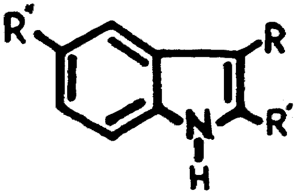
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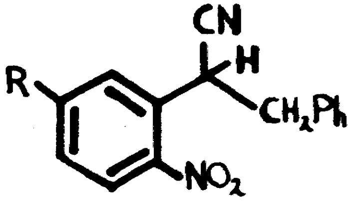
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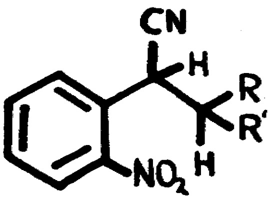
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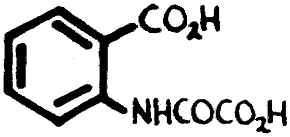
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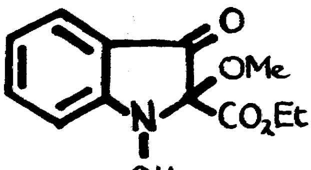
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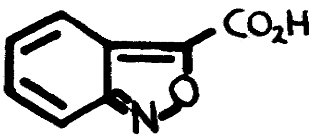

(101)

Heller[121] to prepare 1-acetoxyisatin ((89), R = OCOMe). 1-Hydroxyisatin like other 1-hydroxy indoles shows all the characteristics of a fairly strong acid.

Heller[122] obtained a product by reduction of o-nitromandelic acid ((92), COOH for CN) with zinc and ammonia, to which he assigned the structure of 1-hydroxy dioxindole (93) and this reaction has recently been re-investigated by Mackenzie and Stewart[123].

The Structure of the By-Product obtained in Brand and Loehr's Reaction

Examination of the alkaline mother liquors from the preparation of 2-amino-4-cyano-3-phenylquinoline-1-oxide (cf. Chapter III) led to the isolation of an acidic compound readily recovered from the basic reaction mixture by acidification with dilute mineral acid. The same acid was obtained by warming α-phenyl-o-nitrocinnamonitrile ((94), R = Ph, R' = CN) or α-(o-nitrophenyl) cinnamonitrile (95) with 50% aqueous potassium cyanide followed by acidification of the filtered, alkaline solution, or by merely shaking with aqueous potassium cyanide at room temperature.

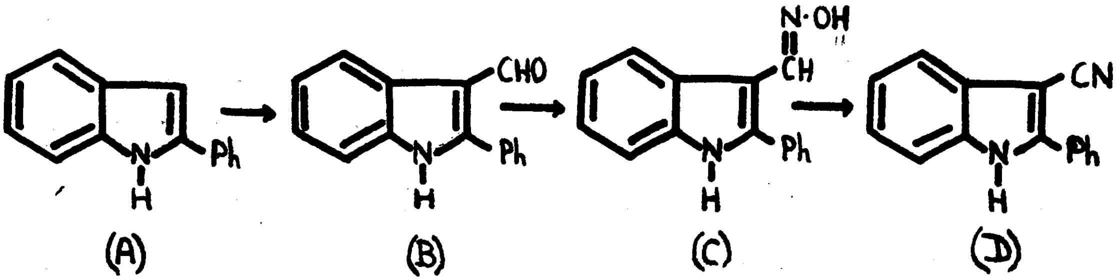
The acid analysed for $C_{15}H_{10}N_2O$ and gave an infra-red spectrum with bands attributable to C-OH, N-OH or N-H

(3200 cm.$^{-1}$) and a high intensity peak at 2200 cm.$^{-1}$ corresponding to a cyano group. The compound gave no colour with alcoholic ferric chloride solution, but behaved as a fairly strong acid, dissolving readily in dilute sodium hydroxide and dilute sodium carbonate solutions from which it was recovered unchanged on acidification. In warm acetic anhydride it formed a monoacetyl derivative which was readily hydrolysed back to the parent acid on warming with dilute alkali. Perhaps the most striking feature of this acetyl derivative was its infra-red spectrum which showed a high intensity peak at 1800 cm.$^{-1}$ characteristic of the cyclic N-acetoxy group[86], and an intact cyano group (2200 cm.$^{-1}$). The appearance of the peak at 1800 cm.$^{-1}$ in the infra-red spectrum of the acetyl derivative was strong evidence for the presence of a cyclic N-hydroxy grouping in the parent acid.

The cyano group in the parent acid proved fairly resistant to hydrolysis but under forcing conditions, namely warming for a short time in 90% aqueous ethylene glycol with potassium hydroxide, it was converted to the known 1-hydroxy indole derivative, 1-hydroxy-2-phenyl indole ((76), R = H, $R' = Ph$, $R'' = H$)[103] identical in every respect with an authentic sample prepared by cyclodehydration of α-benzoin oxime[103]. This established the presence of the 1-hydroxy indole nucleus in the parent acid which could therefore only be

3-cyano-1-hydroxy-2-phenyl indole ((76), R = CN, R$'$= Ph, R$''$= H). If the forcing hydrolysis was continued for a slightly longer period (20-30 min.), the product was 2-phenyl indole ((96), R = H, R$'$= Ph, R$''$= H) and it was confirmed that 1-hydroxy-2-phenyl indole ((76), R = H, R$'$= Ph R$''$= H) was likewise reduced to 2-phenyl indole under similar conditions.

As further proof of the structure the acetyl derivative of the acid, 1-acetoxy-3-cyano-2-phenyl indole ((76), R = CN, R$'$= Ph, R$''$= H, $OCOCH_3$ for OH) was smoothly hydrogenolysed over 5% palladium charcoal affording the indole 3-cyano-2-phenyl indole ((96), R = CN, R$'$= Ph, R$''$= H). This compound had not previously been prepared but it was readily synthesised by the route - (A) ⟶ (D) -



2-Phenyl indole (A)[124] was smoothly formylated in the three-position by treatment with hexamine in refluxing acetic acid giving 2-phenyl indole-3-aldehyde (B). Dehydration of the oxime (C) in acetic anhydride gave a good yield of 3-cyano-

2-phenyl indole (D), identical in melting point, mixed melting point, infra-red spectrum and analysis with the indole obtained by degradation of 3-cyano-1-hydroxy-2-phenyl indole ((76), R = CN, R' = Ph, R'' = H).

1-Hydroxy-2-phenyl indole ((76), R = H, R' = Ph, R'' = H) failed in our hands to give a crystalline acetate but treatment with benzoyl chloride in 10% sodium hydroxide gave a good yield of a crystalline benzoate[125] which had a characteristically high peak at 1780 cm.$^{-1}$ in the infra-red spectrum. The benzoate was smoothly hydrogenolysed over 5% palladium charcoal in ethanol giving a quantitative yield of 2-phenyl indole. 1-hydroxy-2-phenyl indole itself, failed to hydrogenolyse in acetic acid alone but in presence of an excess of acetic anhydride, hydrogen was absorbed giving a reasonable yield of 2-phenyl indole.

It is surprising that whereas 1-hydroxy-2-phenyl indole[103] gives a deep red colour with alcoholic ferric chloride, the 3-cyano derivative does not react with this reagent, and this observation has also been verified in the case of other 3-cyano-2-phenyl-1-hydroxy indoles (see below).

A New Route to 1-Hydroxy Indoles

It had earlier[126] been observed in this department that the nitrile ((97), R = MeO) did not give the corresponding acid on attempted hydrolysis with aqueous ethanolic potassium hydroxide. Instead, a colourless, acidic compound was formed which analysed for $C_{16}H_{12}O_2N_2$. This compound has now been proved, unambiguously, to be a 1-hydroxy indole derivative, namely, 3-cyano-1-hydroxy-5-methoxy-2-phenyl indole ((76), R = CN, R' = Ph, R'' = MeO).

The compound formed a crystalline monoacetate having a peak at 1800 cm.$^{-1}$ in the infra-red spectrum corresponding to a cyclic N-acetoxy group[86]. It was acidic, dissolving readily in dilute alkali and dilute sodium carbonate from which it could be recovered unchanged on acidification. It did not react with alcoholic ferric chloride solution but bands at 3200 cm.$^{-1}$ and 2200 cm.$^{-1}$ in the infra-red spectrum could be attributed to the presence of a cyclic N-hydroxy group and a cyano group respectively. By analogy with 3-cyano-1-hydroxy-2-phenyl indole above, this compound has been assigned the structure 3-cyano-1-hydroxy-5-methoxy-2-phenyl indole ((76), R = CN, R' = Ph, R'' = MeO). Its acetate ((76), R = CN, R' = Ph, R'' = MeO, OCOMe for OH) was hydrogenolysed over 5% palladium charcoal in ethanol to give the indole, 3-cyano-5-methoxy-2-phenyl indole ((96), R = CN, R' = Ph, R'' = MeO).

Similarly base-catalysed cyclisation of the nitrile ((97), R = MeO, $C_6H_2(OMe)_3$ for Ph) gave the 1-hydroxy indole derivative ((76), R = CN, R' = $C_6H_2(OMe)_3$, R'' = MeO, which formed a crystalline monoacetate ((76), R = CN, R' = $C_6H_2(OMe)_3$, R = MeO, OCOMe for OH) having a band at 1800 cm.$^{-1}$ in the infra-red spectrum[86]. The indole derivative ((96), R = CN, R' = $C_6H_2(OMe)_3$, R'' = MeO) was obtained by hydrogenation of the acetate over 5% palladium charcoal in ethanol.

This base-catalysed cyclisation of substituted o-nitrobenzylcyanides of the type (97) constitutes a new synthesis of 1-hydroxy indole derivatives.

Scope and Limitations of the Reaction

Since both α-phenyl-o-nitrocinnamonitrile ((94), R = Ph, R = CN) and α-(o-nitrophenyl) cinnamonitrile ((95) cyclise in aqueous ethanolic potassium cyanide to give 3-cyano-1-hydroxy-2-phenyl indole ((76), R = CN, R' = Ph, R'' = H) it is probable that the adduct ((98), R = CN, R' = Ph), formed by addition of hydrogen cyanide to the double bond in either of these compounds, is an intermediate in the reaction. The similarity between the above reaction and that described by Wellings[86] is then obvious.

In order to test the scope of the reaction and by way of deciding which of the groups, cyano or carbethoxyl would be removed in the course of the reaction, a series of experiments was set up to examine the behaviour of the adduct ((98), R = CN, R' = CO_2Me)[127] obtained by addition of hydrogen cyanide to methyl o-nitrobenzylidenecyanoacetate ((94), R = CN, R' = CO_2Me)[127] when treated with base.

The adduct dissolved in dilute sodium hydroxide in the cold, giving an intense violet solution and when the latter was warmed, cooled and poured into excess dilute sulphuric acid, an acid analysing for $C_9H_7NO_5$ was obtained in 50% yield. No trace of any 1-hydroxy indole derivative could be detected. The ready solubility of the acidic compound in dilute bicarbonate solution and its formation of a dimethyl ester by treatment with ethereal diazomethane, indicated that it was a dicarboxylic acid.

The dimethyl ester was identical in melting point, mixed melting point and infra-red spectrum with an authentic sample of the dimethyl ester of N-oxalyl-anthranilic acid (99)[128]. The melting point of the acid and an authentic sample of N-oxalylanthranilic acid, however, differed by 40°C. though there was no depression of the melting point on admixture. This phenomenon has also been reported by Späth and Bretschneider[129] and by others, and it would appear that since the melting point is in actual fact a decomposition point, the only satisfactory way of characterising N-oxalylanthranilic acid is by way of the dimethyl ester.

Heller and Boessneck[130] obtained N-oxalylanthranilic acid by warming the intermediate (100) obtained by 1:3-addition of methanol in presence of hydrochloric acid, to ethyl isatogen-2-carboxylic acid ((78), R = CO_2Et) with dilute base.

Horner and Klupfel[127] suggest that elimination of hydrogen cyanide from the adduct ((98), R = CN, R' = CO_2Me) occurs very readily and since Pschorr and Wolfes[36] showed that α-phenyl-o-nitrocinnamonitrile ((94), R = Ph, R' = CN) is smoothly converted to N-benzoyl anthranilic acid ((99), COPh for $COCO_2H$) in warm aqueous ethanolic potassium hydroxide, the formation of N-oxalylanthranilic acid in the present case might be explained as proceeding by facile elimination of hydrogen cyanide from the adduct ((98), R = CN, R' = CO_2Me) to give methyl o-nitrobenzylidene cyanoacetate ((94), R = CN, R' = CO_2Me) which could then react with base by analogy with Pschorr's reaction to give N-oxalylanthranilic acid. However, treatment of the benzylidene derivative ((94), R = CN, R' = CO_2Me) with either aqueous ethanolic sodium hydroxide or sodium carbonate gave only o-nitrobenzylidene cyanoacetic acid ((94), R = CN, R' = CO_2H). In presence of cyanide ion however the benzylidene derivative was converted to N-oxalyl anthranilic acid which could also be obtained by merely warming the adduct ((98), R = CO_2Me, R$'$ = CN) with dilute sodium carbonate.

In none of the above experiments could any trace of the expected 1-hydroxy indole derivative be detected.

Further Examples of Base-Catalysed Condensation of Nitro Groups with Methylene Groups

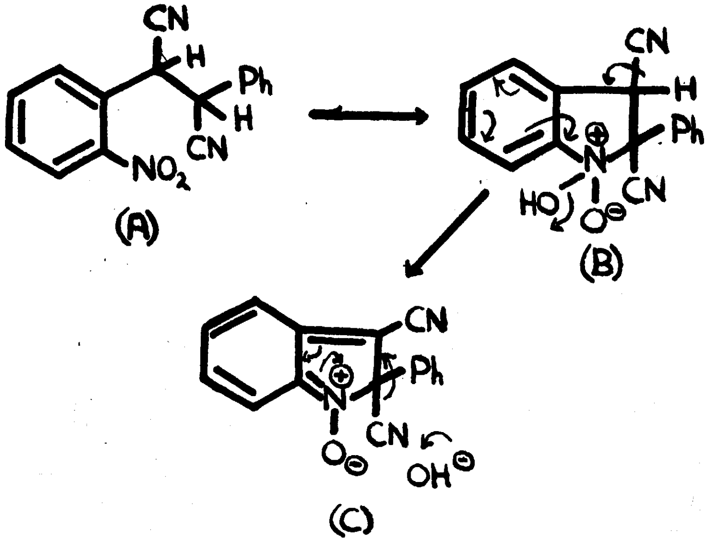
While investigating the scope of base-catalysed cyclisation in ortho-nitro benzene derivatives two new reactions involving this type of condensation were discovered.

ω-Chloro-o-nitroacetophenone ((91), R = CH_2Cl)[4] was treated with aqueous ethanolic sodium hydroxide to give a good yield of the sodium salt of anthranil-3-carboxylic acid (101). The free acid was identical in every respect with a sample obtained by the rearrangement of 1-hydroxyisatin[4] ((89), R = OH). Since the latter compound rearranges in basic media to anthranil-3-carboxylic acid, it is possible that initial cyclisation of ω-chloro-o-nitroacetophenone gives 1-hydroxyisatin which then rapidly rearranges to the anthranil derivative.

o-Nitrobenzoylacetone ((91), R = CH_2COCH_3)[2] was warmed with aqueous ethanolic potassium hydroxide. Careful acidification of the cooled, concentrated alkaline reaction mixture gave an orange red compound identical in every respect with an authentic sample of isatin. Ethyl isatogen-2-carboxylate ((78), R = CO_2Et) is known to be readily hydrolysed in dilute sodium carbonate solution giving isatin[3] and since in the above case condensation might lead to the formation of 2-acetylisatogen ((78), R = COMe) it is possible that a similar type of reaction is taking place.

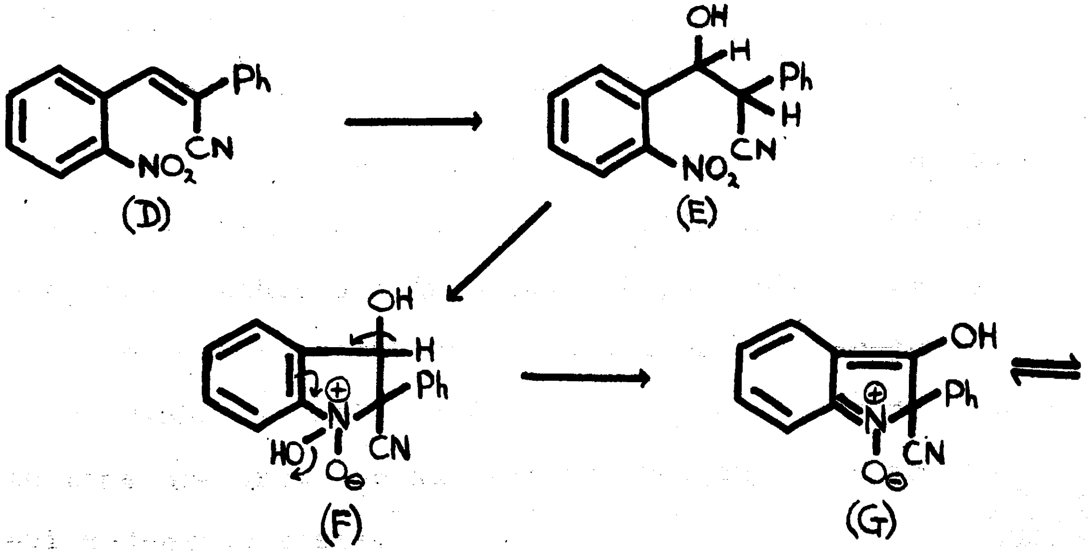
Note on the Mechanism.

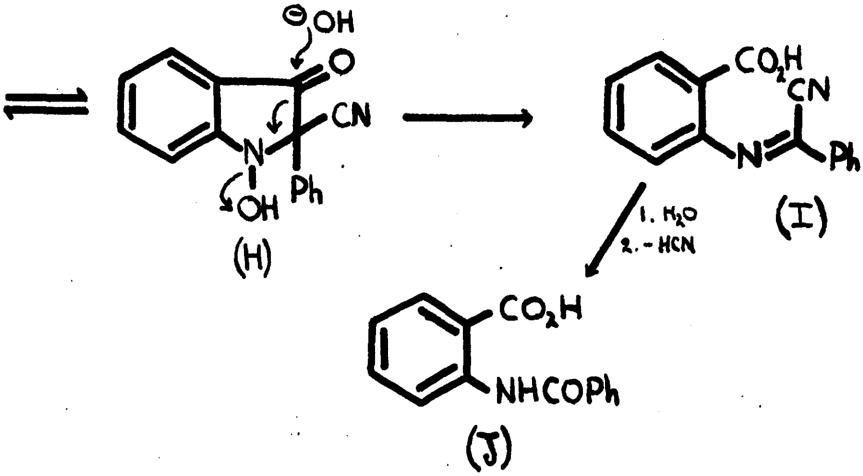
Provided the adduct ((98), R = CN, R' =Ph) may be assumed to be formed initially in the reaction the following mechanism might operate -



The final stage of the reaction would then be hydrolysis of the intermediate (C) to 3-cyano-1-hydroxy-2-phenyl indole ((76), R = CN, R$'$ = Ph, R$''$ = H). Wellings[86] reported a similar type of reaction involving the adduct ((98), R = R$'$ = CO$_2$Et) obtained by addition of hydrogen cyanide to ethyl *o*-nitrobenzylidene malonate ((94), R = R$'$ = CO$_2$Et) and in this case also a mechanism of the above type might apply.

The mechanism (A) ⟶ (C) implies an aldol-type of condensation between the nitro group and the side-chain and this is capable of further extension. Thus Pschorr and Wolfes[36] obtained N-benzoyl anthranilic acid by treatment of *α*-phenyl-*o*-nitrocinnamonitrile with aqueous ethanolic potassium hydroxide and bearing the above mechanism in mind a possible route for this latter reaction could be formulated as follows -





Hydration of the double-bond in (D) would give (E) which could then cyclise as before giving (F), (G) and (H). In the intermediate (H) however, the carbonyl group should be more susceptible to attack by hydroxide ion than the cyano group, giving the azomethine derivative (I). Azomethines of this type are known to be readily converted in base to the N-benzoyl derivatives (J)[131] and Heller and Boessneck[130] claim that an intermediate of the type (H) is readily converted in base to an N-acylanthranilic acid.

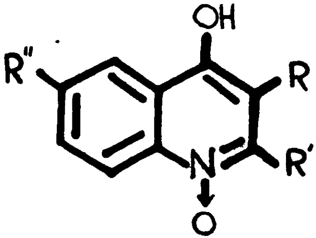
It might be possible to test the validity of the above mechanism by preparing intermediates of type (H) and examining their behaviour in base. A possible route to such an intermediate might be 1:3-addition of hydrogen cyanide to 2-phenyl isatogen ((78), R = Ph) since compounds of this type are known to add various reagents 1:3 to the indolenine-1-oxide system[74].

CHAPTER IV

STUDIES IN THE SYNTHESIS OF 4-HYDROXYQUINOLINE-1-OXIDES

CHAPTER IV

FLOWSHEET (1)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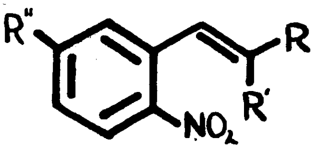
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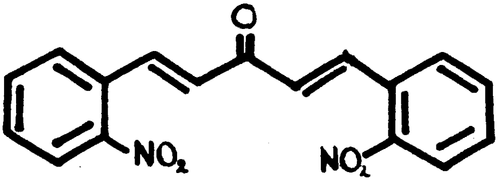
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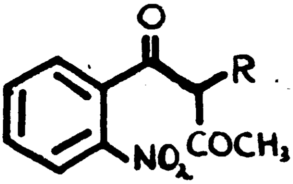
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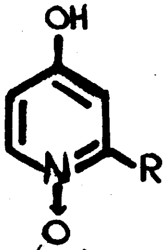
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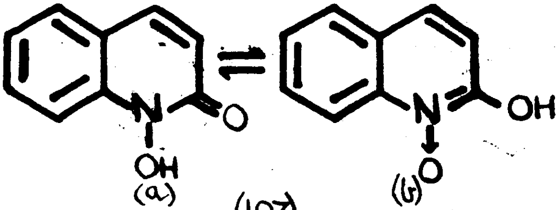
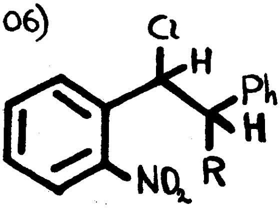

(a) (b)

(107)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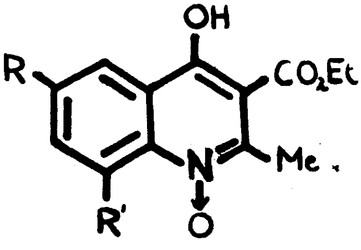
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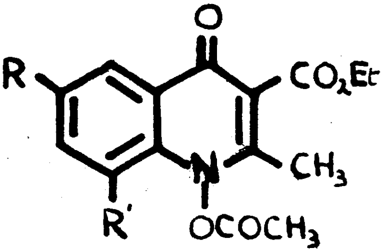
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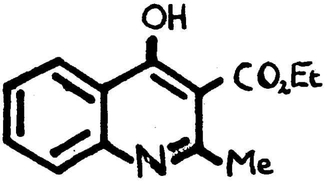
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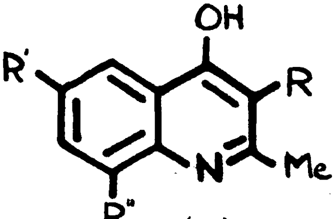
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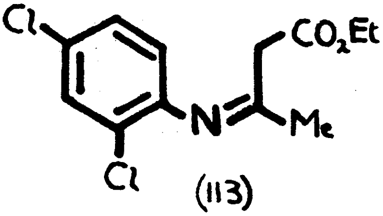

(113)

CHAPTER IV

Studies in the Synthesis of 4-Hydroxyquinoline-1-oxides

When dry hydrogen chloride is passed into an ether solution containing equimolecular proportions of o-nitrobenzaldehyde and ethyl acetoacetate, at room temperature, the main product of the reaction, formed in about 80% yield is ethyl 6-chloro-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide ((102), $R = CO_2Et$, $R' = Me$, $R'' = Cl$)[132]. That some deep-seated reaction must have occurred is obvious from the structure of the product and this is all the more surprising in view of the mild conditions used. Wellings[132] also showed that a similar type of quinoline derivative was obtained using either acetylacetone or acetonedicarboxylic ester. Using ethyl benzoylacetate as the methylene component of the reaction, however, gave only the corresponding benzylidene derivative ((103), $R = COPh$, $R' = CO_2Et$, $R'' = H$) and no evidence of quinoline formation was obtained. Furthermore when acetone was used, the product was bis-o-nitrobenzylideneacetone (104)[132]. At least in the case of acetylacetone, o-nitrobenzylideneacetylacetone ((103), $R = R' = COCH_3$, $R'' = H$) was isolated, as well as the quinoline-1-

oxide, from the reaction mixture, and this benzylidene derivative was smoothly converted to the quinoline-1-oxide ((102), R = $COCH_3$, R' = Me, R'' = Cl) in ethereal hydrogen chloride[132].

Further studies on the mechanism of the above reaction have now been undertaken and the results obtained from these studies constitute the subject matter of this chapter.

Perhaps the first preparation of a 4-hydroxyquinoline-1-oxide was described by Gabriel and Gerhardt[133] who obtained 4-hydroxy-2-methylquinoline-1-oxide ((102), R = H, R' = Me, R'' = H) by the reductive cyclisation of o-nitrobenzoylacetone ((105), R = H) and 4-hydroxy-2-phenylquinoline-1-oxide ((102), R = H, R' = Ph, R'' = H) has been prepared by the similar reduction of o-nitrodibenzoylmethane ((105), R = H, COPh for $COCH_3$)[134]. McLuskey[135] obtained ethyl 4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide ((102), R = CO_2Et, R' = Me, R'' = H) by the reduction of ethyl o-nitrobenzoylacetoacetate ((105), R = CO_2Et) with stannous chloride and hydrochloric acid. Overmeyer[136] examined the scope of the reactions reported by McLuskey, and Gabriel and Gerhardt.

Ochiai[137] obtained 4-hydroxyquinoline-1-oxide

((102), R = R' = R'' = H) by the catalytic hydrogenation of 4-benzyloxyquinoline-1-oxide ((102), R = R' = R'' = H, OCH_2Ph for OH) and Tanaka[138] has also reported a synthesis of the 4-methoxy derivative ((102), R = R' = R'' = H, MeO for OH).

The pyridine analogues, 4-hydroxypyridine-1-oxides ((106), R = H) are also well known. Soliman and El Sayid[139] synthesised a series of 4-hydroxypyridine-1-oxides and the 4-methoxy derivatives of pyridine-and α-picoline-1-oxide ((106), R = H, or Me, MeO for OH) were prepared by Suzucki[140]. Hertog and Combe[141] obtained 4-hydroxypyridine-1-oxide ((106), R = H) itself by refluxing 4-nitropyridine-1-oxide ((106), R = H, NO_2 for OH) with sodium hydroxide.

In general the chemistry of 4-hydroxyquinoline and pyridine-1-oxides has been extensively studied by the Japanese[142], the Dutch[143] and the Italian Schools[144].

In contrast to the corresponding 2-hydroxyquinoline-1-oxides (107) 4-hydroxyquinoline-1-oxides are reported as having no antibactericidal activity[145] though Baltschefsky and Baltschefsky[146] demonstrated the effect of 2-n-heptyl-4-hydroxyquinoline-1-oxide ((102), R = H, R' = n-heptyl, R'' = H) on heart muscle.

Since both 4-hydroxyquinoline- and pyridine-1-oxides represent tautomeric systems, the question of the fine structure of these molecules has been the subject of intensive study. Various groups have attempted to correlate the physical properties of these compounds with the relative stabilities of the two possible tautomeric forms. Among these groups may be mentioned Katritzky[147] and coworkers and Costa et al.[148] who studied the infra-red spectra of various 4-hydroxypyridine-1-oxide derivatives and Jaffe and Doak[149] who made a study of the ultra-violet spectra.

Scope of the Reaction

(a) Using Different Methylene Components.

Experiments were undertaken to determine the scope of the quinoline-1-oxide syntheses discovered by Wellings[132]. The structures of the products obtained when the methylene component of the reaction was varied could then give information about the mechanism involved.

When ethyl cyanoacetate or benzylcyanide was used as the methylene component none of the expected 4-hydroxyquinoline-1-oxide derivative was found and the product of the reaction was the o-nitrobenzylidene derivative, namely ethyl o-nitrobenzylidenecyanoacetate ((103), $R = CN$, $R' = CO_2Et$, $R'' = H$) and o-nitrobenzylidenebenzylcyanide ((103),

$R = CN$, $R' = Ph$, $R'' = H$), respectively. Samples of these compounds prepared in this way were identical in every respect with those prepared by the methods of Riedel[150] and Meyer and Frost[151]. Schimetschek[152] claims that condensation of o-nitrobenzaldehyde with dibenzylketone in acetic acid using hydrogen chloride gives a product to which he has assigned the structure ((108), $R = COCH_2Ph$). Similarly Stobbe and Wilson[153] prepared a mixture of o-nitrobenzylidenedesoxybenzoin ((103), $R = Ph$, $R' = COPh$, $R'' = H$) and the hydrochloride ((108), $R = COPh$) by treating o-nitrobenzaldehyde with desoxybenzoin in ethereal hydrogen chloride.

Benzoyl acetone was condensed with o-nitrobenzaldehyde in ether in presence of hydrogen chloride to give two products corresponding in analysis to o-nitrobenzylidenebenzoylacetone ((103), $R = COCH_3$, $R' = COPh$, $R'' = H$) and a 4-hydroxyquinoline-1-oxide derivative which could either be 3-benzoyl-6-chloro-4-hydroxy-2-methylquinoline-1-oxide ((102), $R = COPh$, $R' = Me$, $R'' = Cl$) or 3-acetyl-6-chloro-4-hydroxy-2-phenylquinoline-1-oxide ((102), $R = COCH_3$, $R' = Ph$, $R'' = Cl$). The ambiguity in the structure of this compound is due to the possibility of cyclisation occurring either with the acetyl or with the benzoyl group. Since there is evidence that the acetyl group tends to cyclise more readily than the benzoyl group, the compound has been assigned the 3-benzoyl-6-chloro-4-hydroxy-2-methylquinoline-1-oxide structure, though this has still to be proved chemically. Like other 4-hydroxyquinoline-1-oxides the above compound gave in warm acetic anhydride a monoacetyl derivative having a peak at 1800 cm.$^{-1}$ in the infra-red[132] characteristic of a cyclic N-acetoxy group, and gave a red colour with alcoholic ferric chloride solution.

Wellings[132] demonstrated that o-nitrobenzylideneacetylacetone ((103), $R = R' = COCH_3$) was an intermediate in the preparation of 3-acetyl-6-chloro-4-hydroxy-2-methylquinoline-1-oxide ((102), $R = COMe$, $R' = Me$, $R'' = Cl$), but similar proof that ethyl o-nitrobenzylideneacetoacetate ((103), $R = COCH_3$, $R' = CO_2Et$, $R'' = H$) was an intermediate in the preparation of ethyl 6-chloro-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide ((102), $R = CO_2Et$, $R' = Me$, $R'' = Cl$) had not been obtained. Heller, Lauth and Buchwaldt[154] report the benzylidene derivative as an oil which they failed to solidify. Ethyl o-nitrobenzylideneacetoacetate has now been prepared as a nicely crystalline solid by condensing o-nitrobenzaldehyde with ethyl acetoacetate in acetic anhydride in presence of potassium bicarbonate and this compound was smoothly converted to ethyl 6-chloro-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide ((102), $R = CO_2Et$, $R' = Me$, $R'' = Cl$) in ethereal hydrogen chloride.

(b) Using Different Aldehyde Components

In the above reaction the 4-hydroxyquinoline-1-oxide derivative is substituted by chlorine in some way at the para position to the nitro group in the original nitrobenzene ring. It was therefore of interest to study the reaction when this para-position was blocked by a substituent such as chlorine or bromine. In practice, condensation of 5-chloro or 5-bromo-2-nitrobenzaldehyde with ethyl acetoacetate in ether in presence of hydrogen chloride gave good yields of ethyl 6:8-dichloro-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide ((109), $R = R' = Cl$) and ethyl 6-bromo-8-chloro-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide ((109), $R = Br$, $R' = Cl$). Therefore, cyclisation still proceeds with substitution by chloride when the para position to the nitro group is blocked. It would be of some interest to examine the reaction using 3:5-dichloro-2-nitrobenzaldehyde in which both the ortho and para positions are blocked.

In both cases the corresponding ethyl 5-halogeno-2-nitrobenzylideneacetoacetate ((103), $R = CO_2Et$, $R' = COCH_3$, $R'' = Cl$ or Br) was isolated as a by-product of the reaction and both of these compounds were converted in good yield in ethereal hydrogen chloride to the corresponding 4-hydroxyquinoline-1-oxide derivative.

Both ethyl 6:8-dichloro-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide and the 6-bromo: 8-chloro compound ((109), R = Br or Cl, R' = Cl) gave the corresponding N-acetoxy derivatives ((110), R = Br or Cl, R' = Cl) in warm acetic anhydride and hydrogenolysis of either of these acetates over 5% palladium charcoal in ethanol gave a good yield of the known quinoline derivative, ethyl 4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide (111), identical in melting point, mixed melting point and infra red spectrum with an authentic sample.

The foregoing evidence proved the 4-hydroxyquinoline-1-oxide structure in both of the dihalogeno derivatives but it did not fix the position of the entering chlorine atom. This was proved for the dichloro compound only, the bromo-chloro compound being regarded as analogous.

Hydrolysis of the ester group with dilute acid gave a good yield of the acid ((109), R = R' = Cl, COOH for CO_2Et). This carboxylic acid was reduced with zinc and acetic acid to give the quinoline carboxylic acid ((112), R = COOH, R' = R'' = Cl) which was smoothly decarboxylated at 250°C to give 6:8-dichloro-4-hydroxyquinaldine ((112), R = H, R' = R'' = Cl).[192] The latter compound was identical in every respect with the quinaldine derivative synthesised by condensing 2:4-dichloroaniline with ethyl acetoacetate in presence of concantrated hydrochloric acid to give the anil (113) followed by cyclisation of the latter in diphenyl ether.

(c) Using a Different Acid Reagent

The similarity between hydrogen bromide and hydrogen chloride suggested that the former like the latter might act as the acid reagent in the synthesis of 4-hydroxyquinoline-1-oxides. As it turned out, hydrogen bromide can be used in the reaction, but with quite a different result from that obtained using hydrogen chloride.

The hydrogen bromide used in the following experiments was satisfactorily prepared by dropping bromine on to tetralin and carrying the gas evolved in a stream of nitrogen through a tower containing phosphorus coated beads to remove any bromine, then through calcium bromide to dry the gas.

Ethyl acetoacetate condensed with o-nitrobenzaldehyde in ethereal hydrogen bromide to give a product which after 48 hrs crystallised from the reaction mixture. The product formed cream needles from ethyl acetate/ethanol and analysed for $C_{13}H_{14}BrO_4N$ (A). It gave a red colour with alcoholic ferric chloride solution, and gave a positive test for ionisable halogen. A broad-band at 2800 $cm.^{-1}$ - 2500 $cm.^{-1}$ in the infra-red spectrum was evidence for strong hydrogen-bonding in the compound and a peak at 1710 $cm.^{-1}$ indicated the presence of an ester group. Peaks due to an intact nitro group were absent. Compound (A) dissolved in dilute sodium carbonate or sodium hydroxide giving a yellow solution from which dilute mineral acid precipitated a second compound (B). When (B) was treated with ethereal hydrogen bromide it was reconverted into (A).

Compound (B) analysed for $C_{13}H_{13}O_4N$ and did not contain halogen, though it did give a red colour with alcoholic ferric chloride. (B) dissolved readily in dilute sodium carbonate and sodium hydroxide giving a yellow solution from which it was recovered unchanged on acidification. The infra-red spectrum showed a broad-band at 2800-2700 cm.$^{-1}$ and an ester peak at 1710 cm.$^{-1}$.

Pyrolysis of compound (A) gave a third compound (C) analysing for $C_{11}H_9O_4N$. The ready solubility of this compound, with effervescence, in dilute sodium bicarbonate indicated that (C) was a carboxylic acid and this was also borne out by the infra-red spectrum which showed broad absorbtion at 2800 cm.$^{-1}$ and a carbonyl peak at 1700 cm.$^{-1}$. Pyrolysis of (C) at a higher temperature gave a fourth compound (D) with loss of carbon dioxide. (D) analysed for $C_{10}H_9O_2N$. It was also shown that compound (C) was obtained by hydrolysis of (B) with dilute alkali.

Compound (B) was finally shown to be identical in every respect with the known compound ethyl 4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide ((102), R = CO_2Et, R' = Me, R'' = H)[135]. Compound (A) was therefore the hydrobromide of (B) while (C) was 4-hydroxy-2-methylquinoline-3-carboxylic acid-1-oxide ((102), R = COOH, R' = Me, R'' = H) and (D), 4-hydroxy-2-methylquinoline-1-oxide ((102), R = H, R' = Me, R'' = H). As a final confirmation of the structure, (B) was converted to the N-acetoxy derivative ((110), R = R' = H) in acetic anhydride, and hydrogenolysis of this acetate over 5% palladium charcoal in ethanol gave the known quinoline, ethyl 4-hydroxy-2-methylquinoline-3-carboxylate (111)[132].

Treatment of ethyl o-nitrobenzylideneaetoacetate ((103), R = $COCH_3$, R = CO_2Et, R'' = H) with ethereal hydrogen bromide gave a good yield of the hydrobromide of ethyl 4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide ((102), R = CO_2Et, R' = Me, R'' = H). Thus, even though hydrogen chloride and hydrogen bromide behave differently in promoting the reaction, the o-nitrobenzylidene derivative would appear to be an intermediate common to both cases.

Condensation of acetylacetone with o-nitrobenzaldehyde in ethereal hydrogen bromide gave the hydrobromide of 3-acetyl-4-hydroxy-2-methylquinoline-1-oxide ((102), R = COMe,

$R' = Me$, $R'' = H$), the free base being readily liberated by treatment with dilute sodium hydroxide followed by acidification with dilute mineral acid. With acetic anhydride, the base gave the N-acetate ((110), $R = R' = H$, $COCH_3$ for CO_2Et) showing the characteristic peak at 1800 cm.$^{-1}$ in the infra-red. Hydrogenolysis of the acetate over 5% palladium charcoal gave the quinoline, 3-acetyl-4-hydroxy-2-methylquinoline ((112), $R = COCH_3$, $R' = R'' = H$) identical in every respect with an authentic sample.

A possible explanation of the difference in behaviour between hydrogen chloride and hydrogen bromide is that the latter being a reducing agent, may be reducing some halogenated intermediate to an unhalogenated derivative. As a means of testing this theory the condensation of 5-chloro- and 5-bromo-2-nitrobenzaldehyde with ethyl acetoacetate was carried out in ethereal hydrogen bromide. The only products isolated in these reactions were the hydrobromides of the known compound ethyl 6-chloro-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide[132] ((102), $R = CO_2Et$, $R' = Me$, $R'' = Cl$) and that of ethyl 6-bromo-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide ((102), $R = CO_2Et$, $R' = Me$, $R'' = Br$). The latter compound formed an N-acetoxy derivative ((110), $R = Br$, $R' = H$) which was smoothly hydrogenated over 5% palladium charcoal giving the known quinoline (111). This verified the structure of the 6-bromo compound.

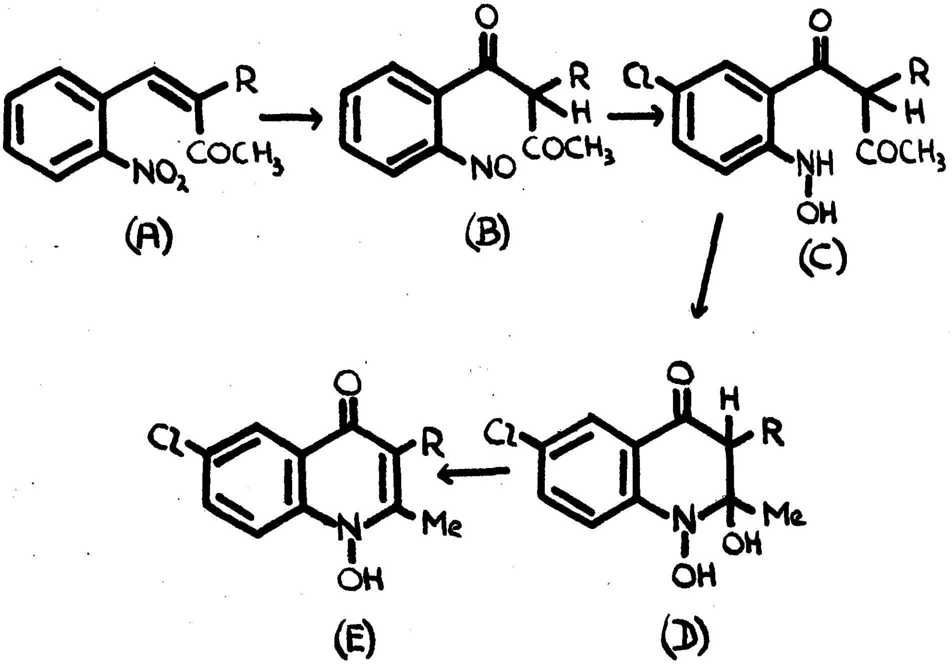
Ethyl 5-bromo- and 5-chloro-2-nitrobenzylidene-acetoacetate ((103), R = CO_2Et, R$'$ = $COCH_3$, R$''$ = Br or Cl) were converted in ethereal hydrogen bromide to ethyl 6-bromo-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide ((102), R = CO_2Et, R$'$ = CH_3, R$''$ = Br) and ethyl 6-chloro-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide ((102), R = CO_2Et, R$'$ = CH_3, R$''$ = Cl) hydrobromides respectively. No evidence for the removal or exchange of halogen during the course of the reaction could therefore be detected.

Experiments Conducted in Presence of Hydroquinone

Condensation of o-nitrobenzaldehydes with ethyl acetoacetate in presence of hydroquinone was carried out in order to determine the effect of hydroquinone on the course of the reaction and the result obtained in this experiment is described later in Chapter V.

Discussion of the Mechanism of the Reaction.

Provided it can be taken for granted that the first step of significance in the above reaction is formation of the benzylidene derivative (this is not strictly valid since the initially formed aldol cannot entirely be ruled out as an intermediate and it has in fact some attraction mechanistically) the following course can be entertained.



The step (A) ⟶ (B) would involve an acid-catalysed oxygen transfer, but there are analogies for this[1,3]. Reduction of the nitrosoketone (B) to the p-chlorohydroxylaminoketone (C) is also feasible since nitrosobenzene is readily converted by hydrochloric acid to p-chlorophenylhydroxylamine[155]. The remainder of the steps (C) ⟶ (E) should not be difficult to invoke. This mechanism does not explain why only the methylketone group undergoes cyclisation. It might, however, explain why hydrogen bromide and hydrogen chloride behave differently, since the critical step would be (B) ⟶ (C) and hydrogen bromide might be expected to bring about direct reduction of the nitroso group as opposed to the indirect pathway chosen by hydrogen chloride with the observed substitution of the nucleus by chlorine.

CHAPTER V

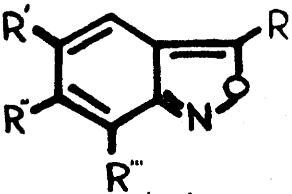
THE SYNTHESIS AND PROPERTIES OF SOME 3-ARYLANTHRANILS

CHAPTER V

THE SYNTHESIS AND PROPERTIES OF SOME 3-ARYLANTHRANILS

CHAPTER V

FLOWSHEET (1)



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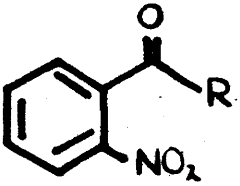

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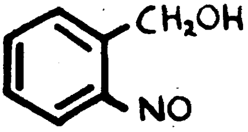

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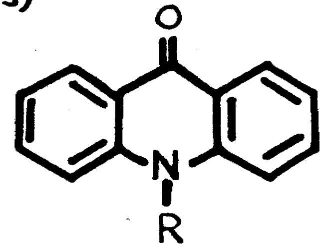

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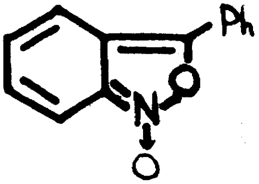

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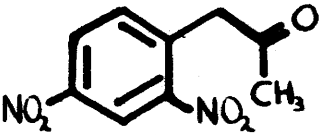

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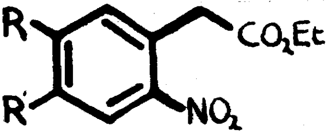

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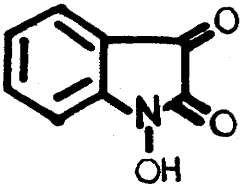

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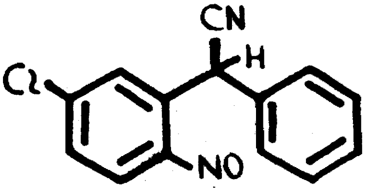

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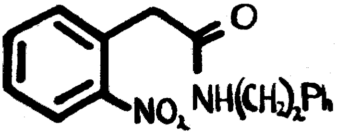

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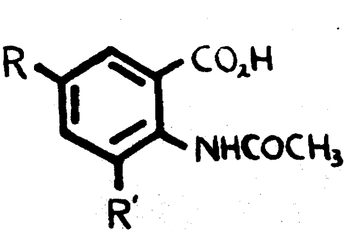

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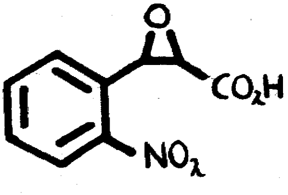

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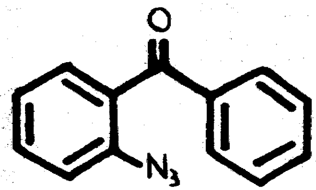

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CHAPTER V

The Synthesis and Properties of Some 3-Arylanthranils.

Anthranils or 2-1-benzisoxazoles (114) were first prepared by reductive cyclisation of o-nitrophenylketones (115)[156] or in the case of anthranil ((114), R = R' = R'' = R''' = H) itself, of o-nitrobenzaldehyde ((115), R = H) a probable intermediate being the o-hydroxylaminoketone ((115), NHOH for NO_2) which readily cyclises with loss of water to give the anthranil. This reductive method is the one most widely used in the synthesis of anthranils[157].

Anthranil is also prepared by the acid dehydration of o-nitrosobenzyl alcohol[158] (116).

Zincke and Prenntzell[159] were the first to describe an anthranil synthesis by means other than deliberate reduction. They condensed o-nitrobenzaldehyde with dimethylaniline in concentrated hydrochloric acid to give 5-chloro-3-(p-dimethylaminophenyl) anthranil ((114),R = p-$C_6H_4N(Me)_2$ R' = Cl, R'' = R''' = H). Similar condensation of o-nitrobenzaldehyde with phenol in ethereal hydrogen chloride gave 5-chloro-3-(p-hydroxyphenyl) anthranil ((114), R = p-C_6H_4OH, R' = Cl, R'' = R''' = H)[160]. Simpson and Stevenson[161] used the latter reaction to synthesise various anthranil derivatives which they then reduced to o-aminobenzophenones required for the synthesis of cinnolines. Ioffe and Belenkii[162] obtained an anthranil derivative by condensing o-nitrobenzaldehyde with guaiacol in ethereal hydrogen chloride.

o-Nitrobenzaldehyde condenses with benzene in sulphuric acid to give a mixture of 3-phenylanthranil ((114), R = Ph, R' = R'' = R''' = H), o-nitrobenzophenone ((115), R = Ph), acridone ((117), R = H) and 1-hydroxyacridone ((117), R = OH)[163]. The mechanism of this reaction and the structure of the products was the subject of much controversy (cf. Adrian Albert in "The Acridines" p.99-101)[164]. Szmant and Harmuth[165] claim to have prepared 3-phenylanthranil-1-oxide (118), a possible intermediate in this reaction.

Tanasescu et al.[166] studied the Kliegl reaction using a range of substituted o-nitrobenzaldehydes and various substituted benzenes and the same school has recently developed the reaction using polyphosphoric acid as the catalyst[167]. Another catalyst employed in this reaction is zinc chloride[168] and using this reagent o-nitrobenzaldehyde condenses with aniline to give 3-(p-aminophenyl) anthranil ((114), R = p-$C_6H_4NH_2$, R' = R'' = R''' = H)[169]. The latter compound is also prepared from the same reagents in acetic acid solution[170].

2:4-Dinitrophenylacetone (119) cyclises in concentrated sulphuric acid to give 6-nitroanthranil ((114), R = H, R' = H, R'' = NO_2, R''' = H)[171] presumably via 6-nitro-3-acetylanthranil ((114), R = $COCH_3$, R' = H, R'' = NO_2, R''' = H).

The formation of anthranils in basic media is also well known.

Gulland[172] on attempting to hydrolyse the ester group in ethyl 4:5-dimethoxyphenylacetate ((120), R = R' = MeO) with dilute sodium hydroxide obtained not the expected phenylacetic acid but 5:6-dimethoxyanthranil-3-carboxylic acid ((114), R = CO_2H, R' = R'' = OMe, R''' = H). Anthroxanic acid ((114), R = CO_2H, R' = R'' = R''' = H) is prepared by base-catalysed rearrangement of 1-hydroxyisatin (121)[6,173] and its ethyl ester by reductive cyclisation of the ethyl ester of o-nitrophenylglycidic acid (122)[174] as well as by more orthodox reduction methods[175]. Scholl[37], Lock[38] and Seibert[40] postulate anthranil as an intermediate in the base-catalysed conversion of o-nitrotoluene to anthranilic acid and Davis and Pizzini obtained 5-chloro-3-phenylanthranil ((114), R = Ph, R' = Cl, R'' = R''' = H)[24] by condensing p-chloronitrobenzene with benzylcyanide in methanolic potassium hydroxide, the probable intermediate in this case being the nitrile (123) which cyclises with loss of hydrogen cyanide to give the anthranil.

Acetic anhydride, phosphorus pentoxide, and phosphorus pentachloride are also effective reagents for the cyclisation of certain o-nitrobenzene derivatives to anthranils. Hey and Palluel[176] in attempting to close the o-nitrophenylethylamide (124) by the Bischler-Napieralski reaction using phosphorus pentoxide, obtained large quantities of the corresponding anthranil ((114), R = $CONH(CH_2)_2Ph$ $R' = R'' = R''' = H$) as well as the expected isoquinoline. When phosphorus pentachloride was used as the catalyst, only the anthranil derivative was isolated. A similar reaction which may involve anthranils as intermediates is the conversion of o-nitrophenylacetic acid ((120), $R = R' = H$, CO_2H for CO_2Et) to N-acetylanthranilic acid((125), $R = R' = H$) in refluxing acetic anhydride[9]. A possible mechanism for this reaction might involve initial cyclisation to give anthroxanic acid ((114), $R = CO_2H$, $R' = R'' = R''' = H$) followed by decarboxylation to anthranil ((114), $R = R' = R'' = R''' = H$) then reaction of the latter with excess acetic anhydride to give N-acetylanthranilic acid. The present writer has in fact shown that anthroxanic acid is converted directly to N-acetylanthranilic acid in warm acetic anhydride.

Schillinger and Wleugl[57] obtained anthranil-3-aldehyde ((114), R = CHO, $R' = R'' = R''' = H$) by steam distillation of o-nitrophenylglycidic acid (122) an example of anthranil formation in a neutral environment.

CHAPTER V

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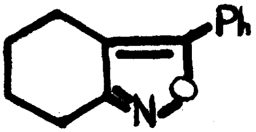

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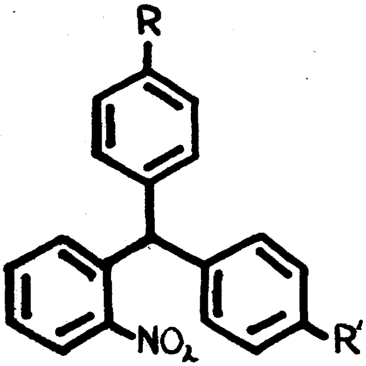

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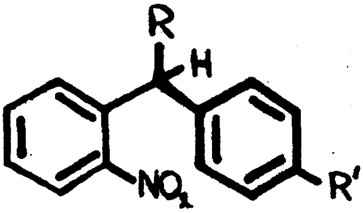

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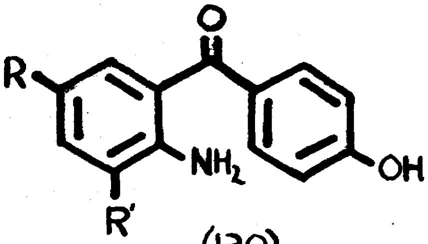

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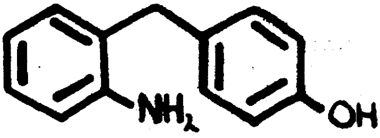

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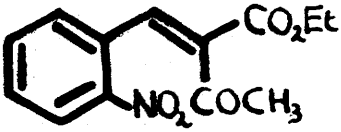

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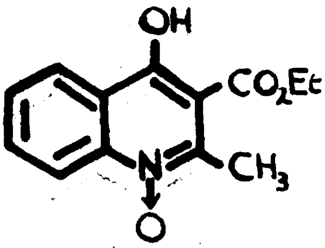

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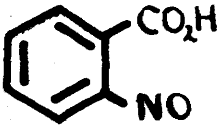

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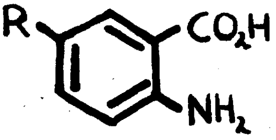

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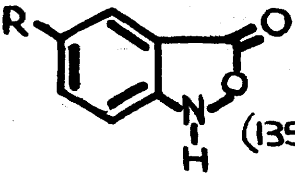

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Oxidative procedures for the synthesis of anthranils are very rare though Bamberger and Demuth[177] obtained anthranil itself by the oxidation of *o*-aminobenzaldehyde. Smith *et al*. obtained good yields of anthranil derivatives by pyrolysis of the corresponding *o*-azidobenzophenones (126)[178]. Tetrahydroanthranil derivatives (127) have also been prepared[179].

The Zincke-Siebert Reaction[160,180,181]

In this reaction *o*-nitrobenzaldehyde is condensed with phenol in acetic acid in presence of hydrogen chloride to give an almost quantitative yield of 5-chloro-3-(*p*-hydroxyphenyl) anthranil ((114), $R = p\text{-}C_6H_4OH$, $R' = Cl$, $R'' = R''' = H$). The striking similarity between this reaction and the synthesis of 4-hydroxyquinoline-1-oxides discussed in Chapter IV prompted a series of experiments which it was hoped might lead to the establishment of a parallel in these two reactions, and hence a clearer understanding of the mechanisms involved.

Driver and Mok[182] condensed phenol with *o*-nitrobenzaldehyde at low temperature in an acetic-sulphuric acid mixture and obtained a good yield of 2-nitro-4':4''-dihydroxytriphenylmethane (128) ($R = R' = NO_2$) a result supported by other workers[183]. Schultz and Geller[184] on the other hand claim that o-nitrobenzaldehyde condenses with phenol in methanolic hydrogen chloride to give 2-nitro-4'-hydroxybenzhydrol ((129), R = R'= OH), but in our hands this reaction yielded only 5-chloro-3-(p-hydroxyphenyl) anthranil ((114), R = p-C_6H_4OH, R' = Cl, R'' = R''' = H)[160] in good yield. This result is not surprising since the benzhydrol derivative might be expected to have only a transient existence in the reaction medium.

Repetition of the Zincke-Siebert reaction in ether or benzene, rather than acetic acid, gave an almost quantitative yield of the anthranil described in the original experiment, and in general it was found that ether was a more satisfactory solvent in which to carry out the reaction. 5-Chloro-3-(p-hydroxyphenyl) anthranil ((114), R = p-C_6H_4OH, R' = Cl, R'' = R''' = H) prepared in this way is a deep yellow phenolic compound forming a sparingly soluble deep red sodium salt. The hydroxyl group is readily methylated and acetylated. Reduction of the anthranil with zinc and acetic acid gave a good yield of 2-amino-5-chloro-4'-hydroxybenzophenone ((130), R = Cl, R' = H) as obtained by Zincke[160]. However sodium dithionite in dilute sodium hydroxide was found to be a much cleaner and more efficient reagent for this reduction, quantitative yields of the aminobenzophenone derivative being obtained. Using palladium charcoal and hydrogen as the reducing agent, the product was a colourless amphoteric substance which analysed for $C_{13}H_{13}ON$ (A). This compound showed peaks in the infra-red spectrum corresponding to a primary amino group (3400 cm.$^{-1}$, 3200 cm.$^{-1}$), and a phenolic hydroxyl group (3100 cm.$^{-1}$). Bands attributable to a carbonyl group were absent. The product formed a diacetyl derivative which was both an acetate (1775 cm.$^{-1}$) and a secondary amide (3200 cm.$^{-1}$, 1670 cm.$^{-1}$, 1550 cm.$^{-1}$) and from the above evidence the structure assigned to compound (A) is that of 2-amino-4'-hydroxydiphenylmethane (131).

Using Zincke's compound, 5-chloro-3-(p-hydroxyphenyl) anthranil as a model compound, a new method of degradation for this type of anthranil was devised. Reduction of the anthranil with sodium dithionite in alkali gave the known compound 2-amino-5-chloro-4'-hydroxybenzophenone and the latter afforded a diacetyl derivative in warm acetic anhydride. Partial hydrolysis of the diacetyl derivative in dilute sodium hydroxide gave 2-acetylamino-5-chloro-4'-hydroxybenzophenone ((130), R = Cl, R' = H, $NHCOCH_3$ for NH_2) which on oxidation in dilute sodium carbonate solution with potassium permanganate gave a good yield of 5-chloro-N-acetylanthranilic acid ((125), R = Cl, R' = H) identified by comparison with an authentic specimen prepared by acetylation of 5-chloroanthranilic acid.

Extensions of the Zincke Reaction

(a) Using Different Aldehyde Components.

As described in Chapter IV, formation of halogenated 4-hydroxyquinoline-1-oxides in ethereal hydrogen chloride still occurs when the 5-position in the starting aldehyde is blocked. Similar behaviour was observed in the case of the Zincke Reaction.

5-Chloro- and 5-bromo-2-nitrobenzaldehyde condense with phenol in ethereal hydrogen chloride to give in each case a single product, namely, a dichloro and a bromo-chloro-3-(p-hydroxyphenyl) anthranil respectively. The gross structure of both of these products was proved by hydrogenation over 5% palladium charcoal in ethanol to give the known compound 2-amino-4'-hydroxydiphenylmethane (131) identical in every respect with a sample prepared by hydrogenation of the anthranil, 5-chloro-3-(p-hydroxyphenyl) anthranil[160] of known structure. The position taken up by the entering chlorine atom was proved for the dichloro compound only, that in the bromo-chloro anthranil being assigned by analogy. Reduction of the dichloro anthranil with sodium dithionite in alkali gave an aminobenzophenone derivative which afforded the diacetyl compound in warm acetic anhydride in presence of sodium acetate. Partial hydrolysis of the latter to the acetylamino phenol, followed by oxidation in dilute sodium carbonate with 2% potassium permanganate solution gave 3:5-dichloro-N-acetyl anthranilic acid ((125), R = R$'$ = Cl) identical with an authentic sample prepared by acetylation of 3:5-dichloroanthranilic acid[185]. This established the structures of the dihalogenated anthranils as 6:8-dichloro-3-(p-hydroxyphenyl) anthranil ((114), R = p-C_6H_4OH, R$'$ = R$''$ = Cl, R$''$ = H) and 6-bromo-8-chloro-3-(p-hydroxyphenyl) anthranil ((114), R = p-C_6H_4OH, R$'$ = Br, R$''$ = H, R$'''$ = Cl) respectively. Substitution by chlorine in the Zincke reaction follows a similar pattern to that encountered in the 4-hydroxyquinoline-1-oxide synthesis (Chapter IV).

(b) Using a Different Acid Catalyst.

By way of further establishing the parallel between the 4-hydroxyquinoline-1-oxide synthesis and the Zincke reaction, the latter reaction was studied in ethereal hydrogen bromide, as well as in ethereal hydrogen chloride.

In practice o-nitrobenzaldehyde condensed with phenol in ethereal hydrogen bromide to give a mixture of two, yellow, crystalline products which were readily separated by fractional crystallisation from methanol. Both compounds gave almost identical infra-red spectra closely similar to that obtained from 5-chloro-3-(p-hydroxyphenyl) anthranil[160].

The lower melting compound (A) analysed for $C_{13}H_9O_2N$ and gave a negative test for halogen while the higher melting compound (B) analysed for $C_{13}H_8BrNO_2$ giving a positive test for halogen. Subsequent preparation of a model compound (see below) proved that compound (B) was in every way identical with 5-bromo-3-(p-hydroxyphenyl) anthranil ((114), $R = p\text{-}C_6H_4OH$, $R' = Br$, $R'' = R''' = H$) and by analogy, compound (A) could only be 3-(p-hydroxyphenyl) anthranil ((114), $R = p\text{-}C_6H_4OH$, $R' = R'' = R''' = H$). The anthranil structure of (A) and (B) was further substantiated by hydrogenation of both of these compounds over 5% palladium charcoal to give 2-amino-4'-hydroxydiphenylmethane (131).

In contrast to the 4-hydroxyquinoline-1-oxide synthesis (Chapter IV), therefore, using ethereal hydrogen bromide in the Zincke reaction leads to a mixture of products.

Condensation of 5-chloro-2-nitrobenzaldehyde with phenol in ethereal hydrogen bromide gave only one product, identical in every respect with a sample of the known compound 5-chloro-3-(p-hydroxyphenyl) anthranil ((114), $R = p\text{-}C_6H_4OH$, $R' = Cl$, $R'' = R''' = H$)[160]. Similarly 5-bromo-2-nitrobenzaldehyde gave 5-bromo-3-(p-hydroxyphenyl) anthranil ((114), $R = p\text{-}C_6H_4OH$, $R' = Br$, $R'' = R''' = H$).

(c) Using a Different Phenolic Component

In the 4-hydroxyquinoline-1-oxide synthesis the use of ethereal hydrogen bromide gave a homogeneous product unsubstituted by halogen (cf. Chapter IV). Similar behaviour in the Zincke reaction was only observed when the aldehyde component of the reaction was substituted in the 5-position, the use of o-nitrobenzaldehyde leading to a mixture of products. A possibility suggested at this stage, was that two distinct mechanisms were operating, namely orthodox substitution by bromine followed by cyclisation, or an "unorthodox" unspecified mechanism, proceeding without substitution by bromine.

Since the only apparent difference between the Zincke reaction and the 4-hydroxyquinoline-1-oxide synthesis was that in the former case phenol was used instead of ethyl acetoacetate, it was decided to vary the phenolic component of the reaction in order to determine the effect of this component on the course of the reaction.

Using resorcinol in the Zincke reaction gave only polymeric material which could not be characterised. More success was obtained using hydroquinone.

Hydroquinone condensed with o-nitrobenzaldehyde in tetrahydrofuran using hydrogen chloride giving only one product in good yield. The compound, (A), which analysed for $C_{13}H_9O_3N$, gave a negative test for the presence of halogen, dissolved readily in dilute sodium hydroxide and gave a deep red colour with alcoholic ferric chloride solution. Oxidation of the compound in dilute acetic acid solution with sodium dichromate gave a monocarboxylic acid (B), which analysed for $C_8H_5O_3N$. (B) was readily converted to N-acetyl anthranilic acid ((125), $R = R' = H$) in refluxing acetic anhydride. Comparison of (B) with an authentic sample of anthranil-3-carboxylic acid ((114), $R = CO_2H$, $R' = R'' = R''' = H$)[96] prepared by base-catalysed rearrangement of 1-hydroxyisatin[6] showed that the two specimens were identical in melting point, mixed melting point and infra-red-spectrum. Compound (A) was therefore the anthranil derivative 3-(2':5' dihydroxyphenyl) anthranil ((114), $R = -C_6H_3(OH)_2$, $R' = R'' = R''' = H$). Similar condensation of either 5-chloro- or 5-bromo-2-nitrobenzaldehyde with hydroquinone gave 5-chloro- and 5-bromo-3-(2':5'dihydroxyphenyl) anthranil ((114), $R = C_6H_3(OH)_2$, $R' = Cl$ or Br, $R'' = R''' = H$).

Condensation of <u>o</u>-nitrobenzaldehyde with hydroquinone using hydrogen bromide in tetrahydrofuran gave a mixture of two products readily separable by fractional crystallisation from methanol. The lower melting compound analysed for $C_{13}H_9O_3N$ and was identical in every respect with a sample of 3-(2$'$:5$'$dihydroxyphenyl)anthranil ((114), $R = C_6H_3(OH)_2$, $R' = R'' = R''' = H$) prepared above. The higher melting compound analysed for $C_{13}H_8BrO_3N$, dissolved in dilute sodium hydroxide, and gave a red colour with alcoholic ferric chloride. This compound was identical in melting point and infra-red spectrum with an authentic sample of 5-bromo-3-(2$'$:5$'$dihydroxyphenyl)anthranil (see above) ((114), $R = C_6H_3(OH)_2$, $R' = Br$, $R'' = R''' = H$) and showed no depression in melting point on admixture with the latter. The structure was further substantiated by oxidation with sodium dichromate in acetic acid giving the known compound[191] 5-bromo-anthranil-3-carboxylic acid ((114), $R = COOH$, $R' = Br$, $R'' = R''' = H$). Similar condensation of 5-bromo-2-nitrobenzaldehyde with hydroquinone in tetrahydrofuran using hydrogen bromide gave only one product in good yield and subsequently shown to be identical with an authentic specimen of 5-bromo-3-(2$'$:5$'$dihydroxyphenyl)anthranil ((114), $R = C_6H_3(OH)_2$, $R' = Br$, $R'' = R''' = H$).

Synthesis of 4-Hydroxyquinoline-1-Oxides in presence of Hydroquinone

The Zincke reaction using ethereal hydrogen chloride in presence of hydroquinone proceeds without substitution by chlorine. Similarly ethyl *o*-nitrobenzylideneacetoacetate (132) was smoothly converted in ethereal hydrogen chloride in presence of hydroquinone to ethyl 4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide (133) identical with an authentic specimen (cf. Chapter IV p.46).

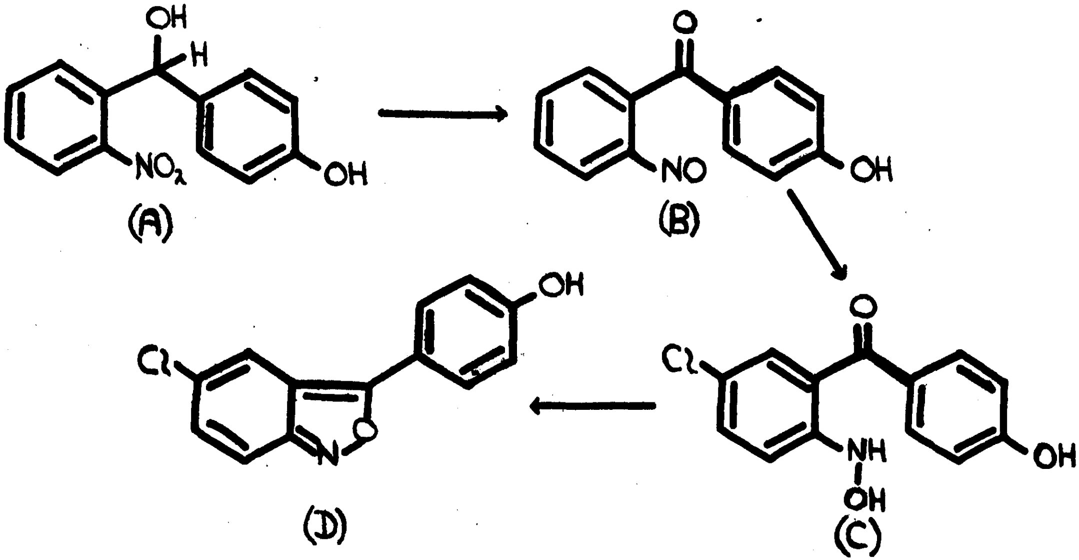
In presence of hydroquinone alone or a mixture of hydroquinone and trichloroacetic acid in ether ethyl *o*-nitrobenzylideneacetoacetate was recovered unchanged.

Reaction of Nitrosobenzoic Acid with Hydrogen Bromide and Hydrogen Chloride

It was hoped that *o*-nitrosobenzoic acid (134) might cyclise on treatment with hydrogen chloride to give 5-chlorobenzisoxazolone ((135), R = Cl). In practice the only product which could be isolated from this reaction was 5-chloroanthranilic acid ((136), R = Cl) identical in every respect with an authentic sample prepared by reducing 5-chloro-2-nitrobenzoic acid. Similarly *o*-nitrosobenzoic acid reacted with hydrogen bromide in tetrahydrofuran to give 5-bromoanthranilic acid ((136), R = Br).

Note on the Mechanism of the Zincke Reaction.

The first intermediate formed in the reaction is probably 2-nitro-4'-hydroxybenzhydrol ((129), $R = R' = OH$). Mr.J.P. Cairns has in fact verified this in the case of 2-nitrobenzhydrol ((129), R=OH,R$'$ = H), and assuming that a similar intermediate is formed in the Zincke reaction, the following reaction sequence might apply -



The step (A) ⟶ (B) may either be considered as acid-catalysed oxygen-transfer (cf. Chapter IV) or as a cyclo-dehydration process. Again, this mechanism like that outlined for the synthesis of 4-hydroxyquinoline-1-oxides in Chapter IV, infers that the nitroso compound (B) is the key intermediate. This would explain why using hydrogen chloride, a product substituted by chlorine is isolated[155], whereas using hydroquinone, a known reducing agent, the nitroso compound is reduced directly to the hydroxylamino compound without the necessity for substitution by chlorine.

What this route (A) → (D) does not explain is the isolation of a mixture of products when *o*-nitrobenzaldehyde is condensed with either phenol or hydroquinone in ethereal hydrogen bromide.

In spite of the fact that the results obtained in Chapters IV and V do not, at present, allow a clearer picture of the mechanism of this type of reaction to be drawn, it is reasonable to suggest that they do infer a parallel between the mechanisms of the Zincke reaction and the 4-hydroxyquinoline-1-oxide synthesis.

EXPERIMENTAL

CHAPTER II

2-Amino-4-cyano-3-phenylquinoline-1-oxide ((62),R=CN, R'=Ph)

(a) Method of Brand and Loehr[85]

o-Nitro-α-phenylcinnamonitrile[151] (8 gm.) was suspended in ethanol (80 ml.) and treated with solutions of potassium cyanide (6 gm.) in water (10 ml.), and ammonium chloride (5 gm.) in water (10 ml.). The reaction mixture was then heated at 100°C for 15 hr. The reaction mixture, still containing some suspended solid was added to water and extracted with chloroform. The dark red chloroform extract was washed with dilute sodium hydroxide solution (at this stage a rather insoluble sodium salt tends to separate), then with water, and the washings combined with the main alkaline extract which was set aside.

The chloroform extract after drying over magnesium sulphate was concentrated giving a gummy solid which on rubbing with benzene gave a hard crystalline solid, the impurities dissolving in the benzene. Crystallisation of the solid from ethanol with charcoaling gave yellow needles of 2-amino-4-cyano-3-phenylquinoline-1-oxide, M.pt.= 235-236°C (3.4 gm.) λ_{max} 227, 265, 335, 404 mu. (ε, 21,000; 31,600; 7000; 8500). ν_{max} 3250, 3400, 2220 $cm.^{-1}$. (found: C, 73.5; H, 4.0; N, 15.9: $C_{16}H_{11}ON_3$ requ: C, 73.6; H, 4.2; N, 16.1).

(b) *o*-Nitro-*α*-phenylcinnamonitrile (2 gm.) was warmed for 5 mins with aqueous potassium cyanide (3 ml.; 50%) and ethanol (12 ml.). On cooling, the above amine (0.2 gm.) separated as fine yellow needles. Separation of the filtered mother liquor into acid and non-acidic fractions gave more of the amine (0.31 gm.).

(c) *α*-(*o*-Nitrophenyl) cinnamonitrile (see below) (0.25 gm.) on warming with aqueous potassium cyanide (2 ml.; 50%) and ethanol (3 ml.) gave a similar yield of the amine (0.05 gm.) when worked up as under (b) above.

α-(*o*-Nitrophenyl) cinnamonitrile (72)

o-Nitrobenzylcyanide (1.5 gm.) and benzaldehyde (1 gm.) were melted together at 65°C and a few drops of piperidine added. The resulting reaction mixture was allowed to stand at room temperature for 48 hr. and at the end of this time, the crystalline benzylidene derivative was collected and crystallised from ethanol, M.pt.= 114-115°C. (*found*: C, 71.85; H, 3.8; N, 11.3; $C_{15}H_{10}O_2N_2$ *requ*: C, 72.0; H, 4.0; N, 11.2.

2-Amino-4-cyano-3-phenylquinoline ((70), R = CN, NH_2 for OH)

2-Amino-4-cyano-3-phenylquinoline-1-oxide (0.5 gm.) was dissolved with warming in acetic acid (4 ml.) and heated for

10 mins. under reflux with iron powder (0.2 gm.). The reaction mixture was cooled and filtered. On basification with ammonia solution, the quinoline separated as a light brown crystalline mass. Recrystallised from ethanol with charcoaling it formed yellow needles, M.pt.= 196°C (found: C, 78.1; H, 4.9; N, 17.3: $C_{16}H_{11}N_3$ requ: C, 78.35; H, 4.5; N, 17.1).

2-Acetamido-4-cyano-3-phenylquinoline-1-oxide ((62, R = CN, R' = Ph, $NHCOCH_3$ for NH_2)

2-Amino-4-cyano-3-phenylquinoline-1-oxide was suspended in acetic anhydride and treated with one drop of concentrated sulphuric acid to effect solution. The reaction mixture was cooled and decomposed with water affording the monoacetyl derivative, M.pt.= 238°C from dimethylformamide, ν_{max} 1550, 1670, 2220 cm.$^{-1}$ giving a weak red colour with alcoholic ferric chloride (found: C, 71.0; H, 4.6; N, 13.7: $C_{18}H_{13}O_2N_3$ requ: C, 71.3; H, 4.3; N, 13.9).

2-Acetamido-3-phenylquinoline-1-oxide ((62), R = H, R' = Ph, $NHCOCH_3$ for NH_2)

2-Amino-3-phenylquinoline-1-oxide[90] treated with sulphuric acid and acetic anhydride as above gave the monoacetyl derivative, M.pt.= 170°C from ethanol, ν_{max} 1550, 1670, 2220 cm.$^{-1}$ giving a weak red colour with alcoholic ferric chloride (found: C, 73.6; H, 5.2; N, 10.1: $C_{17}H_{14}O_2N_2$ requ: C, 73.4; H, 5.1; N, 10.1).

2-Acetamido-4-cyano-3-phenylquinoline ((70), R = CN, NHCOCH$_3$ for OH)

(a) 2-Amino-4-cyano-3-phenylquinoline suspended in acetic anhydride and treated with one drop of sulphuric acid, gave as above, the monoacetyl derivative, yellow needles, M.pt.= 247°C from ethanol ν_{max} 1660, 1550 cm.$^{-1}$ (found: C, 75.3; H, 4.9; N, 14.4; $C_{18}H_{13}ON_3$ requ: C, 75.3; H, 4.5; N, 14.6).

(b) Hydrogenation of 2-acetamido-4-cyano-3-phenylquinoline-1-oxide ((62), R = CN, R$'$ = Ph, NHCOCH$_3$ for NH$_2$) over 5% palladium charcoal in acetic acid gave a compound, M.pt.= 246-247°C from ethanol. Mixed melting point with 2-acetamido-4-cyano-3-phenylquinoline was 247°C and the infra-red spectra of the two samples were identical.

2-Amino-3-phenylquinoline-4-carboxyamide ((70), R=CONH$_2$: NH$_2$ for OH)

2-Amino-4-cyano-3-phenylquinoline ((70), R = CN, NH$_2$ for OH) (0.4 gm.) was warmed with ethylene glycol (1.5 ml.), potassium hydroxide (0.7 gm.) and water (0.5 ml.) for 10 mins.

until a deep red flux was obtained. The reaction mixture was cooled and treated with water to give the crude amide as a pale yellow precipitate. Recrystallised from dimethylformamide it gave pale yellow needles, M.pt.= 346°C; ν_{max} 3270, 3450, 1570, 1610 cm.$^{-1}$ (found: C, 72.5: H, 4.95; N, 15.85: $C_{16}H_{13}ON_3$ requ: C, 73.0; H, 4.9; N, 16.0).

2-Hydroxy-3-phenylquinoline-4-carboxylic acid ((70), $R = CO_2H$)[100]

Isatin (5 gm.) was warmed with an excess of phenylacetic acid (10 gm.) and anhydrous sodium acetate (0.5 gm.) at 200-300°C for 0.5 hr. Water was liberated and the reaction mixture boiled vigorously. The hot reaction mixture was poured into hot acetic acid (30 ml.) and on cooling, the acid separated as a crude, pale brown crystalline solid. The crude acid was washed with benzene, dissolved in dilute sodium carbonate, and filtered. Careful acidification of the carbonate solution gave a white precipitate of the acid which recrystallised from acetic acid formed fine white needles (M.pt.= 292°C; Hubner reports 291°C.).

2-Hydroxy-3-phenylquinoline-4-carbonyl chloride ((70) R = COCl)[100]

2-Hydroxy-3-phenylquinoline-4-carboxylic acid ((70),

$R = CO_2H$) (1 gm.) was refluxed for 3 hr. with excess thionyl chloride (10 cc.). On cooling a crystalline solid separated. This was recrystallised from chloroform-petrol to give cream coloured prisms of the acid chloride, M.pt.= 235°C. The yield was 0.9 gm. (= 84%).

2-Hydroxy-3-phenylquinoline-4-carboxyamide ((70),$R=CONH_2$)[100]

(a) 2-Amino-3-phenylquinoline-4-carboxyamide ((70), $R = CONH_2$, NH_2 for OH) (0.2 gm.) was dissolved in sulphuric acid (1.5 ml.; 90% w/v) and the solution cooled below 30°C. Aqueous 0.5 N sodium nitrite solution (1.6 ml.) was then introduced, dropwise below the surface of the solution and after the addition was complete, the total volume of the reaction mixture was increased to 5 ml. by the addition of water. After standing at room temperature for 1 hr., the suspended solid was collected, dissolved in dilute sodium hydroxide solution, filtered, and recovered from the alkaline filtrate, by acidification with dilute sulphuric acid. After washing with dilute sodium bicarbonate solution to remove a little carboxylic acid also formed in the reaction, the crude amide was crystallised from aqueous acetic acid giving white needles of the monohydrate, M.pt.= 287°C; (*found*: C, 67.8; H, 5.5; N, 9.7: $\underline{C_{16}H_{12}O_2N_2H_2O}$ *requ*: C, 68.1; H, 5.0; N, 9.9). Dehydration at 140°C *in vacuo* gave anhydrous

2-hydroxy-3-phenylquinoline-4-carboxyamide, M.pt.= 299°C; (found: C, 72.4; H, 4.5; N, 10.5: calc. for $C_{16}H_{12}O_2N_2$ C, 72.7; H, 4.6; N, 10.6). Mixed melting point with an authentic specimen prepared as under (b), below, was 299-301°C. The infra-red spectra of the two samples were identical.

(b) 2-Hydroxy-3-phenylquinoline-4-carbonyl chloride ((70), R = COCl)(0.3 gm.) was dissolved with warming in chloroform (30 ml.) and dry ammonia gas was bubbled through the chloroform solution for 0.5 hr. by which time the amide had formed as a cream suspension. The crude amide was collected and crystallised from acetic acid to give white needles M.pt.= 299-301°C. More of the amide was obtained by working up the chloroform mother-liquor (Yield = 96%)

CHAPTER III

3-Cyano-1-hydroxy-2-phenyl indole ((76),R=CN, R'=Ph, R''=H)

(a) When the alkaline mother liquors, obtained from the preparation of 2-amino-4-cyano-3-phenylquinoline-1-oxide in sections (a), (b) or (c) (Chapter III pp. 76-77) were acidified, a curdy yellow precipitate of the crude 1-hydroxy indole was obtained. Crystallised from aqueous ethanol it formed long felted needles, after clarification with charcoal, M.pt.= 195°C; λ_{max} 220, 245, 305 mu (ε , 25300, 24400, 17700) ν_{max} 2220 cm.$^{-1}$ (found: C, 77.2; H, 4.7; N,11.5; $C_{15}H_{10}ON_2$ requ: C, 77.4; N, 4.8; N, 11.3). Treatment of the indole with sodium hydroxide gave a sparingly soluble sodium salt. The indole gave no colour with alcoholic ferric chloride solution.

(b) o-Nitro-α-phenylcinnamonitrile[151] (1 gm.) was suspended in ethanol (6 ml.), treated with aqueous potassium cyanide solution (2 ml.; 50%) and the whole shaken at room temperature for 7 hr. The reaction mixture was filtered to remove unchanged starting material (0.81 gm.) and the blue filtrate on dilution with water, charcoaling, and acidification with dilute sulphuric acid gave 3-cyano-1-hydroxy-2-phenyl indole (0.13 gm.) as above.

1-Acetoxy-3-cyano-2-phenyl indole ((76), R = CN, R$'$ = Ph R$''$ = H, $OCOCH_3$ for OH)

3-Cyano-1-hydroxy-2-phenyl indole ((76), R = CN, R$'$ = Ph, R$''$ = H) was warmed with acetic anhydride for 5 mins. On cooling and pouring into excess water, the acetyl derivative separated as a crude white solid. Crystallised from ethanol it formed colourless needles, M.pt.= 111°C ; ν_{max} 2220 cm.$^{-1}$ 1805 cm.$^{-1}$ (found: C, 74.2; H, 4.3; N, 10.0; $C_{17}H_{12}O_2N_2$ requ: C, 73.9; H, 4.4; N, 10.1).

3-Cyano-2-phenyl indole ((96), R = CN, R$'$ = Ph, R$''$ = H)

(a) 1-Acetoxy-3-cyano-2-phenyl indole (0.5 gm.) was hydrogenated in ethanol (40 ml.) over palladium charcoal (5%; 0.3 gm.). One mole of hydrogen was rapidly absorbed and after filtration through a pad of charcoal to remove the catalyst, the ethanol filtrate was concentrated to give the indole as a white crystalline solid, M.pt.= 243°C from ethanol (found: C, 82.4; H, 4.8; N, 12.8: $C_{15}H_{10}N_2$ requ: C, 82.5; H, 4.6; N, 12.8). Mixed melting point with a sample prepared as under (b) below, was 243°C. The infra-red spectra of the two samples were identical.

(b) 2-Phenyl indole-3-aldoxime (see below)(0.6 gm.) was refluxed for 10 mins. in acetic anhydride (0.5 ml.) and the resulting solution, cooled, concentrated and the residue poured into ice-water (2 ml.). The brown gum formed was slowly hydrolysed at room temperature giving the crude indole. Crystallisation of the crude product from ethanol with charcoaling gave cream needles of 3-cyano-2-phenyl indole, M.pt.= 241-243°C (Yield = 0.09 gm.)

2-Phenyl indole-3-aldehyde[186] ((96), R = CHO, R' = Ph, R'' = H)

2-Phenyl indole[124] ((96), R = H, R' = Ph, R'' = H)(5.8 gm.) was dissolved in acetic acid (9.9 ml.) and diluted with water to 120 ml. Well-powdered hexamine (4.2 gm.) was added and the resulting solution added dropwise over a period of 1 hr. to a refluxing solution of hexamine (4.2 gm.) in acetic acid (15 ml.; 66%). The reaction mixture was cooled, poured into water (450 ml.) and refrigerated overnight. The crude aldehyde which separated was crystallised from ethanol, M.pt.= 253-255°C.

2-Phenyl indole-3-aldoxime[187] ((96), R = CH=NOH,R'=Ph,R''=H)

The aldehyde (1 gm.) and hydroxylamine hydrochloride (1 gm.) were mixed in pyridine (5 ml.) and the resulting solution left overnight in a stoppered flask at room temperature. The reaction mixture after pouring into water (5 ml.) was extracted with ethyl acetate (5 ml.), the ethyl acetate washed with dilute hydrochloric acid, then water, and dried over magnesium sulphate. The ethyl acetate was concentrated to ~ 1 ml. and the crude oxime precipitated with petrol (40-60° B.pt.) as a light brown powder. Recrystallised from ethyl acetate - petrol (40-60° B.pt.) it formed cream needles, M.pt.= 186°C.

1-Hydroxy-2-phenyl indole[103] ((76), R = H, R' = Ph, R'' = H)

3-Cyano-1-hydroxy-2-phenyl indole (0.025 gm.) was suspended in ethylene glycol (0.2 ml.) and treated with potassium hydroxide (0.2 gm.) and water (0.02 ml.). The reaction mixture was warmed for 5-10 mins. until a deep red flux was obtained. The flux was cooled and water added to give 1-hydroxy-2-phenyl indole as orange-red plates. Recrystallised from ethanol with charcoaling it formed orange plates, M.pt.= 172°C. Mixed melting-point with an authentic sample prepared by dehydration of $\underline{\alpha}$-benzoinoxime[103] was 172°C and the infra-red spectra of the two samples were identical.

2-Phenyl indole ((96), R = H, R' = Ph, R'' = H)[124]

(a) When the flux obtained from 3-cyano-1-hydroxy-2-phenyl indole ((76), R = CN, R' = Ph, R'' = H) was warmed a little longer (~ 20 mins.) cream coloured plates of 2-phenyl indole, M.pt.= 186°C (from ethanol) were obtained, on dilution with water. This compound was identified with an authentic sample[124] by mixed melting point and comparison of the infra-red spectra.

1-Hydroxy-2-phenyl indole similarly treated gave 2-phenyl indole identified as above.

(b) 1-Benzoyloxy-2-phenyl indole (see below)(0.25 gm.) was hydrogenated in absolute ethanol (50 ml.) over palladium charcoal (5%; 0.75 gm.). One mole of hydrogen was absorbed in $\sim$ 5 mins. The catalyst was filtered off through a pad of charcoal and the ethanol filtrate on concentration gave white plates of 2-phenyl indole identified by its melting point, mixed melting point and infra-red spectrum with an authentic sample. The yield was o.13 gm.

(c) 1-Hydroxy-2-phenyl indole (0.25 gm.) dissolved in acetic anhydride (25 ml.) and acetic acid (2 ml.), was hydrogenated over palladium charcoal (5%; 0.1 gm.). One mole of hydrogen was slowly absorbed. The catalyst was filtered off through a pad of charcoal and the filtrate concentrated <u>in vacuo</u> to give 2-phenyl indole, identified as above, with an authentic specimen.

No hydrogenolysis of 1-hydroxy-2-phenyl indole occurred in acetic acid alone.

1-Benzoyloxy-2-phenyl indole ((76), R = H, R' = Ph, R'' = H, OCOPh for OH)[125]

1-Hydroxy-2-phenyl indole (0.25 gm.) was dissolved in 10% sodium hydroxide (10 ml.) and benzoyl chloride (0.3 ml.) added in portions with shaking. The reaction mixture was then shaken in a closed flask at room temperature for 0.5 hr. The white precipitate of the benzoate was collected and crystallised from ethanol to give white needles, M.pt.=101°C.

3-Cyano-1-hydroxy-5-methoxy-2(3':4':5'-trimethoxyphenyl) indole ((76), R' = CN, R' = $C_6H_2(OMe)_3$, R'' = MeO)

5-Methoxy-2-nitro-α-(3':4':5'-trimethoxyphenyl) benzyl cyanide[188] (0.5 gm.) was refluxed with aqueous potassium hydroxide (20%; 2 ml.) in ethanol:water (3 ml.: 1ml.) for 1 hr. The deep red reaction mixture was cooled and carefully acidified with dilute sulphuric acid affording the indole as a cream precipitate. Crystallised from ethanol-water, it formed cream needles, M.pt.= 205°C. (found: C, 64.0; H, 5.1; N, 8.0; $C_{19}H_{18}O_5N_2$ requ: C, 64.4; H, 5.1; N, 7.9).

1-Acetoxy-3-cyano-5-methoxy-2(3':4':5'-trimethoxyphenyl) indole ((76), R = CN, R' = $C_6H_2(OMe)_3$, R'' = MeO, $OCOCH_3$ for OH)

The indole ((76), R = CN, R' = $C_6H_2(OMe)_3$, R'' = MeO) suspended in a slight excess of acetic anhydride was warmed gently to effect solution. After warming for a few minutes at 100°C, the reaction mixture was cooled and diluted with water affording the crude acetate. Crystallised from ethyl acetate it formed cream needles, M.pt.= 132°C. ν_{max} = 1805 cm.$^{-1}$ (found: C, 63.4; H, 4.9; N, 7.2: $C_{21}H_{20}O_6N_2$ requ: C, 63.6; H, 5.1; N, 7.1).

3-Cyano-5-methoxy-2(3':4':5'-trimethoxyphenyl) indole ((96), R = CN, R' = $C_6H_2(OMe)_3$, R'' = MeO)

The acetate ((76), R = CN, R' = $C_6H_2(OMe)_3$, R'' = MeO, $OCOCH_3$ for OH) (0.07 gm.) was dissolved in ethanol (15 ml.) and hydrogenated over palladium charcoal (5%: 0.03 gm.). One mole was absorbed in ~ 20 mins. The catalyst was filtered off through a pad of charcoal and the ethanol filtrate concentrated to give the crude indole (0.04 gm.). Crystallised from ethanol-water it formed cream needles, M.pt.= 220°C . (found: C, 67.5; H, 5.4; N, 8.4: $C_{19}H_{18}O_4N_2$ requ: C, 67.4; H, 5.4; N, 8.3).

(With J.McLean)[126]

α-Benzyl-5-methoxy-2-nitrobenzylcyanide ((97), R = OMe)

5-Methoxy-2-nitrobenzylcyanide (1 gm.) in ethanol (13 ml.) was mixed with sodium ethoxide (from 0.13 gm. sodium in 4 ml. ethanol) and treated with benzyl chloride (0.66 gm.). The reaction mixture was then allowed to stand at room temperature for 48 hr. and the cyanide (1.41 gm.) collected. Recrystallised from ethanol it formed cream needles, M.pt.= 107°C. (found: C, 68.2; H, 4.9; N, 9.9: $C_{16}H_{14}O_3N_2$ requ: C, 68.1; H, 5.0; N, 9.9).

Ethyl α-benzyl-5-methoxy-2-nitrophenylacetate ((97), R = Ome, CO_2Et for CN)

α-Benzyl-5-methoxy-2-nitrobenzylcyanide on heating with dilute sulphuric acid in ethanol afforded the crude ester. Crystallised from ethanol it formed cream rhombs, M.pt.= 68°C. (found: C, 65.6; H, 5.5; N, 4.5: $C_{18}H_{19}O_5N$ requ: C, 65.6; H, 5.8; N, 4.3).

α-Benzyl-5-methoxy-2-nitrophenyl acetic acid ((97) R = OMe, CO_2H for CN)

Ethyl α-benzyl-5-methoxy-2-nitrophenylacetate on hydrolysis with aqueous potassium hydroxide in methanol gave the crude acid. Recrystallised from aqueous acetic acid it formed white needles, M.pt.= 134°C. (found: C, 63.8; H, 5.0; N, 4.8: $C_{16}H_{15}O_5N$ requ: C, 63.8; H, 5.0; N, 4.7).

3-Cyano-1-hydroxy-5-methoxy-2-phenyl indole ((76), R = CN, R' = Ph, R'' = OMe)

α-Benzyl-5-methoxy-2-nitrobenzylcyanide (1 gm.) in ethanol (6 ml.) and water (1 ml.) was treated with aqueous potassium hydroxide (4 ml. 20%) and the suspension refluxed for 1 hr. The solid dissolved on heating and the deep red reaction mixture was cooled and worked up as above for 3-cyano-1-hydroxy-5-methoxy-2(3':4':5'-trimethoxyphenyl) indole. Crystallised from aqueous ethanol, the indole formed cream needles, M.pt.= 173°C. (*found*: C, 72.5; H, 4.4; N, 10.8: $C_{16}H_{12}O_2N_2$ *requ*: C, 72.7; H, 4.6; N, 10.6).

1-Acetoxy-3-cyano-5-methoxy-2-phenyl indole ((96), R = CN OCOCH$_3$ for H R' = Ph, R'' = OMe)

The indole ((76), R = CN, R' = Ph, R'' = OMe) was warmed in acetic anhydride at 100°C for 5 mins. The reaction mixture on cooling and dilution with water afforded the crude acetoxy derivative. Crystallised from ethanol it formed colourless needles, M.pt.= 145°C. ν_{max} 1805 cm.$^{-1}$ (*found*: C, 70.6; H, 4.8; N, 9.4: $C_{18}H_{14}O_3N_2$ *requ*: C, 70.6; H, 4.6; N, 9.2).

3-Cyano-5-methoxy-2-phenyl indole ((96), R=CN,R'=Ph,R''=OMe)

1-Acetoxy-3-cyano-5-methoxy-2-phenyl indole (0.18 gm.) dissolved in ethanol (50 ml.) was hydrogenated over palladium charcoal (5%; 0.08 gm.) to give the indole (0.13 gm.), M.pt.= 250^{d}C from ethanol (found: C, 77.2; H, 4.6; N, 11.1: $C_{16}H_{12}ON_2$ requ: C, 77.4; H, 4.8; N, 11.3).

N-oxalyl anthranilic acid (99)

The adduct ((98), R = CO_2Me, R' = CN)[127] (0.1 gm.) was dissolved in 2N sodium hydroxide (1 ml.) and the resulting intense violet solution warmed for 5 mins. on the steam-bath. The reaction mixture was cooled and poured into excess dilute sulphuric acid affording the acid as a crude white solid (0.05 gm.). Recrystallised from hot water it formed white needles, M.pt.= 212°C. (found: C, 51.4; H, 3.3; N, 6.8: calc. for $C_9H_7O_5N$ C, 57.7; H, 3.4; N, 6.7). Mixed melting with an authentic sample[128] was 212°C.

Dimethyl oxanilate-o-carboxylate ((99), CO_2Me for CO_2H)

N-oxalyl anthranilic acid (0.5 gm.) in methanol (10 ml.) and ether (40 ml.) was cooled to 0°C and a solution of ethereal diazomethane (41 ml. of a solution containing 8.4 gm. of diazomethane in 311 ml. of ether) added dropwise. After standing overnight at room temperature the excess diazomethane was destroyed by the addition of a few drops of glacial acetic acid and the ether after washing with dilute sodium bicarbonate then water was dried over magnesium sulphate. Concentration of the ether gave the dimethyl ester as a crude white solid. Crystallised from methanol it formed white needles, M.pt.= 154°C. Mixed melting point with an authentic sample was 154°C and the infra-red spectra of the two samples were identical.

Anthranil-3-carboxylic acid (101)[6]

o-Nitrophenacyl chloride ((91), R = CH_2Cl)[6] (0.1 gm.) was warmed with 1N sodium hydroxide (0.5 ml.) for 10 mins. by which time all the suspended solid had dissolved giving a deep red solution. After warming for a further 5 mins. the reaction mixture was cooled, filtered and carefully acidified with dilute sulphuric to give a cream coloured precipitate (0.06 gm.) of the acid. Recrystallised from hot water it formed white needles, M.pt.= 191-192°C. Mixed melting point with an authentic sample[6] was 192°C and the infra-red spectra of the two specimens were identical.

Isatin ((89), R = H)

o-Nitrobenzoylacetone ((91), R = CH_2COCH_3)[2] (0.2 gm.) suspended in ethanol (2 ml.) was treated with potassium hydroxide (0.2 gm.) in water (2 ml.). On warming the suspended solid dissolved giving a clear red solution which was refluxed for 0.5 hr. The reaction mixture was cooled, concentrated in vacuo, filtered and carefully acidified with dilute sulphuric acid to give an orange-red precipitate of isatin. Crystallised from methanol it formed deep red needles, M.pt.= 205°C. (found: C, 65.6; H, 3.7; N, 9.3: calc. for $C_8H_5O_2N$ C, 65.3; H, 3.5; N, 9.5). Mixed melting point with an authentic sample of isatin was 205°C and the infra-red spectra of the two samples were identical.

CHAPTER IV

Ethyl o-nitrobenzylidenecyanoacetate[150] ((103), R = CN, R' = CO_2Et, R'' = H)

o-Nitrobenzaldehyde (2.5 gm.) was dissolved with ethyl cyanoacetate (1.88 gm.) in dry ether (10 ml.) and while cooling in a water bath, the solution was saturated with dry hydrogen chloride. The flask was stoppered and left at room temperature for 24 hr. The crystalline precipitate of the benzylidene derivative (3.5 gm.) was collected, washed with a little ether, then with water and dried. Recrystallised from ethanol it gave cream coloured plates, M.pt.= 101°C identical in every respect with an authentic sample.

α-Phenyl-o-nitrocinnamonitrile[151] ((103), R = CN, R' = Ph,R'' =H)

A mixture of o-nitrobenzaldehyde (2.5 gm.) and benzyl cyanide (1.95 gm.) in ethereal hydrogen chloride (10 ml.) as above, gave the benzylidene derivative, M.pt.= 130°C from ethanol. The o-nitrobenzylidene benzyl cyanide was identified by comparison with an authentic sample[151].

o-Nitrobenzylidene benzoyl acetone ((103), R = $COCH_3$, R' = COPh, R'' = H)

o-Nitrobenzaldehyde (1.5 gm.) and benzoyl acetone (1.6 gm.) in dry ether (5 ml.) was saturated with dry hydrogen chloride at room temperature. After standing in a stoppered flask at room temperature for 24 hr., no solid had separated but the reaction mixture was deep red in colour. The ether and excess hydrogen chloride were removed in vacuo and the gummy residue redissolved in ether, washed with a little dilute sodium carbonate, and the aqueous layer set aside. After drying over magnesium sulphate, the ether was concentrated to give the benzylidene derivative (2 gm.), M.pt.= 77°C from methanol (found: C, 69.2; H, 4.6; N, 4.7: $C_{17}H_{13}O_4N$ requ: C, 69.2; H, 4.4; N, 4.8).

3-Acetyl-6-chloro-4-hydroxy-2-phenylquinoline-1-oxide ((102) $R = COCH_3$, $R' = Ph$, $R'' = Cl$)

or

3-Benzoyl-6-chloro-4-hydroxy-2-methylquinoline-1-oxide((102) $R = COPh$, $R' = Me$, $R'' = Cl$)

(a) Careful acidification of the sodium carbonate extract in the preparation of o-nitrobenzylidene benzoyl acetone, above, gave a cream precipitate of the N-oxide (0.5 gm.). Crystallised from dimethyl formamide it formed cream needles, M.pt.= 254°C. (found: C, 65.3; H, 4.0; N, 4.4; $C_{17}H_{12}ClO_3N$ requ: C, 65.1; H, 3.8; N, 4.5).

(b) Treatment of o-nitrobenzylidene benzoyl acetone (0.2 gm.) with ethereal hydrogen chloride (3 ml.) for 48 hr. gave a white crystalline precipitate of the hydrochloride of the N-oxide ((102), R = $COCH_3$ or COPh, R = Ph or Me, R'' = Cl) too unstable for analysis. Treatment of the hydrochloride with dilute sodium hydroxide followed by acidification with dilute mineral acid gave the free N-oxide (0.15 gm.), M.pt.= 254°C from dimethylformamide, identical in every respect with the sample obtained in (a) above.

Ethyl *o*-nitrobenzylideneacetoacetate ((103), R = $COCH_3$, R' = CO_2Et.)

o-Nitrobenzaldehyde (3.0 gm.), ethyl acetoacetate (2.7 gm.) and potassium bicarbonate (3 gm.) were warmed together in acetic anhydride (1.9 ml.) at 100°C for 2 hr. The mixture was cooled, poured into water and extracted with ether (3 x 20 ml.). The ether extract after washing with dilute sodium bicarbonate, then water, was dried over magnesium sulphate. Concentration of the ether gave a gum which was dissolved in warm methanol, and refrigerated to give the benzylidene derivate (2.5 gm.) as cream plates from ethanol, M.pt.= 69°C. (found: C, 59.3; H, 5.1; N, 5.4: $C_{13}H_{13}O_5N$ requ: C, 59.3; H, 5.0; N, 5.3). Concentration of the ethanol mother liquors gave an oil which was set aside.

Ethyl 6:8-dichloro-4-hydroxy-2-methylquinoline-3-carboxylate -1-Oxide ((109), R = R' = Cl)

(a) A mixture of 5-chloro-2-nitrobenzaldehyde[189] (5 gm.) and ethyl acetoacetate (3.2 ml.) was treated with ethereal hydrogen chloride (25 ml.) at room temperature and the reaction mixture left in a stoppered flask at room temperature for 24 hr. The reaction mixture became red in colour but after 24 hr. no solid had separated. After resaturation with dry hydrogen chloride and standing at room temperature for a further 24 hr., the hydrochloride of the N-oxide separated as a crystalline mass (5.64 gm.) too unstable for analysis. Concentration of the ether mother liquor gave a further quantity (0.7 gm.) of the hydrochloride. It dissolved in dilute sodium hydroxide (a rather insoluble sodium salt may be formed), giving a yellow solution which was carefully acidified with dilute sulphuric acid affording the N-oxide as a creamy precipitate. Crystallised from ethanol it formed cream needles, M.pt.= 203°C, (*found*: C, 49.4; H, 3.8; N, 4.6: $C_{13}H_{11}Cl_2O_4N$ *requ*: C, 49.4; H, 3.5; N, 4.4).

(b) *Ethyl 5-chloro-2-nitrobenzylideneacetoacetate ((103), R = $COCH_3$, R$'$ = CO_2Et, R$''$ = Cl)* (see below) (0.3 gm.) was treated for 48 hr. with ethereal hydrogen chloride (5 ml.) at room temperature to give an almost quantitative yield of the hydrochloride of the N-oxide. Liberation of the free base by successive treatment with dilute sodium hydroxide, then dilute sulphuric acid gave the N-oxide, M.pt.= 203°C from ethanol, identical with a sample prepared as under (a) above.

Ethyl 5-chloro-2-nitrobenzylideneacetoacetate ((103), R = $COCH_3$, R$'$ = CO_2Et, R$''$ = Cl).

Evaporation of the ethereal residues in the preparation of ethyl 6:8-dichloro-4-hydroxy-2-methylquinoline-4-carboxylate-1-oxide, above, gave a gummy solid. This solid was redissolved in ether, the ether washed with dilute sodium carbonate solution, water, then dried over magnesium sulphate. Concentration of the ether gave the benzylidene derivative as a crude crystalline solid. Recrystallised with charcoaling from ethanol, it formed cream coloured rhombs, M.pt.= 101°C, (found: C, 52.4; H, 4.2; N, 4.7: $C_{13}H_{12}ClO_5N$ requ: C, 52.4; H, 4.0; N, 4.7).

Ethyl 1-acetoxy-6:8 dichloro-2-methylquinol-4-one-3-carboxylate ((110), R = R' = Cl)

The N-oxide ((109), R = R' = Cl) in warm acetic anhydride gave the acetoxy derivative as white needles, M.pt.= 130°C from ethanol, (found: C, 50.5; H, 3.8; N, 4.2; $C_{15}H_{13}Cl_2O_5N$ requ: C, 50.3; H, 3.6; N, 3.9).

Ethyl 6-bromo-8-chloro-4-hydroxy-2-methylquinoline-3& carboxylate-1-oxide ((109), R = Br, R' = Cl).

(a) 5-Bromo-2-nitrobenzaldehyde (2.3 gm.)[190] was treated with ethyl acetoacetate (1.3 ml.) in dry ether (25 ml.) and the solution saturated with dry hydrogen chloride at room temperature. Using the same procedure as above, the N-oxide (2 gm.) was obtained as cream needles from ethanol, M.pt.= 193°C (found: C, 43.6; H, 3.3; N, 3.8: $C_{13}H_{11}BrClO_4N$ requ: C, 43.3; H, 3.1; N, 3.9).

(b) Treatment of ethyl 5-bromo-2-nitrobenzylidene acetoacetate (0.3 gm.) with ethereal hydrogen chloride (5 ml.) for 48 hr. gave no precipitate. The reaction mixture was concentrated to ~ 1 ml. and petrol (40-60°B.pt.) was added giving a fine white precipitate of the hydrochloride of ethyl 6-bromo-8-chloro-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide, which on treatment with dilute sodium hydroxide and acidification with dilute sulphuric acid gave the N-oxide as a curdy precipitate, M.pt.= 193°C from ethanol. Mixed melting point with an authentic sample was 193°C and the infra-red spectra were identical.

Ethyl 5-bromo-2-nitrobenzylideneacetoacetate ((103), R = COMe, R' = CO_2Et, R'' = Br).

Working up the ether mother liquor in the preparation of ethyl 6-bromo-8-chloro-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide, above, as already described for ethyl 5-chloro-2-nitrobenzylideneacetoacetate ((103), R = $COCH_3$, R' = CO_2Et, R'' = Cl) gave the 5-bromo derivative, cream prisms from ethanol, M.pt.= 106°C, (found: C, 45.7; H, 3.8; N, 3.9: $C_{13}H_{12}BrO_5N$ requ: C, 45.6; H, 3.5; N, 4.1).

Ethyl 1-acetoxy-6-bromo-8-chloro-2-methylquinol-4-one-3-carboxylate ((110), R = Br, R' = Cl)

The N-oxide ((109), R = Br, R' = Cl) was warmed with acetic anhydride for 5 mins. at 100°C and after working up in the usual manner, the crude acetoxy derivative was crystallised from ethanol giving white needles, M.pt.= 122°C, (found: C, 45.0; H, 2.9; N, 3.8: $C_{15}H_{13}BrClO_5N$ requ: C, 44.7; H, 3.2; N, 3.5).

6:8-Dichloro-4-hydroxy-2-methylquinoline-3-carboxylic acid-1-oxide ((109), $R = R' = Cl$, CO_2H for CO_2Et).

The ester ((109), $R = R' = Cl$) (1.1 gm.) was dissolved with warming in acetic acid (5.5 ml.), water (11 ml.) and concentrated sulphuric acid (1.4 cc.) and the solution refluxed for 3 hr. Concentration of the reaction mixture gave the acid as a cream powder. Crystallised from dimethylformamide it formed cream needles, M.pt.= 258°C (found: C, 46.3; H, 3.0; N, 5.0: $C_{11}H_7Cl_2O_4N$ requ: C, 45.8; H, 2.4; N, 4.9). (Better analytical figures were unobtainable.)

6:8-Dichloro-4-hydroxy-2-methylquinoline-3-carboxylic acid ((112), $R = CO_2H$, $R' = R'' = Cl$).

The carboxylic acid ((109), $R = R = Cl$, CO_2H for CO_2Et) (0.7 gm.) was refluxed for 1 hr. with zinc dust (1.5 gm.) in acetic acid (40 cc.), the zinc being added in portions to the refluxing solution. The cooled, filtered reaction mixture afforded fine cream needles of the acid. Crystallised from dimethylformamide it formed white needles, M.pt.= 258-259°C (decomp.) (found: C, 48.9; H, 2.7; N, 5.1: $C_{11}H_7Cl_2O_3N$ requ: C, 48.5; H, 2.6; N, 5.1).

6:8-Dichloro-4-hydroxy-2-methylquinoline[192] ((112), $R=H$, $R''=R'=Cl$)

(a) The acid ((112), $R = CO_2H$, $R' = R'' = Cl$) (0.09 gm.) was warmed at 250°C in a hard glass test tube. Carbon dioxide was evolved and after 5 mins., the tube was cooled and the residue crystallised twice from dimethylformamide with charcoaling gave the quinoline as white needles, M.p.= 298°C, (found: C, 52.7; H, 3.2; N, 6.3; $C_{10}H_7Cl_2ON$ requ: C, 52.6; H, 3.1; N, 6.1).

(b) Preparation of the Anil (113)

Ethyl acetoacetate (6.5 gm.) and 2:4-dichloroaniline (8.1 gm.) were mixed and two drops of concentrated hydrochloric acid added. The whole was shaken by hand for 5 mins. to dissolve all the suspended solid and the reaction mixture left at room temperature in a stoppered flask for 5 hr. Ether was added and the solution dried over magnesium sulphate. Removal of the ether in vacuo gave the crude anil as a mobile liquid which was not further purified.

The anil prepared above was added drop by drop to well stirred and refluxing diphenyl ether. After addition was complete, the solution was boiled with continual stirring for 0.5 hr. On cooling, cream needles of 6:8-dichloro-4-hydroxy-2-methylquinoline separated. The quinoline was collected, washed with petrol and crystallised from dimethylformamide to give white needles, M.pt.= 298°C. Mixed melting point with a sample prepared above was 298°C and the infra-red spectra of the two samples were identical.

(a) Ethyl 4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide hydrobromide.

o-Nitrobenzaldehyde (10 gm.) snd ethyl acetoacetate (8.7 gm.) dissolved in dry ether (30 ml.) was saturated with dry hydrogen bromide at room temperature. The stoppered flask was left at room temperature for 24 hr. and the white crystalline solid which separated was collected and recrystallised from ethyl acetate - ethanol to give white needles of the hydrobromide, M.pt.= 138-140°C, (**found**: C, 47.4; H, 4.0; N, 4.5: $C_{13}H_{14}BrO_4N$ requ: C, 47.6; H, 4.3; N, 4.3). The yield was ~60%.

(b) Ethyl o-nitrobenzylidene acetoacetate ((103), R = COMe, $R' = CO_2Et$, $R'' = H$) was treated with ethereal hydrogen bromide at room temperature for 48 hr. to give an almost quantitative yield of the hydrobromide of ethyl 4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide identical in melting point (140°C), infra-red spectrum and mixed melting point with an authentic sample (see (a) above).

Ethyl 4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide[139] ((109), R = R' = H).

Careful acidification of the red solution obtained by dissolving the hydrobromide (see above) in 4N sodium hydroxide solution, with dilute sulphuric acid gave a gream precipitate of the N-oxide. Crystallised from ethanol it formed cream needles, M.pt.= 175°C, (found: C, 63.2; H, 5.3; N, 6.0: calc. for $C_{13}H_{13}O_4N$: C, 63.2; H, 5.3; N, 5.7).

4-Hydroxy-2-methylquinoline-3-carboxylic acid-1-oxide[135]

((109), $R = R' = H$, CO_2H for CO_2Et)

(a) The hydrobromide of the N-oxide ((109), $R = R' = H$) was heated in a hard glass test tube at 150°C in an oil bath, for 10 mins. The crude residue crystallised with charcoaling from methanol afforded the acid as white needles, M.pt.= 215°C, (decomp.) (found: C, 59.9; H, 4.1; N, 6.3: calc. for $C_{11}H_9O_4N$: C, 60.2; H, 4.1; N, 6.4).

(b) Ethyl 4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide ((109), $R = R' = H$) was refluxed for 2 hr. with 3% sodium hydroxide solution. Careful acidification of the cooled reaction mixture with dilute sulphuric acid, gave the acid as a cream precipitate. Crystallised from methanol it formed white needles, M.pt.= 215°C. Mixed melting point with an authentic specimen was 215°C and the infra-red spectra were identical.

4-Hydroxy-2-methylquinoline-1-oxide ((109), R = R' = H, H for CO_2Et)[135]

The acid ((109), R = R' = H, CO_2H for CO_2Et) was decarboxylated at 220°C in a hard glass test tube to give the N-oxide. After two crystallisations from dimethylformamide it gave white needles, M.pt.= 248°C, (found: C, 68.8; H, 5.5; N, 7.5: $C_{10}H_9O_2N$ requ: C, 68.6; H, 5.2; N, 8.0).

3-Acetyl-4-hydroxy-2-methylquinoline-1-oxide ((102), R = COMe, R' = Me, R'' = H)

A mixture of *o*-nitrobenzaldehyde (10 gm.) and acetylacetone (6.7 gm.) in dry ether (30 ml.) was treated as above with hydrogen bromide, to give the hydrobromide of the N-oxide (60% yield). The hydrobromide dissolved in dilute (4N) sodium hydroxide giving a red solution which on careful acidification with dilute sulphuric acid afforded the N-oxide as a cream precipitate. Crystallised from dimethylformamide it formed cream needles, M.pt.= 261°C, (found: C, 66.1; H, 4.9; N, 6.7: $C_{12}H_{11}O_3N$ requ: C, 66.4; H, 5.1; N, 6.5).

1-Acetoxy-3-acetyl-2-methylquinol-4-one ((110), R = R' = H, $COCH_3$ for CO_2Et)

The N-oxide ((102), R = COMe, R = Me, R = H) was warmed in acetic anhydride for 5 mins. Working up in the usual manner, gave the acetoxy derivative as cream needles from ethanol, M.pt.= 135-137°C, (<u>found</u>:- C, 65.0; H, 4.6; N, 5.6: $C_{14}H_{13}O_4N$ <u>requ</u>:- C, 64.9; H, 5.0; N, 5.4).

<u>3-Acetyl-4-hydroxy-2-methylquinoline ((112), R = COMe, R' = R'' = H)</u>

The N-acetate ((110), R = R' = H, COMe for CO_2Et) was smoothly hydrogenolysed in ethanol over 5% palladium charcoal giving 3-acetyl-4-hydroxy-2-methylquinoline, M.pt.= 255°C from dimethylformamide (<u>found</u>: C, 72.0; H, 5.5; N, 7.3: $C_{12}H_{11}O_2N$ <u>requ</u>: C, 71.6; H, 5.5; N, 7.0).

<u>Ethyl 6-chloro-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide hydrobromide</u>

(a) 5-Chloro-2-nitrobenzaldehyde (2.5 gm.) and ethyl acetoacetate (1.7 ml.) in dry ether (30 ml.) were treated with dry hydrogen bromide at room temperature. After standing stoppered for 24 hr., the white solid which separated was collected (2 gm.) and crystallised from ethyl acetate - ethanol to give white needles of the hydrobromide, M.pt.= 133-135°C (decomp.) (<u>found:</u> C, 43.1; H, 3.8; N, 4.1; $C_{13}H_{13}BrClO_4N$ <u>requ</u>: C, 43.0; H, 3.6; N, 3.9).

The hydrobromide dissolved in 4N sodium hydroxide giving a deep yellow solution which on acidification afforded the free base as a cream precipitate. Crystallised from ethanol it formed cream needles, M.pt.= 226°C. Mixed melting point with an authentic sample of ethyl 6-chloro-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide[132] was 226°C and the infra-red spectra were identical.

(b) Ethyl 5-chloro-2-nitrobenzylideneacetoacetate ((103), R = COMe, $R' = CO_2Et$, $R'' = Cl$) treated for 48 hr. at room temperature with ethereal hydrogen bromide gave a good yield of the above hydrobromide, identified by its infra-red spectrum and mixed melting point with an authentic sample (135°C), and also by its conversion by base to the known compound ethyl 6-chloro-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide ((109), R = Cl, $R' = H$).

<u>Ethyl 6-bromo-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide hydrobromide</u>.

(a) 5-Bromo-2-nitrobenzaldehyde (4.6 gm.) and ethyl acetoacetate (2.6 ml.) treated as above with ethereal hydrogen bromide for 24 hr. gave the hydrobromide (2.2 gm.) as white needles from ethyl acetate - ethanol, M.pt.= 138-140°C, (<u>found</u>: C, 38.1; H, 3.2; N, 3.5: $C_{13}H_{13}Br_2O_4N$ <u>requ</u>: C, 38.3; H, 3.2; N, 3.4). A small amount (1 gm.) of starting material was recovered on working up the ether mother liquor as well as a further quantity (0.5 gm.) of the N-oxide.

(b) Ethyl 5-bromo-2-nitrobenzylideneacetoacetate ((103), R = COMe, R' = CO_2Et, R'' = Br)(0.3 gm.) treated at room temperature with ethereal hydrogen bromide (3 ml.) for 48 hr. gave a crystalline precipitate of the hydrobromide (0.15 gm.). M.pt.= 138-140°C from ethyl acetate - ethanol. Mixed melting point with a sample prepared as under (a) above was 138-140°C and the infra-red spectra were identical.

Ethyl 6-bromo-4-hydroxy-2-methylquinoline-3-carboxylate-1-oxide ((109), R = Br, R' = H).

The yellow solution obtained by dissolving the above hydrobromide in 4N. sodium hydroxide was acidified with dilute sulphuric acid to give the N-oxide. Crystallised from ethanol it formed cream needles, M.pt.= 219°C. (found: C, 47.6; H, 3.8; N, 4.1: $C_{13}H_{12}BrO_4N$ requ: C, 47.9; H, 3.7; N, 4.3).

Ethyl 1-acetoxy-6-bromo-2-methylquinol-4-one-3-carboxylate ((110), R = Br, R' = H)

The N-oxide ((109), R = Br, R' = H) was warmed with acetic anhydride to give the N-acetoxy derivative. M.pt.= 211°C

CHAPTER V

2-Amino-5-chloro-4'-hydroxybenzophenone[160] ((130), R=Cl,R'=H)

The anthranil derivative ((114), R = p-C_6H_4OH; R' = Cl, R'' = R''' = H) (1 gm.) dissolved in 10% sodium hydroxide (10 ml.) (a rather insoluble, red sodium salt tends to be formed, but dissolves on warming), was warmed for 20 mins. with portions (0.5 gm.) of sodium dithionite, a total of 3 gms being added. The reaction mixture was cooled before the addition of each portion. As reduction proceeds the deep orange-red colour of the anthranil salt is replaced by the pale yellow colour of the amino-phenol salt. The cooled reaction mixture was acidified with acetic acid giving a yellow crystalline precipitate of the amine (3 gm.), M.pt.= 176-177°C from aqueous methanol (found: C, 63.2; H, 4.3; N, 5.9: calc. for $C_{13}H_{10}ClO_2N$: C, 63.0; H, 4.1; N, 5.7).

4'-Acetoxy-2-acetylamino-5-chlorobenzophenone ((130), R = Cl, R' = H, $NHCOCH_3$ for NH_2, $OCOCH_3$ for OH).

The amine ((130), R = Cl, R' = H) was warmed with acetic anhydride and the solution decomposed with water to give the crude diacetyl derivative. Recrystallised from aqueous ethanol it formed colourless rhombs, M.pt.= 135-137°C. (found: C, 61.5; H, 4.3; N, 4.3: $C_{17}H_{14}ClO_4N$ requ: C, 61.5; H, 4.2; N, 4.2).

2-Acetylamino-5-chloro-4'-hydroxybenzophenone ((130), R = Cl, R' = H, $NHCOCH_3$ for NH_2)

The diacetyl compound ((130), R = Cl, R' = H, $NHCOCH_3$ for NH_2, $OCOCH_3$ for OH) was warmed on the steam bath with 0.5N. sodium hydroxide giving a yellow solution. This was cooled and acidified with dilute sulphuric acid to give the crude phenol as a pale yellow precipitate. Recrystallised from aqueous ethanol it formed yellow prisms, M.pt.= 174°C (found: C, 62.3; H, 4.3; N, 5.0: $C_{15}H_{12}ClO_3N$ requ: C, 62.2; H, 4.2; N, 4.8).

N-Acetyl-5-chloroanthranilic acid ((125), R = Cl, R' = H).

The phenol ((130), R = Cl, R' = H, $NHCOCH_3$ for NH_2) (0.1 gm.) was suspended with gentle warming in 0.2N. sodium carbonate solution (4 ml.) and mixed at 40-45°C with 2% potassium permanganate solution (15 ml.). After standing at 45°C overnight, the reaction mixture was filtered to remove the precipitated manganese dioxide, and carefully acidified with dilute sulphuric acid giving a cream coloured precipitate. This was extracted with chloroform and the chloroform washed with a little sodium bicarbonate solution. Careful acidification of the latter gave the acid as a cream precipitate (0.04 gm.) Recrystallised from aqueous methanol it gave cream rhombs, M.pt. = 202°C. Mixed melting point with an authentic sample of

N-acetyl-5-chloroanthranilic acid was 202°C and the infra-red spectra were identical.

5:7-Dichloro-3-(p-hydroxyphenyl) anthranil ((114), $R = p\text{-}C_6H_4OH$, $R' = R''' = Cl$, $R'' = H$)

5-Chloro-2-nitrobenzaldehyde[189] (3.0 gm.) and phenol (3.1 gm.) were dissolved in dry ether (30 ml.) and the solution saturated at room temperature with dry hydrogen chloride. After standing for 24 hr. in a stoppered flask the reaction mixture deposited a fine, yellow, crystalline mass of the anthranil (3.6 gm.) which was collected, washed with ether, then water and dried *in vacuo*. Working up the ether mother liquor afforded a further quantity of product (1.0 gm.). Recrystallised from ethanol the anthranil formed deep yellow needles, M.pt.= 251°C (*found*: C, 55.5; H, 2.8; N, 5.1: $C_{13}H_7Cl_2O_2N$ *requ*: C, 55.7; H, 2.5; N, 5.0).

5-Bromo-7-chloro-3-(p-hydroxyphenyl) anthranil ((114), $R = p\text{-}C_6H_4OH$, $R' = Br$, $R'' = H$, $R''' = Cl$).

5-Bromo-2-nitrobenzaldehyde[190] (2.3 gm.) and phenol (1.88 gm.) treated as above, with ethereal hydrogen chloride (30 ml.) for 24 hr. at room temperature gave the anthranil (3.0 gm.) as deep yellow needles from aqueous dimethylformamide, M.pt.= 240-241°C (*found*: C, 48.1; H, 2.1; N, 4.5: $C_{13}H_7BrClO_2N$

requ: C, 48.1; H, 2.2; N, 4.3).

2-Amino-6:8-dichloro-4'-hydroxybenzophenone ((130),R=R'=Cl)

The anthranil ((114), R = p-C_6H_4OH, R = R''' = Cl, R'' = H) (1 gm.) treated with sodium dithionite (3 gm.) in boiling sodium hydroxide (10%, 15 ml.) as for 5-chloro-3-(p-hydroxyphenyl) anthranil, gave on acidification of the cooled, alkaline, reaction mixture, a deep yellow, crystalline precipitate of the amine (1.1 gm.). Crystallised from aqueous ethanol it formed deep yellow needles, M.pt.= 162°C, (found: C, 55.5; H, 3.3; N, 5.1: $C_{13}H_9Cl_2O_2N$ requ: C, 55.4; H, 3.2; N, 5.1).

4'-Acetoxy-2-acetylamino-6:8-dichlorobenzophenone ((130), R = R' = Cl, NHCOCH_3 for NH_2, OCOCH_3 for OH).

The aminophenol ((130), R = R = Cl) was warmed for 0.5 hr. with sodium acetate in acetic anhydride. The excess acetic anhydride was removed in vacuo and the solid residue on trituration with water afforded the crude diacetyl derivative. Crystallised from acetic acid it gave colourless prisms, M.pt. = 193°C (found: C, 56.0; H, 3.6; N, 3.7: $C_{17}H_{13}Cl_2O_4N$ requ: C, 55.8; H, 3.6; N, 3.8).

2-Acetylamino-6:8-dichloro-4'-hydroxybenzophenone ((130), $R = R' = Cl$, $NHCOCH_3$ for NH_2)

The diacetyl compound ((130), $R = R' = Cl$, $NHCOCH_3$ for NH_2, $OCOCH_3$ for OH) was warmed with 0.5N. sodium hydroxide giving a pale yellow solution which after cooling was acidified to give the phenol as a cream precipitate. Crystallised from aqueous ethanol it formed cream prisms, M.pt.= 278-280°C (found: C, 55.6; H, 3.5; N, 4.1: $C_{15}H_{11}Cl_2O_3N$ requ: C, 55.6; H, 3.4; N, 4.3).

N-Acetyl-3:5-dichloroanthranilic acid ((125), $R = R' = Cl$)

Oxidation of the phenol (0.1 gm.) ((130), $R = R' = Cl$, $NHCOCH_3$ for NH_2) with 2% potassium permanganate solution (15 ml.) in 0.2N. sodium carbonate (4 ml.) gave as for 2-acetylamino-5-chloro-4'-hydroxybenzophenone ((130), $R = Cl$, $R' = H$, $NHCOCH_3$ for NH_2), N-acetyl 3:5-dichloroanthranilic acid, white needles from aqueous ethanol, M.pt.= 205°C. Mixed melting point with an authentic sample prepared by acetylation of 3:5-dichloroanthranilic acid[185], was 205°C and the infra-red spectra of the two samples were identical.

2-Amino-4'-hydroxydiphenylmethane (131).

Hydrogenolysis of 5-chloro-, 5-bromo-, 5:7-dichloro-, or 5-bromo-7-chloro-3-(p-hydroxyphenyl) anthranil over palladium charcoal (5%) in ethanol gave after removal of the catalyst and concentration of the ethanol filtrate, a pale green gum which on trituration with dilute sodium bicarbonate solution afforded the crude diphenylmethane derivative. Crystallised from ethanol it formed white needles, M.pt.= 117°C (found: C, 78.7; H, 6.8; N, 7.1: $C_{13}H_{13}ON$ requ: C, 78.4; H, 6.5; N, 7.1).

4'-Acetoxy-2&acetylaminodiphenylmethane ((131), $NHCOCH_3$ for NH_2, $OCOCH_3$ for OH).

The diphenylmethane derivative (131) was warmed with acetic anhydride, affording the crude diacetyl derivative on pouring into water. Crystallised from ethanol it gave white needles, M.pt.= 175°C (found: C, 72.1; H, 6.1; $C_{17}H_{17}O_3N$ requ: C, 72.1; H, 6.0).

Reaction of o-Nitrobenzaldehyde with Phenol in Ethereal Hydrogen Bromide.

o-Nitrobenzaldehyde (3.0 gm.) and phenol (3.9 gm.) in dry ether (30 ml.) was treated with dry hydrogen bromide at room temperature until the solution was saturated. The reaction flask was left stoppered, for 24 hr. at room temperature and the crude orange-yellow solid which separated collected (4-5 gm.) and fractionally crystallised from methanol to give

5-bromo-3-(p-hydroxyphenyl) anthranil ((114), R = p-C_6H_4OH, R' = Br, R'' = R''' = H) as deep yellow needles from aqueous dimethylformamide, M.pt.= 243°C. Mixed melting point with an authentic sample (see below) was 243°C and the infra-red spectra were identical.

Successive fractions gave 3-(p-hydroxyphenyl) anthranil ((114), R = p-C_6H_4OH, R' = R'' = R''' = H) as pale yellow needles from methanol, M.pt.= 205°C (found: C, 74.1; H, 4.2; N, 6.8: $C_{13}H_9O_2N$ requ: C, 73.9; H, 4.3; N, 6.7).

5-Chloro-3-(p-hydroxyphenyl) anthranil ((114), R = p-C_6H_4OH, R' = Cl, R'' = R''' = H).

5-Chloro-2-nitrobenzaldehyde (2.5 gm.) and phenol (2.6 gm.) were treated with ethereal hydrogen bromide (30 ml.) for 24 hr. as in the above experiment. The deep yellow, crystalline solid (0.5 gm.) which separated, was collected, washed with ether, then water and dried in vacuo. Crystallised from aqueous dimethylformamide it gave deep yellow needles, M.pt.= 241°C (found: C, 63.2; H, 3.3; N, 5.9; calc. for $C_{13}H_8ClO_2N$, C, 63.5; H, 3.3; N, 5.7). Mixed melting point with an authentic specimen of 5-chloro-3-(p-hydroxyphenyl) anthranil[160] was 241-242°C and the infra-red spectra were identical. The ether mother liquor on working up gave more of the anthranil (0.2 gm.) and also 5-chloro-2-nitrobenzaldehyde (1.5 gm.) identical in every respect with an authentic specimen of starting material.

5-Bromo-3-(p-hydroxyphenyl) anthranil ((114), $R = p\text{-}C_6H_4OH$, $R' = Br$, $R'' = R''' = H$)

Treatment of a mixture of 5-bromo-2-nitrobenzaldehyde (4.6 gm.) and phenol (3.8 gm.) with ethereal hydrogen bromide (40 ml.) for 24 hr. at room temperature as described above gave fine yellow needles of the anthranil (1 gm.), M.pt.= 243°C from aqueous dimethylformamide (found: C, 53.4; H, 2.6; N, 5.1: $C_{13}H_8BrO_2N$ requ: C, 53.8; H, 2.8; N, 4.8).

Working up the ether mother liquor gave more of the anthranil (0.3 gm.) and 5-bromo-2-nitrobenzaldehyde (2.0 gm.) identical in every respect with an authentic specimen of starting material.

3-(2':5'-dihydroxyphenyl) anthranil ((114), $R = C_6H_3(OH)_2$, $R' = R'' = R''' = H$).

o-Nitrobenzaldehyde (4.0 gm.) and hydroquinone (6 gm.) in dry tetrahydrofuran (25 ml.) were saturated at room temperature with dry hydrogen chloride. After standing stoppered for 24 hr. at room temperature the excess hydrogen chloride and tetrahydrofuran were removed in vacuo to give the anthranil as a crude orange-red solid (3.0 gm.) which crystallised from aqueous ethanol in the form of golden-yellow needles, M.pt.= 200°C (found: C, 68.6; H, 4.1; N, 6.0: $C_{13}H_9O_3N$ requ: C, 68.7; H, 4.0; N, 6.2).

5-Chloro-3-(2':5'-dihydroxyphenyl) anthranil ((114), $R = C_6H_3(OH)_2$, $R' = Cl$, $R'' = R''' = H$).

A mixture of 5-chloro-2-nitrobenzaldehyde (1 gm.) and hydroquinone (1.2 gm.) in dry tetrahydrofuran (5 ml.) was treated with dry hydrogen chloride as above. Removal of the excess hydrogen chloride and tetrahydrofuran in vacuo after 24 hr. at room temperature gave the anthranil as a crude orange solid (0.9 gm.). Crystallised from methanol with charcoaling it formed golden-yellow plates, M.pt.= 254°C (found: C, 59.3; H, 2.9; N, 5.6: $C_{13}H_8ClO_3N$ requ: C, 59.6; H, 3.1; N,5.4).

5-Bromo-3-(2':5'-dihydroxyphenyl) anthranil ((114), $R = C_6H_3(OH)$, $R' = Br$, $R'' = R''' = H$).

(a) 5-Bromo-2-nitrobenzaldehyde (2.3 gm.) and hydroquinone (2.2 gm.) dissolved in tetrahydrofuran (10 ml.) were treated with hydrogen chloride at room temperature to give, after 48 hr. at room temperature, a crude orange solid (1.5gm.). Crystallised from methanol the anthranil formed deep yellow needles, M.pt.= 260°C (found: C, 51.0; H, 2.8; N, 4.6: $C_{13}H_8BrO_3N$ requ: C, 51.0; H, 2.6; N, 4.6). Concentration of the tetrahydrofuran mother liquor gave a further quantity of the anthranil derivative (0.8 gm.).

(b) 5-Bromo-2-nitrobenzaldehyde[190] (2.3 gm.) and hydroquinone (2.2 gm.) treated with hydrogen bromide in tetrahydrofuran (10 ml.) at room temperature for 48 hr., as above, gave a crude orange solid (0.6 gm.) insoluble in the reaction mixture. Crystallised from methanol with charcoaling it formed deep yellow needles, M.pt.= 260°C. Mixed melting point with 5-bromo-3-(2':5'-dihydroxyphenyl) anthranil was 260°C and the infra-red spectra were identical. Concentration of the tetrahydrofuran mother liquor gave more of the anthranil (1.5 gm.).

Reaction of o-Nitrobenzaldehyde and Hydroquinone with Hydrogen Bromide in Tetrahydrofuran.

o-Nitrobenzaldehyde (4 gm.) and hydroquinone (6 gm.) dissolved in dry tetrahydrofuran (25 ml.) were treated with dry hydrogen bromide at room temperature. After standing for 48 hr. in a stoppered flask at room temperature, the tetrahydrofuran and excess hydrogen bromide were removed *in vacuo* to give a crude orange solid (4.6 gm.). This was collected, washed with ether, water, and then dried *in vacuo*. The product was fractionally crystallised from methanol to give-

(a) 3-(2':5'-dihydroxyphenyl) anthranil (2 gm.), M.pt. =

198-200°C from methanol. Mixed melting point with an authentic sample (see above) was 198-200°C and the infra-red spectra were identical.

(b) 5-Bromo-3-(2':5'-dihydroxyphenyl) anthranil (2.3 gm.), M.pt.= 258-260°C, from methanol. Mixed melting point with an authentic sample (see above) was 258-260°C and the infra-red spectra of the two samples were identical.

Anthranil-3-carboxylic acid (anthraxanic acid)[6] ((114), $R = CO_2H$, $R' = R'' = R''' = H$)

3-(2':5'-Dihydroxyphenyl) anthranil ((114), $R = C_6H_3(OH)_2$, $R' = R'' = R''' = H$) (0.5 gm.) dissolved in warm aqueous acetic acid (70%: 15 ml.) was treated with sodium dichromate (0.9 gm.) in small portions while warming on the steam bath (5-10 mins.). The reaction mixture became deep red in colour and after cooling, it was diluted with water (5 ml.) and extracted with chloroform (3 x 25 ml.). The chloroform extract was dried over magnesium sulphate and concentrated *in vacuo* to ~ 5 ml. Addition of petrol (60-80 B.pt.) gave the acid as an amorphous precipitate (0.2 gm.). Crystallised with charcoaling from hot water it formed white needles, M.pt.= 191-192°C (*found*: C, 58.5; H, 3.5; N, 8.8: *calc. for* $C_8H_5O_3N$ C, 58.8; H, 3.1; N, 8.6). Mixed melting point with an authentic sample[6] was 191-192°C and the infra-red spectra were identical.

N-Acetylanthranilic acid ((125), R = R' = H).

Anthranil-3-carboxylic acid (0.1 gm.) was refluxed with acetic anhydride (2 ml.) for 1 hr. Removal of the acetic anhydride *in vacuo* gave a gum which was digested in dilute sodium hydroxide and the alkaline solution acidified with dilute sulphuric acid afforded the acid as a cream precipitate (0.08 gm.). Crystallised from aqueous alcohol it formed white needles, M.pt.= 188°C (*found*: C, 60.4; H, 5.0; N, 7.7: *calc. for* $C_9H_9O_3N$, C, 60.3; H, 5.0; N, 7.8). Mixed melting point with a sample prepared by acetylation of anthranilic acid was 188°C and the infra-red spectra were identical.

5-Bromo-anthranil-3-carboxylic acid ((114), R = CO_2H, R' = Br R'' = R''' = H)[191].

5-Bromo-3-(2':5'-dihydroxyphenyl) anthranil (0.2 gm.) was treated at 100°C in 70% acetic acid (12 ml.) with sodium dichromate (0.5 gm.) as for the above anthranil giving a 50% yield of 5-bromoanthranil-3-carboxylic acid, M.pt.= 201-202°C from hot water (*found*: C, 39.8; H, 1.9; *calc. for* $C_8H_4BrO_3N$, C, 39.7; H, 1.7).

5-Chloroanthranilic acid ((136), R = Cl).

o-Nitrosobenzoic acid (134)[23] (0.65 gm.) in tetrahydrofuran

(60 ml.) was saturated with dry hydrogen chloride at room temperature. After standing in a closed flask overnight at room temperature, the colour of the reaction mixture had changed from an emerald green to a deep red. Concentration of the reaction mixture to ~10 ml. in vacuo and addition of ether (30 ml.) gave a light brown amorphous precipitate, of the acid hydrochloride (0.4 gm.). The crude hydrochloride was dissolved in dilute sodium carbonate solution, filtered, and acidified with a slight excess of acetic acid. On standing, the free acid separated as a crude brown solid. Recrystallised from aqueous ethanol with charcoaling, it formed dun coloured needles, M.pt.= 205-206°C. Mixed melting point with an authentic sample was 206°C and the infrared spectra of the two samples were identical.

5-Bromo-anthranilic acid ((136), R = Br).

o-Nitrosobenzoic acid (0.5 gm.) in tetrahydrofuran (60 ml.) was saturated at room temperatüre with dry hydrogen bromide. After standing at room temperature for 24 hr. in a stoppered flask, the reaction mixture was worked up as for 5-chloro-anthranilic acid, giving light sandy needles of 5-bromo-anthranilic acid (0.34 gm.). M.pt.= 217-218°C from ethanol after clarification with charcoal (found: C, 39.4; H, 2.9; N, 6.1: $C_7H_6BrO_2N$ requ: C, 39.8; H, 2.8; N, 6.5).

Reaction of Ethyl o-Nitrobenzylideneacetoacetate with Hydrogen Chloride and Hydroquinone in Tetrahydrofuran.

Ethyl o-nitrobenzylideneacetoacetate (132) (cf.Chapter IV) (0.3 gm.) and hydroquinone (0.13 gm.) in dry tetrahydrofuran (3 ml.) were treated at room temperature with dry hydrogen chloride. After 48 hr. the reaction mixture was concentrated to ~1 ml. in *vacuo*. Dilution with ether gave a pale cream solid (0.3 gm.) which dissolved in dilute sodium hydroxide and was recovered unchanged on acidification. Crystallised from ethanol it formed cream needles, M.pt.= 175°C. Mixed melting point with ethyl 4-hydroxy-2-methylquinoline carboxylate 1-oxide was 175°C and the infra-red spectra of the two samples were identical.

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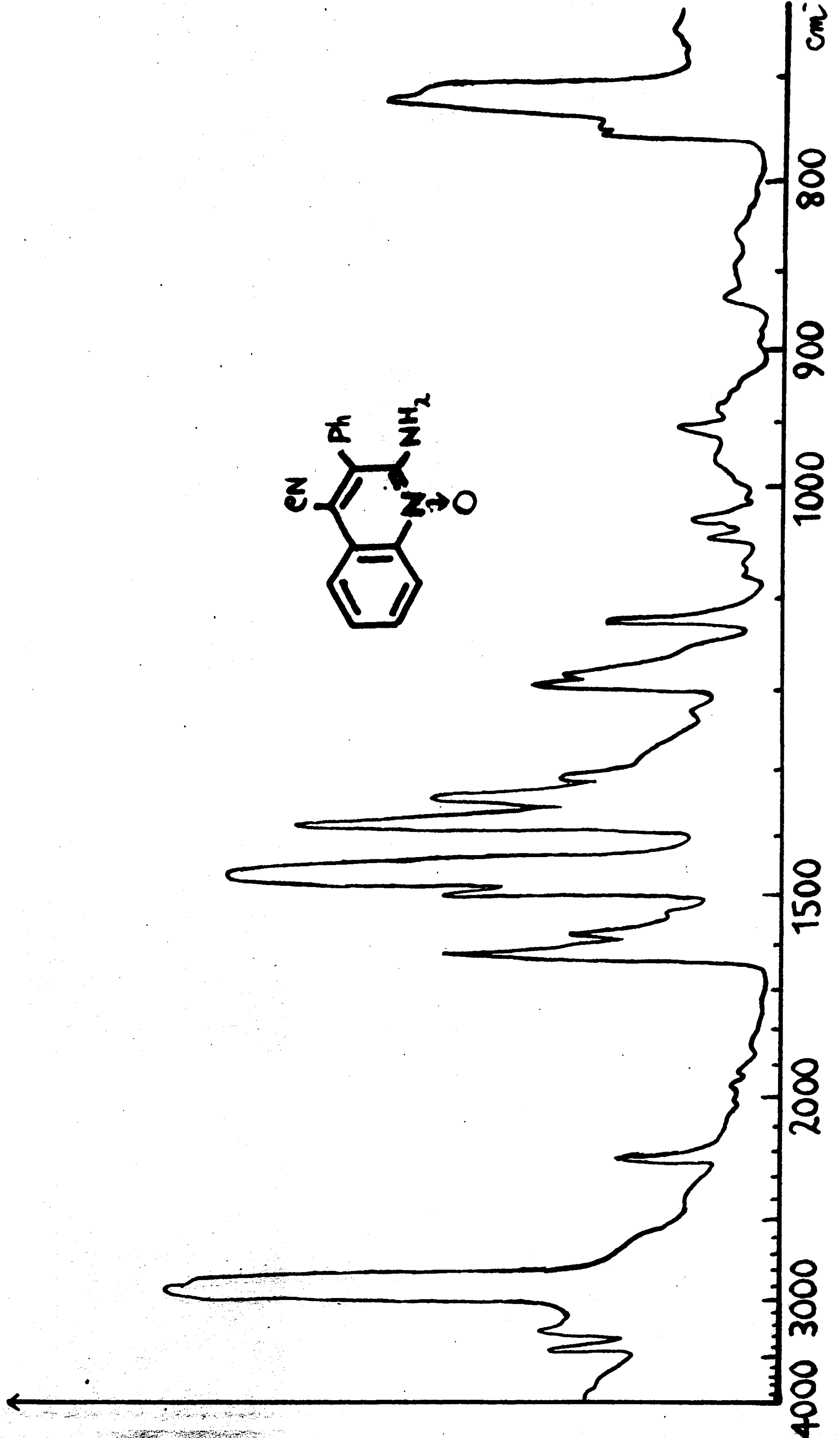
INFRA - RED GRAPHS



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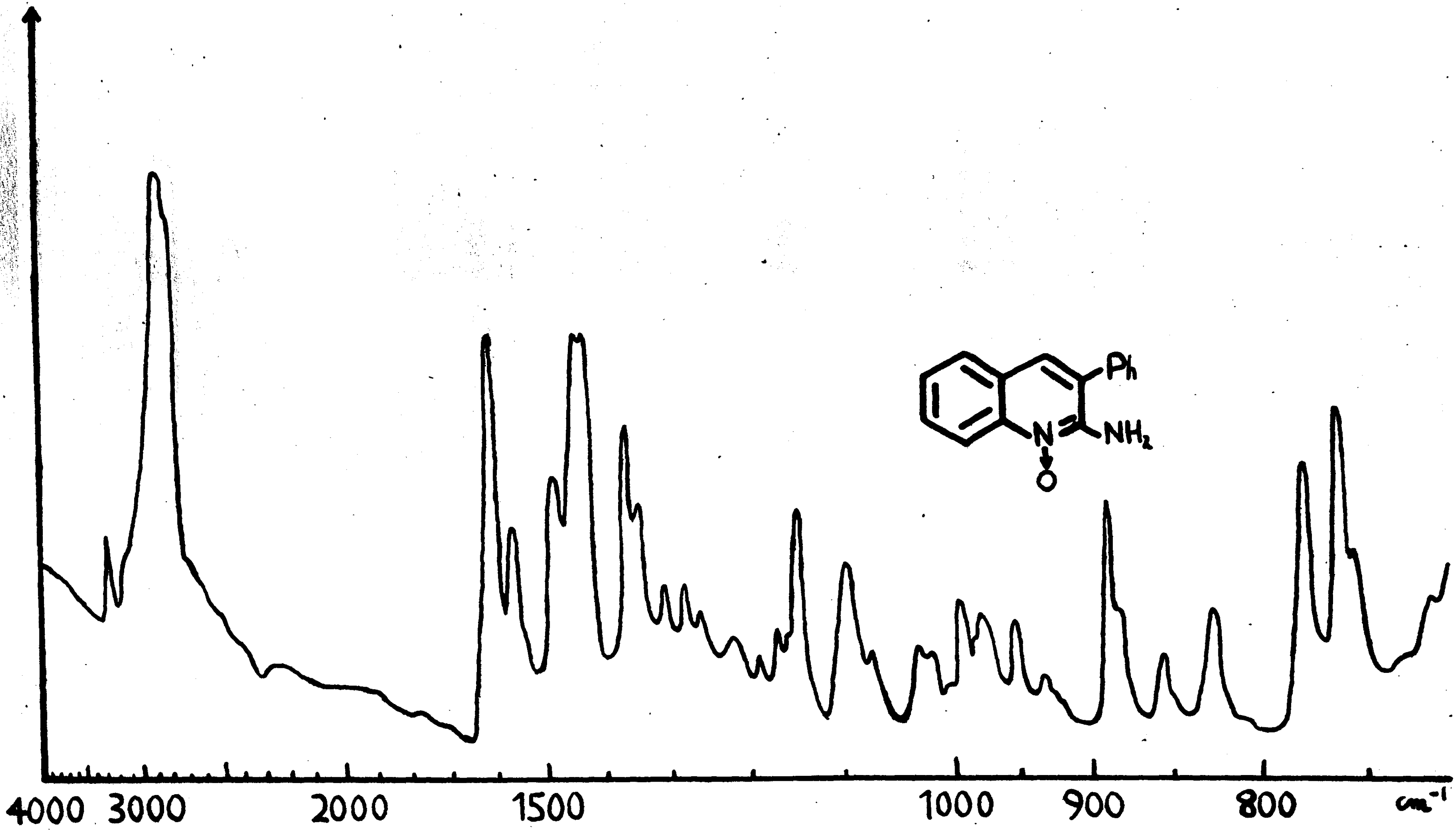
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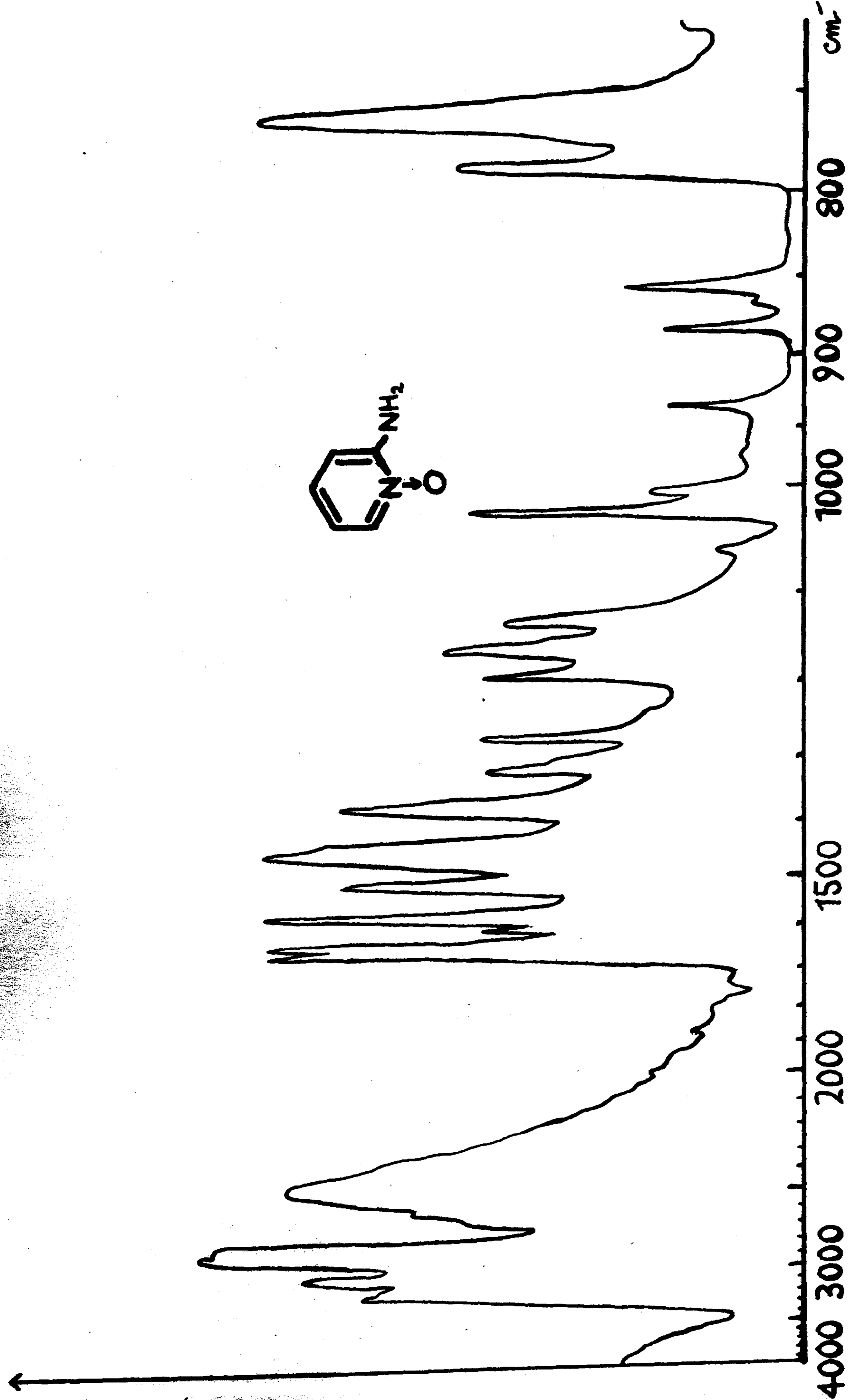
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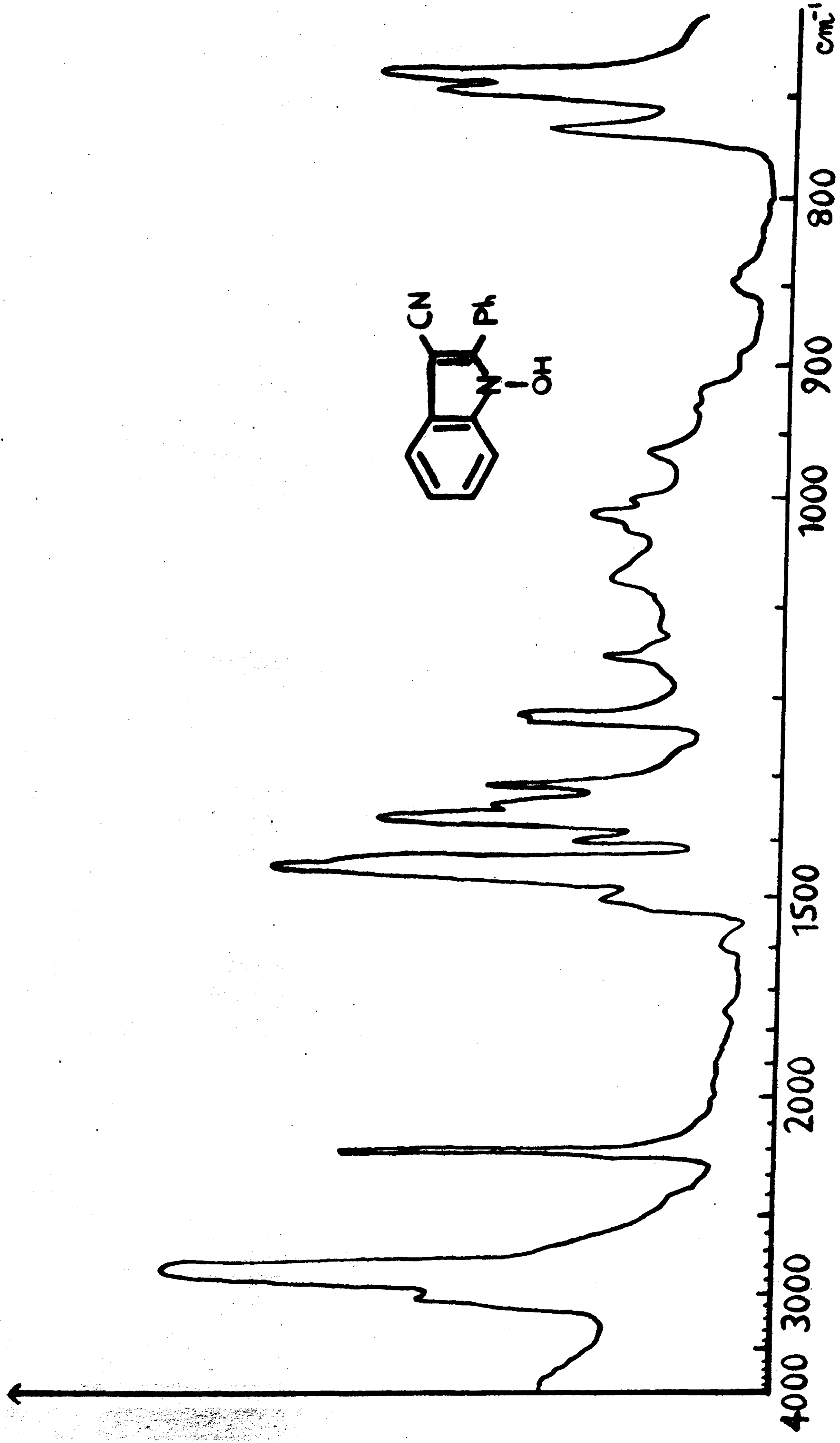
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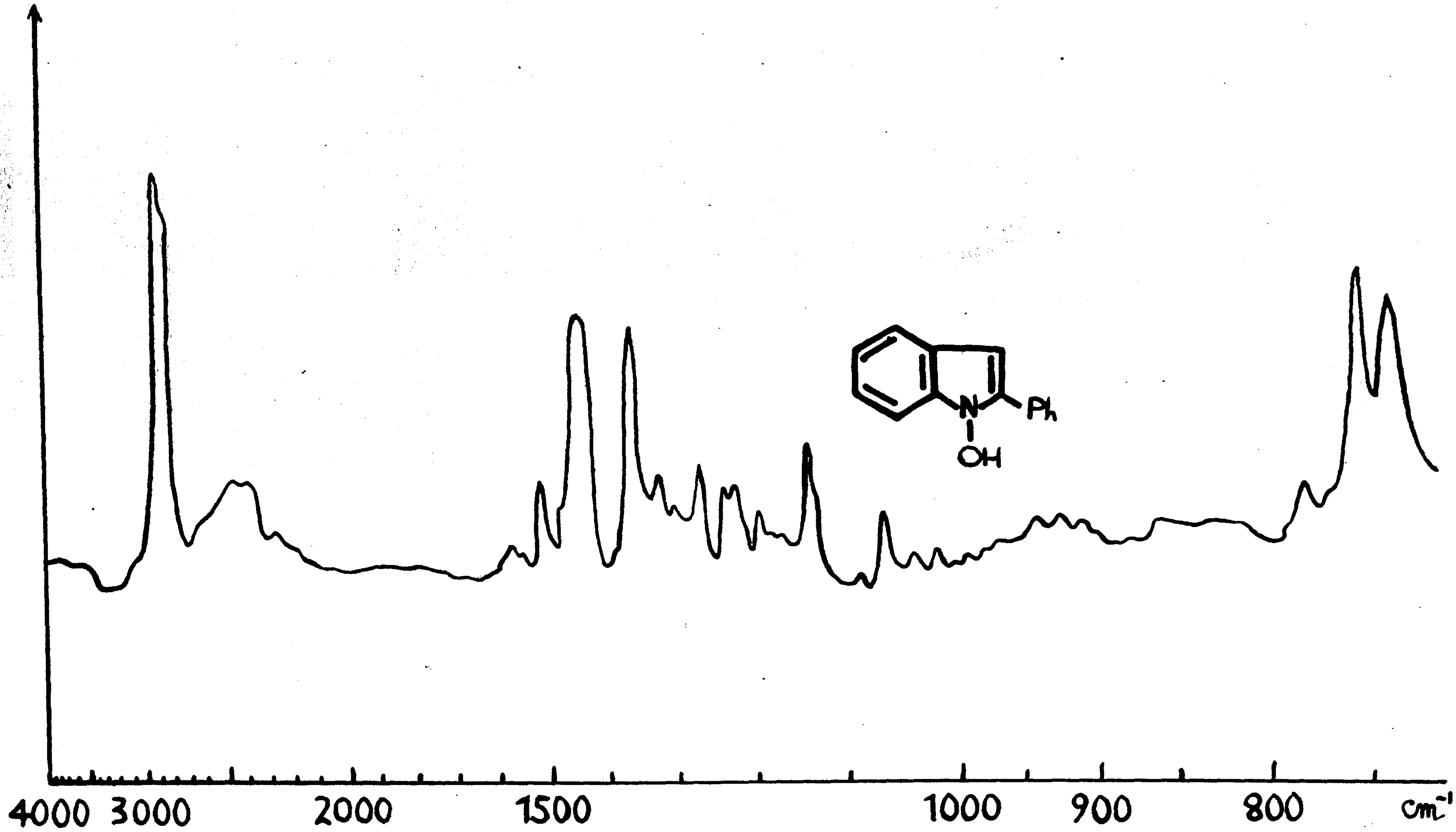
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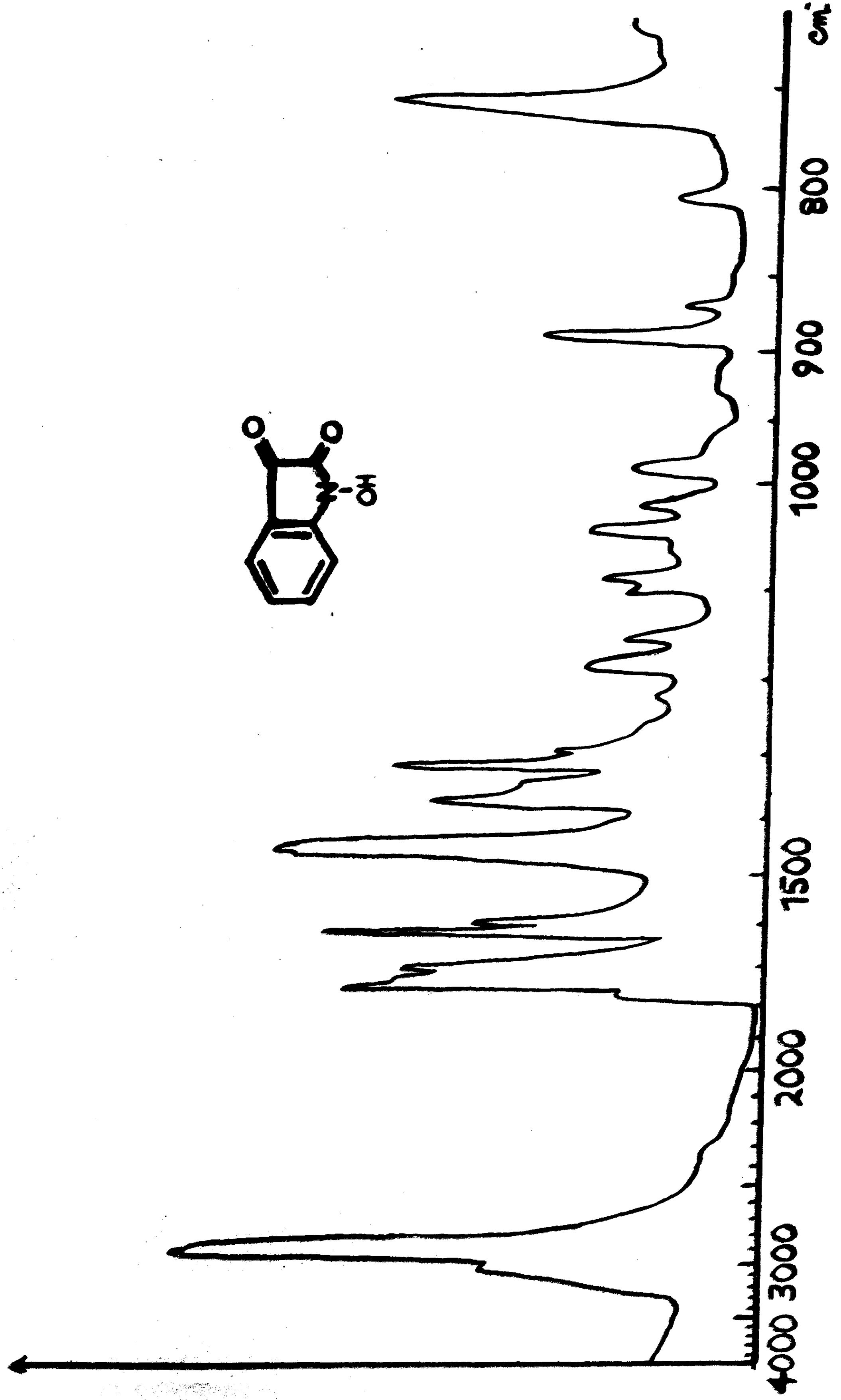
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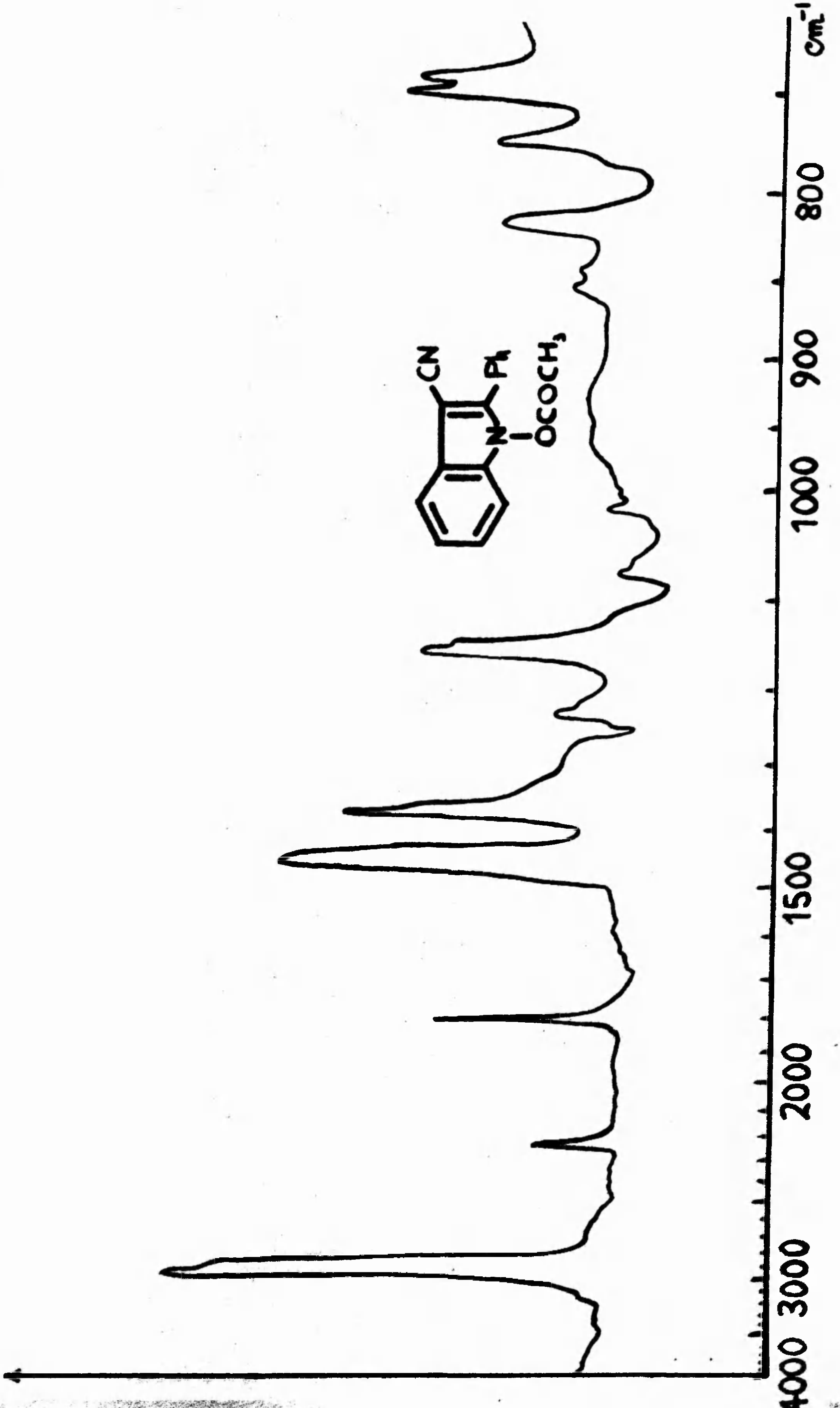
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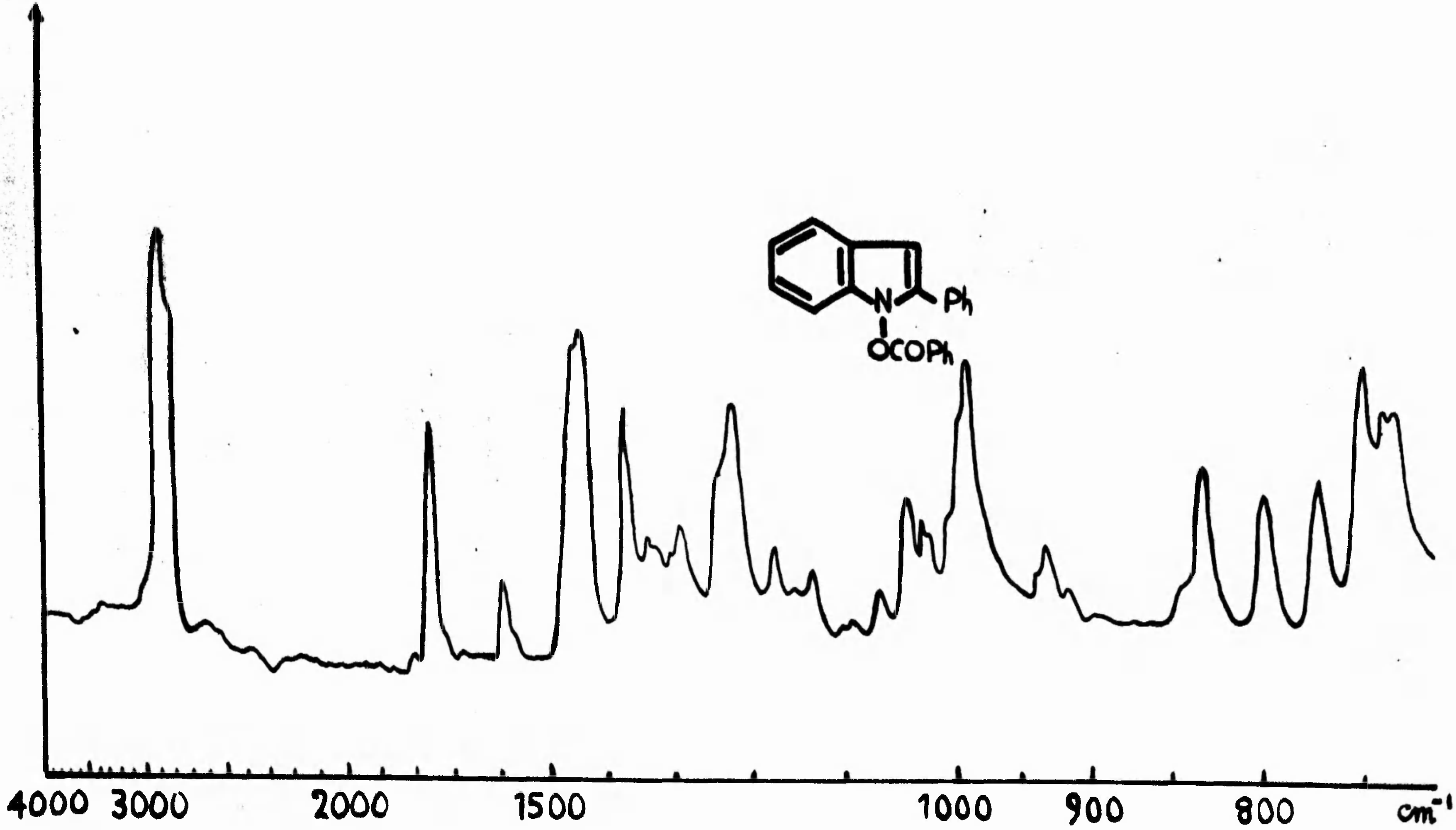
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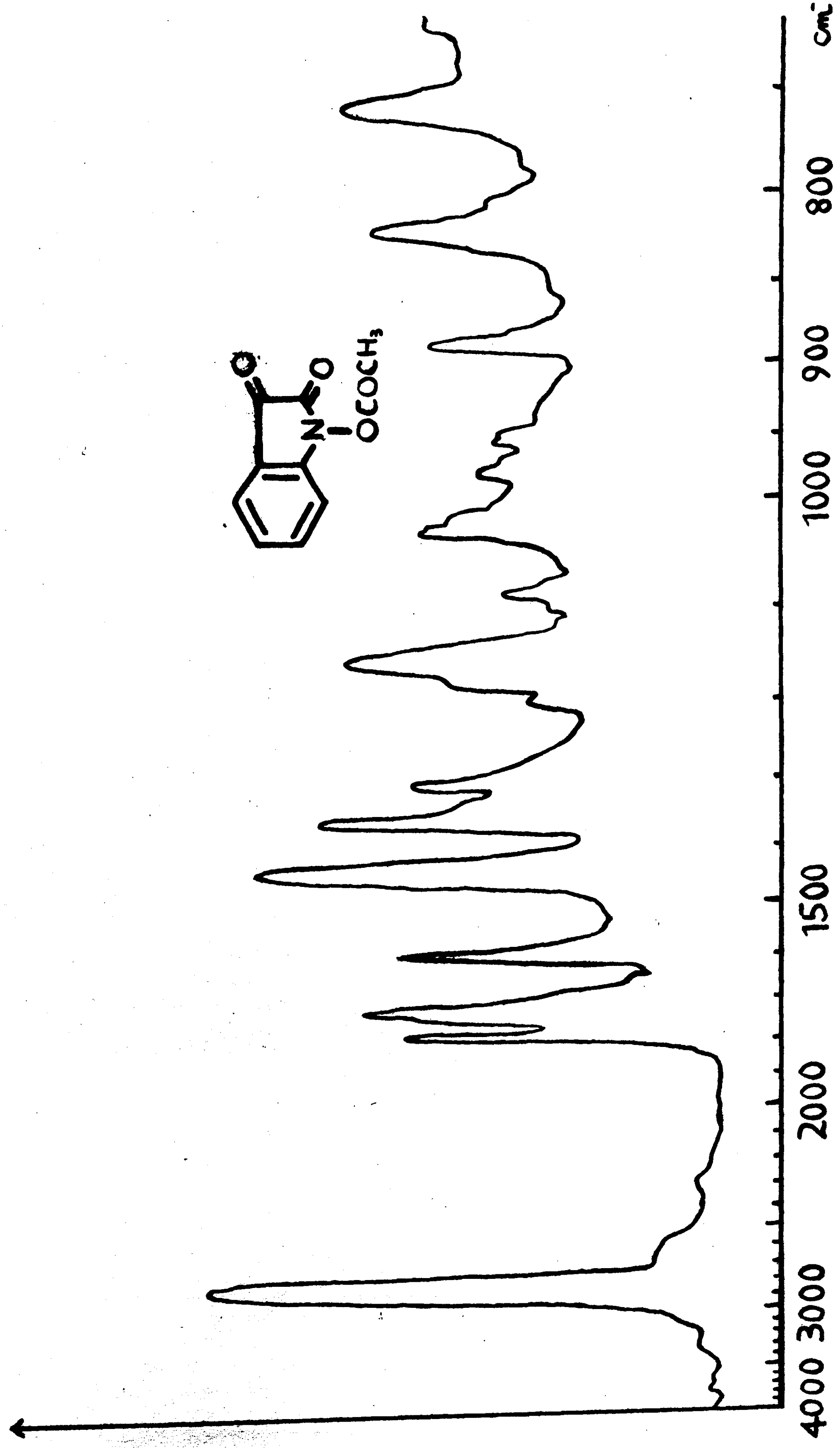

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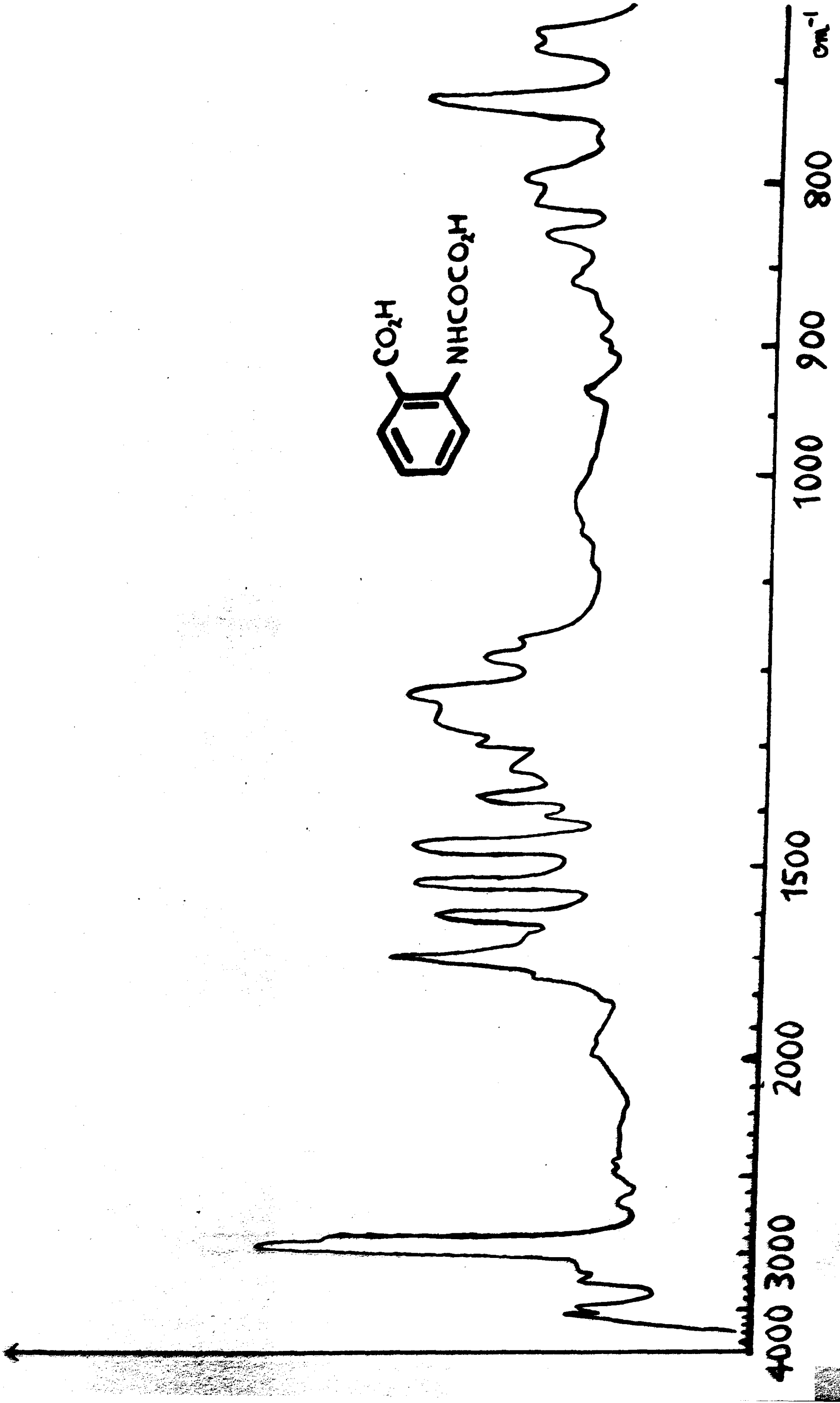
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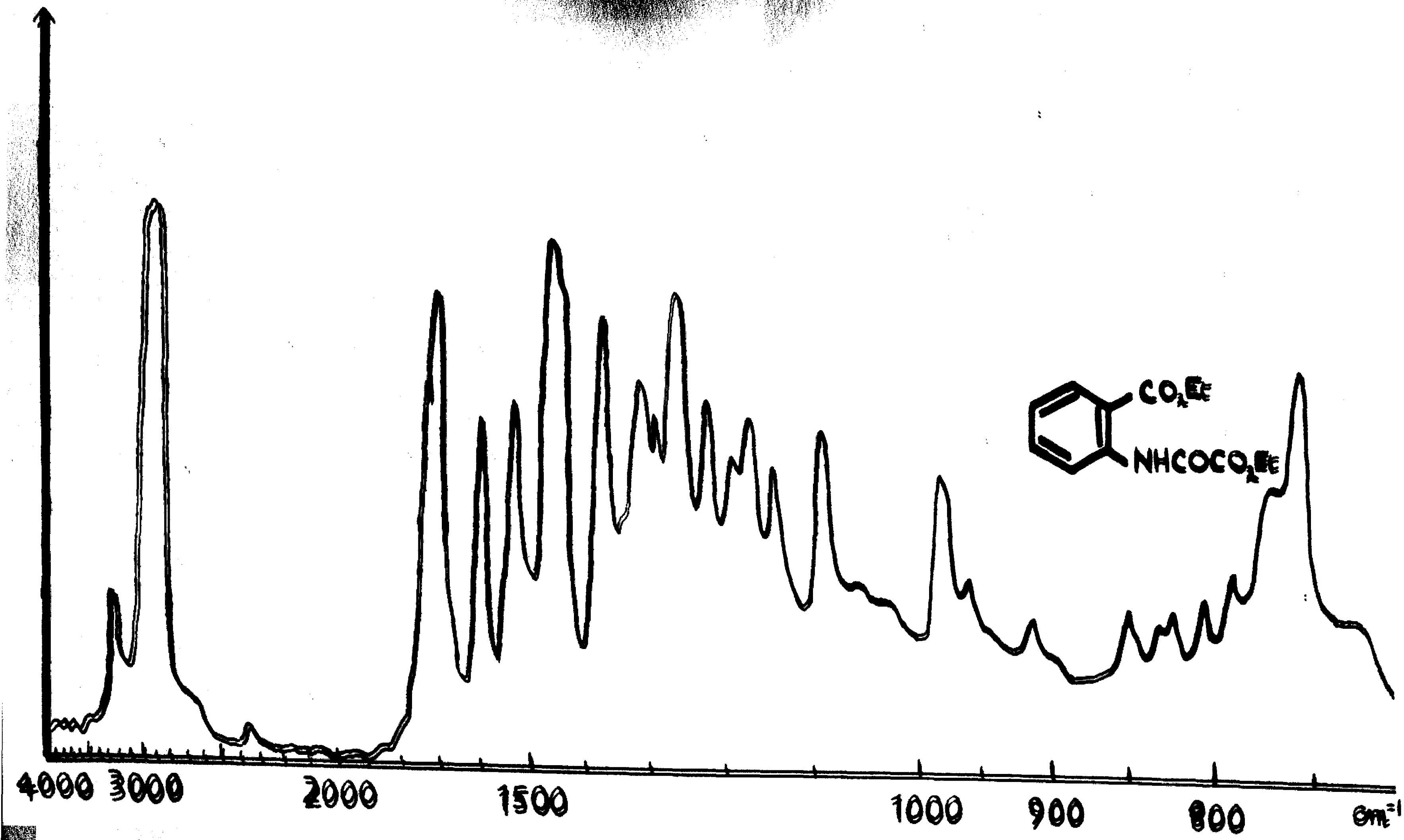
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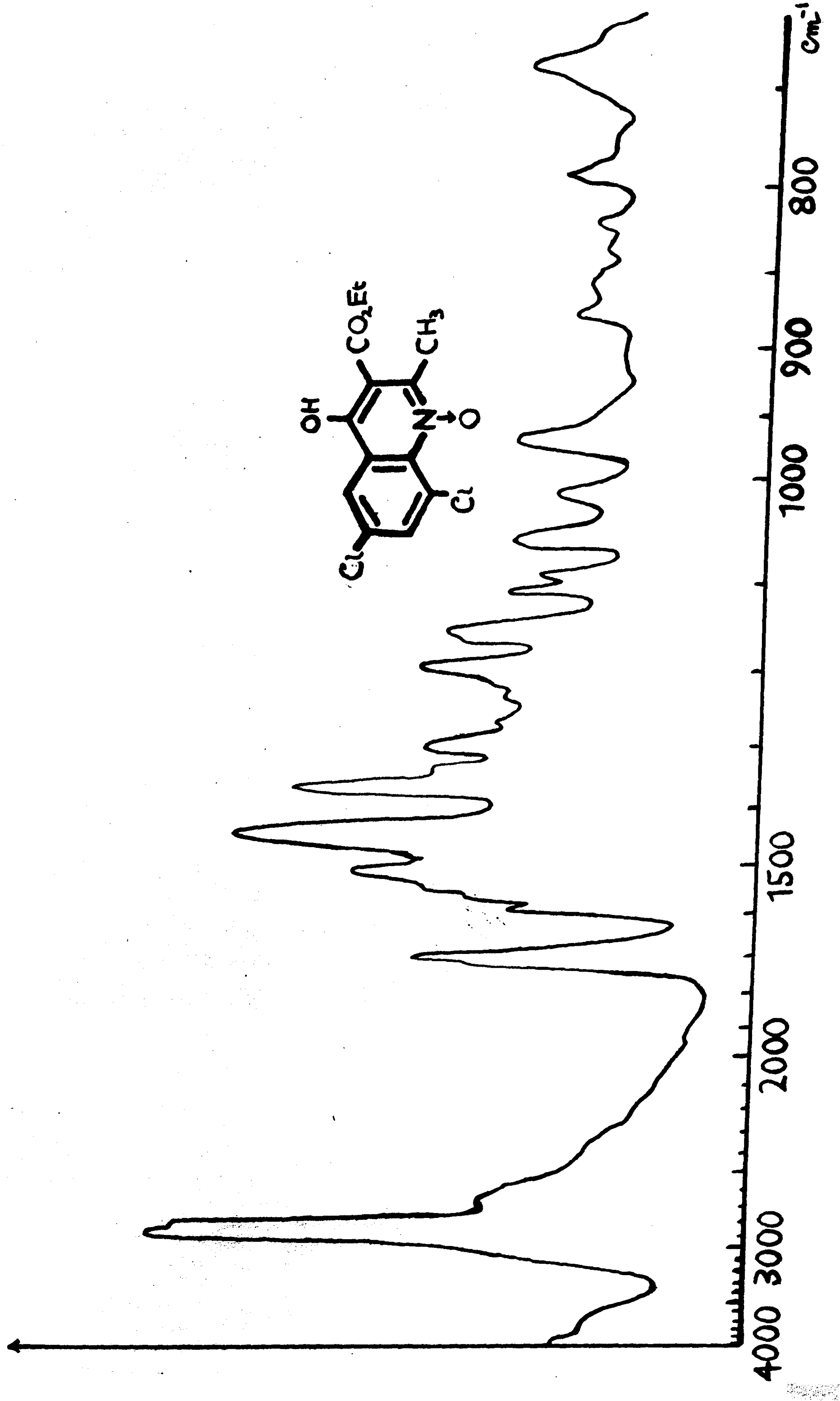
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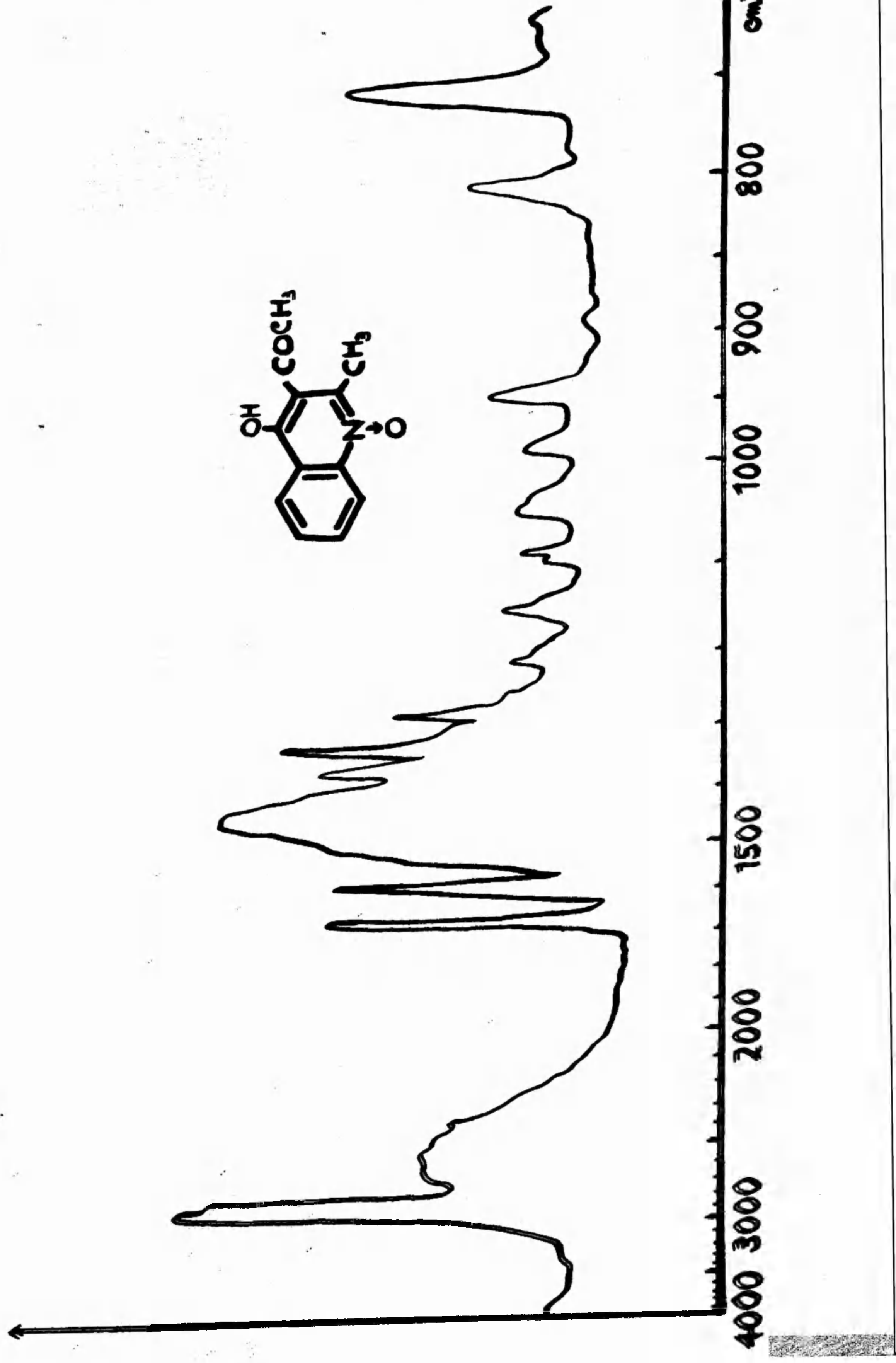
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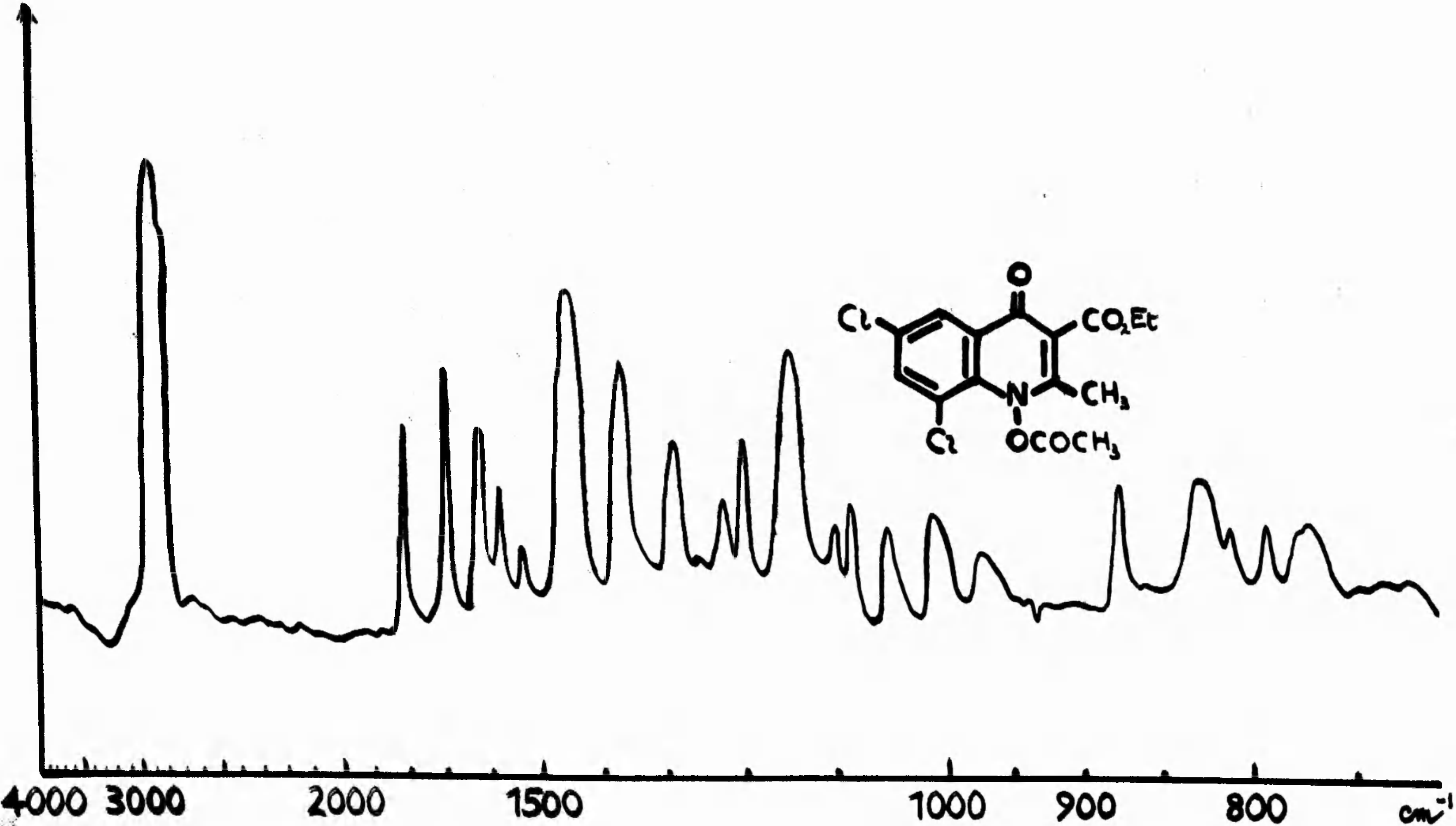
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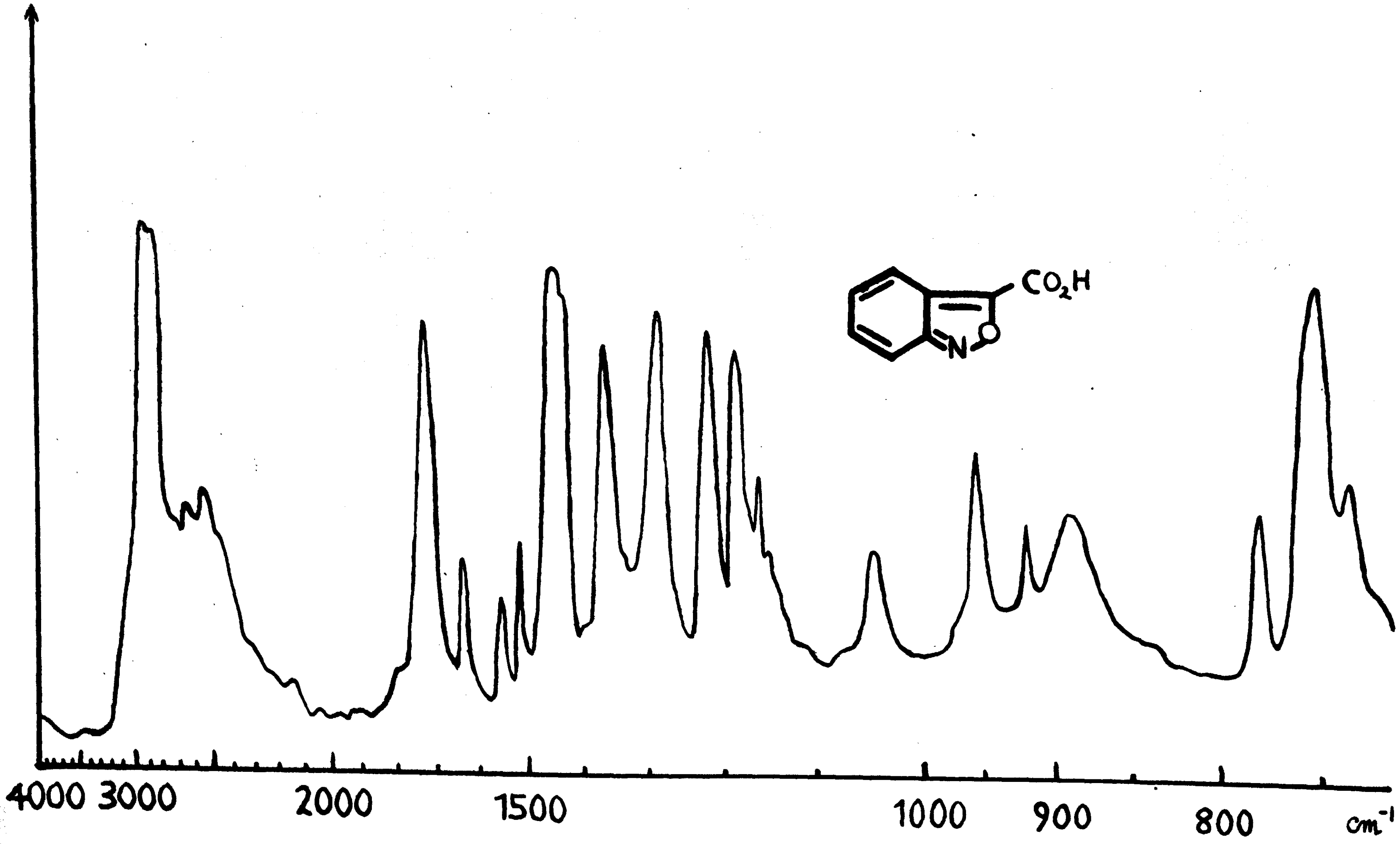
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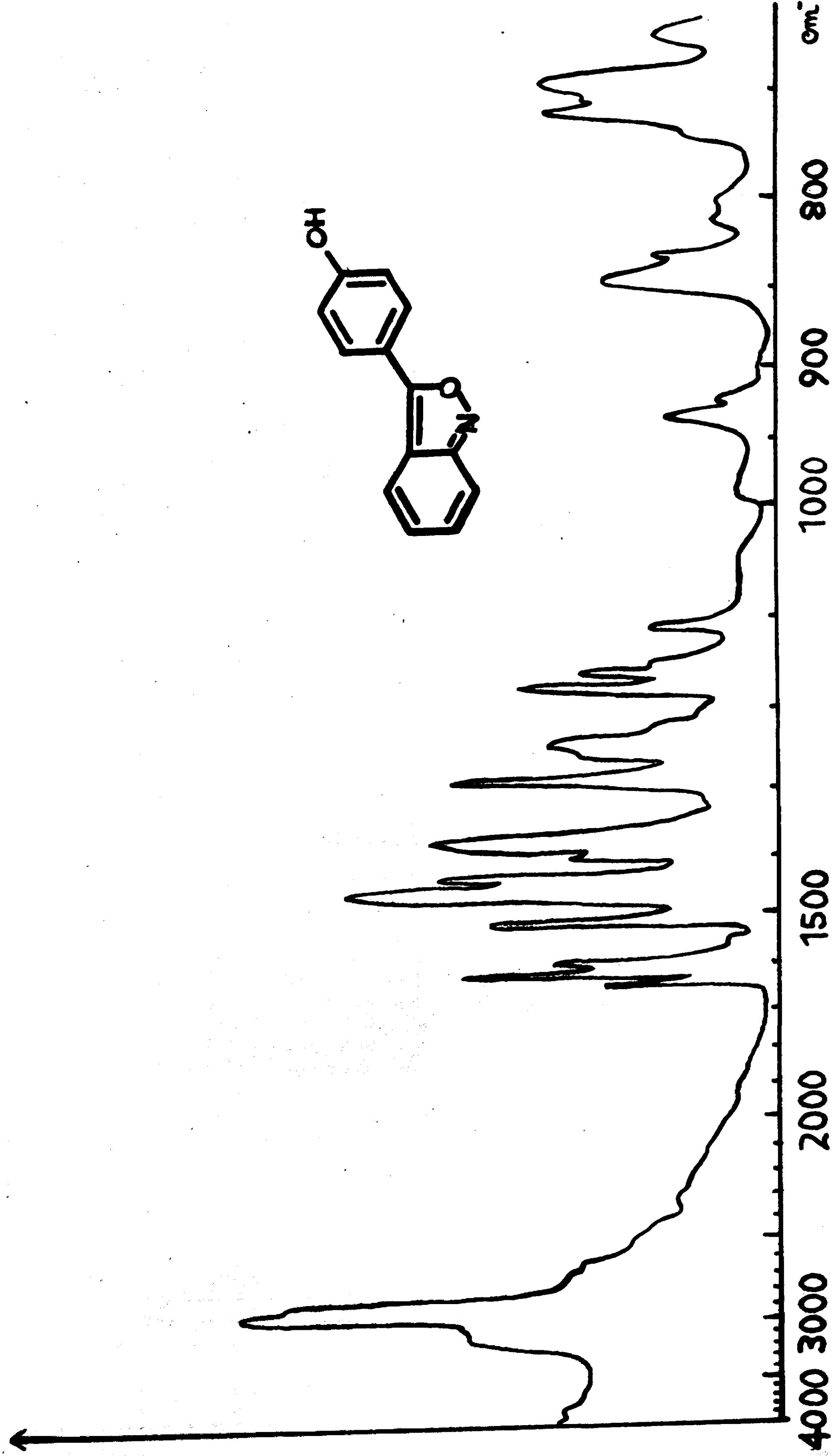
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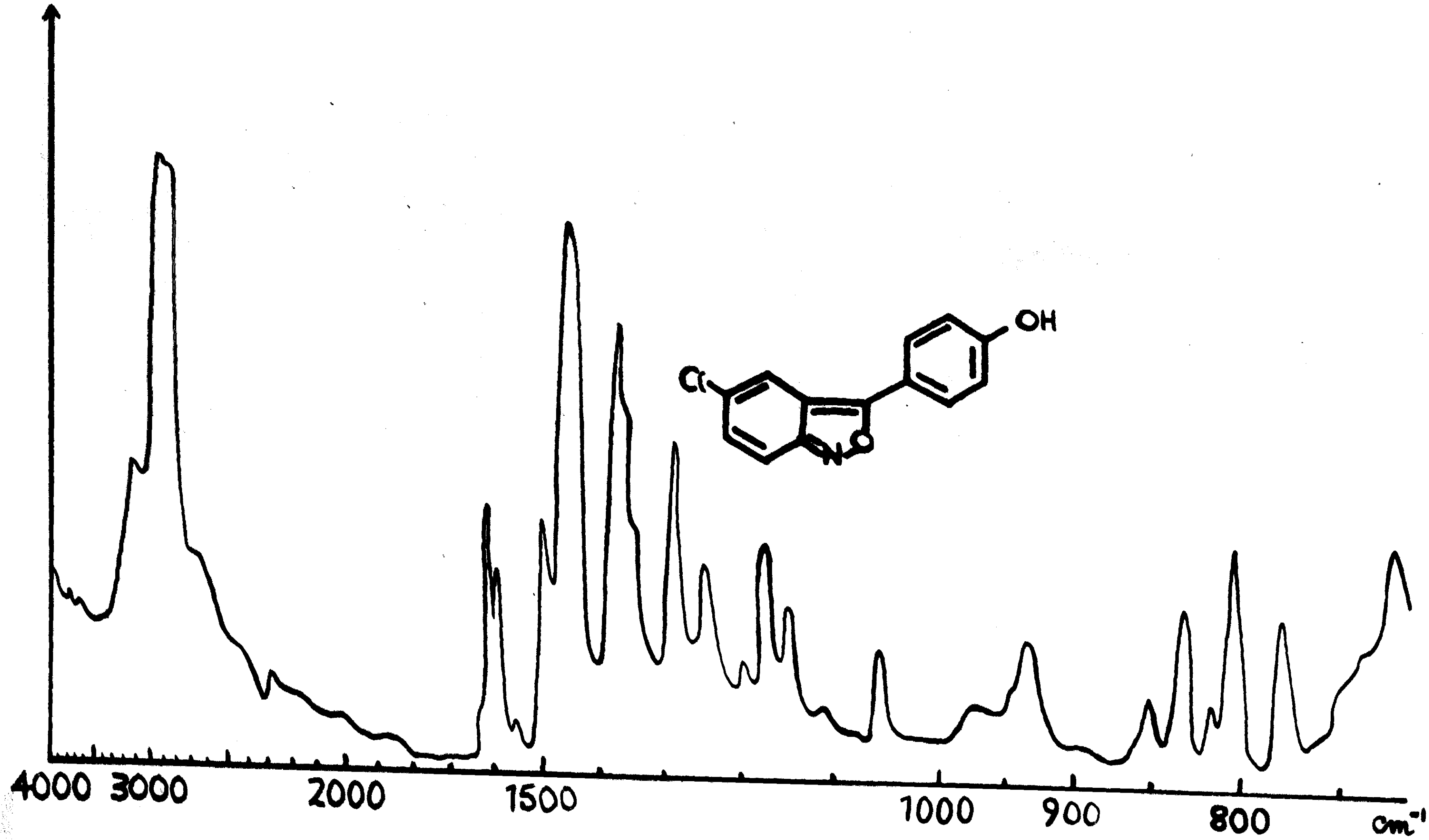
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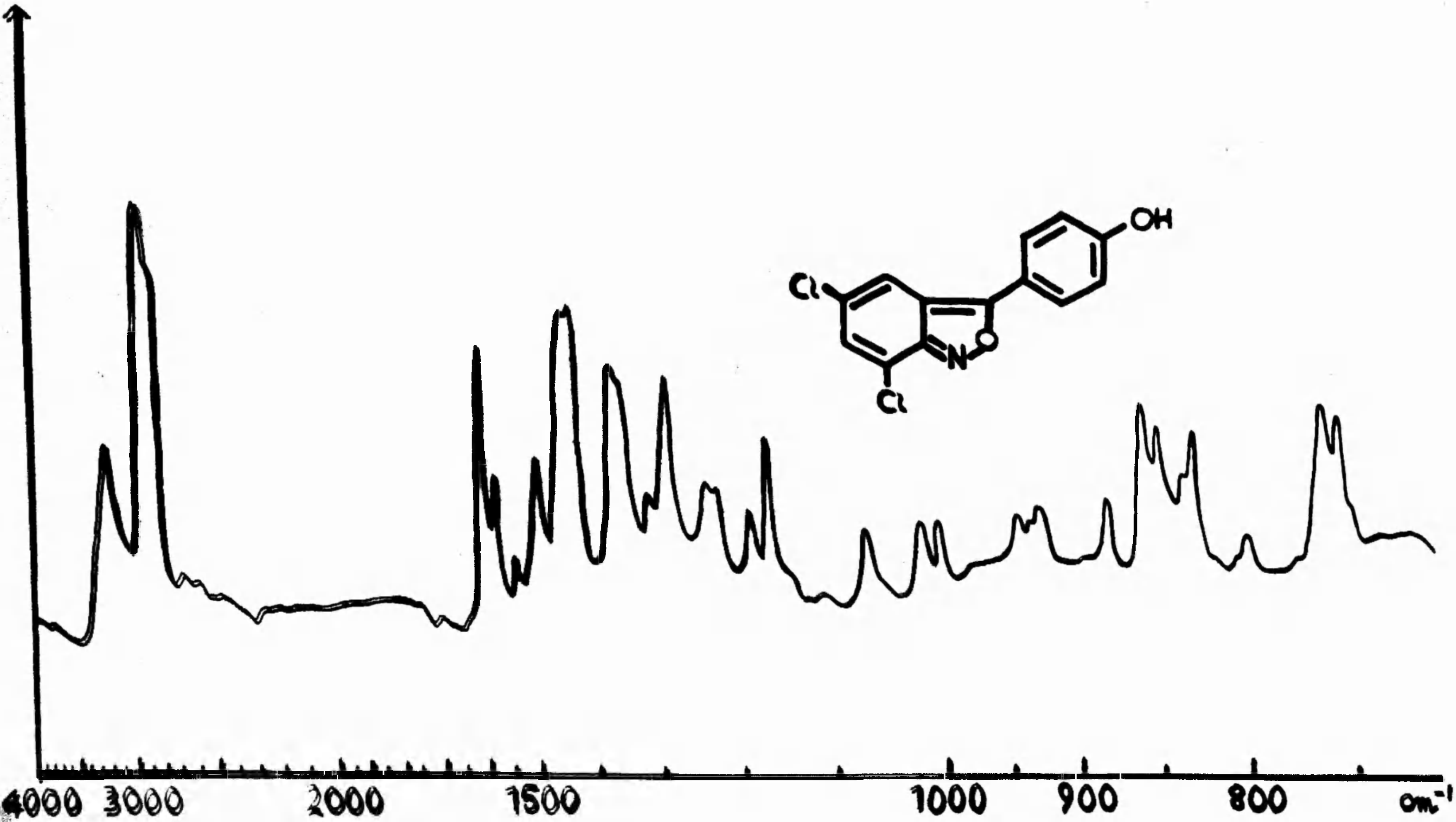
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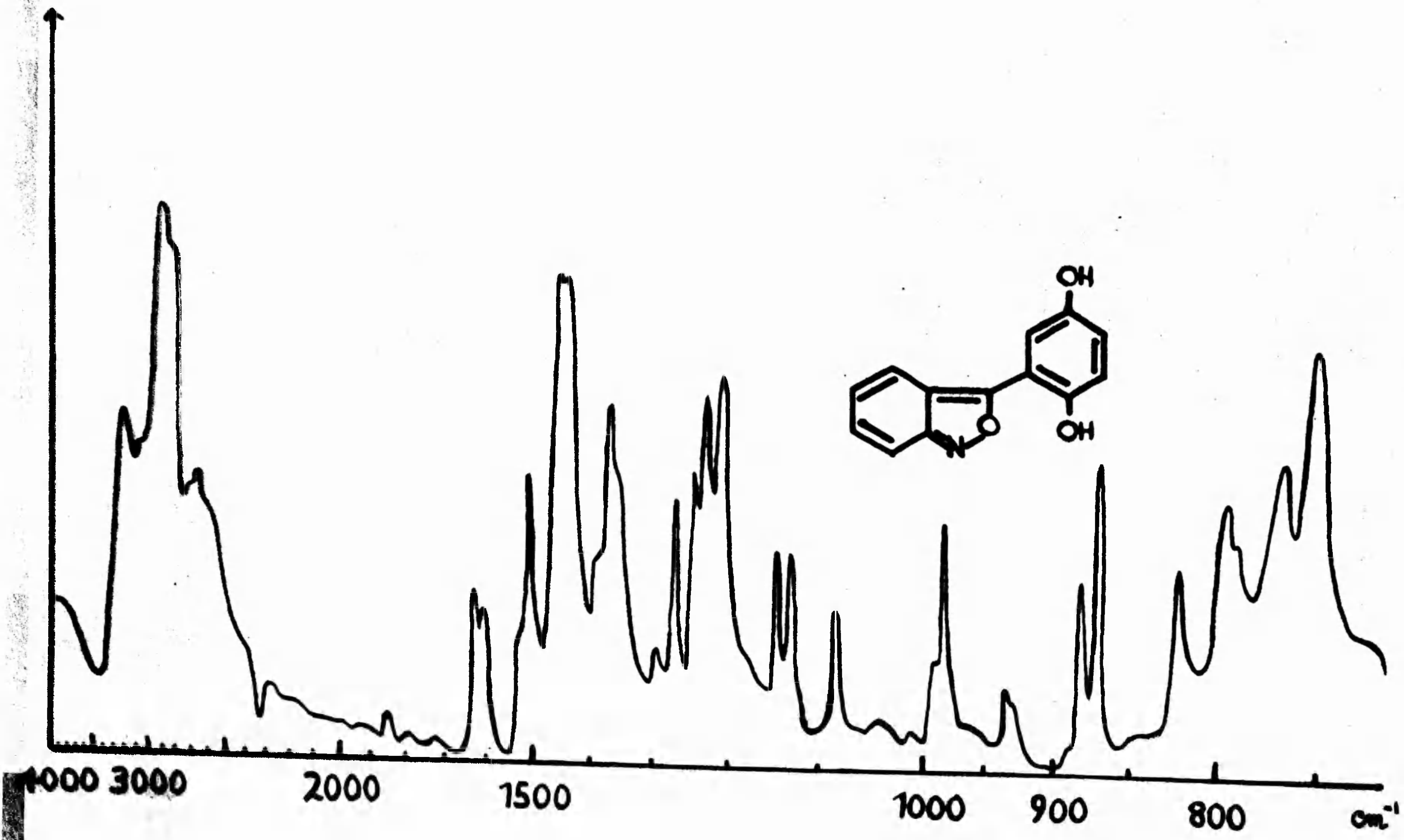

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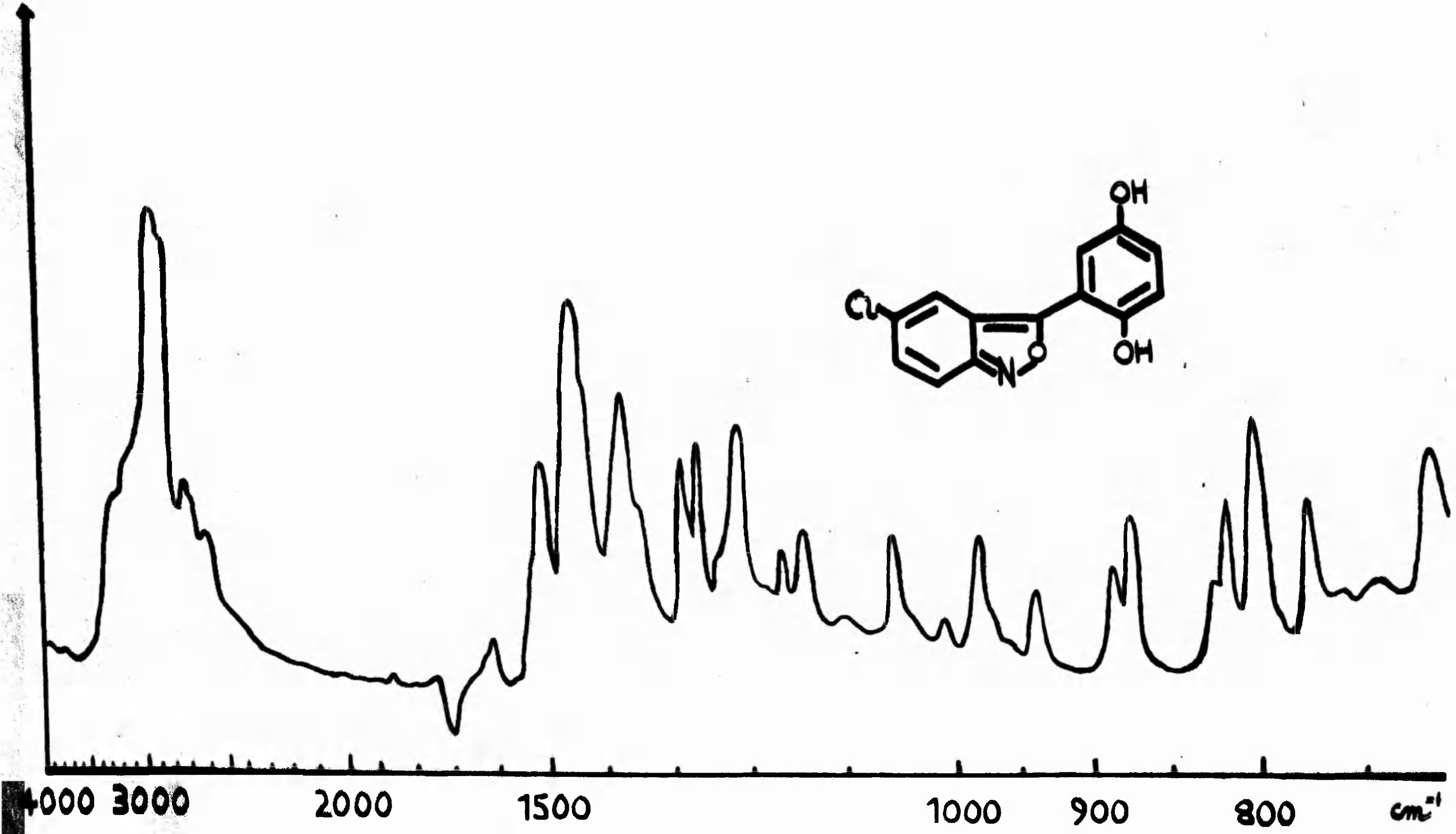
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