SUBSTITUENT INTERACTIONS IN ORTHO-SUBSTITUTED NITROBENZENES

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J. P. CAIRNS, B.Sc.

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CONTENTS

CHAPTER 1

BASE-CATALYSED CYCLISATIONS

INTRODUCTION

Examples of the preparation of benzo-heterocycles by base-catalysed aldol-like condensations between a nitro-group and a carbanion in an ortho-side-chain are widely dispersed in the literature. An attempt will now be made to group some of these reactions into sets, within each of which it seems likely that a common mechanism might operate. It is obvious, however, that for many specific compounds it is impossible to define the precise mechanism with any certainty.

When the nitro-group and side-chain cannot influence each other through the aromatic ring because of the absence of an α-hydrogen, their interaction must occur across space. A generalised form for a reaction of this type is shown in the scheme (1) → (2). The mode of further reaction of the isatogen product (2) is dependent on the nature of the group R. When R = Cl, hydroxyl ion can effect a substitution leading to 1-hydroxyisatin (3), while if R is a carbonyl function, e.g. $CO \cdot CH_3$, CO_2Et, attack by hydroxyl ion on the intermediate (4; R=Me, OEt) can produce isatin (5). Several examples of this type of reaction are known.

In the conversion of ω-chloro-2-nitroacetophenone

(1; R=Cl) into anthranil-3-carboxylic acid (6) by aqueous ethanolic sodium hydroxide,[1] a possible intermediate is 1-hydroxyisatin (3) which is known to rearrange to the acid (6) under basic conditions.[2] A similar reaction under comparable conditions is involved in the formation of isatin (5) from o-nitrobenzoylacetone (1; R=CO·CH_3). A possible intermediate in this case is 2-acetylisatogen (2; R=CO·CH_3), since ethyl isatogen-2-carboxylate (2; R=CO_2Et) is readily converted into isatin by dilute sodium carbonate.[3] Baeyer obtained isatin[4] by the action of dilute alkali on 2-nitrophenylpropiolic acid (7) possibly *via* 2-nitrobenzoylacetic acid (1; R=CO_2H) and isatogen-2-carboxylic acid (2; R=CO_2H).[5]

Other examples of the base-catalysed condensation of a carbanion with an unmodified nitro-group seem to be provided in the reaction of various derivatives of biphenyl (8) to give phenanthridine N-oxides (9).[6,7] The necessity for sufficient activation of the methylene hydrogens is emphasised by the fact that whereas the compounds (8; R=CN, CO_2Me, $CONH_2$) were successfully cyclised to the corresponding phenanthridine N-oxides (9; R=CN, CO_2Me, CO·NH_2), no reaction occurred with the derivatives (8; R=H, OH, Br, CO_2H, Ph).

It is also possible that an unmodified nitro-group is

involved in the reaction (10) $\longrightarrow$(11), where the α-hydrogens of the side-chain are subject to activation only by the nitro-group, whereas formation of a carbanion at the β-carbon of the side-chain is promoted by the two activating groups, R and R'.

Reissert[8] obtained 1-hydroxyindole-2-carboxylic acid (11; R=CO_2H) by base-catalysed cyclisation of 2-nitrobenzylmalonic acid (10; R=R'=CO_2H), while Gabriel *et al.*[9] reported the formation of a mixture of 1-hydroxyindole-2-carboxylic acid (11; R=CO_2H) and its ethyl ester (11; R=CO_2Et) by treatment of ethyl 2-nitrobenzylacetoacetate (10; R=CO_2Et, R'=$CO\cdot CH_3$) with dilute alkali.

When the *ortho*-side-chain also contains a strongly activating group in the α-position, as in the compound (12), it seems reasonable to invoke an alternative mechanism which involves initial abstraction of the more acidic α-proton to give the intermediate *aci*-nitro-compound (13). Subsequent removal of the β-proton can then be followed by immediate condensation of the β-anion with the nitro-group to form the ring structure (14) which would be rapidly converted into the 1-hydroxyindole (15).

An alternative mode of reaction of the dianion formed from the intermediate (13) proceeds through the nitroso

compound (16), which is the net result of the alkali-promoted transfer of both acidic hydrogen atoms from the side-chain to the nitro-group in (12). The nitroso compound can then cyclise according to the scheme (16) ⟶ (17) ⟶ (15).

Many reactions which can be considered as involving an aci-nitro-intermediate have been reported. Diethyl (α-cyano-2-nitrobenzyl)-malonate (18; R=CN, R'=R"=CO_2Et, R'"=H) and diethyl (α-carbamoyl-2-nitrobenzyl)-malonate (18; R=$CONH_2$, R'=R"=CO_2Et, R'"=H) are cyclised by sodium carbonate solution to the 1-hydroxyindoles (19; R=CO_2Et, R'=CN, R"=H) and (19; R=CO_2Et, R'=$CO\cdot NH_2$, R"=H) respectively.[10] Treatment of the nitrile (18; R=CN, R'=Ph, R"=H, R'"=OMe) with aqueous ethanolic potassium hydroxide gives the 1-hydroxyindole (19; R=Ph, R'=CN, R"=OMe).[11]

Where the α-substituent is a hydroxyl group, the reaction can take a different course. Kröhnke[12] effected a synthesis of 2-phenylisatogen (2; R=Ph) by heating the pyridinium salt (20) in sodium carbonate solution. The presumed intermediate (21) might undergo dehydration to the N-hydroxy compound (22) which would give the isatogen by elimination of pyridine. A reaction which might be considered as proceeding by a similar path is the rapid

transformation, in aqueous ethanolic alkali, of α-phenyl-2-nitrocinnamonitrile (23) into N-benzoylanthranilic acid (24).[13] Here the proposed intermediate (25), formed in a similar manner to the analogous intermediate (22) but lacking such a good leaving group, is attacked by hydroxyl ion at the carbonyl group, and the ring is opened to form the azomethine (26) which is readily converted into the product (24) by base.[14]

Reactions are also known involving condensation of a nitro-group with an amino- or substituted amino-group in an ortho-side-chain.

Treatment of o-nitrophenylhydrazine (27; R=R'=H) with aqueous ammonia rapidly gave the 1-hydroxybenzotriazole (28; R=R'=H),[15] while the triazole (28; R=Me, R'=NO_2) was prepared by treatment of 3,5-dinitro-o-cresol-methyl ether with hydrazine hydrate,[16] the hydrazine (27; R=Me, R'=NO_2) being the presumed intermediate.

2-Phenyl-3-cyanoindazole 1-oxide (29; R=Ph, R'=CN, R"=R"'=H)[17] was obtained by cyclisation of α-anilino-2-nitrobenzyl cyanide (30) with aqueous sodium carbonate, and alcoholic sodium carbonate was used by Secareanu and Lupas[18] to convert 2,4,6-trinitrobenzylideneaniline (31; R=R'=NO_2) into 3-hydroxy-4,6-dinitro-2-phenylindazole

1-oxide (29; R=Ph, R'=OH, R"=R'"=NO_2). The same authors[19] obtained a mixture of the indazole (29; R=Ph, R'=OH, R"=H, R'"=NO_2, N-H for N-O) and its 1-oxide by longer treatment of 2,4-dinitrobenzylideneaniline (31; R=H, R'=NO_2) with the same reagent, the indazole being formed by reduction of the oxide in the basic medium, while 2-nitrobenzylidene aniline itself (31; R=R'=H) failed to cyclise under comparable conditions.

The presence of an activated α-hydrogen in the reactant molecule is a feature common to the successful cyclisations involving a side-chain nitrogen mentioned above, the activation being provided by the substituted phenyl nucleus and the presence of electronegative side-chain substituents. Since the formation of a N-N bond can be effected by mild base, it seems likely that the side-chain nitrogen uses its lone pair electrons for condensation with the nitro-group. Hence the more basic the side-chain nitrogen, the more readily the reaction would be expected to occur.

The reaction of the benzylidene compounds (31) presumably proceeds by addition of water to the carbon nitrogen double bond to give the intermediate (32). This can then cyclise to the unstable conjugate acid (33) which

would quickly lose a proton to give the intermediate (34). Ring-opening of this compound can occur (35) leading to regeneration of the benzylidene compound (31), or the α-hydrogen can be removed by base (36) resulting in formation of the product (37).

For the product to be formed, it is thus necessary that process (36) should be faster than the alternative (35). Reaction path (36) would be favoured by increased activation of the α-hydrogen, and in the reaction with sodium carbonate it would appear that the presence of at least one additional nitro-group in the ring (36; R=H, R'=NO_2) is necessary to provide sufficient activation of the α-hydrogen for the reaction to go to completion. Where a more powerful side-chain activating group is present, as when CN replaces OH in (32; R=R'=H) to give (30), the reaction can be carried out in sodium carbonate solution in the absence of additional nitro-groups.

An example of a direct condensation between a primary aromatic amino-group and a nitro-group is provided by the conversion of 2-amino-2'-nitrobiphenyl (38) into benzocinnoline 1-oxide (39) by methanolic sodium hydroxide.[7]

SECTION I

In the course of previous work in this department,[10] the adduct (40) from hydrogen cyanide and diethyl 2-nitrobenzylidenemalonate was converted, in an alkaline medium, into the 1-hydroxy-2-quinolone (41) or the 1-hydroxyindole (42), depending on the conditions used. The formation of the 1-hydroxyindole is an example of the type of reaction mentioned in the Introduction, but the hydroxyquinolone was a novel type of product which could only arise by external reduction.

The mechanism of formation of the hydroxyquinolone could involve the nitroso-intermediate (43), which might cyclise to the hydroxyindole (42) as represented for the analogous intermediate (16). However the nitroso-group could also undergo reduction to the hydroxylamine which would rapidly cyclise to the hydroxyquinolone (41). It can be seen[10] that when the reaction was carried out using strongly reducing conditions (potassium cyanide or potassium hydroxide in aqueous ethanol), the quinolone (41) was the main product, while when the medium had little or no reducing action (aqueous ethanolic sodium carbonate or aqueous sodium hydroxide) only the indole (42) was produced.

There is another possible course for the reaction (40)⟶(41) involving direct reduction to the hydroxylamine and proceeding *via* the 3,4-dihydro-derivative of the quinolone (41). In order to explore the situation further, the adduct (40) was treated with zinc dust in cold ammonium chloride solution, conditions which had been reported by Todd and his co-workers[20] as being of general utility in the reduction of *δ*-nitro-carbonyl compounds to 1-pyrroline 1-oxides, e.g. (44). It has now been shown that such a reduction of the adduct (40) yields the decyano-quinolone (41; H for CN).

While this result, because of the difference in the operating conditions, does not provide final proof, it certainly suggests that in the strongly alkaline medium the decyano-quinolone (41; H for CN) would have been the final product if the reaction had followed this course. Hence it supplies support for the view that the nitroso-compound (43) is an intermediate.

It was also of interest to discover whether a 3,4-dihydro-1-hydroxy-2-quinolone would aromatise under the reaction conditions. To this end, the available nitro-ester (45) was subjected to similar reduction conditions, but the product in this case, the dihydro-

carbostyril (46), indicated that further reduction of the hydroxylamino-group had been preferred to condensation with the ethoxycarbonyl group.

The intermediate amino-ester (45; NH_2 for NO_2) was isolated in this reaction. The given structure was assigned on the basis of infra-red evidence, $\nu_{max.}$ 3300, 3250, 3150 (NH_2), 1710 (CO_2Me) $cm.^{-1}$, and from the fact that it could be diazotised and coupled to alkaline β-naphthol with the formation of a red dye. The amino-intermediate was cyclised to the product (46) in the course of the work-up.

The dihydrocarbostyril (46) had bands in the infra-red at 3120 (sh.) (NH), 1675 and 1630 (CO·NH) $cm.^{-1}$, and had a melting point of 238°, similar to that reported by Perkin[21] (235°).

SECTION II

In 1943, Zaki and Iskander[22] prepared ethyl α-2,4-dinitrophenyl-γ-phenylacetoacetate (47) as an intermediate for the preparation of 2,4-dinitrodibenzyl ketone (48). They reported that the ester was resinified by concentrated sulphuric acid, and was unchanged by dilute mineral acids.

Treatment with dilute alkali was claimed to give the dihydroxynaphthalene (49; R=H), while alcoholic sodium ethoxide was alleged to convert the ester into the monoethyl ether (49; R=Et). Further it was stated that the ether gave the dihydroxy-compound (49; R=H) on being boiled with dilute alkali.

It seemed much more likely that the product obtained by ethoxide treatment of the ester was actually the quinoline 1-oxide (50; R=Et), formed by base-catalysed cyclodehydration between the ortho-nitro-group and the active methylene in the side-chain. This compound would be readily hydrolysed to the acid (50; R=H) by dilute alkali.

It was decided therefore to reinvestigate the action of alkali on the ester (47), which had been synthesised by the action of ethyl γ-phenylacetoacetate (sodio-

derivative) on 1-chloro-2,4-dinitrobenzene in absolute alcohol. This method of synthesis gave a poor yield of product, and an alternative procedure, which entailed forming the sodium salt of the ester in ethereal solution and adding the halobenzene in ether, was preferred. The β-keto-ester (47) showed strong bands in the infra-red at 1665 (br.) (chelated ester carbonyl), 1520 and 1350 (nitro) $cm.^{-1}$.

The ester was heated in ethanolic sodium ethoxide to give a product whose melting point corresponded to that quoted for the alleged naphthalene (49; R=Et). An improvement in yield was obtained by reducing the reaction time from 4 hours to 30 minutes. The infra-red spectrum of the product is quite inconsistent with the structure (49; R=Et) but is in accord with the salicylic ester type of compound (50; R=Et). The spectrum showed bands at 1645 (chelated ester carbonyl), 1495 and 1350 (nitro) $cm.^{-1}$

The carboxylic acid (50; R=H) was obtained by the action of dilute sodium hydroxide on either the ester (50, R=Et) or the starting-ester (47). This acid, unlike the ester (50; R=Et), was soluble in sodium bicarbonate solution. The infra-red spectrum showed the expected changes on going from the ester to the acid, namely the

appearance of broad absorption in the region 2,200-3,000 (hydrogen bonded OH) cm.$^{-1}$ and of a broad salicylic acid carbonyl band at 1650 cm.$^{-1}$

The acid was not purified, and the crude compound melted at 280-285° and resolidified to melt finally at 305-310°. This behaviour was suggestive of a decarboxylation taking place, and this interpretation was confirmed by heating the acid in nitrobenzene and ascertaining that the product, presumably (50; H for CO_2R), showed no carbonyl frequency in the infra-red.

Since these last two compounds could not be satisfactorily purified by crystallisation, it was decided to reduce the N-oxide grouping in (50; R=Et) in the hope of obtaining degradation products which could be crystallised more easily. The N-oxide was dissolved in a solution of triethylphosphite in diethyleneglycol diethyl ether and left at room temperature for 75 hours. This method has been used for the deoxygenation of pyridine and 4-nitropyridine N-oxide, though the latter reaction proceeded very slowly.[23] In the present case, the organic material was contaminated with phosphorous compounds which were presumably covalently bound to the organic material since the total product was soluble in ether and cold benzene.

Treatment of the N-oxide with phosphorous trichloride in dry chloroform at 0°, the method employed by Essery and Schofield[24] for the deoxygenation of 4-nitropyridine N-oxides, gave largely recovery of starting material.

Although the work presented in this section is incomplete, on the grounds of the chemical evidence and of the infra-red spectra, there is reason to question Zaki and Iskander's interpretation of these reactions, and to infer that the reaction products were in fact the quinoline-ester (50; R=Et) and the corresponding acid (50; R=H).

The ketone (48) was obtained using less drastic acid conditions than those employed by Zaki and Iskander in their unsuccessful attempts to prepare this compound. The infra-red spectrum contained bands at 1705 (ketone), 1520 and 1350 (nitro) $cm.^{-1}$, which were also present in the spectrum of 2,4-dinitrophenylacetone (51).

SECTION III

Arndt's[25] cyclisation of the o-nitrophenylurea-derivatives (52; X=NH, O, S) to benzotriazine 1-oxides (53; X=NH, O, S) with dilute sodium hydroxide suggested that analogous synthesis of the cinnoline ring system might be effected. Thus it was hoped to convert o-nitrophenylacetamide derivatives (54; X=NH, O) into cinnoline 1-oxides (55; X=NH, O), providing a new route to 3-hydroxy- and 3-amino-cinnolines.

The only known cyclisation procedure for the synthesis of 3-hydroxycinnoline (56; R=H) was devised by Neber and Bossel[26] who, after diazotisation and reduction of o-aminomandelic acid (57), cyclised the o-hydrazino-mandelic acid so formed in boiling acid solution. This method was extended by Alford and Schofield[27] who converted o-nitromandelic acid into 3-hydroxycinnoline in 60% yield, and also prepared the 6-chloro- and 6-hydroxy-analogues (56; R=Cl, OH). The same authors also obtained 3-hydroxy-cinnoline in good yield by reacting 3-bromocinnoline with sodium methoxide in undried methanol.[28] Using anhydrous conditions the expected 3-methoxy-compound was obtained.

3-Aminocinnoline was formed by reduction of the 3-nitro-compound,[29] and was produced when 3-bromo- or

3-chloro-cinnoline was reacted with ammonia under pressure in the presence of copper sulphate.[28]

All attempts to condense o-nitrophenylacetamide (54; X=O) to 3-hydroxycinnoline 1-oxide (55; X=OH) failed. As reported in the literature for sodium hydroxide,[7,30] potassium amide in liquid ammonia, sodium amide in benzene, and potassium ethoxide in ethanol did not cause cyclisation. Treatment of the amidine (54; X=NH) with alkali led only to recovery of carboxylic acid. Although identification of all the products of the above reactions was not carried out, their infra-red spectra lacked two strong bands present in the spectrum of the cyclised product, 3-hydroxycinnoline 1-oxide (55; X=O), namely $\sim$ 2,500 (bonded OH) and 1125 $cm.^{-1}$

As was mentioned in the Introduction, the basicity of the side-chain nitrogen would be expected to be an important factor in its condensation with a nitro-group. Since an amide nitrogen is very feebly basic, it was thought that an important role of the alkali in the cyclisation of the urea (52; X=O) was the formation of the anion (58). This should contain a more basic and hence a more reactive amino-group.

This concept suggested that a requisite for the

cyclisation of an amide nitrogen with a nitro-group was the presence of an active α-hydrogen. This is present in the urea (52; X=O) but is absent in the unreactive acetamide (54; X=O). To test this hypothesis, it was decided to examine the action of alkali on o-nitrophenylcyanoacetamide (62) which was prepared[30] by the reaction sequence (59) ⟶ (62).

The rearrangement of the o-nitrobenzenesulphonamide (61) was effected in dilute alkali. This process is related to the Smiles rearrangement,[31] which is a base-catalysed reaction of the general form (63) ⟶ (64), involving substitution of the group X at a positive carbon by a more reactive nucleophile Y. Thus 2-hydroxy-2'-nitrodiphenylsulphone (65) is converted into 2-nitro-2'-sulphinodiphenyl ether (66) by dilute alkali, the more powerful nucleophile ($-O^{(-)}$) displacing the sulphone group from the positive centre ortho to the nitro-group.

The reaction has been extended[32] to produce p-nitrophenylguanidines (67) by the rearrangement of compounds of the type (68) in dilute alkali, sulphur dioxide being lost under the reaction conditions. When the activating nitro-group was in the ortho-position (69), only the benzotriazine 1-oxide (53; X=NH) was isolated.

Nitrophenylacetamides (o- and p-) have been prepared in an analogous manner,[30] the p-nitrosulphonamides (70; R=CN, Ph) giving the corresponding acetamides (71; R=CN, Ph), while the sulphonamides (70; R=CO_2Et, $COCH_3$), on treatment with sodium carbonate, gave the acetamide (71; R=H), a product of further hydrolysis. The ortho-compound (72; R=$CO\cdot CH_3$) gave o-nitrophenylacetamide, but the sulphonamide (72; R=Ph) underwent a more deep-seated rearrangement, resulting in the formation of 3-phenyl-indazole (73).

In the abstract of the preparation of the chloro-compound (60), the acylation of the amide (59) was reported[30] as being carried out in alkaline solution, the product being obtained in 24% yield by neutralisation of the solution with acetic acid. In the present work, neutralisation gave only unchanged sulphonamide (59), further acidification with mineral acid being necessary to cause precipitation of the more acidic acylsulphon-amide product (60). Making allowance for recovered starting-material, a yield of 82% of pure product was obtained.

o-Nitrophenylcyanoacetamide (62), whose infra-red spectrum contained no nitrile band, was readily converted

by dilute alkali into a high-melting compound whose chemical behaviour, analysis, and infra-red spectrum are consistent with its formulation as 4-cyano-3-hydroxycinnoline 1-oxide (74). The infra-red spectrum of this strongly acidic compound lacked the bands due to the amide and nitro-groups characteristic of the acetamide (62), and contained new bands at 2,200 (m.) (ArCN) and 1135 cm.$^{-1}$ There was no carbonyl band present, and broad absorption in the 2400-3200 cm.$^{-1}$ region indicated the presence of a strongly hydrogen-bonded hydroxyl group. The product gave a pale wine colour with alcoholic ferric chloride.

The nitrile (74) was hydrolysed with 10% sodium hydroxide solution to the carboxylic acid (75) which gave a wine-red colour with alcoholic ferric chloride. The nature of the change was confirmed by the replacement of the nitrile frequency in the spectrum of (74) by an acid carbonyl frequency (1630 cm.$^{-1}$). The product (75) is an o-hydroxyaromatic acid, in which the carbonyl frequency is lowered by formation of strong hydrogen bonds. The acid (75) was also obtained in good yield by prolonged alkaline treatment of the sulphonamide (61).

Decarboxylation of the acid (75) in hot diphenyl ether gave 3-hydroxycinnoline 1-oxide (55; X=O), which

gave a pale wine colour in alcoholic ferric chloride and whose spectrum showed no carbonyl band but contained broad absorption centred at 2550 (m) $cm.^{-1}$ due to the hydrogen bonded hydroxyl group. The presence of a new band at 1000 (m) $cm.^{-1}$ was used to detect the presence of the decarboxylated compound (55; X=O) among the major product (75) of alkaline hydrolysis of the nitrile (74). The strong acidity of 3-hydroxycinnoline 1-oxide was shown by its solubility in sodium hydrogen carbonate solution.

While on the basis of infra-red evidence this compound seems to exist in the enol form in the solid state, the deoxygenated compound, 3-hydroxycinnoline (56; R=H), has been reported[33] as showing a strong carbonyl band at 1660 $cm.^{-1}$ and so seems to be largely in the amide form.

The N-oxide (55; X=O) was reduced with sodium dithionite in alkali to convert it into the known 3-hydroxycinnoline. Two reduction products were isolated, neither corresponding to the expected compound. Further reduction of 3-hydroxycinnoline would be expected to give 1,2-dihydro-3-hydroxycinnoline (76), and this reaction has been reported[26] as being effected with zinc and sulphuric acid. It has recently been shown,[34] however, that the structure of the reduction product was in fact

N-aminooxindole (77), it being postulated that the intermediate dihydro derivative (76) undergoes acid hydrolysis to the ion (78) which then recyclises to form a five-membered ring.

One product of reduction of the N-oxide (55; X=O) has been shown to be identical with an authentic specimen of N-aminooxindole (77), prepared by cyclisation of o-hydrazinophenylacetic acid.[34] This is consistent with the proposed structure (55; X=O) for the starting-material, being the expected result of further reduction of the primary product (56; R=H).

The second reduction product is thought to be the unrearranged dihydro compound (76). This compound melts at ~145° with gas evolution, and resolidifies to melt finally over a range with upper limit 198°. The melting point of 3-hydroxycinnoline[27] is 201-203°, and so it seems possible that the dihydro compound loses hydrogen on melting to form this aromatic product. In a small-scale dehydrogenation experiment, using 10% palladium-charcoal in boiling xylene, the dihydro compound was converted into a product of melting point 195-201° (crude), probably 3-hydroxycinnoline.

The infra-red spectrum of the dihydro compound showed

bands at 3200, 3140 (NH), 1640 (carbonyl) and 1125 (m) cm.$^{-1}$ Each of the compounds (74), (75), (55; X=O), and (76) has a band in the 1125-1135 cm.$^{-1}$ region which seems characteristic of the cinnoline nucleus. A chloroform-solution spectrum of the dihydro compound contained a band at 1675 cm.$^{-1}$, while the approximate model compound, β-acetylphenylhydrazine (79), had a carbonyl band at 1685 cm.$^{-1}$.[34]

When the dihydro compound was treated with benzoyl chloride in pyridine, a mixture of the mono- (80) and di-benzoyl (81) derivatives of the isomeric N-amino-oxindole was obtained. Baumgarten *et al.*[34] reported that only the monobenzoylated derivative was formed on similar treatment of N-aminooxindole itself, though earlier workers[35,36] had obtained both products.

Thus the dihydro compound must be rearranged during the course of the reaction. In pyridine alone, no re-arrangement occurred. This suggests that either the rearrangement is acid-catalysed, being induced by benzoic acid present in the benzoyl chloride used, or, less likely, that benzoylation precedes rearrangement.

The above evidence strongly suggests that the desired cyclisation of o-nitrophenylcyanoacetamide (62) to the

cinnoline 1-oxide (74) has been accomplished.

In order to test the generality of the above cyclisation, an acetamide (83) with a different activating α-substituent, Ar-SO_2, was synthesised from the chloro-compound (60) via the sulphonamide (82). As the rearrangement of the sulphonamide (82) to the acetamide (83) in aqueous alkali took place, the product separated from the alkaline solution.

While both the chloro-compound (60) and the cyano-compound (61) showed carbonyl absorption in the infra-red at 1750 $cm.^{-1}$, the carbonyl frequency of the sulphone (82) was lowered to 1710 $cm.^{-1}$ The spectrum of the acetamide (83) showed bands at 3390, 3175 (NH_2), 1685, 1660 ($CONH_2$), 1530, 1350 (NO_2), 1315 and 1145 ($-SO_2-$) $cm.^{-1}$

On being heated at 75° for 1 hour in 10% aqueous ethanolic alkali, the amide (83) was converted into the sulphone (85). This ready loss of an amide grouping has been observed before in β-sulphonyl carboxyamides, the sulphone (87), for example, being produced by boiling the amide (86) in 5% aqueous alkali for 2½ minutes.[37] The structure of the sulphone product (85) was confirmed by comparison with an authentic sample prepared by heating equimolar amounts of sodium p-toluenesulphinate and

o-nitrobenzyl chloride in alcohol.[38]

When the amide (83) was refluxed in alcoholic sodium hydroxide for 5 hours the product ran on a chromatoplate as at least 4 compounds. After similar treatment for 1 hour, the crude product was completely soluble in dilute alkali, and hence did not contain appreciable amounts of either the starting amide (83) or the sulphone (85). No pure compound could be isolated from this reaction. The amide (83) was recovered unchanged after being refluxed for 1½ hours with a suspension of sodium amide in toluene.

These results suggest that the labile sulphone molecule (83) was cyclised too slowly under the reaction conditions to prevent its decomposition.

An alternative source of activation of the α-hydrogens in a side-chain would be provided by the presence of additional nitro-groups in the aromatic ring. It would be interesting from this point of view to examine the effect of alkali on 2,4-dinitrophenylacetamide (88) in the hope of effecting a cyclisation to the 3-hydroxy-cinnoline 1-oxide (89).

Preparation of o-Nitrobenzaldehyde

For the work described in this thesis and for other allied work in this department, large amounts of o-nitrobenzaldehyde, a common starting-material, were required. The aldehyde was not then commercially available, and although subsequently it has again come on to the market, its price is still very high.

The method considered most suitable for large scale preparatory work involved the reaction of o-nitrobenzene-diazonium chloride with formaldoxime and hydrolysis of the resultant oxime.[45] On each of 10 runs yields of 30-42 g. (32-45%) were obtained, the product being sufficiently pure to be used without crystallisation.

[illegible] solution of potassium cyanide [illegible] g.) in water [illegible] and ethanol (200 ml.) there was added, with [illegible] g. dilute acetic acid (50 g. of solution containing [illegible] glacial acetic acid) and then finely powdered

EXPERIMENTAL

Infra-red spectra were run in nujol mulls unless otherwise stated. The given bands are all strong, exceptions being denoted as medium (m) or weak (w).

SECTION I

Diethyl 2-Nitrobenzylidenemalonate.[10]

A solution of o-nitrobenzaldehyde (15 g.) and diethyl malonate (16 g.) in acetic anhydride (50 ml.) was heated with potassium hydrogen carbonate (15 g.) at 100° for 2 hr. Addition of the cooled mixture to water (100 ml.) gave an oil. An ethereal solution of the product, washed with aqueous sodium carbonate, then with water, was dried ($MgSO_4$) and concentrated, affording the ester (10 g.), m.p. 49° (from ethanol). Literature m.p. 53°.

Diethyl (α-Cyano-2-nitrobenzyl) malonate (40).[10]

To a solution of potassium cyanide (7 g.) in water (25 ml.) and ethanol (200 ml.) there was added, with cooling, dilute acetic acid (50 g. of solution containing 5 g. of glacial acetic acid) and then finely powdered diethyl 2-nitrobenzylidenemalonate (25 g.). The mixture was shaken for at least 2 hr., and the crystalline adduct was filtered off, the filtrate being poured into water to

give more product. The combined solids were crystallised from ethanol to give a total yield of 16 g. adduct, m.p. 55° (Literature[10] quotes 46°), identical in infra-red spectrum with an authentic sample.

3-Ethoxycarbonyl-1-hydroxy-2-quinolone (41; H for CN).

Zinc dust (2.8 g.) was added to a solution of ester (40) (1 g.) and ammonium chloride (0.6 g.) in 50% aqueous alcohol (20 ml.). The suspension was stirred at room temperature for 4 hr., when the bright yellow solid was separated by decantation and chloroform-extraction from unreacted zinc. The yellow zinc salt was added to dilute hydrochloric acid (15 ml., 2.5N), and the free organic acid was extracted with chloroform. Crystallisation from ethanol gave the orange-yellow hydroxyquinolone (41; H for CN) (0.2 g.), m.p. and mixed m.p. with an authentic sample,[10] 168°. The hydroxamic acid gave a blood-red colour with alcoholic ferric chloride, and its infra-red spectrum was identical with that of an authentic sample.

3,4-Dihydro-6,7-methylenedioxycarbostyril (46).

Zinc dust (3.54 g.) was added to a suspension of the nitro-ester (45) (1 g.) in an aqueous solution (25 ml.) of ammonium chloride (0.76 g.). The mixture was stirred at room temperature for 5½ hr., when the yellow suspension

had become colourless. This colourless material (45; NH_2 for NO_2), m.p. ~118°, $\nu_{max.}$ 3300, 3250, 3150, 1710 cm.$^{-1}$, could be diazotised and coupled with alkaline β-naphthol to give a deep red dye. The reaction mixture was treated with a small amount of dilute sodium hydroxide and extracted with ether. The alkaline solution was separated from the zinc by decantation, acidified (H_2SO_4), and extracted with ether to give a trace amount of the product (46).

The ether extracts of the alkaline solution were washed with dilute sulphuric acid to remove basic material, and the ether, on evaporation, gave a colourless crystalline solid (46), m.p. 234° (0.1 g.; from aqueous methanol). The acid washings were made alkaline and chloroform-extraction gave a colourless crystalline solid, m.p. 235° (0.4 g.; from ethanol). This compound was relatively insoluble in dilute sulphuric acid and after several crystallisations from ethanol it had m.p. 238° (Perkin[21] reported 235°), $\nu_{max.}$ 3120 (sh.), 1675, 1630 cm.$^{-1}$

SECTION II

Phenacetyl Chloride

Phenylacetic acid (280 g.) and freshly distilled thionyl chloride (262 g.) in benzene (750 ml.) were refluxed for 3 hr., the benzene and excess thionyl chloride were removed, and the product was distilled, 205 g. (b.p. 90°/6 mm.).

Ethyl α-Phenacetylacetoacetate (Method of Metzner[39])

Sodium (30 g., 1.26 mol.) was added to a solution of ethyl acetoacetate (170 g., 1.30 mol.) in ether (300 ml.), and phenacetyl chloride (101 g., 0.63 mol.) was dripped in over 24 hr. with stirring and ice-cooling. Sodium and phenacetyl chloride were then added in the following amounts during a further 4 days:

Sodium (g.)	15	7.5	3.75	1.88
Phenacetyl chloride (g.)	50.4	25.2	12.6	6.3

In all, phenacetyl chloride (195 g., 1.26 mol.) and sodium (58 g., 2.53 mol.) were added. The yellow crystalline sodium salt was filtered off and washed with ether, dissolved in water, and the solution was acidified with acetic acid and extracted with ether. The washed (sodium hydrogen carbonate solution, then water) ethereal solution was dried and concentrated to give the product (213 g.).

Ethyl δ-Phenylacetoacetate.[40]

Ethyl α-phenacetylacetoacetate (213 g.) was vigorously stirred for 1 hr. with 0.5% ammonia (16.7 ml. 0.88 ammonia diluted to 1160 ml. with water). The solution was extracted with ether, the combined extracts were washed with sodium hydrogen carbonate solution and water, and the dried ($MgSO_4$) ethereal solution was concentrated and fractionally distilled to give the product (55 g.), fraction, b.p. 118°/0.25 mm. (Lit.[40] b.p. 153-5°/0.9 mm.).

Ethyl α-2,4-Dinitrophenyl- δ-phenylacetoacetate (47).

(a)[22] Ethyl δ-phenylacetoacetate (5.17 g., 0.025 mol.) was dissolved in a solution of sodium (0.58 g., 0.025 mol.) in ethanol (65 ml.), and 1-chloro-2,4-dinitrobenzene (2.54 g., 0.0125 mol.) in ether (25 ml.) was added in portions with vigorous shaking. After 24 hr., water was added and the ethereal layer was separated and washed with dilute sodium hydroxide. The combined alkaline solutions were acidified with dilute hydrochloric acid and extracted with ether to give the product (47), m.p. 128° (0.25 g.; from ethanol), $\nu_{max.}$ 1665, 1520, 1350 $cm.^{-1}$, giving a red colour with ferric chloride in ethanol (Found: C, 58.1; H, 4.5; N, 7.5. Calc. for $C_{18}H_{16}N_2O_7$: C, 58.1;

H, 4.3; N, 7.5%). Literature[22] m.p. 127°.

(b) Ethyl δ-phenylacetoacetate (26 g., 0.127 mol.) was added to atomised sodium (2.93 g., 0.129 mol.) in ether (200 ml.), and 1-chloro-2,4-dinitrobenzene (17 g., 0.084 mol.) in ether (100 ml.) was added portionwise with vigorous shaking. After 24 hr., water was added and the ethereal layer was separated and washed with dilute sodium hydroxide solution. Acidification of the alkaline solutions followed by ether-extraction gave the ester (47), m.p. 128° (4.2 g.; from ethanol).

4-Ethoxycarbonyl-3-hydroxy-7-nitro-2-phenylquinoline 1-Oxide (50; R=Et)

The keto-ester (47) (0.5 g.) in an equivalent amount of sodium ethoxide in absolute ethanol (8 ml.) was heated at 100° for 30 min. The alcohol was removed, the dark oily residue was dissolved in water, and the solution was acidified with dilute hydrochloric acid and extracted with chloroform (3 x 10 ml.). The chloroform solution was washed with water, sodium hydrogen carbonate solution, and water, and after drying ($MgSO_4$), was concentrated to give the orange N-oxide (50; R=Et), m.p. 178° (0.24 g.; from ethanol), $\nu_{max.}$ 1645, 1495, 1350 $cm.^{-1}$, giving a brown colour with ferric chloride in ethanol (Found: C, 61.0;

H, 4.0; N, 7.9. $C_{18}H_{14}N_2O_6$ requires C, 61.0; H, 4.0; N, 7.9%). Zaki and Iskander[22] give m.p. 179°.

4-Carboxy-3-hydroxy-7-nitro-2-phenylquinoline 1-Oxide (50; R=H).

(a) The keto-ester (47) (0.2 g.) was refluxed for 30 min. with 5% sodium hydroxide solution (5 ml.), the solution was then cooled, acidified with dilute hydrochloric acid, and filtered. The crude product (0.04 g.), $\nu_{max.}$ 3000-2200, 1650, 1520 (m), 1330 $cm.^{-1}$, was completely soluble in sodium hydrogen carbonate solution, and had m.p. 280-5°, resolidifying to melt finally at 305-310°. (Lit.[22] m.p. 279°).

(b) The quinoline-ester (50; R=Et) (0.1 g.) was refluxed for 5 min. with dilute sodium hydroxide (3 ml.). Acidification of this solution gave the quinoline-acid (50; R=H) (0.075 g.).

3-Hydroxy-7-nitro-2-phenylquinoline 1-Oxide (50; H for CO_2R)

A solution of the quinoline-acid (50; R=H) (0.13 g.) in nitrobenzene (4 ml.) was boiled for 10 min., cooled and filtered, and the residue was washed with a little ether. The nitrobenzene solution was extracted with dilute sodium hydroxide (3 x 4 ml.), and the alkaline extracts were then treated with ether to remove traces of nitrobenzene.

Acidification of the alkaline solution with concentrated sulphuric acid gave more product which was filtered off and washed with water. The crude product (0.1 g.), $\nu_{max.}$ 1520 (m), 1320 $cm.^{-1}$, could not be purified by crystallisation.

Attempted Reduction of the Quinoline 1-Oxide (50; R=Et)

(a) A solution of the N-oxide (50; R=Et) (0.1 g.) and triethylphosphite (4.15 g.) in diethyleneglycol diethyl ether (25 ml.) was left at room temperature for 75 hr. The orange-red solution was then extracted with dilute sodium hydroxide (2 x 10 ml.), and the aqueous extracts were acidified with concentrated sulphuric acid and then taken back to the alkaline side with sodium hydrogen carbonate solution. Ether-extraction gave an oil (0.19 g.) which was soluble in cold benzene and which could not be purified.

(b) Phosphorus trichloride (0.24 g.) was added dropwise to a well-stirred ice-cold solution of the N-oxide (0.05 g.) in dry chloroform (2 ml.), and the solution was stirred for a further $1\frac{1}{2}$ hr. The reaction mixture was poured over crushed ice, basified (sodium carbonate), and extracted with chloroform to give the product (0.04 g.) which, on the basis of m.p. (165-7°) and infra-red spectrum, was

largely the starting N-oxide.

2,4-Dinitrodibenzyl Ketone (48)

The keto-ester (47) (0.2 g.) was heated at 100° for 30 min. in a mixture of concentrated sulphuric acid (4 ml.) and acetic acid (4 ml.). The cooled solution was poured into water, extracted with chloroform (3 x 10 ml.), and the combined extracts were washed with water, sodium hydrogen carbonate solution, and water. Concentration of the dried ($MgSO_4$) solution yielded the ketone as colourless needles, m.p. 113° (0.1 g.; from ethanol), $\nu_{max.}$ 1705, 1520, 1350 cm.$^{-1}$ (Found: C, 59.8; H, 3.9; N, 9.4. $C_{15}H_{12}N_2O_5$ requires C, 60.0; H, 4.0; N, 9.3%).

[illegible] m.p. 141° (lit. m.p. 141°).

[illegible] (54; X=O).[43]

[illegible]ophenylacetic acid (9 g.) was added in small

SECTION III

o-Nitrophenylacetic Acid.[41,42]

Ethyl oxalate (58.4 g., 0.4 mol.) was added slowly to an ice-cold suspension of potassium ethoxide (15.6 g. granulated potassium and 30 ml. ethanol) in ether (400 ml.). To the resulting solution, after 20 min., o-nitrotoluene (54.8 g., 0.4 mol.) was added portionwise with ice-cooling. The deep red solution was left for 18 hr., when the red crystals were filtered off and washed with alcoholic and then pure ether. This potassium salt was dissolved in water (600 ml.) and left for 24 hr., when the deep red colour of the ester had given way to the much paler colour of the pyruvic acid. Hydrogen peroxide solution (30%) was added slowly until a test portion of the reaction mixture gave no red colour with aqueous alkali. The solution was then acidified (concentrated hydrochloric acid) to liberate the free acid (44 g.; from aqueous ethanol), m.p. 141° (Lit. m.p. 141°).

o-Nitrophenylacetamide (54; X=O).[43]

o-Nitrophenylacetic acid (5 g.) was added in small portions to a suspension of ground phosphorus pentachloride (5 g.) in ether (20 ml.). The red solution was warmed briefly on the water-bath and was then left at

room-temperature for 18 hr. Volatile material was removed at 30-40°/1 mm., and the residue was dissolved in benzene (25 ml.) and ether (35 ml.) and treated with ammonia gas. The separated precipitate was washed with ether and treated with water (25 ml.). Filtration gave the amide, m.p. 160160° (3.2 g.; from ethanol), $\nu_{max.}$ 3380, 3300 (sh), 3190, 16516̲5̲0̲,̲ ̲1̲6̲2̲0̲,̲ ̲1̲5̲2̲0̲,̲ ̲1̲3̲3̲5 cm.$^{-1}$ Literature[43] m.p. 160°.

Treatment of o-Nitrophenylacetamide (54; X=O) with:

(a) Potassium Amide in Liquid Ammonia.

o-Nitrophenylacetamide (0.5 g.) was added portionwise to a suspension of potassium amide (0.3 g. potassium) in liquid ammonia (25 ml.). The initial red colour of the solution rapidly changed to violet, and after 1 hr. ammonium chloride was added and the ammonia was evaporated. To the residue was added water (15 ml.) and dilute sodium hydroxide (5 ml.), the mixture was filtered, and the filtrate was extracted with chloroform (35 ml.). From the residue and the chloroform solution was obtained unchanged amide (0.22 g.). The alkaline filtrate on acidification yielded a sandy coloured precipitate, the mixture was extracted with chloroform (50 ml.), and the insoluble material was separated (0.02 g.), $\nu_{max.}$ 1770 (w), 1720, 1675, 1520, 1340 cm.$^{-1}$ The chloroform solution on

evaporation gave a red oil (0.04 g.), $\nu_{max.}$ 1770 (m), 1720, 1520, 1340 cm.$^{-1}$

When this experiment was repeated using potassium (1.5 g.) in liquid ammonia (50 ml.) for 18 hr., less unchanged amide was isolated. The chloroform extract of the acidified solution was extracted with sodium carbonate solution which removed the red colour and gave, on acidification, a yellow solid $\nu_{max.}$ 1690 (v.s.), 1640, 1520 (m), 1330 cm.$^{-1}$

(b) Sodium Amide in Benzene.

o-Nitrophenylacetamide (0.5 g.) was added portionwise to a refluxing suspension of sodium amide (1.5 g.) in benzene (25 ml.), and the solution was refluxed for a further 6 hr. On cooling, a colourless precipitate separated, and addition of water gave a red aqueous layer. The precipitate (0.25 g.; from ethanol), m.p. 160°, had an infra-red spectrum identical with that of the starting amide. Ether-extraction of the acidified aqueous layer gave a red coloured oil, $\nu_{max.}$ 1700-1650, 1520, 1340 cm.$^{-1}$ Subsequent chloroform-extraction gave a small amount of starting amide, which was also recovered from the benzene layer.

(c) Potassium Ethoxide in Ethanol.

o-Nitrophenylacetamide (0.5 g.) was added to a solution

of potassium (1.5 g.) in ethanol (25 ml.). The red solution was left at room temperature for 24 hr., and was finally refluxed for 2 hr.

Once again the product fractions showed no infra-red bands at 2500 or 1125 $cm.^{-1}$, and so the presence of cyclised 3-hydroxycinnoline 1-oxide was never detected.

o-Nitrophenylacetamidine Hydrochloride (54; X=NH) was prepared in the usual manner from the nitrile *via* the imino ether.

Treatment with Alkali

o-Nitrophenylacetamidine hydrochloride (0.2 g.) in water (0.5 ml.) was treated with 30% sodium hydroxide solution (2 ml.). The liberated amidine dissolved on heating at 100° to give a deep red solution from which an oil rapidly separated. After 45 min. the very deep red solution appeared clear, and it was cooled, acidified, and extracted with ether. After being washed (water) the ether was extracted with sodium carbonate solution, which gave only o-nitrophenylacetic acid on acidification. The acid reaction mixture was basified, but no product was obtained on ether-extraction.

2-Nitrobenzenesulphonamide (59)

2-Nitrobenzenesulphonyl chloride was formed in the usual way[44] by passing chlorine into a mixture of di-2-nitrophenyl disulphide, concentrated hydrochloric acid and concentrated nitric acid. The crude chloride (227 g.) was ground and treated with a mixture of concentrated ammonia (400 ml., 0.88) and water (200 ml.). The mixture was heated at 100° for 30 min., and the cooled reaction product was acidified (concentrated sulphuric acid), diluted with water, and filtered. The crude sulphonamide was dissolved in dilute sodium hydroxide, filtered, and recovered by acidification, m.p. 171-192° (from aqueous ethanol). It was suspected that the impurity was 2-nitrobenzenesulphenamide (m.p. ~ 124°, decomp. at ~170°), and so the crude product was oxidised.

Crude sulphonamide (122 g.) was dissolved in acetic acid (1650 ml.) and treated with 30% hydrogen peroxide (910 ml.) at 100° for 30 min. The red colour of the solution faded to a pale yellow, and the cooled solution was poured into water to give the colourless sulphonamide (59) (101 g.), m.p. 192°. Literature gives 193°.

N-Chloroacetyl-2-nitrobenzenesulphonamide (60).[30]

Chloroacetyl chloride (28 g.) was added dropwise to

a stirred ice-cooled solution of 2-nitrobenzenesulphonamide (40 g.) in 4.4% sodium hydroxide solution (400 ml.). Towards the end of the addition a heavy colourless precipitate separated, and the mixture was stirred for a further 1½ hr. at 0-5°, acidified (dilute hydrochloric acid), and filtered. The residue was redissolved in 10% sodium hydroxide, and the alkaline solution was neutralised with acetic acid to precipitate unchanged sulphonamide (28.9 g.), m.p. 192°. Addition of concentrated sulphuric acid to the filtrate gave pure product (60), m.p. 128° (12.7 g.), $\nu_{max.}$ 3240, 1750, 1530, 1340 $cm.^{-1}$ Literature gives m.p. 127-8°.

N-Cyanoacetyl-2-nitrobenzenesulphonamide (61).[30]

A solution of chloro-compound (60) (8 g.) and sodium carbonate (1.6 g.) in water (40 ml.) was treated with sodium cyanide (2 g.), and the deep red solution was heated at 70° for 2 hr. The cooled solution was acidified (concentrated hydrochloric acid), extracted with ethyl acetate (40 ml., then 2 x 30 ml.) and the combined extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated to give the crude product (6.85 g.), m.p. 140-160°. Repeated crystallisation from ethanol gave the cyano-compound (61), m.p. 168°, $\nu_{max.}$ 3300, 1750, 1540,

1355 cm.$^{-1}$ Literature[30] gives m.p. 168-170°.

The crude product was normally a mixture of the cyano-sulphonamide (61) and the cyano-acetamide (62), and was used for the next step without purification.

2-Nitrophenylcyanoacetamide (62).[30]

The cyano-sulphonamide (61) (3 g.) was heated with sodium hydroxide (1.8 g.) in water (20 ml.) at 50° for 30 min. Acidification (concentrated hydrochloric acid) of the cooled solution gave crude product (2.1 g.), m.p. ~170°. The cyano-acetamide (62) had m.p. 172-3° (from ethanol), $\nu_{max.}$ 3400 (m), 3260 (m), 3150 (w), 1690, 1520, 1345 cm.$^{-1}$ (Lit.[30] m.p. 171-171.5°).

When the mixture, (61) and (62), was used as starting-material for this reaction, the product was the mixture, (62) and (74).

4-Cyano-3-hydroxycinnoline 1-Oxide (74)

The acetamide (62) (0.1 g.) in 10% sodium hydroxide (1 ml.) was heated at 75° for 1 hr., and the cooled clear red solution was acidified (concentrated sulphuric acid) to give the crude product (0.08 g.), m.p. 270-5° (decomp.). The pure cinnoline (74) was obtained as pale yellow crystals, m.p. 277° (decomp.) (from ethanol), $\nu_{max.}$ 3200-2400, 2220 (m), 1135 cm.$^{-1}$ (Found: C, 57.9;

H, 2.9; N, 22.4. $C_9H_5N_3O_2$ requires C, 57.8; H, 2.7; N, 22.5%). This compound was soluble in sodium hydrogen carbonate solution, and gave a pale wine colour with alcoholic ferric chloride.

4-Carboxy-3-hydroxycinnoline 1-Oxide (75)

(a) The nitrile (74) (0.2 g.) was refluxed in 10% sodium hydroxide (2 ml.) for 7 hr. The cooled solution was poured into excess dilute hydrochloric acid, and the precipitate was filtered off, washed with water, and dried. The solid was treated with hot ethanol, the mixture was filtered, and the filtrate was evaporated to give crude carboxylic acid (75) (0.17 g.), obtained as cream needles, m.p. 153° (decomp.) (from benzene-methanol), $\nu_{max.}$ 3200-2400, 1630, 1125 $cm.^{-1}$ (Found: C, 52.6; H, 3.1. $C_9H_6N_2O_4$ requires C, 52.4; H, 2.9%), giving a wine-red colour with alcoholic ferric chloride. On melting, this compound resolidified to melt finally at ~195°.

(b) The cyano-sulphonamide (61) (1 g.) in 10% sodium hydroxide (20 ml.) was heated at 70° for 30 min. and then refluxed for 6 hr. The reaction mixture was treated as in (a) to produce crude product (0.5 g.), crystallised from benzene-methanol to give pure carboxylic acid (75) (0.37 g.).

3-Hydroxycinnoline 1-Oxide (55; X=O)

The carboxylic acid (75) (1 g.) was suspended in diphenyl ether (5 ml.) and heated in an oil-bath at ~165° for a few minutes until evolution of carbon dioxide had ceased. The cooled mixture was diluted with petrol, filtered, and the residue (0.76 g.) was well washed with petrol. Crystallisation from ethanol gave cream needles, m.p. 195° (decomp.), $\nu_{max.}$ 2550 (br), 1125, 1000 (m) $cm.^{-1}$, giving a pale wine colour with alcoholic ferric chloride (Found: C, 59.2; H, 3.9; N, 17.2. $C_8H_6N_2O_2$ requires C, 59.3; H, 3.7; N, 17.3%). This compound was soluble in sodium hydrogen carbonate solution, and was often detected as a minor product of the hydrolysis of the nitrile (74).

Reduction of 3-Hydroxycinnoline 1-Oxide

A warm deep red solution of the N-oxide (55; X=O) (1.49 g.) in 2% aqueous sodium hydroxide (25 ml.) was treated portionwise with sodium dithionite (9 x 0.5 g.). The mixture was then heated at 100° for 1½ hr., having a final pale orange colour. Constant ether-extraction of the neutralised (with acetic acid) reaction mixture gave a solid which, after being dried, was treated with boiling benzene (20 ml.), and the crystalline insoluble portion of the product was filtered off (A).

The benzene-soluble fraction (0.4 g.) contained a mixture of products, and chromatoplate evidence suggested that two of these were the compound (A) and N-amino-oxindole (77). A pure sample of N-aminooxindole, obtained by sublimation of the reaction mixture at ~110°/0.4 mm., formed colourless plates, m.p. 126° (from benzene), identified by mixed m.p. and infra-red spectrum.[34]

The benzene-insoluble product (A) (0.25 g.) was obtained as pale yellow plates from chloroform, m.p. ~145° (decomp.) resolidifying to melt finally at 185-198°, $\nu_{max.}$ 3200, 3140, 1640, 1125 (m) cm.$^{-1}$, $\nu_{max.}$ ($CHCl_3$) 3375 (w), 3250 (w), 1675 cm.$^{-1}$. (Found: C, 65.1; H, 5.6; N, 18.7. $C_8H_8N_2O$ requires C, 64.9; H, 5.4; N, 18.9%). These experimental facts are consistent with the structure (76) for compound (A).

3-Hydroxycinnoline (56; R=H)

A solution of compound (A) (0.01 g.) in xylene (1.5 ml.) was boiled with 10% palladium-charcoal (0.01 g.) for 3 hr. The xylene was evaporated, the product was treated with hot chloroform, and the mixture was filtered through a pad of celite. Removal of the chloroform gave the crude product (0.008 g.), m.p. 195-201° (Lit.[27] m.p. 201-3°), which ran just ahead of the starting-material on

a chromatoplate ($CHCl_3$).

N-Aminooxindole (77)

was prepared from 2-nitrophenylacetic acid by the method of Baumgarten et al.[34] The nitro-acid was hydrogenated to the amino-acid which was diazotised and added to a solution of stannous chloride in concentrated hydrochloric acid. It was reported that at this point a "tin-salt" was precipitated, but in the present work only a small amount of yellow solid had separated after 48 hr., and this was treated with hot water, dried, and sublimed as described in the published method to give colourless plates, m.p. 125° (from benzene), $\nu_{max.}$ 3400 (m), 3275 (m), 3175 (m), 1680, 1640, 1610 (m) $cm.^{-1}$, $\nu_{max.}$ ($CHCl_3$) 1705, 1661 (w), 1632 (m) $cm.^{-1}$ (Lit. m.p. 127.5 - 128°).

Benzoylation of Compound (A)

An ice-cold solution of (A) (0.05 g.) in pyridine (0.05 ml.) was added to benzoyl chloride (0.1 g.) cooled in ice. A colourless suspension formed, and the mixture was left at room temperature for 18 hr., when it was poured over crushed ice (5 g.) in dilute sulphuric acid (2.5 ml.) and the solid product was separated and washed with water. The dried product (0.082 g.) was chromatographed over silica using benzene-chloroform (1:1) as eluant. The

first compound eluted (0.036 g.) was the dibenzoyl derivative (81) of N-aminooxindole, which was obtained as colourless needles, m.p. 166° (from ethanol) (Lit.[36] m.p. 167°), $\nu_{max.}$ 1740, 1700 (sh), 1690 cm.$^{-1}$ (Found: C, 73.9; H, 4.7; N, 8.0. $C_{22}H_{16}N_2O_3$ requires C, 74.1; H, 4.5; N, 7.9%). The second product eluted was treated with aqueous sodium hydrogen carbonate to remove any benzoic acid, and the dried residue (0.028 g.), N-benzoylaminooxindole (80), formed colourless needles, m.p. 200° (from ethanol) (Lit.[34] m.p. 199°), $\nu_{max.}$ 3150 (w), 1690, 1660 cm.$^{-1}$, $\nu_{max.}$ ($CHCl_3$) 3340 (w), 1690, 1655 cm.$^{-1}$ (Found: C, 71.7; H, 4.7; N, 11.1. Calc. for $C_{15}H_{12}N_2O_2$: C, 71.4; H, 4.8; N, 11.1%).

N-Benzoylaminooxindole (80), when treated with benzoyl chloride in pyridine, gave the dibenzoyl derivative (81), identified by m.p., mixed m.p., and infra-red spectrum.

N-Aminooxindole was benzoylated as for the dihydro-compound (A) and only the monobenzoyl derivative was detected, as found by Baumgarten *et al.*[34]

Pyridine Treatment of Compound (A)

The dihydro-compound (A) (0.01 g.) was left in dry pyridine (0.2 ml.) at room temperature for 70 hr. The pale yellow solution became deep red, but the product ran

on a chromatoplate as a single spot, corresponding to the starting-material (A).

N-*p*-Tolylsulphonylacetyl-2-nitrobenzenesulphonamide (82)

A solution of the chloro-sulphonamide (60) (0.5 g.), sodium carbonate (0.1 g.), and sodium *p*-toluenesulphinate (0.36 g.) in water (3 ml.) was heated at 100° for 20 min. The ethyl acetate extracts of the cooled, acidified (dilute hydrochloric acid) solution were washed with brine (2 x), dried ($MgSO_4$), and concentrated to give the product (0.68 g.), m.p. 170° (from ethanol), $\nu_{max.}$ 3150, 1710, 1540, 1360, 1310, 1150 $cm.^{-1}$ (Found: C, 45.4; H, 3.6; N, 7.2. $C_{15}H_{14}N_2O_7S_2$ requires C, 45.2; H, 3.5; N, 7.0%).

When similar reaction conditions were used as for the formation of the cyano-compound (61), namely excess sodium *p*-toluenesulphinate (1 g., ~ 3 mol.), and heating at 70° for 2 hr., a solid (0.17 g.) was isolated as colourless needles, m.p. 75° (from ethanol), $\nu_{max.}$ 1320, 1135, which was identified as the thiolsulphonate (84) by comparison, using m.p., mixed m.p., and infra-red spectrum, with an authentic sample (supplied by Dr. J.D. Loudon).

α-*p*-Tolylsulphonyl-2-nitrophenylacetamide (83)

A solution of the sulphonamide (82) (0.22 g.) in 5% sodium hydroxide (2 ml.) was heated at 55°. Solid soon

began to separate, and at the end of 30 min. the cooled mixture was filtered to give a cream crystalline solid (0.16 g.), m.p. ~ 195°. Crystallisation from ethanol gave the acetamide (83) as colourless needles, m.p. 203° (sealed tube), $\nu_{max.}$ 3390, 3175, 1685 (m), 1660, 1530, 1350, 1315, 1145 $cm.^{-1}$ (Found: C, 54.0; H, 4.3; N, 8.5. $C_{15}H_{14}N_2O_5S$ requires C, 53.9; H, 4.2; N, 8.4%).

Alkali Treatment of the Acetamide (83)

(a) The acetamide (0.06 g.) in 10% sodium hydroxide (1 ml.) was heated at 75° for 1 hr. with enough ethanol for complete solution. The ethanol was boiled off, the cooled solution was filtered, and the washed (water) residue was crystallised from ethanol to give 2-nitrobenzyl-*p*-tolyl-sulphone (85), m.p. and mixed m.p. with an authentic sample,[38] 131°.

(b) The acetamide (0.1 g.) in alcoholic sodium hydroxide (0.3 g. sodium hydroxide in 9 ml. ethanol) was heated at 100° for 1 hr. The ethanol was evaporated, and enough water was added to give a clear red solution which was acidified (concentrated hydrochloric acid) and extracted with chloroform. The red chloroform extracts were washed with brine, dried, and concentrated to give an oil (0.076 g.) whose infra-red spectrum showed broad absorption in the

regions 3500-3200 cm.$^{-1}$ and 1800-1630 cm.$^{-1}$

The oil was chromatographed on an alumina column (1.5 g. Grade V, neutral). Using chloroform as eluant, the first fraction (5 ml.) contained 0.03 g., $\nu_{max.}$ 3440 (m), 3300, 1775 (m), 1680, 1520, 1350, 1315, 1135 cm.$^{-1}$ The last fraction (0.009 g.), eluted with methanol, had $\nu_{max.}$ ($CHCl_3$ film) 3420 (m), 3300, 1725 cm.$^{-1}$, along with the nitro- and sulphone absorption. In all, only 0.045 g. were recovered from the column even after eluting with acetic acid. The first fraction (0.03 g.) was re-chromatographed using petrol-benzene (1:1) as eluant, and the first fraction of this run (0.008 g.) had $\nu_{max.}$ ($CHCl_3$ film) 1790 (m), 1775 (sh.)(m), 1740 (w), 1700-1690 (m), 1520 (m), 1320, 1140 cm.$^{-1}$

(c) The acetamide (0.1 g.) was refluxed for 1½ hr. with a suspension of sodium amide (0.06 g.) in toluene (10 ml.). The suspension was filtered off, and the toluene was evaporated to give a solid (0.08 g.), m.p. ~185°, whose infra-red spectrum was identical to that of the starting-material.

o-Nitrobenzaldehyde

Paraformaldehyde (28.75 g.) and hydroxylamine hydrochloride (65.75 g.) in water (425 ml.) were heated to give a clear solution, hydrated sodium acetate (127.5 g.) was added, and the solution was boiled gently for 15 mins.

Finely ground o-nitroaniline (86.25 g.) in concentrated hydrochloric acid (142.5 ml.) and water (125 ml.) was stirred for 15 mins., crushed ice (250 g.) was added, and a solution of sodium nitrite (43.75 g.) in water (63 ml.) was added dropwise with stirring, the temperature being kept at 0-2°. The solution was then made neutral to Congo Red by addition of sodium acetate (55 g.) in water (88 ml.). The neutral diazonium solution was filtered through a plug of glass wool, and was immediately introduced below the surface of the formaldoxime solution, to which had been added copper sulphate (31.25 g.), anhydrous sodium sulphite (2.5 g.), and sodium acetate (412.5 g.) in water (450 ml.), at 10-15° with efficient stirring (Hershberg). Stirring was continued for 1 hr., and then the mixture was made acid to Congo Red with concentrated hydrochloric acid. The solid oxime was separated by suction filtration, and boiled under reflux for 1 hr. with a solution of ferric ammonium sulphate (720 g.) in water (1250 ml.).

Crude aldehyde, which was isolated by steam-distillation, extraction of the distillate (~5 l.) with ether (2.5 l.), and subsequent distillation of the ether, was shaken with aqueous sodium hydrogen sulphite (125 ml.; 40%); and water (250 ml.) at 50° was added. After removal of the non-aldehydic material by extraction of the cooled solution with ether (3 x 100 ml.), aldehyde was regenerated by treatment of the aqueous solution with concentrated sodium hydroxide until the solution became cloudy, and then precipitation was completed using dilute sodium carbonate solution. Product was then removed in ether (5 x 250 ml.), dried ($MgSO_4$), and the solvent was removed by distillation under reduced pressure to give o-nitrobenzaldehyde (42 g.), m.p. 41°.

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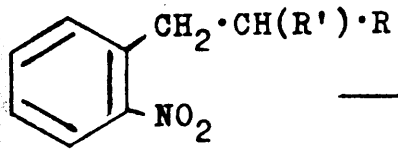

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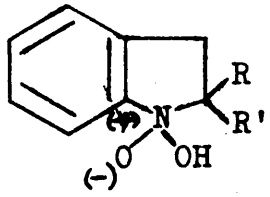

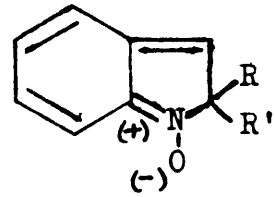

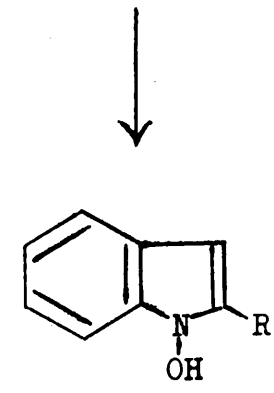

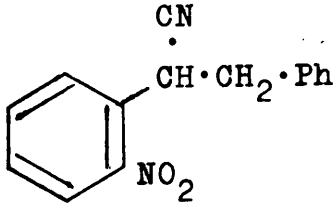

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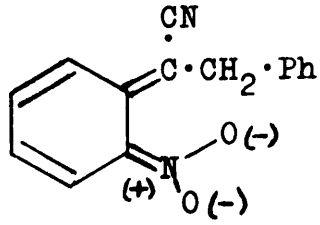

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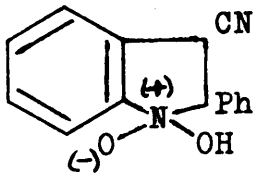

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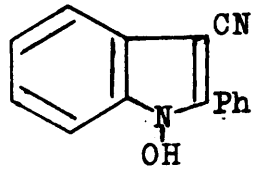

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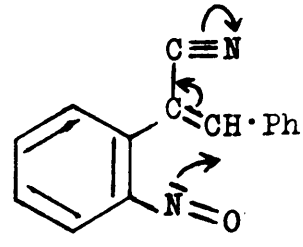

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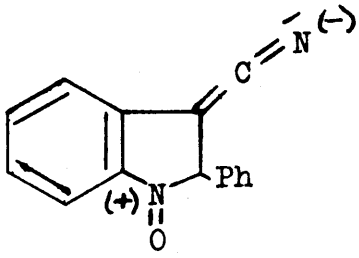

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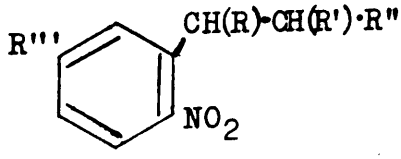

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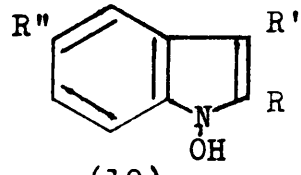

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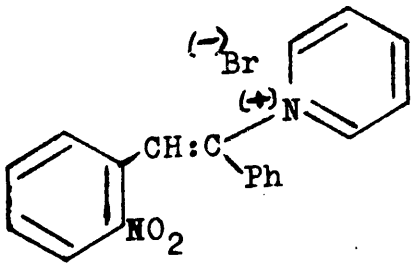

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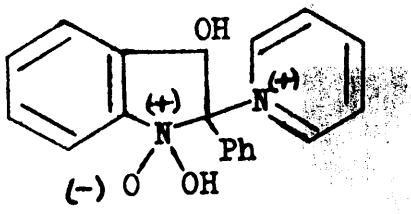

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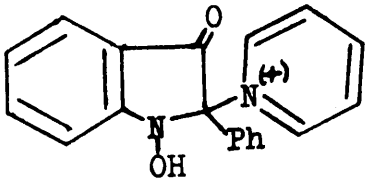

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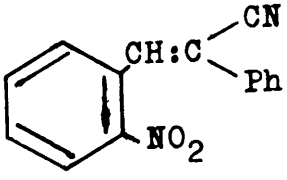

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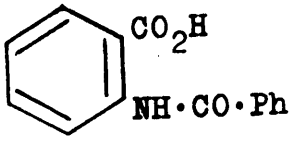

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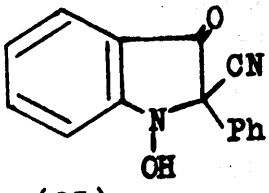

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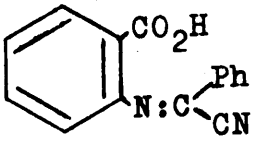

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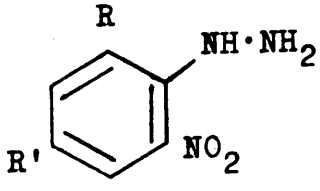

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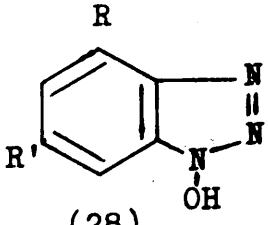

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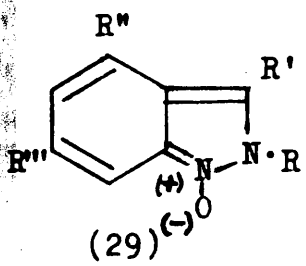

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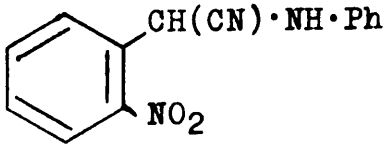

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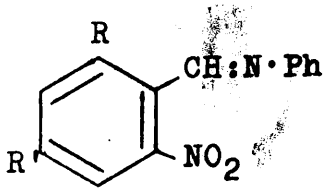

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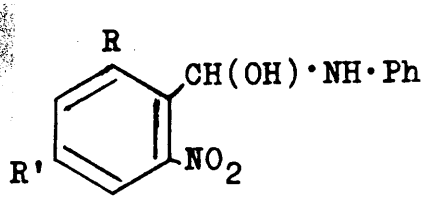

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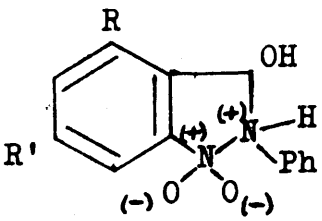

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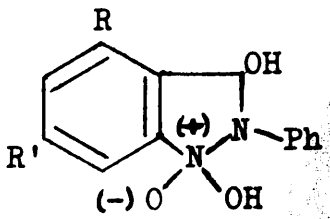

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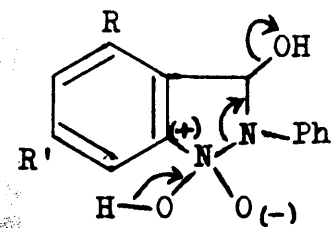

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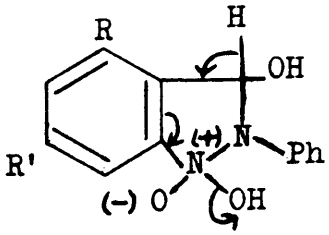

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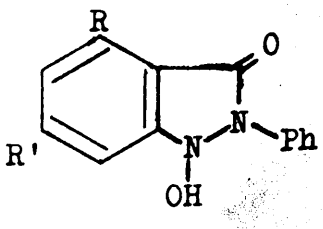

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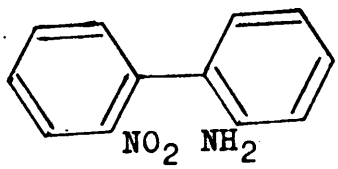

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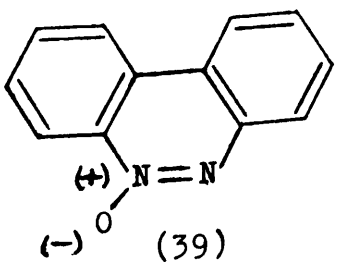

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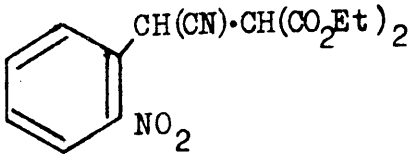

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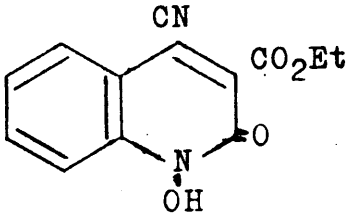

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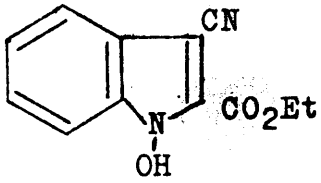

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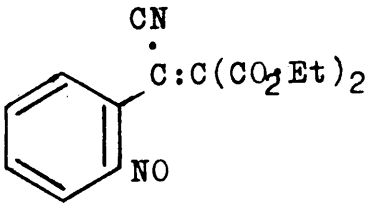

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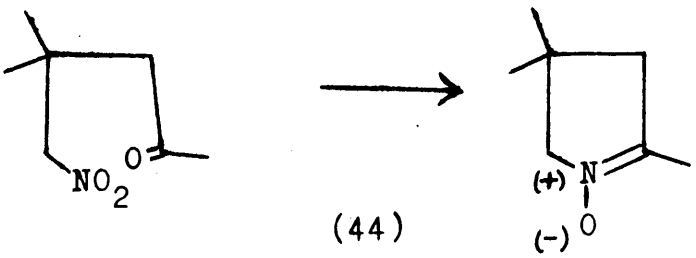

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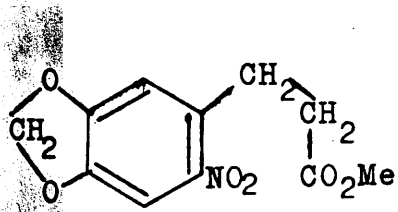

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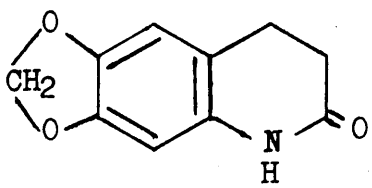

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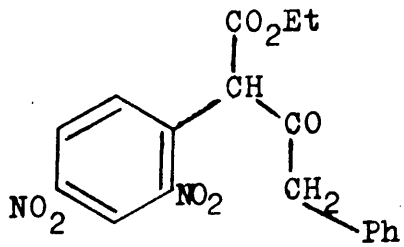

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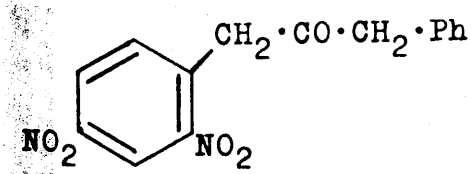

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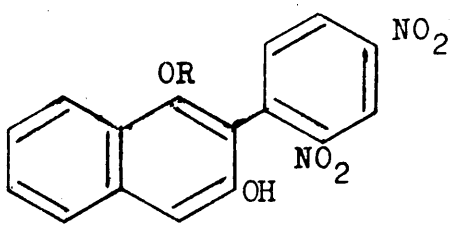

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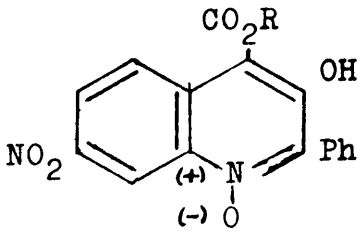

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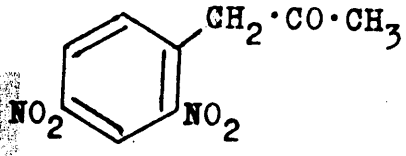

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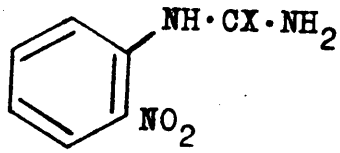

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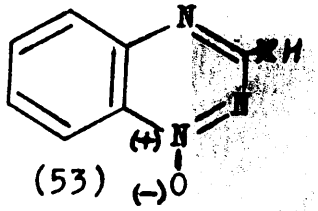

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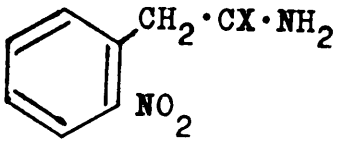

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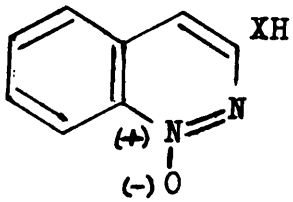

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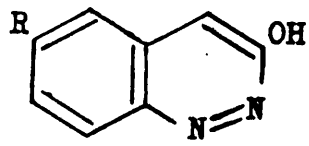

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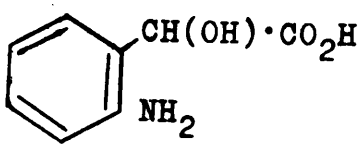

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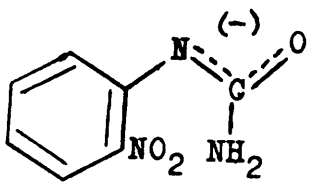

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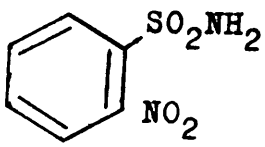

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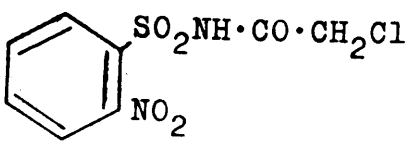

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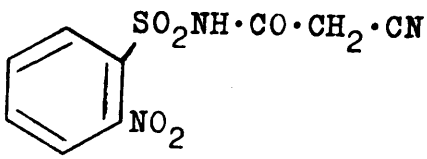

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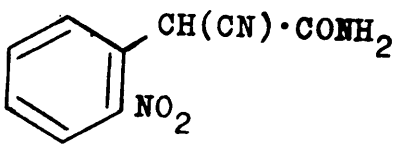

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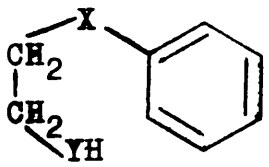

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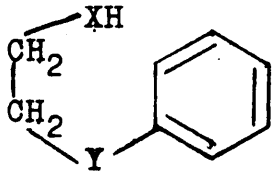

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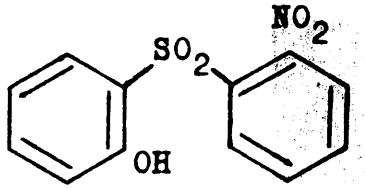

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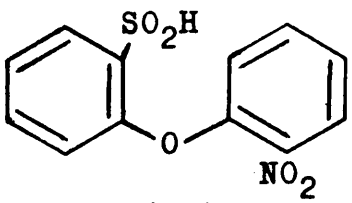

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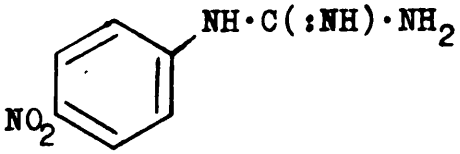

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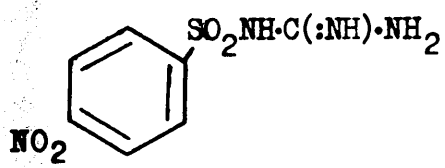

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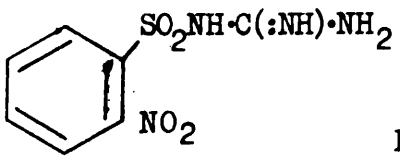

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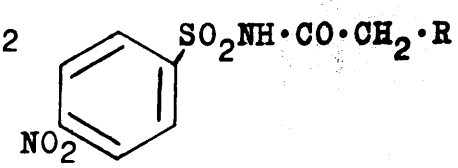

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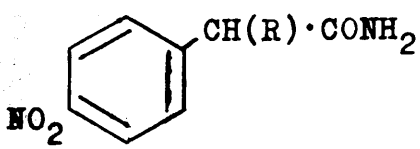

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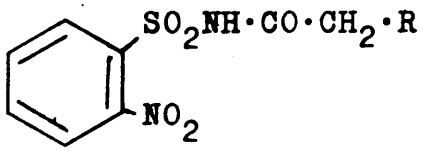

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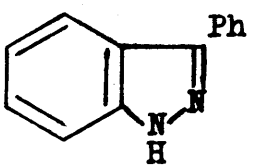

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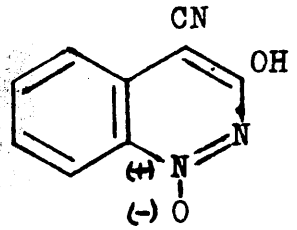

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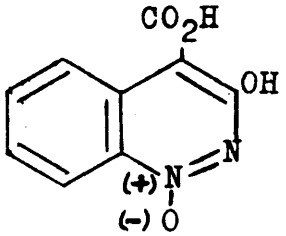

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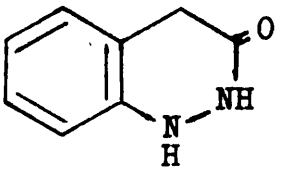

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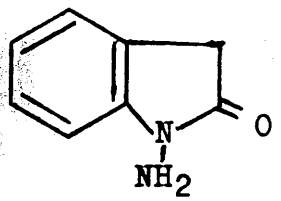

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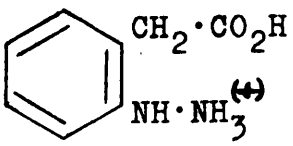

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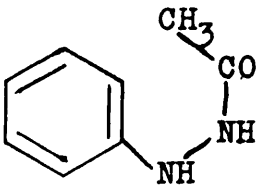

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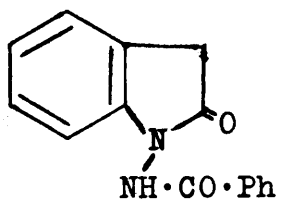

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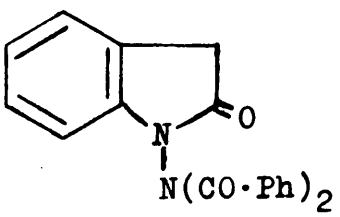

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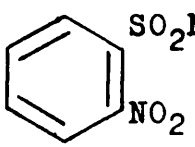

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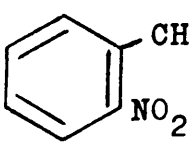

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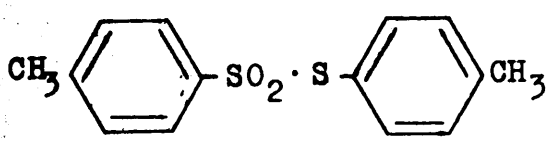

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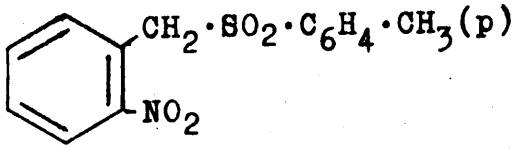

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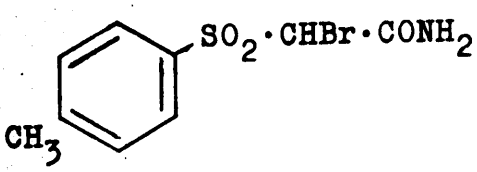

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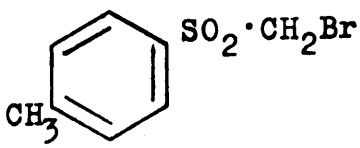

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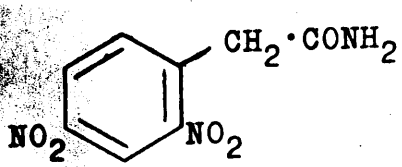

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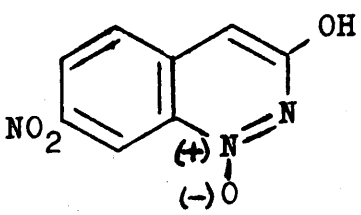

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CHAPTER 2

ACID-CATALYSED CYCLISATIONS

INTRODUCTION

While base-catalysed condensation between a nitro-group and an ortho-side-chain is well known, acid-catalysed interactions are comparatively rare. Some reactions of this latter type appear to involve an oxygen-transfer from the nitro-group to the α-position of the side-chain, and this kind of behaviour will now be examined.

An early instance was reported by Baeyer[1] who obtained ethyl isatogenate (1) by the action of cold concentrated sulphuric acid on ethyl o-nitrophenylpropiolate (2). It was later shown[2] that ethyl o-nitrobenzoylacetate (3; R=Et) was not an intermediate in the reaction, since similar treatment of this compound merely caused hydrolysis to the carboxylic acid (3; R=H). Arndt et al.[3] found that o-nitrophenylethylene oxide (4) was converted into o-nitroso-benzoylcarbinol (5) under acid conditions, and 3-formyl-anthranil (6) was formed by acetic acid treatment of β-2-nitrophenylglycidic acid (7).[4]

These cases may involve an interaction between the δ−-nitro-oxygen and the side-chain α-carbon which is made δ+ either by being the positive end of a polarised multiple-bond or by carrying an electronegative substituent. An oxygen-transfer reaction is also observed in

cases in which it would appear that transfer proceeds *via* an *aci*-nitro-form, and this type of reaction has been effected with either acid or base. Thus, 2,4-dinitrophenylacetone (8) is converted into 6-nitroanthranil (9) by the action of concentrated sulphuric acid,[5] while *o*-nitrotoluene gives anthranilic acid on being treated with strong base, anthranil being an intermediate.[6]

SECTION I

In Glasgow, it has recently been shown[7] that o-nitrobenzaldehyde reacts with ethyl acetoacetate in the presence of hydrogen chloride to form the 1-hydroxyquinolone (10; R=Me, R'=CO_2Et). The mechanism of this reaction presents an interesting problem, and the work reported in this section was undertaken in order to provide information about the reaction sequence involved.

In addition to the ester mentioned above, o-nitrobenzaldehyde has been successfully condensed with acetylacetone and diethyl acetonedicarboxylate giving the 1-hydroxyquinolones (10; R=Me, R'=CO·Me) and (10; R=CH_2·CO_2Et, R'=CO_2Et).[7] Condensation of the aldehyde with benzoylacetone[8] gave a cyclised product whose structure is either (10; R=Me, R'=CO·Ph) or (10; R=Ph, R'=CO·Me). This ambiguity might be resolved if the product, when treated with acetic anhydride, underwent the kind of acetate rearrangement described in Chapter 3.

Use of other active methylene components led only to the recovery of the 2-nitrobenzylidene derivatives. Thus with benzyl cyanide,[8] ethyl cyanoacetate,[8] and ethyl benzoylacetate,[7] only the 2-nitrobenzylidene compounds (11), (12; R=OEt, R'=CN), and (12; R=Ph, R'=CO_2Et) were obtained, and with acetone[7] the di-2-nitrobenzylidene derivative was

formed. When desoxybenzoin was used,[9] the hydrogen chloride adduct of the benzylidene compound (12; R=R'=Ph) was isolated.

The 2-nitrobenzylidene derivatives of the respective ketones are potential intermediates in these cyclisation reactions, and in some cases they have been isolated from the reaction mixture and converted into the 1-hydroxy-quinolones by renewed treatment with hydrogen chloride. Thus any proposed mechanism must explain the inactivity of those benzylidene compounds which resist further reaction.

The formation of the product (10) from the benzylidene derivative (12) is explicable through stepwise formation of the intermediates (13) and (14). The oxygen-transfer, (12) $\longrightarrow$ (13), is an example of the type of acid-catalysed reaction mentioned in the Introduction, and the known formation of *p*-chlorophenylhydroxylamine from hydrogen chloride and nitrosobenzene[10] provides analogy for the step (13) $\longrightarrow$ (14).

However it has not yet proved possible to effect the oxygen-transfer reaction with acids other than hydrogen halides. Trichloroacetic acid has been reported[11] as causing no reaction of benzylidene compounds (12), and it has now been found that the 2-nitrobenzylidene compound (12; R=Me, R'=CO_2Et) is unchanged by cold concentrated

sulphuric acid. This suggests that acid-catalysed oxygen-transfer is not the first step, and it is proposed that attack by halide ion and oxygen-transfer are concerted, as in (15), leading to the intermediate (14).

The reactivity of the benzylidene compounds seems to be relateable to the degree of polarisation of the side-chain double-bond. In those compounds which react further with hydrogen halide, the double-bond is always activated by an alkyl ketone and another carbonyl function. It would thus appear that the nucleophilic halide ion only substitutes the aromatic ring if this is made sufficiently electron-deficient by the interaction of the nitro-oxygen with the $\delta+$ α-carbon atom of the unsaturated side-chain.

An electron-releasing group in the benzene ring, ortho or para to the nitro-group, would increase the nucleophilicity of the nitro-oxygen atoms, and would decrease the "back-polarisation" of the side-chain double-bond caused by the nitro-group. Hence, such a modification might be expected to cause reaction to occur in a previously inactive benzylidene compound. In support of this hypothesis, Mr. D. M. Smith has found that whereas o-nitrobenzaldehyde and ethyl benzoylacetate gave only the benzylidine derivative (12; R=Ph, R'=CO_2Et) on treatment with hydrogen chloride, when 5-hydroxy-2-nitro-

benzaldehyde was used the reaction went to completion giving the 1-hydroxyquinolone (16; R=Ph, R'=OH).

It has been shown[11] that when the position *para* to the nitro-group in the starting nitro-aldehyde is blocked by a halogen atom (Cl or Br), the reaction can proceed normally, chlorine entering *ortho* to the nitro-group. Thus with ethyl acetoacetate and 5-halogeno-2-nitro-benzaldehyde, hydrogen chloride gave the dihalogeno-compound (16; R=Me, R'=Cl or Br).

It was thought desirable to examine the behaviour of a blocked nitro-aldehyde, and for this purpose 3,5-dichloro-2-nitrobenzaldehyde (17) was synthesised. Chlorination of anthranilic acid with sulphuryl chloride gave 3,5-dichloroanthranilic acid, and this was deaminated by treating the diazonium compound with hypophosphorous acid. The resulting 3,5-dichlorobenzoic acid was converted into the acid chloride, and reduced with lithium tri-t-butoxyaluminohydride to give 3,5-dichlorobenzaldehyde, a convenient method introduced by Brown *et al*.[12] The required nitro-aldehyde (17) was obtained in good yield on nitration with potassium nitrate in concentrated sulphuric acid.

Since this aldehyde has no vacant position *ortho* or *para* to the nitro-group, if the derived benzylidene compound

reacts initially by an acid-catalysed oxygen-transfer step of the form (12) ⟶ (13) it should be possible to isolate the nitroso-intermediate analogous to (13), as this cannot react further by nuclear substitution by chloride ion. However, when 3,5-dichloro-2-nitrobenzaldehyde (17) and ethyl acetoacetate were treated with ethereal hydrogen chloride, over 50% of the aldehyde was recovered. In addition a small amount of an unidentified intermediate was formed which gave 3,5-dichloroanthranilic acid on treatment with strong base in the cold.

The unreactivity of the dichloronitrobenzaldehyde (17) compared with o-nitrobenzaldehyde itself is not surprising, since it is thought that the main factor which determines the reactivity of aldehydes in acid-catalysed condensations is the concentration of oxonium ion formed by protonation of the carbonyl oxygen.[13] Electron-withdrawing groups in the aromatic ring would not favour the formation of the protonated form, and so such substituents should decrease the reactivity of the aldehyde. Accordingly, substituents operate in opposite directions in acid- and in base-catalysed reactions. In the latter, nuclear electron-withdrawing groups increase the electron deficiency of the carbonyl group and hence increase the rate of reaction with the carbanion formed from the active methylene compounds.

In view of the above finding, the benzylidene compound (18) was preformed using basic conditions and was treated with ethereal hydrogen chloride. No reaction ensued, the benzylidene compound being recovered unchanged. This result is consistent with concerted process (15) being the first step in the further reaction of the benzylidene intermediate.

In comparable reactions using hydrogen bromide as condensing agent, similar cyclisations are achieved, but the products are unsubstituted by bromine.[11] Thus o-nitrobenzaldehyde condenses with ethyl acetoacetate in the presence of hydrogen bromide forming the halogen-free 1-hydroxyquinolone (10; R=Me, R'=CO_2Et, H for Cl). This same product is obtained using hydrogen chloride in the presence of the reducing agent hydroquinone.[11] The course of the reaction seems to involve a reduction step which can be effected directly by hydrogen bromide or hydroquinone but which is otherwise accomplished in the case of hydrogen chloride.

When the dichloronitrobenzylidene compound (18) was treated with ethereal hydrogen bromide, there was produced a high-melting alkali-soluble product of probable structure (16; R=Me, R'=Cl, $CO\cdot CH_3$ for CO_2Et). Although the product was not obtained analytically pure, the result serves to

emphasise the difference in mechanism between reactions effected by hydrogen chloride and hydrogen bromide.

SECTION II

The formation of 5-chloro-3-*p*-hydroxyphenylanthranil (22; R=*p*-C_6H_4·OH, R'=Cl) from *o*-nitrobenzaldehyde, phenol, and hydrogen chloride in acetic acid and of the analogous compound 5-chloro-3-*p*-dimethylaminophenylanthranil (22; R=*p*-C_6H_4·NMe_2, R'=Cl) reported by Zincke[14] has features in common with the condensation reaction mentioned above leading to the quinolone (10).

The reaction scheme leading to the anthranil product (22) can be written as involving the intermediates (19) ⟶ (21). The first postulated intermediate (19; R=*p*-C_6H_4·OH) has now been synthesised and shown to yield the expected anthranil (22; R=*p*-C_6H_4·OH, R'=Cl) on treatment with hydrogen chloride in ether.

It was suggested in Section I that for benzylidene compounds of the type (12), a requisite for reaction with hydrogen chloride is the presence on the *α*-carbon atom of an adequate $\delta+$ charge to secure interaction with the nitro-oxygen. The same factor would seem to be involved in the anthranil reaction.

The three substituted 2-nitrobenzyl alcohols (19; R=Me), (19; R=Ph), and (19; R=*p*-C_6H_4·OH) would be expected, under the influence of acid, to give benzyl carbonium ions of increasing stability, and hence to be

arranged in order of increasing activity in the anthranil reaction. This prediction is now confirmed. The alcohol (19; R=Me) was unaffected by ethereal hydrogen chloride, the alcohol (19; R=Ph) yielded the anthranil (22; R=Ph, R'=Cl) only slowly, while the alcohol (19; R=p-C_6H_4·OH), which could form the stabilised carbonium ion (25), rapidly afforded the anthranil (22; R=p-C_6H_4·OH, R'=Cl).

Anthranil formation can also be effected by hydrogen bromide.[11] 5-Halogeno-2-nitrobenzaldehyde reacts with phenol in ethereal hydrogen bromide to give 5-halogeno-3-p-hydroxyphenylanthranil (22; R=p-C_6H_4·OH, R'=Hal.), similar behaviour to that found in the quinolone reaction. However, with unsubstituted o-nitrobenzaldehyde the product is a mixture of 3-p-hydroxyphenylanthranil (22; R=p-C_6H_4·OH, R'=H) and its 5-bromo-derivative (22; R=p-C_6H_4·OH, R'=Br).

When 2-nitrodiphenylmethanol (19; R=Ph) was treated with hydrogen bromide in ether, the product was largely 2-amino-5-bromobenzophenone (23; R=NH_2, R'=Br) accompanied by 5-bromo-3-phenylanthranil (22; R=Ph, R'=Br). Separation of the products of this reaction proved difficult.

Attempts to remove the amine by dissolution in mineral acid failed. This type of behaviour has also been

noticed by Sternbach and Reeder[15] who reported that 2-amino-5-chlorobenzophenone (23; R=NH_2, R'=Cl) was not basic enough to form a salt with 3N hydrochloric acid, and could be extracted from an acidic reaction mixture with ether. The mixed product was treated in dry ether with hydrogen chloride gas, but the amine hydrochloride did not separate.

Chromatography over alumina did not give a clean separation, but did give a pure sample of each component. In practice separation was effected by treating the crude reaction product with benzene or ether which dissolved mainly the anthranil, leaving the amine hydrobromide. The anthranil structure was confirmed by isomerisation to 2-bromoacridone (24; R=Br) on treatment with sodium nitrite in concentrated sulphuric acid.

The mode of formation of the amino-ketone is not clear. Reduction of the bromo-anthranil by hydrogen bromide is unlikely, since the related chloro-anthranil (22; R=Ph, R'=Cl) was unchanged by prolonged exposure to ethereal hydrogen bromide. It is known that o-nitroso-benzoic acid is converted into 5-bromoanthranilic acid by hydrogen bromide,[11] and reaction of the postulated intermediate (20; R=Ph) in a similar way could account for the formation of the amino-ketone (23; R=NH_2, R'=Br) in the present case.

o-Nitrobenzaldehyde reacts with an aromatic hydrocarbon in the presence of a strong dehydrating agent to give an anthranil. Thus with benzene in concentrated sulphuric acid at 0° for 4 days, o-nitrobenzaldehyde (5 g.) yielded 3-phenylanthranil (22; R=Ph, R'=H) (1.3 g.), 2-nitrobenzophenone (0.03 g.), and N-hydroxyacridone (24; N·OH for NH, R=H) (0.35 g.).[16] The presumed intermediate, 2-nitrodiphenylmethanol (19; R=Ph), undergoes reduction to form the anthranil and oxidation to form the ketone, and hence one would expect equivalent amounts of these two products. This reaction seems to provide an example of an acid-catalysed oxygen-transfer which does not involve entry of halide ion into the aromatic nucleus.

By using polyphosphoric acid at 100° for 5 hours as the dehydrating agent, Tanasescu[17] obtained only acridone (24; R=H) in poor yield, but this reaction was complicated by self-condensation of o-nitrobenzaldehyde. Since the use of polyphosphoric acid seemed preferable in this type of reaction, its interaction with 2-nitrodiphenylmethanol in the cold for two hours has now been studied, thus avoiding self-condensation of the aldehyde. This relatively mild treatment of 2-nitrodiphenylmethanol (0.25 g.) gave unchanged starting-material (0.04 g.), 2-nitrobenzophenone (~ 0.08 g.), and 3-phenylanthranil (~0.05 g.), and has

confirmed 2-nitrodiphenylmethanol as an intermediate.

The ketone-anthranil mixture obtained as reaction product proved difficult to separate, and even using chromatography pure anthranil was never obtained. The presence of anthranil ($\nu_{max.}$ ($CHCl_3$) 1640 $cm.^{-1}$) was detected in the infra-red spectrum of the eluate fractions, and in any one fraction its approximate concentration could be obtained by treating the mixture in sulphuric acid with sodium nitrite when the anthranil was isomerised into the easily separable acridone (24; R=H).

When the starting 2-nitrodiphenylmethanol (0.1 g.) was treated for 1 hour in the cold with sodium nitrite in sulphuric acid, there was formed acridone (0.04 g.) and 2-nitrobenzophenone (0.032 g.) accompanied by a trace amount of unchanged starting-material. This result suggests the initial formation of equivalent amounts of 3-phenylanthranil and 2-nitrobenzophenone.

It seems reasonable that 2-nitrodiphenylmethanol (19; R=Ph) initially undergoes an acid-catalysed oxygen-transfer to give 2-nitrosobenzophenone (20; R=Ph) which by disproportionation could give rise to 2-nitrobenzophenone and 2-hydroxylaminobenzophenone (21; R=Ph, H for Cl), the latter cyclodehydrating to form the found 3-phenylanthranil. The intermediate 2-nitrosobenzophenone could alternatively

be reduced to the hydroxylamino-compound by the starting-material which would thereby be oxidised to 2-nitrobenzophenone.

The substituted 2-nitrobenzyl alcohols used in the above experiments were prepared by reducing the corresponding ketones with sodium borohydride. 2-Nitroacetophenone was prepared[18] by acylation of the ethoxymagnesium derivative of diethyl malonate with o-nitrobenzoyl chloride, followed by acid hydrolysis and decarboxylation of the two ester groups of the resulting diethyl acylmalonate.

Since 2-nitrobenzophenone cannot be satisfactorily prepared by a Friedel-Crafts reaction using o-nitrobenzoyl chloride and benzene,[19] it was formed by oxidation of 2-nitrodiphenylmethane with chromium trioxide in acetic acid.[20] 2-Nitrodiphenylmethanol was also prepared directly[21] by reaction of o-nitrobenzaldehyde with phenylmagnesium bromide at -70°, 2-nitrobenzophenone also being formed in this reaction.

Reaction of o-nitrobenzaldehyde with 4-methoxyphenylmagnesium bromide at -70° yielded 4-methoxy-2'-nitrodiphenylmethanol and the corresponding ketone. This mixture was oxidised to the pure methoxy-ketone with chromium trioxide in acetic acid, and this was then

demethylated by treatment with hydrogen bromide in refluxing acetic acid for six hours. Using these conditions, about one third of the methoxy-ketone was recovered unchanged, but when the amount of hydrogen bromide used was increased and the reaction time extended to fifteen hours, although the yield of alkali insoluble material became negligible, the phenolic product was a mixture of two bromine containing compounds (positive Beilsten test).

The 4-hydroxy-2'-nitrobenzophenone formed by demethylation melted over the range 160-9°, gave a good analysis, and ran on a chromatoplate as a single spot. It formed a sharp-melting acetate which, on hydrolysis, gave the phenol melting over the same range.

The phenolic ketone proved more difficult to reduce than 2-nitrobenzophenone, using sodium borohydride in aqueous dioxan at room temperature the reduction was incomplete after 24 hours. Heating the ketone with a suspension of sodium borohydride in dioxan was more successful, but again starting-ketone contaminated the product, possibly due to the ketone being removed from the dioxan solution as its insoluble sodium salt. Satisfactory results were obtained by reducing the acetyl derivative, the free phenolic alcohol (19; R=$\underline{p}$-C_6H_4·OH) being obtained

after work-up.

The preparation of this compound (m.p. 105°) has finally disproved a claim for its isolation from a solution of hydrogen chloride, phenol, and o-nitrobenzaldehyde in methanol.[22] It is likely that the compound formed in that reaction (m.p. 229°) was in fact the chloro-anthranil (22; R=p-C_6H_4·OH, R'=Cl), as has already been suggested,[11] since the melting-point of that compound (240°) is considerably depressed unless it is determined using a sealed tube.

EXPERIMENTAL

Ethyl α-2-nitrobenzylideneacetoacetate (12; R=Me, R'=CO_2Et).[11]

A mixture of o-nitrobenzaldehyde (3 g.), ethyl acetoacetate (2.7 g.), acetic anhydride (4.9 ml.), and potassium hydrogen carbonate (3 g.) was heated at 100° for 2 hr., then cooled and poured into water, and the whole was extracted with ether. Evaporation of the washed (aqueous sodium hydrogen carbonate, then water) and dried ($MgSO_4$) extract gave the ester, m.p. 69° (from ethanol).

Treatment with Concentrated Sulphuric Acid

The benzylidene compound (12; R=Me, R'=CO_2Et) (0.1 g.) was dissolved in cold concentrated sulphuric acid (1 ml.). After 20 hr. at room temperature the solution was poured into water, and the precipitated solid was filtered off (0.035 g.). The filtrate was extracted with chloroform and the pale red chloroform extracts were washed with aqueous sodium hydrogen carbonate which removed most of the colour. No material could be recovered from the acidified alkaline washings, and the chloroform gave a solid (0.02 g.). The combined recovered solid ran on a chromatoplate (Kieselgel) as a single spot, and was shown by m.p. and infra-red spectrum to be unchanged starting-ester.

3,5-Dichloroanthranilic Acid.[23]

A solution of sulphuryl chloride (250 ml.) in thiophene-free benzene (300 ml.) was added dropwise to a cooled, well-stirred mixture of anthranilic acid (150 g.) in benzene (600 ml.). The resulting suspension was heated on a steam-bath for 4 hr., cooled, and diluted with one volume of petrol (b.p. 80-100°). The crude product, after filtration and drying, had m.p. 192-8° (174 g.) and was not further purified. Atkinson and Lawler[23] give m.p. 231°.

3,5-Dichlorobenzoic Acid.[24]

A suspension of 3,5-dichloroanthranilic acid (174 g.) in glacial acetic acid (830 ml.) and concentrated hydrochloric acid (270 ml.) was refluxed until solution was complete. On cooling the hydrochloride of the acid crystallised. The flask was fitted with an efficient stirrer, the mixture cooled to -5°, and a solution of sodium nitrite (60.5 g.) in water (168 ml.) was added dropwise, the stirring being continued for 1 hr. at -1°. The resulting solution was cooled to -25°, and ice-cold aqueous hypophosphorous acid (434 ml.; 50%) was added dropwise with stirring, the temperature rising to -15°. The turbid solution was stirred overnight, and the heavy

colourless precipitate was filtered off and washed with water. The acid filtrate was chilled overnight in a refrigerator to yield a second crop. Crystallisation (from ethanol) yielded crude 3,5-dichlorobenzoic acid (133 g.), m.p. ~165°. Elderfield and Kreuger[24] give m.p. 186-8°.

3,5-Dichlorobenzoyl Chloride.[25]

A mixture of 3,5-dichlorobenzoic acid (50 g.) and thionyl chloride (45 g.) was refluxed until evolution of hydrogen chloride ceased, and the acid chloride was recovered by distillation, b.p. ~ 135°/25 mm.

3,5-Dichlorobenzaldehyde.

Dry t-butyl alcohol (11.25 g., 0.15 mol.) was added with stirring to a turbid solution of lithium aluminium hydride (1.9 g., 0.05 mol.) in dry ether (125 ml.). The colourless precipitate was allowed to settle, the ether decanted and the solid was largely dissolved in diglyme (80 ml.).

Acid chloride (10.5 g., 0.05 mol.) in diglyme (25 ml.) was placed in a flask fitted with a stirrer, dropping funnel, and nitrogen inlet and outlet. The flask was flushed with dry nitrogen and was cooled to -75° by being immersed in a bath of Drikold and trichloroethylene, more

diglyme being added to keep the acid chloride in solution. The solution of lithium tri-t-butoxy-aluminohydride in diglyme was added dropwise, the mixture was allowed to reach room temperature over an hour, and the contents of the flask were poured onto crushed ice. This mixture was steam-distilled, and filtration of the distillate (~ 500 ml.) gave the aldehyde (4.4 g.), m.p. ~55°. Crystallisation (petrol) gave 3.7 g., m.p. 63° (Literature[26] gives m.p. 65°). Ether-extraction of the steam-involatile material gave 3,5-dichlorobenzoic acid (1.4 g.).

3,5-Dichloro-2-nitrobenzaldehyde (17)

3,5-Dichlorobenzaldehyde (5 g.) was added portionwise to a well stirred solution of potassium nitrate (3.1 g.) in concentrated sulphuric acid (31 ml.) at 0°. The mixture was left at room temperature overnight, and was then poured over crushed ice. The crude product (6.2 g.), obtained from the ethereal extract, had m.p. 83-6° while the pure nitro-aldehyde had m.p. 89° (from petrol), $\nu_{max.}$ 1700, 1550, 1360 $cm.^{-1}$. Asinger[27] gives m.p. 91.5°.

Reaction with Ethyl Acetoacetate

A solution of 3,5-dichloro-2-nitrobenzaldehyde (0.59 g.) and ethyl acetoacetate (0.35 g.) in ether (7 ml.) was saturated with hydrogen chloride at room temperature.

After 24 hr., the ether was evaporated under reduced pressure to give a colourless oily solid which was heated at 100° under reduced pressure to remove hydrogen chloride. The product was redissolved in ether, and the ethereal solution was extracted several times with aqueous sodium hydrogen carbonate. No material could be recovered from the alkaline extracts.

The colourless ethereal solution was then washed several times with very dilute sodium hydroxide solution until the aqueous washings were no longer coloured. The ether gave a crystalline solid (0.27 g.) whose infra-red spectrum and melting-point identified it as the starting nitro-aldehyde. The pale green alkaline extracts quickly became yellow, depositing a green-blue scum which was filtered off. The filtrate was acidified with sulphuric acid and ether extraction gave an oily solid (0.2 g.) whose infra-red spectrum showed both amino- and nitro-absorption. An ethereal solution of this solid was extracted with saturated sodium hydrogen carbonate solution. Acidification (acetic acid) of the aqueous solution followed by ether extraction gave 3,5-dichloroanthranilic acid (0.1 g.), m.p. 226° (from methanol), $\nu_{max.}$ 3500 (w), 3370 (w), 1680, 1620 (m), 1210 $cm.^{-1}$ The carbonate-insoluble fraction was recovered from the ether and proved to be starting nitro-aldehyde.

3,5-Dichloro-2-nitrobenzylideneacetylacetone (18).

A mixture of 3,5-dichloro-2-nitrobenzaldehyde (0.88 g.), acetylacetone (0.4 g.), acetic anhydride (4 ml.), and potassium hydrogen carbonate (0.6 g.) was heated at 100° for 1 hr., and was poured into a mixture of saturated sodium carbonate and crushed ice. After several hours the alkaline mixture was extracted with ether which was washed with brine and dried ($MgSO_4$). The product, recovered from the ether, was crystallised from methanol, m.p. 122° (0.45 g.), $\nu_{max.}$ 1705, 1660, 1630 (m), 1530, 1355 $cm.^{-1}$ (Found: C, 47.7; H, 3.1; N, 4.5. $C_{12}H_9Cl_2NO_4$ requires C, 47.7; H, 3.0; N, 4.6%).

Reaction with -

(a) Hydrogen Chloride

The nitro-benzylidene compound (18) (0.1 g.) in ether (15 ml.) was saturated with hydrogen chloride. After 14 hr. the pale yellow ethereal solution was washed (water, aqueous sodium carbonate, and brine), dried ($MgSO_4$), and concentrated to give starting-material (0.096 g.), m.p. 120° (from methanol). The product was run on a chromatoplate (Kieselgel) and no other compound was detected.

(b) Hydrogen Bromide

The nitro-benzylidene compound (0.1 g.) in ether

(30 ml.) was saturated with hydrogen bromide and left 42 hr. at room temperature. The ethereal solution was extracted with dilute sodium hydroxide solution which, on acidification (dilute sulphuric acid) and filtration, gave a brown solid (0.08 g.). This was dissolved in acetic acid, treated twice with charcoal, and recovered as a non-crystalline solid, m.p. ~ 205° (decomp.).

o-Nitroacetophenone

This was prepared by the method of Reynolds and Hauser[18] in 53% yield, b.p. ~ 174°/34 mm., n_D^{21} 1.550, $\nu_{max.}$ (liq. film) 1700, 1520, 1350 $cm.^{-1}$. Product solidified on standing, m.p. 26°. Literature quotes n_D^{20} 1.551,[18] and m.p.[28] 24.5°.

α-Methyl-2-nitrobenzyl Alcohol (19; R=Me)

Sodium borohydride (3.22 g.) in water (8 ml.) was added portionwise to a cooled (water) solution of o-nitroacetophenone (3.5 g.) in methanol (40 ml.). After 18 hr. the excess borohydride was decomposed with dilute hydrochloric acid and the solution was heated under reduced pressure at 100° to remove the methanol. The reaction mixture was extracted with ether (6 x 25 ml.) and the combined ether extracts were washed (saturated sodium hydrogen carbonate solution), dried ($MgSO_4$), and evaporated to give

a yellow oil (3 g.), n_D^{22} 1.5537, $\nu_{max.}$ (film) 3500-3200 (br.), 1520, 1350 (br.), 1100 $cm.^{-1}$ Literature[28] gives n_D^{20} 1.5517.

Treatment with Hydrogen Chloride

The nitro-carbinol (19; R=Me) (0.16 g.) in ether (2 ml.) was saturated four times with hydrogen chloride at 24 hr. intervals. The oil recovered from the ether was identical in infra-red spectrum with the starting nitro-carbinol.

o-Nitrobenzyl Chloride.[20]

o-Nitrobenzyl alcohol (26 g.) was dissolved in dry chloroform (175 ml.) and treated with phosphorus pentachloride (35 g.) portionwise, the reaction flask being immersed in cold water. The chloroform solution was washed with water, dried ($MgSO_4$), and concentrated to give a dark oily residue. This was extracted several times with hot petroleum ether (b.p. 40-60°), and the halide was obtained by crystallisation, m.p. 48° (20 g.). Literature[20] value, m.p. 49°.

2-Nitrodiphenylmethane.[20,29]

Aluminium chloride (40 g.) and o-nitrobenzyl chloride (20 g.) in dry benzene (400 g.) were left at room temperature for 3 days and then poured into acidified ice-water.

The benzene layer was separated, washed several times with concentrated sulphuric acid until the colour was largely removed, and after being washed with water and dried ($MgSO_4$) was evaporated to give a pale orange oil (15.5 g.).

2-Nitrobenzophenone.[20]

Chromium trioxide (7.5 g.) in water (7.5 ml.) was mixed with acetic acid (135 g.) and added dropwise over 6 hr. to a refluxing solution of 2-nitrodiphenylmethane (5 g.) in acetic acid (10 g.). The solution was concentrated, poured into cold water, and the mixture was neutralised with ammonia and filtered. The residue was boiled with dilute sodium carbonate solution, filtered off, washed with water, and crystallised from ethanol to give 2-nitrobenzophenone (2.5 g.), m.p. 103°. Literature[20] m.p. 105°.

2-Nitrodiphenylmethanol (19; R=Ph)

1. A solution of 2-nitrobenzophenone (2.1 g.) in dioxan (125 ml.) was treated with sodium borohydride (2.2 g.) in water (7 ml.). After 30 hr. the dioxan was removed under reduced pressure and the excess sodium borohydride was decomposed with dilute hydrochloric acid. Ether was added with enough water (~ 90 ml.) to give two clear layers. The combined ether extracts (~ 400 ml.) were

washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated to give an oily solid. This was extracted with hot petroleum ether (b.p. 40-60°) (250 ml.) leaving a small residue, and from the petrol was obtained the crystalline product (1.4 g.), m.p. 59°, $\nu_{max.}$ 3250 (br.), 1520, 1350 cm.$^{-1}$ Literature[21] m.p. 59-60°.

2.[21] A solution of o-nitrobenzaldehyde (6 g.) in sodium-dried toluene (100 ml.) was cooled to -70° (a precipitate appeared) in a Drikold cooling-bath while a stream of dried nitrogen was passed. Phenylmagnesium bromide, prepared from bromobenzene (7 g.) and magnesium (1.08 g.) in dry ether (25 ml.), was added dropwise over 30 min. with vigorous stirring. The temperature was kept at -70° for a further 2 hr. and then allowed to rise to -10° when alcohol (5 ml.) was added to decompose any unchanged Grignard reagent. The solution was poured into ammonium chloride (7.5 g.) in ice-water (150 ml.) and left overnight in the refrigerator. The organic layer was separated, dried ($MgSO_4$), and concentrated to give a brown oil, $\nu_{max.}$ (film) 3500-3300, 1700, 1520, 1350 cm.$^{-1}$ This oil was treated with a solution of sodium hydrogen sulphite (20 ml., 30%) followed by water (40 ml.) at 50° with stirring, and the cooled mixture was extracted with ether.

The aqueous solution yielded o-nitrobenzaldehyde (0.8 g.) on being made alkaline (Na_2CO_3). The ether contained a red oil (6.8 g.), $\nu_{max.}$ 3500-3300, 1520, 1350 $cm.^{-1}$, which was split into two fractions by distillation. Fraction 1, b.p. 60-150° (0.1 mm.), $\nu_{max.}$ (film) 3500-3300, 1700 (m), 1520, 1350 $cm.^{-1}$, consisted of a pale yellow oily solid (1.7 g.) which was a mixture of 2-nitrodiphenylmethanol and 2-nitrobenzophenone. The latter compound was identified by its m.p. (104°) and infra-red spectrum. Fraction 2, b.p. 155° (0.13 mm.), m.p. 60° (from petrol), consisted of pure 2-nitrodiphenylmethanol (4.1 g.).

Treatment of 2-Nitrodiphenylmethanol with -

1. Hydrogen Chloride

5-Chloro-3-phenylanthranil (22; R=Ph, R'=Cl)

A solution of 2-nitrodiphenylmethanol (0.4 g.) in anhydrous ether (5 ml.) was saturated 6 times at room temperature at intervals of 24 hr. The ether was washed (water), dried ($MgSO_4$), and evaporated to give an oily solid which was chromatographed on Grade I Woelm alumina. Elution with benzene-petrol (1:4) gave the anthranil (0.15 g.), m.p. 115° (from petrol), $\nu_{max.}$ 1625 $cm.^{-1}$ (Found: C, 67.7; H, 3.4; N, 6.0. Calc. for $C_{13}H_8ClNO$:

C, 68.0; H, 3.5; N, 6.1%). Literature[30] m.p. 115-7°. Elution with benzene gave unchanged starting-material.

2. Hydrogen Bromide

A solution of 2-nitrodiphenylmethanol (0.2 g.) in anhydrous ether (4 ml.) was saturated with hydrogen bromide at room temperature. After 24 hr., the solution was re-saturated and left a further 24 hr. when an oily solid had separated. The ether was evaporated and the residue was triturated with dry benzene leaving a cream amine hydrobromide, m.p. ~180° (decomp.), which gave a precipitate with silver nitrate in acetonitrile. Treatment with aqueous sodium carbonate liberated the yellow free base (0.16 g.), 2-amino-5-bromobenzophenone (23; R=NH_2, R'=Br), m.p. 112° (from methanol), $\nu_{max.}$ 3425, 3325, 1625 $cm.^{-1}$ (Found: C, 56.3; H, 3.8; N, 5.1. Calc. for $C_{13}H_{10}BrNO$: C, 56.5; H, 3.7; N, 5.1%). Literature[31] m.p. 111°.

The benzene-soluble material (0.05 g.) was washed with aqueous sodium carbonate and water, and crystallisation from methanol gave 5-bromo-3-phenylanthranil (22; R=Ph, R'=Br) as pale yellow needles, m.p. 115°, $\nu_{max.}$ 1620 $cm.^{-1}$ (Found: C, 57.0; H, 3.2; N, 5.0. Calc. for $C_{13}H_8BrNO$: C, 56.9; H, 2.9; N, 5.1%). Literature[30] gives m.p. 116-8°.

Treatment of 5-Chloro-3-phenylanthranil with Hydrogen Bromide

The chloro-anthranil (0.07 g.) in ether (5 ml.) was saturated 4 times with hydrogen bromide at intervals of 24 hr. The ethereal solution was washed with dilute sodium hydroxide and water, and, after drying ($MgSO_4$), was evaporated to give a solid (0.063 g.) which was shown to be starting-material from m.p. and infra-red spectrum.

2-Bromoacridone (24; R=Br).[30]

Sodium nitrite (0.065 g.) was added portionwise with stirring to a solution of 5-bromo-3-phenylanthranil (0.013 g.) in concentrated sulphuric acid (1 ml.) at -10°. The mixture was then left at room temperature for 18 hr., when it was poured into ice-water, and the solid was filtered off, washed well with water, and dried (0.012 g.). Crystallisation from glacial acetic acid gave a pale yellow solid, m.p. > 360° (Literature[30] m.p. 382-5°), $\nu_{max.}$ 1630 cm.$^{-1}$

4-Methoxy-2'-nitrodiphenylmethanol (19; R=C_6H_4·OMe (p)).

A solution of o-nitrobenzaldehyde (24 g.) in sodium-dried toluene (450 ml.) was cooled to -70° (solid carbon dioxide bath) whilst a stream of dried nitrogen was passed in. To this solution p-methoxyphenylmagnesium bromide,

prepared from p-bromoanisole (33.4 g.) and magnesium (4.3 g.) in ether (100 ml.), was added dropwise over 1½ hr. with vigorous stirring. The temperature was kept at -70° for a further 3 hr. and then allowed to rise to -10°, when ethanol (20 ml.) was added to decompose any unchanged Grignard reagent and the solution was poured into ammonium chloride (30 g.) in ice-water (600 ml.) and left overnight at 0°. The organic layer was separated and evaporated, the residue was treated with sodium hydrogen sulphite solution (50 ml., 30%), and to the mixture was added water (50 ml.) at 50°. Ether-extraction of the mixture gave the product freed from o-nitrobenzaldehyde.

Distillation of the crude product gave a fraction (15 g.), b.p. 195-210° (0.4 mm.). Chromatography of this over Grade I alumina, eluting successively with benzene and benzene-ether mixtures, revealed the presence of three reaction products, 4,4'-dimethoxybiphenyl, m.p. 175° (from petrol), 4-methoxy-2'-nitrobenzophenone, m.p. 102° (from ethanol) (Lit.[19] m.p. 105°), $\nu_{max.}$ 1660, 1520, 1345 cm.$^{-1}$, and 4-methoxy-2'-nitrodiphenylmethanol. This last compound did not solidify, and the structure was assigned on the basis of its infra-red spectrum, $\nu_{max.}$ (film) 3500-3300, 1520, 1340 cm.$^{-1}$, and its oxidation product, 4-methoxy-2'-nitrobenzophenone. The combined weight of

alcohol and ketone was 14 g.

4-Methoxy-2'-nitrobenzophenone (Method of Hey and Mulley[21])

A hot solution of chromium trioxide (4.4 g.) in acetic acid (30 ml.) was added over ½ hr. to a refluxing solution of 4-methoxy-2'-nitrodiphenylmethanol (6.7 g.) in acetic acid,(11 ml.). The solution was refluxed for a further ½ hr., and poured into cold water (300 ml.). Chloroform-extraction gave the ketone (5.5 g.), m.p. 102° (from ethanol).

4-Hydroxy-2'-nitrobenzophenone (Method of Stoemer[32])

4-Methoxy-2'-nitrobenzophenone (1.5 g.) in acetic acid (15 ml.) was refluxed with hydrogen bromide (3 ml., S.G. 1.49) for 6 hr. The solution was made alkaline (concentrated sodium hydroxide) and extracted with ether. The ether layer was washed with dilute alkali and water, and the dried ($MgSO_4$) extract yielded starting-material (0.49 g.). The combined alkaline solutions on acidification (concentrated sulphuric acid) and ether-extraction gave the phenol (0.81 g.), m.p. 160-9° (from benzene), $\nu_{max.}$ 3240, 1650, 1520, 1340 $cm.^{-1}$ (Found: C, 64.3; H, 3.8; N, 6.0. $C_{13}H_9NO_4$ requires C, 64.2; H, 3.7; N, 5.8%).

4-Acetoxy-2'-nitrobenzophenone

4-Hydroxy-2'-nitrobenzophenone (0.5 g.) in 10% sodium hydroxide (1.5 ml.) was stirred for 5 min. with crushed ice (1.5 g.) and acetic anhydride (0.4 ml.). The ether extracts of this solution were washed twice with dilute alkali and finally with water. The dried ($MgSO_4$) ethereal solution gave the acetate (0.45 g.), m.p. 87° (from petrol), $\nu_{max.}$ 1760, 1670, 1525, 1340 $cm.^{-1}$ (Found: C, 63.4; H, 3.9. $C_{15}H_{11}NO_5$ requires C, 63.1; H, 3.9%).

4-Hydroxy-2'-nitrodiphenylmethanol (19; R=C_6H_4·OH (p)).

4-Acetoxy-2'-nitrobenzophenone (1.1 g.) was heated at 100° for 3 hr. with a suspension of sodium borohydride (2 g.) in dioxan (27 ml.), during which time the initial pale yellow colour slowly changed to a deep orange-yellow. The dioxan was removed under reduced pressure, and the residue was heated on the water-bath with water, a clear red solution being obtained. Acidification (dilute hydrochloric acid) followed by ether-extraction gave the product as an oil (0.9 g.) which was crystallised as a pale yellow solid (from chloroform, after charcoal treatment), m.p. 105°, $\nu_{max.}$ 3375, 3200, 1520, 1340 $cm.^{-1}$ (Found: C, 63.4; H, 4.2; N, 5.8. $C_{13}H_{11}NO_4$ requires C, 63.65; H, 4.5; N, 5.7%).

5-Chloro-3-p-hydroxyphenylanthranil (22; R=$C_6H_4 \cdot OH$ (p), R'=Cl)

The diphenylmethanol (19; R=$C_6H_4 \cdot OH$ (p)) (0.05 g.) in ether (1 ml.) was saturated with hydrogen chloride, the ethereal solution being cooled in a water-bath. After 1 hr. the yellow colour of the solution had deepened markedly, and after 48 hr. the precipitated anthranil was filtered off, washed with a little water, and crystallised from ethanol, identified (m.p. 238° (sealed tube) and infra-red spectrum) by comparison with an authentic sample.[11] Literature m.p. 242°.

Treatment of 2-Nitrodiphenylmethanol with Polyphosphoric Acid

2-Nitrodiphenylmethanol (0.25 g.) in dry benzene (3 ml.) was stirred with polyphosphoric acid (2.5 g., available from B.D.H. containing ~80% P_2O_5) at room temperature for 2 hr. Crushed ice and solid sodium carbonate was added, and after a further 1½ hr. the mixture was extracted with ether. The washed (aqueous sodium carbonate, then water) and dried ($MgSO_4$) extracts yielded an oil (0.17 g.), $\nu_{max.}$ (film) 3350 (w) (br.), 1665, 1630 (m), 1520, 1350 $cm.^{-1}$ When this oil was chromatographed over Grade I alumina using benzene as eluant, a satisfactory separation was not obtained. The

first fractions were rich in 2-nitrobenzophenone, identified by m.p. 103° (from ethanol) and infra-red spectrum. Later fractions showed a more intense infra-red peak at 1640 cm.$^{-1}$ ($CHCl_3$ film), assigned as being due to 3-phenylanthranil. Unchanged starting-material (0.04 g.) was eluted from the column with chloroform. From the infra-red spectra of the eluate fractions, the product consisted of ketone ($\sim$0.08 g.) and anthranil ($\sim$0.05 g.).

Isomerisation of Anthranil to Acridone

A reaction product mixture of 2-nitrobenzophenone and 3-phenylanthranil (0.022 g. in all) was dissolved in concentrated sulphuric acid (0.6 ml.) and treated with sodium nitrite (0.025 g.). After 1 hr. the solution was poured into ice-water (3 ml.), and the precipitated solid was filtered off, washed well with water and then ether, and sublimed to give acridone (0.009 g.), m.p. 358°, $\nu_{max.}$ 1630 cm.$^{-1}$ From the ether was isolated 2-nitrobenzophenone (0.01 g.).

Treatment of 2-Nitrodiphenylmethanol with Sulphuric Acid - Sodium Nitrite

2-Nitrodiphenylmethanol (0.1 g.) in concentrated sulphuric acid (2 ml.) was treated with sodium nitrite (0.1 g.) and left at room temperature for 1 hr. The

solution was poured into ice-water, the precipitated solid was filtered off, and was washed with water and ether. The insoluble solid was acridone (0.04 g.), identified by m.p. and infra-red spectrum. The ether gave a mixture (0.032 g.) of 2-nitrobenzophenone, identified by m.p. and infra-red spectrum, and a small amount of the starting 2-nitrodiphenylmethanol, $\nu_{max.}$ (film) 3250 (br.) $cm.^{-1}$

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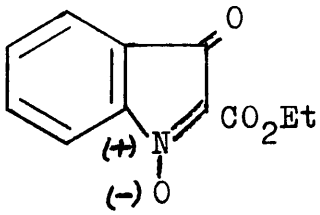

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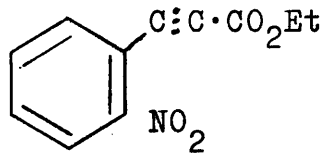

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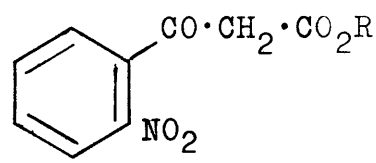

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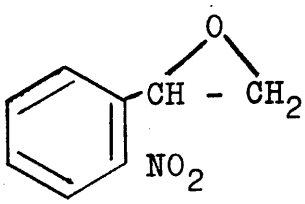

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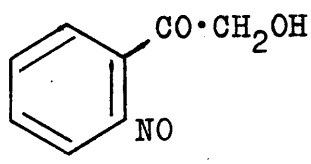

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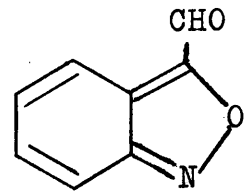

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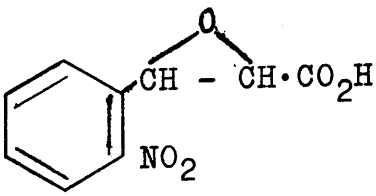

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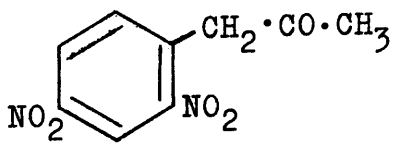

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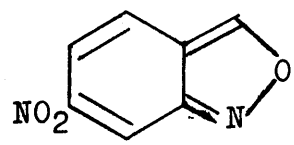

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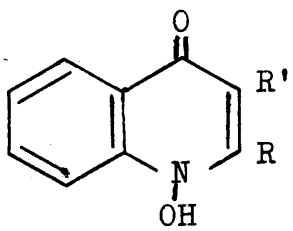

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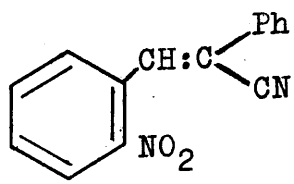

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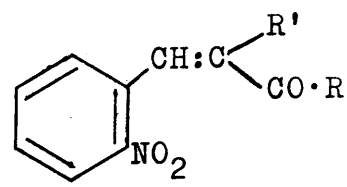

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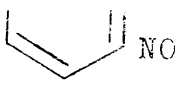

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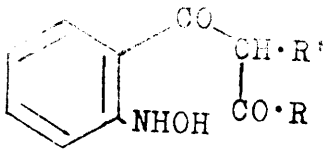

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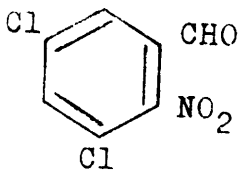

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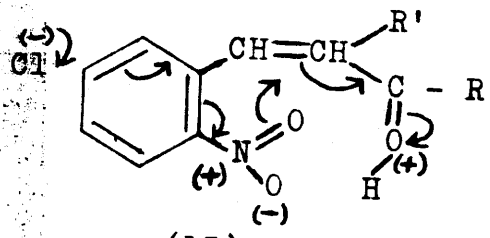

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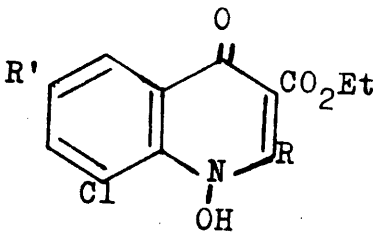

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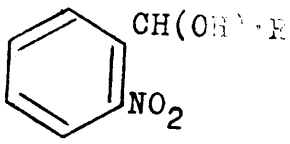

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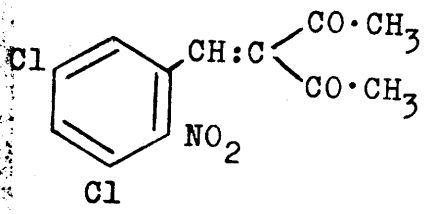

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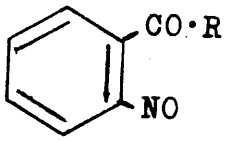

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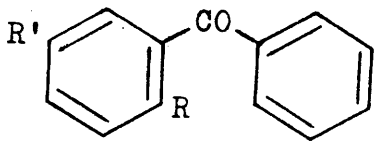

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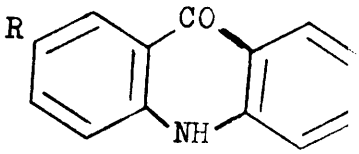

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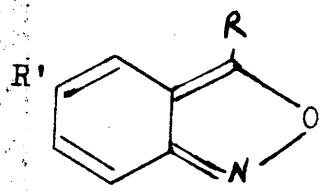

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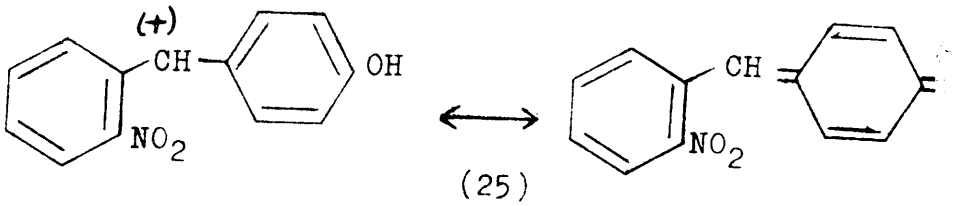

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CHAPTER 3

REARRANGEMENT OF QUINOLINE N-ACETATES

INTRODUCTION

Heteroaromatic N-oxides, when heated with carboxylic acid anhydrides, are acylated with rearrangement to the corresponding 2-acyloxyheterocycles, examples having been reported in the pyridine[1,2], quinoline[3,4], iso-quinoline[5], and benzimidazole[3] series. Thus reaction of pyridine N-oxide (1) with acetic anhydride gives 2-acetoxy-pyridine (2).

However, when an alkyl group is in the 2- or 4-position, rearrangement gives the corresponding 2- or 4-acyloxyalkyl derivative, the acetoxy group having displaced an α-hydrogen of the side chain. This was first reported by Japanese workers[6] who, by treating 2-picoline N-oxide (3) with acetic anhydride, obtained, after hydrolysis, 2-hydroxymethylpyridine (4). The reaction was discovered independently by two American groups[2,7] and examples of this type of rearrangement are now known in the pyridine[2,7,8], quinoline[2], and pyrimidine[9] series.

While a convenient route to heterocyclic carbinols is thus available, attempts to extend the reaction to the preparation of carbonyl compounds have proved less successful. The best method of synthesis of pyridine-2-aldehyde (6) is provided by repetition of the N-oxide rearrangement,

the product (5) of primary rearrangement of 2-picoline N-oxide (3) being oxidised again to an N-oxide which is reacted with acetic anhydride to give, after hydrolysis, the pyridine aldehyde in 36% overall yield.[2] This approach, however, proved less satisfactory in other cases, the N-oxide (7), on treatment with acetic anhydride, giving the 2,6-diacetoxymethylpyridine (8),[2] while an attempted analogous synthesis of a 2-pyridylketone failed when it proved impossible to rearrange 2-(α-acetoxyethyl) pyridine N-oxide (9).[2]

Both ionic and free-radical mechanisms have been proposed for the rearrangement of the type exemplified by the conversion of the N-oxide (3) into the rearranged ester (5) by acetic anhydride. Each involves as the initial step the formation of 1-acetoxy-2-methylpyridinium acetate (10).

The ionic path was suggested by Pachter[10] to explain a similar rearrangement in which quinaldine N-oxide (11) was transformed by benzoyl chloride and alkali into the 2-benzoyloxymethylquinoline (12), and was extended to the pyridine system by others.[2,8] This pathway proceeds through the anhydro base (13) which results from the N-acetate by abstraction of an acidic hydrogen from the 2-methyl group by acetate ion. Conversion to

2-acetoxymethylpyridine follows either by an intramolecular cyclic rearrangement (14a),[11] or by a nucleophilic attack of acetate anion on the methylene carbon with elimination of acetate anion (14b).[10]

Evidence for the intramolecular nature of the rearrangement was provided by the fact that no 2-acetoxymethylpyridine was isolated when 2-picoline N-oxide was reacted with butyric anhydride and sodium acetate.[11] Japanese workers[12] rejected such ionic mechanisms because of the discordance between the calculated and found enrichment of the products (4) and (5) by ^{18}O derived from ^{18}O-enriched acetic anhydride.

Since for many of the examples investigated there was an induction period followed by an exothermic reaction, a chain reaction involving radicals was suggested.[2] A proposed free-radical chain mechanism[13] involves homolytic cleavage of the nitrogen oxygen bond in the N-acetate leading to the chain reaction shown in scheme (a). The rate of the reaction was found to be little affected by the nature of the solvent, even with solvents varying in polarity over the range from acetonitrile to benzene, and this was considered compatible with a free-radical reaction but difficult to explain on the basis of an ionic mechanism. Further, the isolation of polystyrene was

reported when the reaction was performed in the presence of styrene.

A free-radical chain reaction was rendered unlikely by the work of Traynellis and Martello[11] who established that the addition of inhibitors in sufficient concentration drastically to decrease or stop polymerisation of styrene had little effect upon the yield of product ester. Thus the free radicals present did not appear to be involved in the origin of the product. Traynellis and Martello suggested that the anhydro base (13) might react by cleavage of the nitrogen oxygen bond, either homolytically or heterolytically, the two parts then recombining to give the ester product. This mechanism, involving homolytic cleavage of the nitrogen oxygen bond, is favoured by the Japanese group[12] on the basis of results obtained in tracer experiments using ^{18}O-enriched acetic anhydride. The found enrichment of the products (4) and (5) suggests that the reaction proceeds via a free-radical pair in a solvent cage.

In a similar investigation into the mechanism of rearrangement of 4-picoline N-oxide, Traynellis and Martello[14] found that by having present a sufficiently high concentration of inhibitor they were able to decrease the yield of product. This is an accord with the concept of

a radical pair undergoing an intramolecular rearrangement, when a relatively high concentration of inhibitor is necessary before intervention is significant.

In reactions of this kind, minor products are sometimes obtained, resulting from the acetoxy group substituting in the β-position in the ring.[8,14,15,16] Rearrangement of 2-picoline N-oxide has been reported[15] as giving 3- and 5-hydroxy-2-methylpyridine, (15) and (16), in addition to the main product 2-hydroxymethylpyridine (4). This behaviour is compatible with the 2-picolyl radical being an intermediate. Of the contributing structures (A) - (D), (B), because of the resonance stabilisation derived from the intact aromatic ring, might be expected to make the greatest contribution to the total structure of the hybrid. Hence the major product should result by attachment of the acetoxy radical to the side chain, as found, with minor products corresponding to combination at the β-positions in the ring.

3-Ethoxycarbonylquinoline N-Acetate

In the course of work mentioned in the previous section, Wellings[17] found that monoacetylation of the tautomeric N-oxide (17) gave an N-acetate (18) whose formation and infra-red frequency (1800 $cm.^{-1}$) had

diagnostic value for the presence of the N-hydroxy-structure. However the formative conditions required careful control, and use of more vigorous conditions gave a compound A, whose analysis suggested it to be isomeric with the N-acetate (18).

Repetition of Wellings' procedure yielded two compounds, A and B, with almost identical analysis figures. The infra-red spectra of both products contained an ethoxycarbonyl band, while A showed an acetate carbonyl at 1776 $cm.^{-1}$ and B showed a carbonyl band at 1746 $cm.^{-1}$ These spectra were perplexing, and the situation was not resolved by the discovery that on heating with acetic anhydride, B was converted into A. In the end the simplest interpretation of this finding proved correct, namely that the function of the acetic anhydride was merely to introduce a second acetyl group into B. The fact that A was a diacetate was not immediately obvious, since the analysis figures and the infra-red spectrum were both consistent with its formulation as a monoacetate. Inspection of the analysis figures for A revealed that these also fitted a diacetate and the presence of two acetate groups was then confirmed by an O-acetyl analysis.

Redetermination of the infra-red spectrum of A, using the Unicam S.P.100, resolved the anomaly. Using a nujol

mull preparation, it was seen that the second acetate peak appeared as a shoulder (1737 $cm.^{-1}$) on the ethoxycarbonyl band (1733 $cm.^{-1}$). A spectrum run in carbon tetrachloride gave three well-resolved bands at 1790, 1750 (acetates), and 1733 (ester) $cm.^{-1}$. The frequency of the infra-red band at 1776 $cm.^{-1}$ in the spectrum of A corresponds to a phenolic acetate, while the spectrum of B shows a band at 1746 $cm.^{-1}$ which is assigned as a benzylic acetate, this latter peak being moved to lower frequency (1737 $cm.^{-1}$) in the nujol mull spectrum of A.

Structures for A and B consistent with the above information are given by (19) and (20) respectively.

In order to minimise the formation of acetic acid which was found to convert di- into monoacetate, experiments using acetic anhydride were conducted on the N-acetate (18) rather than on the N-oxide (17). In all reactions carried out in acetic anhydride, the solution became very deep red, and the product required considerable purification, resulting in loss of material. In acetic anhydride as solvent, 1 g. of N-acetate gave, after 1 hour's refluxing, 0.32 g. of diacetate (19) and 0.38 g. of monoacetate (20).

In an attempt to reduce the decomposition taking place in acetic anhydride solution, and since the acetic

anhydride seemed to be acting merely as a base in the conversion of the N-acetate (18) into monoacetate (20), it was decided to try to effect this reaction in pyridine. At room temperature no reaction was detected after 3 days, while using reflux conditions, although the necessary reaction time was reduced to half an hour, the product still proved difficult to purify. 1 g. of N-acetate gave 0.46 g. of monoacetate using this method.

It was noticed that a solution of the N-acetate in acetic acid coloured very rapidly on warming. This observation led to the discovery that the rearrangement of N-acetate to monoacetate is also acid-catalysed, and indeed the acid-catalysed reaction has proved the most successful. The optimum conditions for the rearrangement involve heating the N-acetate in acetic acid at 100° for half an hour. This procedure effects complete conversion of N-acetate to monoacetate with the minimum decomposition. In acetic acid, 1 g. of N-acetate gave 0.70 g. of monoacetate. The diacetate is readily obtained by acetic anhydride treatment of monoacetate.

To test whether the rearrangement could be effected without a catalyst, and also to determine whether the contamination of the product was simply due to thermal decomposition of the N-acetate (18), (18) was heated at

100° for 2 hours in toluene. The toluene remained a pale yellow colour throughout, no trace of rearranged product (20) was detected, and decomposition was negligible.

The evidence so far presented for the structure of A is in complete accord with its representation as (19). The number of acetate groups was given by an O-acetyl analysis, and this was confirmed by the infra-red spectrum which further indicated that one was a phenolic acetate and the other a benzylic acetate. The diacetate was produced by acetylation of the monoacetate B, reaction being marked by the appearance of an acetate frequency (1776 $cm.^{-1}$) assigned as phenolic acetate.

The structure of the diacetate (19) was confirmed by a stepwise degradation to establish the relative positions of the functional groups.

The diacetate contained one very labile acetate group which, as already stated, could be removed by treatment with warm glacial acetic acid. The infra-red spectrum of the product (20) lacked the phenolic acetate peak (1776 $cm.^{-1}$), showed the carbonyl frequency (1746 $cm.^{-1}$) expected for a benzylic acetate[18a], and a band at 1700 $cm.^{-1}$ attributed to the ethoxycarbonyl group (expected frequency would be $\sim$1720 $cm.^{-1}$ [18a]), and contained a new band (1616 $cm.^{-1}$) characteristic of a

4-quinolone.[19] The monoacetate gave an orange-red colour with alcoholic ferric chloride, in contrast to the N-acetate and diacetate which caused no colour change.

The above information is consistent with B being related to A as mono- (20) to diacetate (19).

Both acetates gave a clear solution with cold dilute alkali, acidification giving the same product which was relatively insoluble in the common organic solvents. The ready solubility of the monoacetate (20) derives from the 4-quinolone system, which is produced in the case of the diacetate (19) by rapid hydrolysis of the labile phenolic acetate group.

The analysis of the product and its infra-red spectrum, containing a single carbonyl band (1740 $cm.^{-1}$) in addition to the quinolone carbonyl band (1620 $cm.^{-1}$), were in accord with the lactone structure (21). The infra-red frequency of a phthalide carbonyl is quoted as $\sim$1750 $cm.^{-1}$ [18b], and it seems that hydrogen bonding here lowers the frequency of the 3-carbonyl function in both this compound and the monoacetate (20). The same compound (21) was also obtained from either (19) or (20) by acid hydrolysis.

The lactone was recovered unchanged from boiling dilute alkali, but heating in concentrated alkali gave the hydroxyacid (22). Since acidification of an alkaline

solution of the hydroxyacid did not cause lactonisation, it would appear that dilute alkali is unable to open the lactone ring. It seems likely that the enhanced stability of the lactone is derived from the presence of the 4-hydroxyquinoline anion which would be expected to hinder approach of a negative species to the lactone ring.

The hydroxyacid was soluble in sodium hydrogen carbonate solution and was reconverted into the lactone by acetic anhydride. The infra-red spectrum showed bands at 3,295 (OH), 1660 (hydrogen bonded aromatic carboxylic acid), and 1620 (quinolone) $cm.^{-1}$ Unlike the lactone, the acid gave a weak orange colour with alcoholic ferric chloride.

Decarboxylation in boiling quinoline afforded the hydroxymethylquinoline (23), whose infra-red spectrum contained the expected bands at 3030 (bonded OH), and 1615 (quinolone) $cm.^{-1}$, and which gave a pale orange colour with alcoholic ferric chloride. The molecular weight was confirmed by a mass spectrometric determination.

The above degradative evidence is in accord with the structure (19) for the diacetate which is thus considered to be confirmed.

3-Acetylquinoline N-Acetate

Attempts to extend this enquiry to compounds derived from the 1-hydroxyquinolone (24)[17], wherein the complicating ethoxycarbonyl is lacking, met with disappointment in that rearrangement in this series proceeded more slowly, and the compounds proved more liable to decomposition. Whereas the ester (17) was converted into the N-acetate (18) by warming at 100° for 3 minutes in acetic anhydride, longer heating causing the appearance of rearrangement products, (19) or (20), the ketone (24) gave only N-acetate after warming at 100° for 15 minutes.

The N-acetate decomposed extensively on heating, and proved very slow to rearrange. Pyridine treatment at 100° for 1 hour produced only a trace of rearranged product (25), though heating in acetic anhydride - sodium acetate for 2 hours at 100° caused partial conversion of N-acetate into monoacetate (25). Heating in boiling acetic acid for half an hour did not cause complete conversion of N-acetate into monoacetate (25), and the product was contaminated with resinous material.

In an effort to avoid the use of heat in the rearrangement, catalysis by mineral acids was tried. A solution of the N-acetate in acetic acid containing a catalytic amount of concentrated sulphuric acid gave only

the hydrolysis product (24). A similar result was obtained by treating an ethereal solution of the N-acetate with dry hydrogen chloride gas.

The infra-red spectrum of the monoacetate (25) showed only two carbonyl bands, at 1740 (benzylic acetate) and 1660 (ketone) $cm.^{-1}$ The fact that no quinolone carbonyl band could be seen, added to the presence of a band at 3330 (bonded OH) $cm.^{-1}$, suggests that, in contrast to the analogous compound (20), the monoacetate exists largely in the form (26). The monoacetate gave a pale amber colour in alcoholic ferric chloride.

In view of the difficulties experienced in this series due to the instability of the compounds and the decreased rate of rearrangement, it was decided to discontinue work on this line.

Discussion of Mechanism

Whereas in 1-acetoxyquinaldinium acetate (27), presumed to be the immediate product of attack by acetic anhydride on quinaldine N-oxide, the methyl substituent is activated by a cationic ring, a different situation obtains in the acetate (28) which is formed when the ring carries a 4-hydroxyl group. Here the activating nucleus is neutral and hence less effective.

Heterocyclic N-oxides with a 2- or 4-methyl group readily react with aldehydes under mild basic conditions (e.g. (29)→(30)), while nitrogen heterocycles with a 2- or 4-hydroxyl group as well as a 4- or 2-methyl group (e.g. (31)), will not condense with aldehydes.[20] Thus the base-catalysed rearrangement of the acetate (28), depending as a first step on the removal of a methyl proton, would be expected to proceed less readily than in the case of quinaldine N-acetate itself.

No example can be found in the literature of an acetate rearrangement having been carried out in a ring with a 2- or 4-hydroxyl group as well as a 4- or 2-methyl group. The work described in this section involves such a rearrangement.

A possible path for the acetic anhydride induced rearrangement of the N-acetate (18) to the diacetate (19) is shown in scheme (b), acetic anhydride acting as a weak base to give the anhydro base (32) which is then rearranged and acetylated to give (19), or else acetylation precedes rearrangement, the reaction then involving the intermediate (33) as shown. On the available evidence one cannot distinguish between the two possible pathways. When the reaction is effected in the stronger base pyridine, the rearrangement (18) →(20) must involve either the anhydro

base (32) or its conjugate acid (34).

Since protonation of the N-acetate (18) would cause increased activation of the methyl group by the cationic ring (35), an explanation of the rearrangement as catalysed by acetic acid is provided. Moreover, since diacetate formation is both unlikely and unobserved under these conditions, the reaction appears to be the equivalent of that effected by acetic anhydride on compound (27).

[illegible] the free base. Crystallisation from [illegible] g., m.p. 226°. (decomp.).

[illegible] experiments the ester product was contaminated with [illegible] carboxylic acid (17; CO_2H for CO_2Et). To prevent [illegible] anhydrous magnesium sulphate (1 g.) was added [illegible] solution before saturation with hydrogen [illegible] and was separated from the product by dissolu- [illegible] ether.

[illegible] was formed by warming the N-oxide [illegible] anhydride (0.1 ml.) at 100° until

EXPERIMENTAL

6-Chloro-3-ethoxycarbonyl-4-hydroxy-2-methylquinoline 1-Oxide (17).[17]

A solution of o-nitrobenzaldehyde (3.02 g.) and ethyl acetoacetate (2.6 ml.) in dry ether (7 ml.) was saturated with dry hydrogen chloride, the solution being cooled in a water-bath. After 24 hr., the crystalline precipitate was filtered off, and the filtrate was resaturated with hydrogen chloride. At the end of a further 24 hr. the precipitate was collected, and the combined solids, the hydrochloride of the cyclic ester (17), were treated with water to liberate the free base. Crystallisation from ethanol gave 3.8 g., m.p. 226° (decomp.).

In some experiments the ester product was contaminated with the carboxylic acid (17; CO_2H for CO_2Et). To prevent hydrolysis, anhydrous magnesium sulphate (1 g.) was added to the ethereal solution before saturation with hydrogen chloride, and was separated from the product by dissolution in water.

The N-Acetate of (17)[17] was formed by warming the N-oxide (0.1 g.) in acetic anhydride (0.1 ml.) at 100° until solution was complete. The solution was cooled and diluted with ether to give the N-acetate (18), m.p. 152°

(from ethanol).

The N-acetate (18) (0.1 g.) was heated at 100° in dry toluene (3 ml.) for 2 hr. On cooling, the pale yellow solution deposited unchanged N-acetate (0.084 g.), identified by m.p. and infra-red spectrum. Evaporation of the toluene gave more N-acetate. This material ran on a Kieselgel chromatoplate ($CHCl_3$) as two spots. One corresponded to N-acetate, the other was unidentified, not being due to product (20).

4-Acetoxy-2-acetoxymethyl-6-chloro-3-ethoxycarbonyl-quinoline (19)

(a) The N-acetate (18) (1 g.) was refluxed in acetic anhydride (5 ml.) for 1 hr. The acetic anhydride was removed under reduced pressure, and the brown solid was dissolved in the minimum amount of hot ethanol. Crystallisation gave largely the diacetate (19), which formed colourless needles, m.p. 127° (0.32 g.; from ethanol, after treatment with charcoal), $\nu_{max.}$ 1776, 1737 (sh.), 1733 $cm.^{-1}$, $\nu_{max.}$ (CCl_4) 1790, 1750, 1733 $cm.^{-1}$ (Found: C, 55.5; H, 4.3; N, 4.1; OAc, 31.3. $C_{17}H_{16}ClNO_6$ requires C, 55.8; H, 4.4; N, 3.8; 2 x OAc, 32.3%).

(b) Diacetate (19) was formed by heating the monoacetate (20) (0.1 g.) in acetic anhydride (2 ml.) for 2 hr. at 130°.

2-Acetoxymethyl-6-chloro-3-ethoxycarbonyl-4-hydroxyquinoline (20)

(a) The mother liquor from the crystallisation in (a) above, on crystallisation, afforded the monoacetate as cream needles, m.p. 206° (0.38 g.; from ethanol, after charcoal treatment), $\nu_{max.}$ 1746, 1700, 1616 (m) cm.$^{-1}$, giving an orange-red colour with alcoholic ferric chloride (Found: C, 55.5; H, 4.3; N, 4.2. $C_{15}H_{14}ClNO_5$ requires C, 55.6; H, 4.3; N, 4.3%).

(b) The N-acetate was unchanged by pyridine at room temperature.

The N-acetate (0.5 g.) in dry pyridine (3 ml.) was refluxed for 30 min. The pyridine was removed under reduced pressure, and crystallisation from ethanol (charcoal) gave 0.23 g. monoacetate.

(c) The N-acetate was unchanged by acetic acid at room temperature.

The N-acetate (0.5 g.) in glacial acetic acid (3 ml.) was heated at 100° for 30 min. The solvent was removed under reduced pressure, and crystallisation gave 0.35 g. monoacetate (from ethanol).

(d) The diacetate (19) was converted into the monoacetate (20) on being heated in glacial acetic acid at 100° for 30 min.

6-Chloro-4-hydroxy-2-hydroxymethyl-3-quinolinecarboxylic Acid Lactone (21)

(a) The diacetate (19) or monoacetate (20) was dissolved in warm dilute sodium hydroxide and the solution was made just acid with dilute hydrochloric acid. The precipitated solid was filtered off, washed with water, and crystallised from aqueous dimethylformamide to give the lactone (21) as colourless needles, m.p. $> 360°$. The crystalline material contained occluded dimethylformamide, and for analytical purposes the purified compound was dissolved in hot ethylene glycol, and the solution was cooled to precipitate the non-crystalline but solvent-free lactone, m.p. $> 360°$, $\nu_{max.}$ 1740, 1620 $cm.^{-1}$ (Found: C, 55.8; H, 2.6; N, 5.9. $C_{11}H_6ClNO_3$ requires C, 56.1; N, 2.6; N, 5.9%).

(b) Water (4 ml.) was added to a refluxing solution of mono- (20) or diacetate (19) (0.2 g.) in glacial acetic acid (2 ml.) and concentrated sulphuric acid (0.3 ml.). A colourless precipitate appeared after ~ 2 min., the cooled mixture was treated with water (10 ml.), and the crude lactone was collected by filtration.

0.2 g. (19) gave 0.11 g. lactone.

0.2 g. (20) gave 0.14 g. lactone.

(c) The hydroxyacid (22) (0.1 g.) was heated at 130° in acetic anhydride (3 ml.) for 30 min. Cooling and filtering gave the lactone (0.08 g.) identified by its infra-red spectrum.

3-Carboxy-6-chloro-4-hydroxy-2-hydroxymethylquinoline (22)

(a) The lactone (21) (0.12 g.) was refluxed in sodium hydroxide solution (3 ml., 15%) for 5 min. The cooled solution was made just acid (conc. sulphuric acid) then filtered to recover the crude product (22) (0.1 g.) which, after washing with water, was crystallised from aqueous dimethylformamide to give colourless needles, m.p. ~ 270° (decomp.), $\nu_{max.}$ 3295, 1660, 1620 cm.$^{-1}$, giving a weak orange colour with ferric chloride in ethanol. (Found: C, 52.2; H, 3.0; N, 5.3. $C_{11}H_8ClNO_4$ requires C, 52.1; H, 3.2; N, 5.5%).

(b) The monoacetate (0.97 g.) was boiled in sodium hydroxide solution (20 ml., 15%) for 5 min. The solution was cooled, water being added if necessary to keep the sodium salt in solution, carefully acidified (conc. sulphuric acid), and filtered. Crystallisation from aqueous dimethylformamide gave 0.57 g. acid.

6-Chloro-4-hydroxy-2-hydroxymethylquinoline (23)

The acid (22) was unchanged by refluxing pyridine.

The acid (0.2 g.) in quinoline (2 ml.) was refluxed for 10 min., during which time a precipitate separated. The cooled mixture was diluted with ether, filtered, and the residue (0.13 g.) was washed with ether. Crystallisation from dimethylformamide gave cream plates, m.p. ~295° (decomp.), $\nu_{max.}$ 3030, 1615 (m) $cm.^{-1}$ The analytical sample was purified by sublimation, and gave a weak orange colour with ferric chloride in ethanol. (Found: C, 57.4; H, 4.2; N, 7.0. $C_{10}H_8ClNO_2$ requires C, 57.3; H, 3.9; N,6.7%).

Mass spectrometric molecular weight determination (Found: 209.5; $C_{10}H_8ClNO_2$ requires 209.6).

3-Acetyl-6-chloro-4-hydroxy-2-methylquinoline 1-Oxide (24)[17]

A solution of o-nitrobenzaldehyde (3.02 g.) and acetylacetone (2.06 ml.) in dry ether (15 ml.) was saturated with dry hydrogen chloride at room temperature. After 36 hr., the mixture was filtered, and the filtrate was resaturated with hydrogen chloride. After a further 12 hr. the product was filtered, and the combined solids, the hydrochloride of the cyclic ketone (24), were treated with water to liberate the free base, which was crystallised from dimethylformamide to give 4 g. (24), m.p. 286° (decomp.).

The N-Acetate[17] of (24) was formed by warming the N-oxide (0.2 g.) in acetic anhydride (5 ml.) at 100°, m.p. 166° (from ethanol).

2-Acetoxymethyl-3-acetyl-6-chloro-4-hydroxyquinoline (25)

(a) The N-acetate (0.1 g.) and fused sodium acetate (0.1 g.) were heated at 100° in acetic anhydride for 2 hr. The acetic anhydride was removed under reduced pressure, and the organic material was separated by chloroform extraction of the residue. After 2 crystallisations from chloroform-petrol (charcoal), the monoacetate (25) was obtained as colourless needles (0.03 g.), m.p. ~190° (decomp.), rapid heating being required, $\nu_{max.}$ 3330, 1740, 1660 cm.$^{-1}$ (Found: C, 57.4; H, 4.2; N, 5.0. $C_{14}H_{12}ClNO_4$ requires C, 57.3; H, 4.1; N, 4.8%). The monoacetate gave a pale amber colour with alcoholic ferric chloride.

(b) The N-acetate (0.45 g.) was refluxed in acetic acid (10 ml.) for 30 min., and the solvent was then removed under reduced pressure. The crude product (infra-red spectrum showed a band at 1800 cm.$^{-1}$ characteristic of the N-acetate grouping) was largely dissolved in chloroform, filtered, and the solution was concentrated to give relatively clean crystals followed by a brown solid. At

this point the precipitated solid was filtered off, and crystallised twice (from chloroform-petrol, after charcoal treatment) to give monoacetate (0.14 g.).

Use of Mineral Acid Catalysis

(a) A solution of N-acetate (0.1 g.) in glacial acetic acid (2 ml.) and concentrated sulphuric acid (3 drops) was left at room temperature for 1 hr. The solution was poured into ice-water, and the precipitated solid was filtered (infra-red spectrum indicated presence only of (24)), and crystallised to give N-oxide (24) (0.07 g.; from dimethylformamide).

(b) A solution of N-acetate (0.04 g.) in dry benzene (10 ml.) and dry ether (90 ml.) was saturated with dry hydrogen chloride with careful exclusion of moisture. After 18 hr., the solvent was removed under reduced pressure and the residue was crystallised to give N-oxide (24) (0.025 g.; from ethanol), m.p. 284° (decomp.). The ethanol mother liquor was concentrated to give a solid whose infra-red spectrum indicated the presence of only N-oxide.

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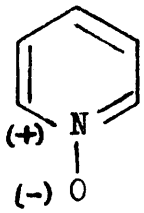

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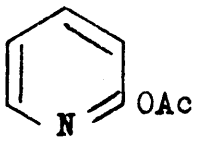

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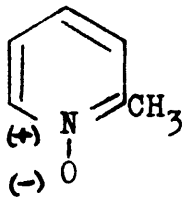

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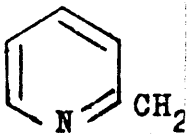

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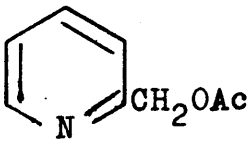

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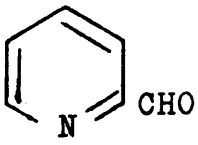

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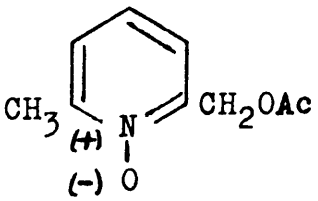

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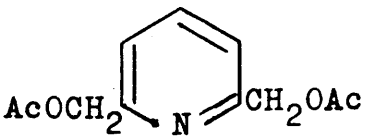

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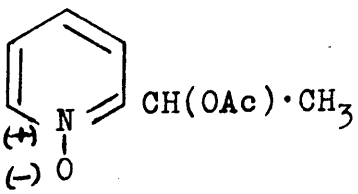

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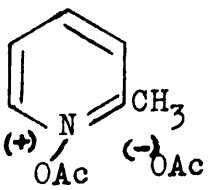

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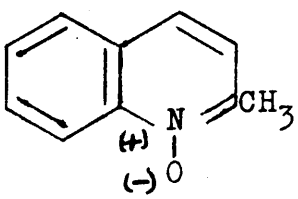

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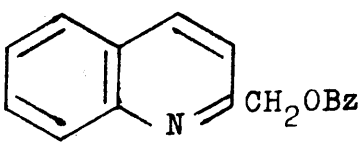

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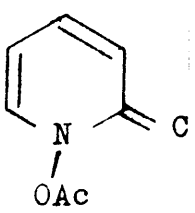

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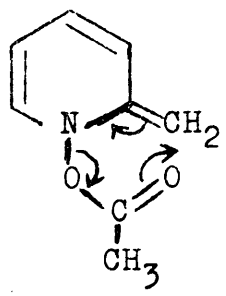

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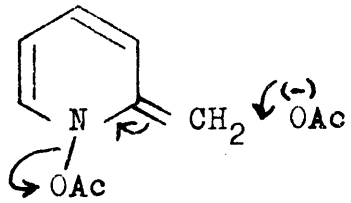

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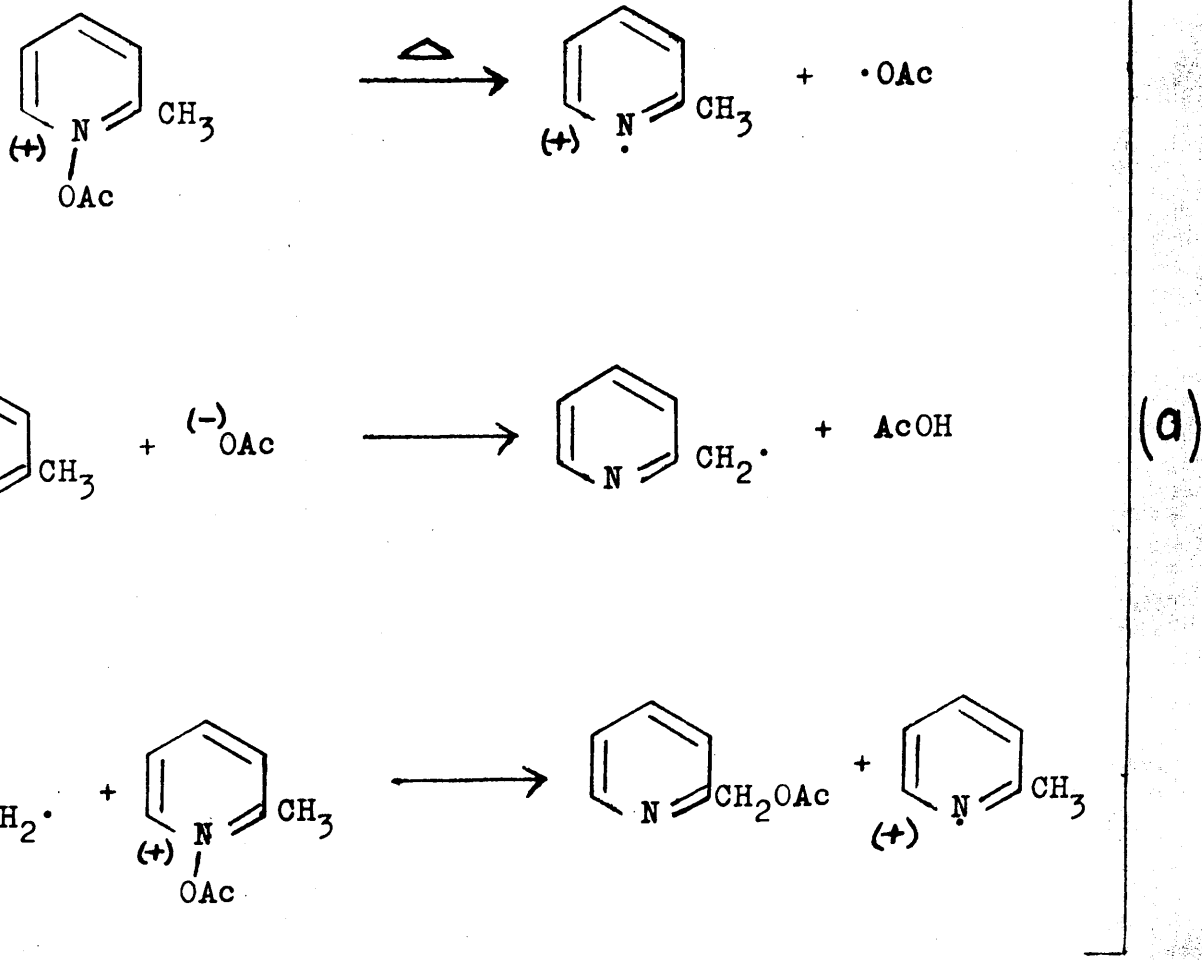

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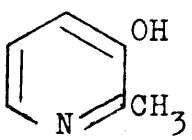

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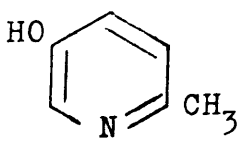

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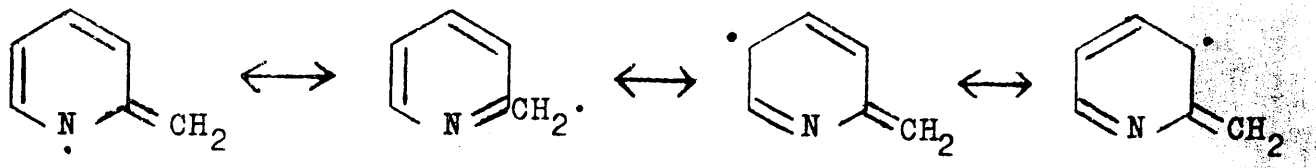

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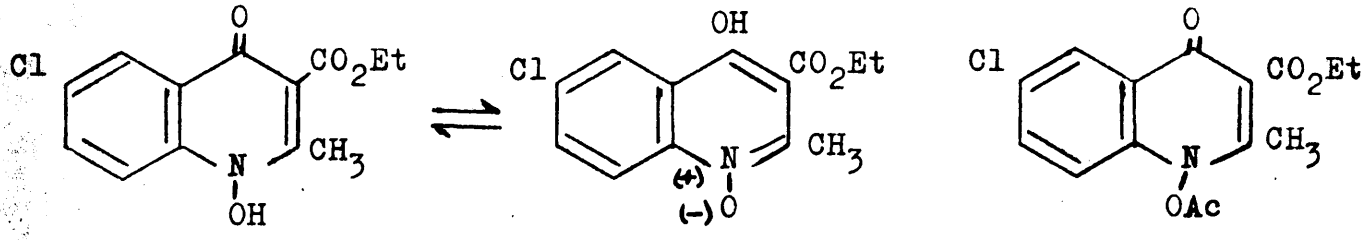

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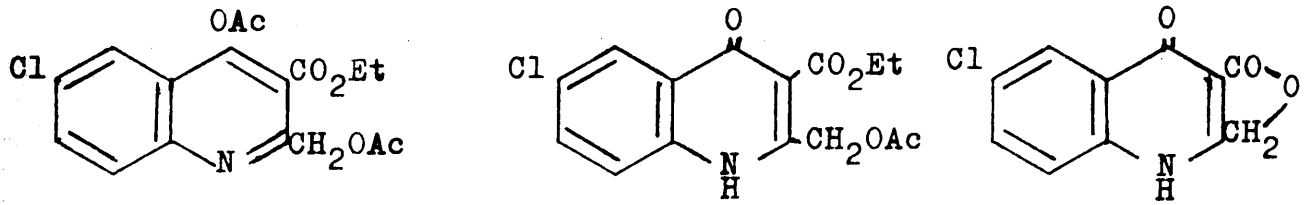

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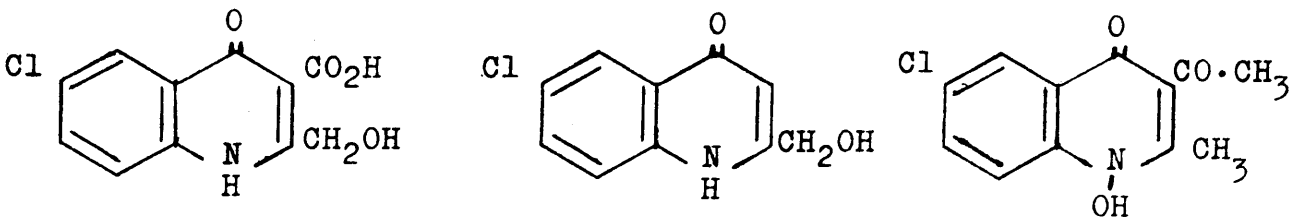

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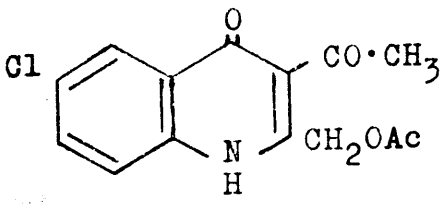

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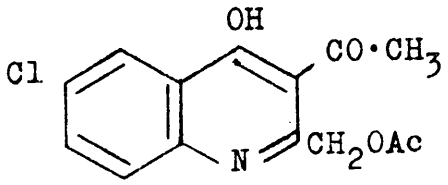

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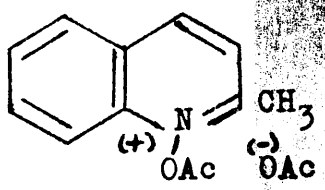

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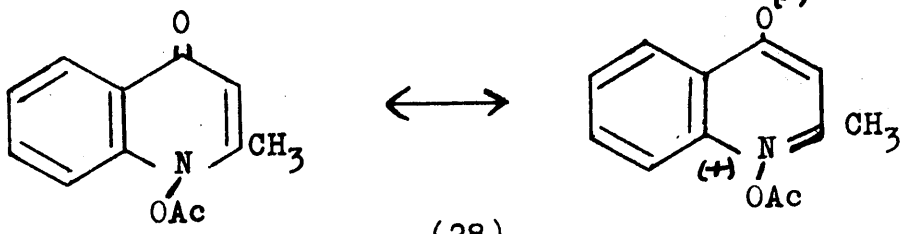

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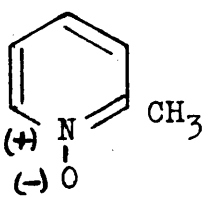

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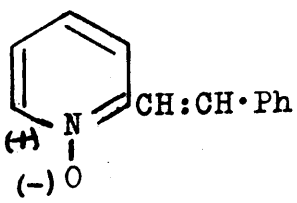

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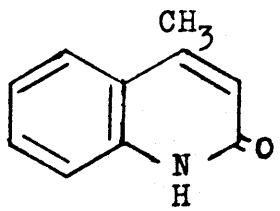

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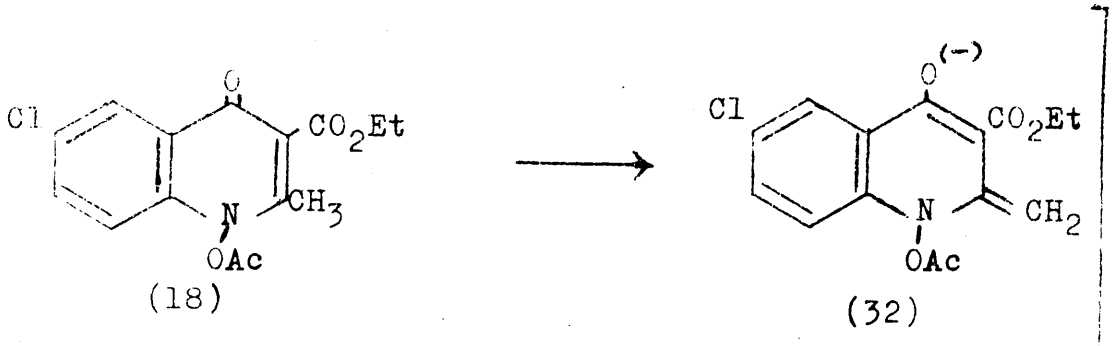

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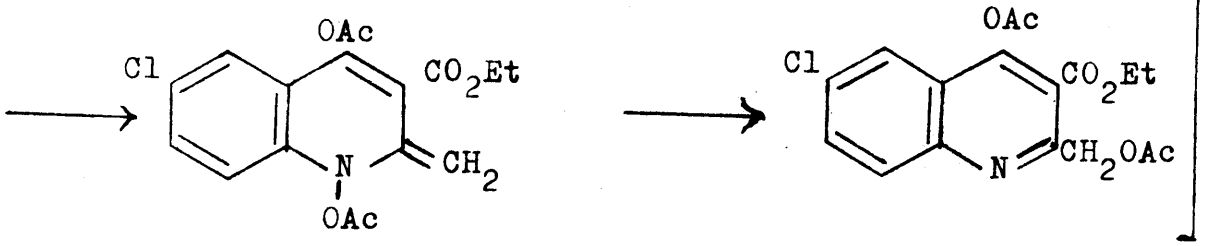
(b)



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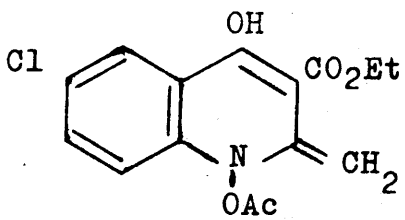

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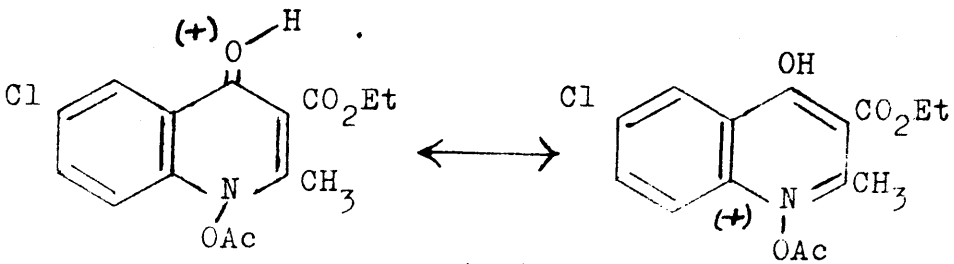

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