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Thesis

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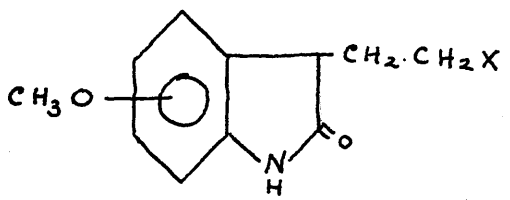
PREFACE

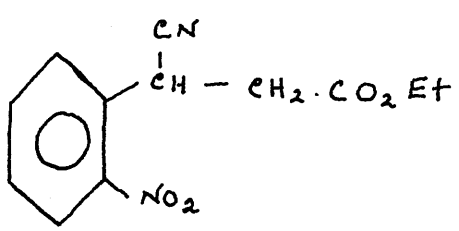
The work described in this thesis emerged from a project related to the chemistry of mitragyna alkaloids and designed to discover a flexible synthesis of 3-substituted oxindoles of type I.



I

where x = OH, NR_2, or halogen.

Ethyl β-cyano-β-o-nitrophenylpropionate II, was considered a suitable starting compound on which to model such a synthesis, which would proceed by elaboration of the requisite side chain from the ester grouping, followed by oxindole ring-formation through the cyano- and nitro-groups.



II

It was realised from the start that the nitro-group could be a complicating factor in this scheme, and in fact, as the work progressed, the original project was completely superseded by the challenge and interest of the novel reactions encountered. These reactions and their study form the subject matter of this thesis.

CONTENTS

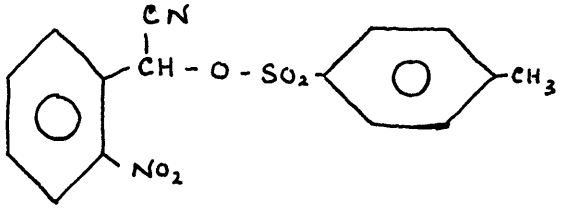
CHAPTER I

Studies in Mandelonitrile Sulphonates

CONTENTS

DISCUSSION

The well established alkylating properties of alkyl arenesulphonates suggested the possibility of forming diethyl (α-cyano-2-nitrobenzyl)-malonate (II) by condensation between diethyl sodiomalonate and α-cyano-2-nitrobenzyl toluene-p-sulphonate (I).



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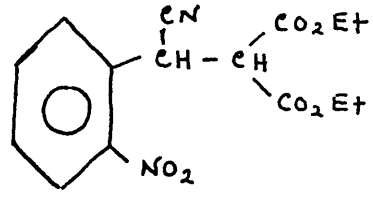
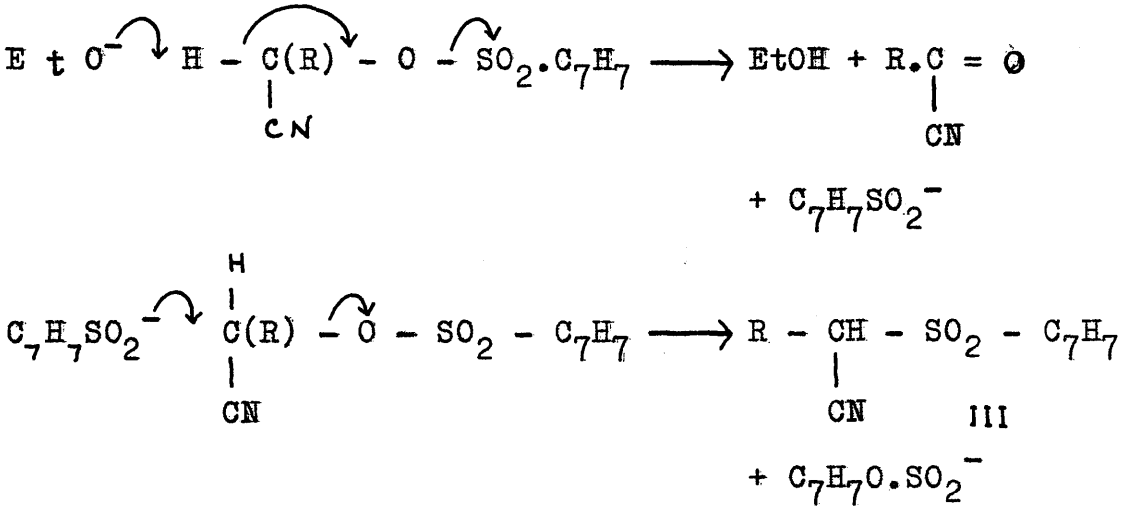


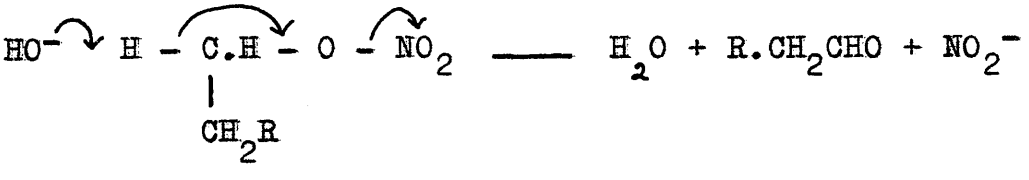
II

In practice the product [$C_{15}H_{12}O_4N_2S$] isolated from this attempted condensation differed from the reagent tosylate (I) in having one oxygen atom less in its molecular formula. This surprising result became more intelligible when it was found that the tosylate (I) reacted in a normal way with sodium toluene-p-sulphinate affording the sulphone (III) and that this sulphone was indeed the unexpected product [$C_{15}H_{12}O_4N_2S$]. It thus became clear that the diethyl malonate plays only a minor role in the original reaction and that the tosylate (I) might be

providing as well as reacting with toluene-p-sulphinate anions in the alkaline environment. Later work showed that this was indeed the case.



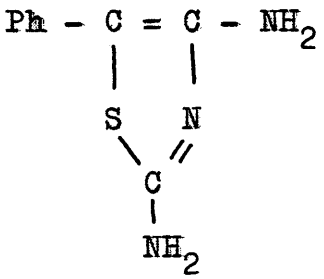
This is the only case of sulphinate elimination from a sulphonic ester known to the author, although sulphinate elimination from sulphonamides has been reported[1,2]. A close analogy to this reaction is found in the work of Baker and others on the hydrolytic elimination of nitrite from nitric esters[3] which takes place in the following manner:-



Few α-cyanobenzyl sulphonates have been reported

in the literature, as the method of preparation[4,5] consisting of the interaction of an arylaldehyde, potassium cyanide, and a sulphonyl chloride in water, is very limited. A more general synthesis was achieved in many cases by the use of an aqueous-dioxan medium for the reaction (see Experimental section).

The sulphonates have been studied mainly in the role of non-lachrimatory substitutes for α-cyanobenzyl halides, in which they react with thiourea[5] to form the substituted thiazole(IV)



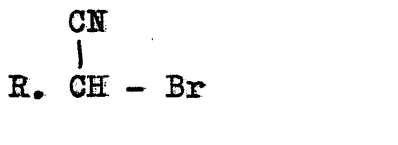
IV

They react similarly with the substituted thioureas, dithiocarbamates, or thioamides[6], forming the corresponding derivatives of thiazole. With sulphonyl chlorides in the presence of thiourea they form alkyl- or aryl-sulphonyl-acetonitriles[7], and with aluminium chloride and aromatic hydrocarbons they undergo Friedel-Crafts reactions to give diarylacetonitriles[8] of type,(V)

V

The above examples of nucleophilic substitution of the α-cyanobenzyl sulphonates, with displacement of the sulphonate group, were extended in a series of experiments which, while not comprehensive, were designed to show the general nature of this type of substitution.

On attack by bromide, mercaptide, p-nitrophenoxide and toluene-p-sulphinate ions the sulphonates afforded the corresponding α-cyanoalkylbromide, (VI), the thioether, (VII), the ether, (VIII), and the sulphone, (IX).



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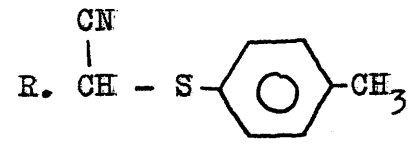
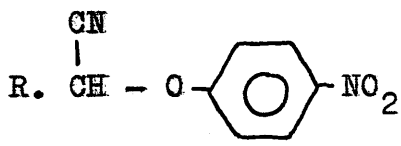
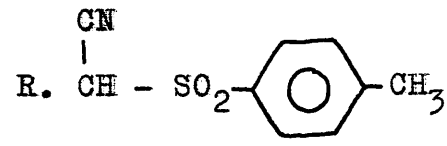


VII



VIII



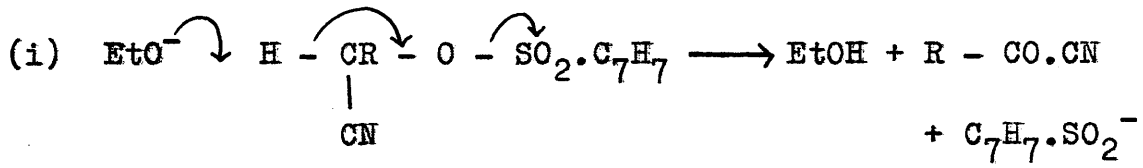
IX

The analogous formation of ethers and thioethers from nitric esters[9], by nucleophilic attack on the α-carbon atom of the nitrate, demonstrates a further similarity

between the reactions of these two series of esters.

Hydrogenation of α-cyano-2-chlorobenzyl toluene-p-sulphonate over a palladised charcoal catalyst occurred with the uptake of three moles of hydrogen yielding 2-chlorophenethylamine. In this respect the sulphonates resemble the O-acylmandelonitriles[10].

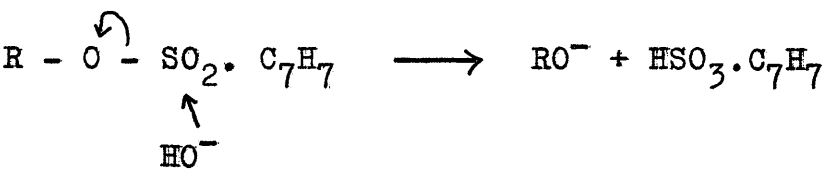
In contrast to the above displacement reactions the α-cyanobenzyl toluene-p-sulphonates, on treatment with sodium ethoxide in cold anhydrous ethanol give sodium toluene-p-sulphinate in high yield (ca. 90%). The benzoyl cyanide, undoubtedly formed as another product of this reaction, is not isolated, as it readily undergoes reaction with ethoxide ion to yield the corresponding ethyl ester (or sodium salt) of the acid.



I

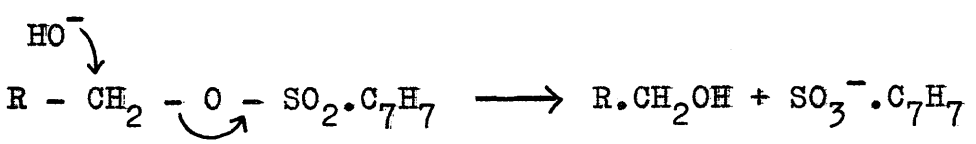
abstracts a proton from the α-carbon atom, is in sharp contrast to the action of base on toluene-p-sulphonic esters of phenols or alcohols.

The action of base on the phenolic ester (X, R = aryl) is known to proceed by the following mechanism:-



X

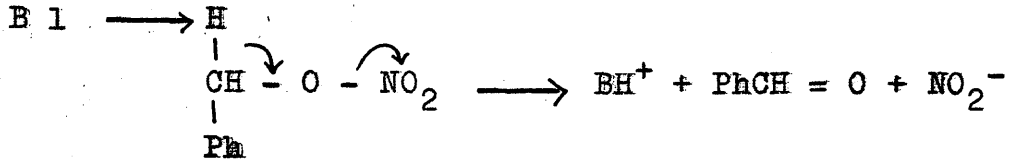
in which nucleophilic attack of the hydroxyl ion occurs at the sulphur atom of the sulphonate group. In the case of the alkyl ester (XI; R = alkyl) attack of the base takes place on the α-carbon atom of the alkyl substituent.



XI

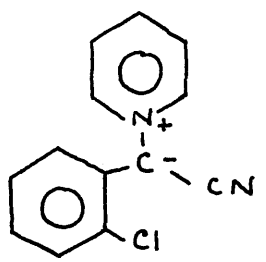
In an attempt to isolate the aroyl cyanide formed in the above elimination reaction (i), the α-cyanobenzyl toluene-p-sulphonate was treated with the milder base triethylamine. The use of this reagent was suggested

by the work of Baker[9] in the nitric ester series, where he demonstrated the production of benzaldehyde from the treatment of benzyl nitrate,(XII)with triethylamine.



XII

However treatment of 2-chloro-α-cyanobenzyl toluene-p-sulphonate with triethylamine afforded the sulphone (III; R = o - Cl. C_6H_4) and an oil from which no o-chlorobenzoyl cyanide could be obtained. The same ester with pyridine gave a pyridinium salt from which a betaine type of product,(XIII) was obtained by treatment with alkali.



XIII

It seems reasonable to expect that sulphinate elimination should also take place from sulphonic esters of type,(XIV) from thiosulphonic esters of type(XV) and

from sulphonamides of type(XVI)

$R.CO.CH.ROSO_2C_7H_7$ $R.CO.CH_2.S.SO_2.C_7H_7$

XIV XV

$R.CO.CH_2.N.R.SO_2Ph$

XVI

The benzene sulphonate of benzoin[11] and the toluene-p-sulphonate of 2-oxo-3-phenyl propan-1-ol were prepared and examined, but elimination of sulphinate could not be detected. Attempts to prepare phenacyl toluene-p-thiolsulphonates (XV; R = Ar) from phenacyl bromides led chiefly to phenacyl p-tolyl sulphones presumably via sodium toluene-p-sulphinate formed by decomposition of the sodium toluene-p-thiolsulphonate used as reagent. Takata[1], however, has shown that compounds allied to type(XVI)yield sulphinates when heated with potassium ethoxide in non-hydroxylic solvents. This has been confirmed for the particular case (XVI; R = R = Ph) and it has been shown that the oil (phenylglyoxal or its anil) simultaneously formed affords 2-phenylquinoxaline on treatment with o-phenylenediamine.

EXPERIMENTAL

α-Cyanobenzyl Arenesulphonates I. [See Table I] -

In a typical preparation potassium cyanide (0.66 g.) was added with stirring to a solution of o-chlorobenzaldehyde (1.4 g.) and toluene-p-sulphonyl chloride (1.9 g.) in dioxan (2 cc.) and water (4 cc.), the temperature being kept below 5°. The mixture was then allowed to stand at 0-5° for one hour with stirring. The solid was collected, dissolved in a mixture of acetone, ethanol, and water (5 c.c. ; 2:2:1) and filtered if necessary to remove any undissolved material. The addition of ice (3 g.) to the cold filtrate afforded an oil which solidified to the crude product on standing.

Elimination of Sulphinate - (i) A solution of sodium ethoxide (from 0.12 g. of sodium in 2 c.c. of ethanol) was added to a solution of α-cyano-2-nitrobenzyl toluene-p-sulphonate (1.66 g.) in ethanol (10 c.c.) at room temperature. After standing for 15 min. the solvent was removed in vacuo and the residue was extracted with benzene, leaving sodium toluene-p-sulphinate (0.77 g.) which was identified as the sulphinic acid (m.p. and mixed m.p. 84°) and as the derived 2:4-dinitrophenylsulphone (m.p. and mixed m.p. 187°). Chromatography of the benzene solution

Table I

α-Cyano (substituted) benzyl toluene-p-sulphonates I

Subst.	M.p.	Yield (%)	Formula	Found(%) C	H	N	Required (%) C	H	N
H	60°[4]	72							
2-Br	104	75	$C_{15}H_{12}O_3NBrS$	49.4	3.2	3.9	49.2	3.3	3.8
2-Cl	86	78	$C_{15}H_{12}O_3NClS$	55.9	3.6	4.6	56.0	3.7	4.4
3-MeO	52	55	$C_{16}H_{15}O_4NS$	60.5	4.7	4.4	60.6	4.8	4.4
2-NO_2	111	72	$C_{15}H_{12}O_5N_2S$	54.1	3.9	8.3	54.2	3.6	8.4
2:4-Cl_2 ..	78	72	$C_{15}H_{11}O_3NCl_2S$	50.6	3.4	4.0	50.5	3.2	3.9
2-Cl-5-NO_2	118*	70	$C_{15}H_{11}O_5N_2ClS$	49.3	3.4	7.7	49.2	3.1	7.6

* From benzene - light petroleum (b.p. 60-80°): the others from ethanol.

From 2:5-dichlorobenzenesulphonyl chloride there were prepared in the same way α-cyanobenzyl, m.p. 102° (from ether) (Found: C, 49.0; H, 2.6; N, 4.5. $C_{14}H_9O_3NCl_2S$ requires C, 49.1; H, 2.6; N, 4.1%), and 4-chloro-α-cyanobenzyl 2:5-dichlorobenzenesulphonate, m.p. 86° [from benzene - light petroleum (b.p. 60-80°)] (Found: C, 44.8; H, 2.2; N, 4.3. $C_{14}H_8O_3NCl_3S$ requires C, 44.8; H, 2.1; N, 3.7%).

on alumina afforded ethyl o-nitrobenzoate (0.68 g.) m.p. 30° (Found: N, 7.3. Calc. for $C_9H_9O_4N$: N, 7.2%) which was hydrolysed to o-nitrobenzoic acid. (m.p. and mixed m.p. 147°).

(ii) High yields of the appropriate sulphinic acid were similarly obtained from the other sulphonates described in the above table. The 2:5-dichlorobenzene sulphinic acid had m.p. and mixed m.p. 122°.

(iii) When diethyl sodiomalonate replaced the sodium ethoxide of (i) the solid precipitated in the reaction contained (water-soluble) sodium toluene-p-sulphinate and α-cyano-2-nitrobenzyl p-tolyl sulphone, m.p. and mixed m.p. 167° (cf. below). An oil, recovered from the reaction mother liquor on evaporation, was hydrolysed by 5N- sodium hydroxide, affording o-nitrobenzoic acid.

(iv) 2-Chloro-α-cyanobenzyl toluene-p-sulphonate (1.5 g.) was heated for 30 min. with triethylamine (5 c.c.) at 100°. The oil obtained by concentration in vacuo was rubbed with benzene-light petroleum (b.p. 60-80°; 1:1) affording 2-chloro-α-cyanobenzyl p-tolyl sulphone, m.p. and mixed m.p. 112° (cf. below) and an oily extract which, after hydrolysis, gave o-chlorobenzoic acid m.p. and mixed m.p. 142°.

(v) From N-phenacylbenzenesulphonanilide

A solution of sodium ethoxide (from 0.046 g. of sodium in 3 c.c. of ethanol) was added to a solution of the anilide[1] (0.73 g.) in ethanol (10 c.c.). After standing for 30 min. the precipitated sodium toluene-p-sulphinate was collected and identified as in (i). An ethereal extract of the evaporated filtrate gave an oil, which, on heating with excess o-phenylenediamine in ethanol for 15 min., yielded 2-phenylquinoxaline m.p. 78°. (Found: C, 81.6; H, 4.7; N, 13.2. Calc. for $C_{14}H_{10}N_2$; C, 81.5; H, 4.9; N, 13.6%).

Replacement of Sulphonate - α-cyanobenzyl bromide, b.p. 137-139°/15 m.m., m.p. 29°, was recovered in ether (yield 70%) after a solution of α-cyanobenzyl toluene-p-sulphonate (2.87 g.) in methanol (20 c.c.) had been heated with sodium bromide (1.53 g.) under reflux for 1 hr. and the resultant mixture concentrated.

2-Chloro-α-cyanobenzyl p-tolyl sulphide - A solution of 2-chloro-α-cyanobenzyl toluene-p-sulphonate (0.32 g.), thio-p-cresol (0.13 g.), and sodium hydroxide (0.04 g.) in ethanol-water (8 c.c.; 4:1) was heated under reflux for 30 min. On cooling, the mixture was poured into water (30 c.c.), extracted with ether, and the dried ether extract concentrated in vacuo to give the sulphide m.p. 62° (from

methanol; yield 85%). (Found: C, 65.7; H, 4.1; N, 5.3. $C_{15}H_{12}NClS$ requires C, 65.8; H, 4.3; N, 5.1%).

2-Chloro-α-cyanobenzyl p-tolyl sulphone - A solution of 2-chloro-α-cyanobenzyl toluene-p-sulphonate (0.32 g.), and sodium toluene-p-sulphinate (0.27 g.) in ethanol (5 c.c.) was heated under reflux for 30 min. On cooling, the mixture was poured into water (20 c.c.) precipitating the sulphone m.p. 112° (from ethanol; yield 85%). (Found: C, 59.0; H, 4.1; N, 4.8. $C_{15}H_{12}O_2NClS$ requires C, 59.0; H, 4.0; N, 4.6%).

α-cyano-2-nitrobenzyl p-tolyl sulphone, m.p. 167° (from ethanol). (Found: C, 56.8; H, 3.8; N, 8.8. $C_{15}H_{12}O_4N_2S$ requires C, 57.0; H, 3.8; N, 8.9%), and α-cyanobenzyl p-tolyl sulphone, m.p. 152° (Found: C, 66.3; H, 4.8; N, 5.4. $C_{15}H_{13}O_2NS$ requires C, 66.4; H, 4.8; N, 5.2%) were similarly prepared from the appropriate toluene-p-sulphonates.

α-Cyano-2-nitrobenzyl p-nitrophenyl ether - A solution of p-nitrophenol (0.85 g.), α-cyano-2-nitrobenzyl toluene-p-sulphonate (0.33 g.) and sodium ethoxide (from 0.034 g. of sodium in 3 c.c. ethanol) in ethanol (10 c.c.) was heated under reflux for 48 hr. The solvent

was removed in vacuo and the residue was extracted with ether. The ether extract was washed with dilute sodium hydroxide, then with water, dried, and concentrated to yield the ether m.p. 157° (from ethanol; yield 33%) (Found: C, 56.2; H, 2.8; N, 13.9. $C_{14}H_9N_3O_5$ requires C, 56.2; H, 3.0; N, 14.0%).

1-(2-Chloro-α-cyanobenzyl) pyridinium toluene-p-sulphonate slowly crystallised at 0° from a solution of 2-chloro-α-cyanobenzyl toluene-p-sulphonate (1.6 g.) in anhydrous pyridine (2 c.c.). It formed colourless crystals, m.p. 101° [from benzene-light petroleum (b.p. 60-80°) containing a trace of ethanol] (Found: C, 60.5; H, 4.2; N, 6.8. $C_{20}H_{17}O_3NClS$ requires C, 60.0; H, 4.2; N, 7.0%), and when treated with 5N- sodium hydroxide afforded a betaine as dark red crystals, m.p. 138° (from ethanol; yield 70%) (Found: C, 68.5; H, 4.2; N, 12.1. $C_5H_4N^+ - C^-(CN).C_6H_4Cl$ requires C, 68.5; H, 3.9; N, 12.3%).

2-Chlorophenethylamine - 2-Chloro-α-cyanobenzyl toluene-p-sulphonate (0.32 g.) was hydrogenated in acetic acid (3 c.c.) containing concentrated sulphuric acid (0.05 c.c.) and in the presence of 10% palladium charcoal (0.15 g.). Absorption of hydrogen (3 mol.) was complete after 3 hr. The filtered solution was basified and the amine, recovered in ether, was precipitated as the picrate[12] m.p. 186°

(from benzene; yield 60%) (Found: C, 44.2; H, 3.3; N, 14.5. Calc. for $C_{14}H_{14}O_7N_4$: C, 44.2; H, 3.4; N, 14.6%).

[With G. Tennant]. 2-oxo-3-phenylpropyl toluene-p-sulphonate - To a stirred solution of diazomethane (~ 10 g.) in anhydrous ether (500 c.c.) was added phenacetyl chloride (15.5 g.) in ether (50 c.c.) and, after several hours, powdered toluene-p-sulphonic acid (17 g.). After 12 hr. at 20° the solvent was removed and the gummy solid afforded the ester m.p. 63° (from ethanol) (Found: C, 63.0; H, 5.4. $C_{16}H_{16}O_4S$ requires C, 63.15; H, 5.3%).

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CHAPTER II

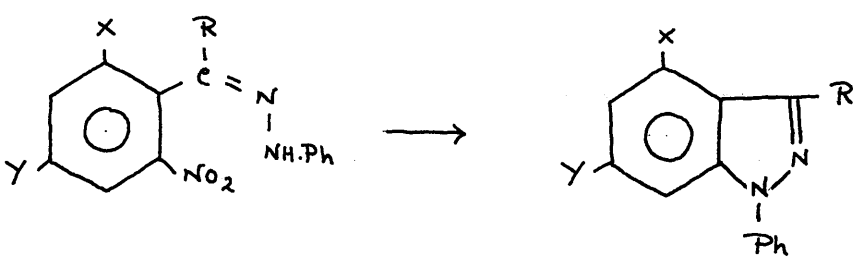
The Preparation and Properties of some Heterocyclic N-hydroxy Compounds.

CONTENTS

INTRODUCTION to CHAPTERS

II and III

o-Nitrobenzene derivatives are common starting materials for the synthesis of a wide variety of benzo-heterocyclic systems. In a few cases the heterocycle is formed and its attachment to the benzene ring secured, through elimination of the nitro-group as nitrous acid (or nitrite), as in the cyclisation of the phenylhydrazone (I) to the substituted indazole (II)[1],

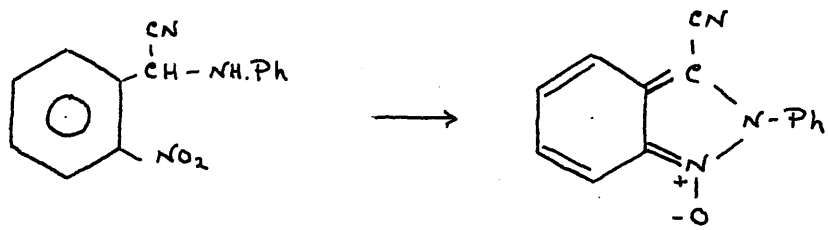


I II

subject to the provisions (a) X = NO_2 or halogen, where R = H (b) Y = NO_2, where R = Me, COMe or CO_2Me. In the vast majority of cases the nitrogen atom of the nitro-group is retained as an aza-atom in the heterocycle. Cyclisations of this type frequently involve reduction -

deliberately effected, so that the precursor molecule is an amino - or hydroxylamino - compound. There are also examples of cyclisation in which it appears probable that the nitro-group as such condenses with a suitable centre in the ortho-situated side-chain.

Heterocyclic N-oxides are among the cyclic products formed by this last type of interaction. In a recent review of these N-oxides, Katritzky[2] describes three examples of their preparation in which the N=O bond of a nitro compound undergoes a reaction of the carbonyl-addition type. α-Amino-o-nitrophenylacetonitriles (as III) are cyclised to indazole 1-oxides (IV) by treatment with alkali[3].

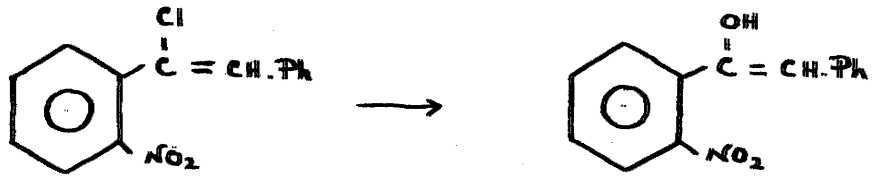


III IV

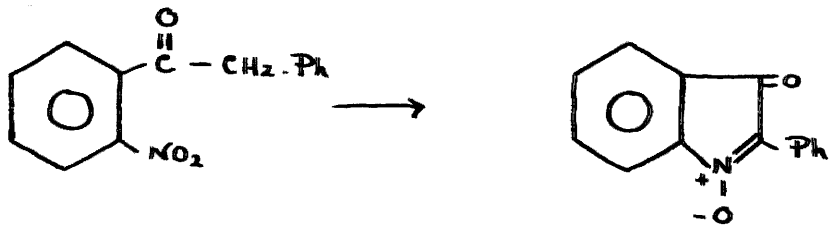
Similar treatment of o-nitrophenylurea derivatives (V, X = O, S, NH, NPh) gives benzatriazine 1-oxides[4] (VI).

V VI

The preparation of isotogens[5] (as VIII), by heating or irradiating 1-O-nitrophenylvinyl chlorides (VII) in pyridine, is believed by Katritzky to be of the same type.

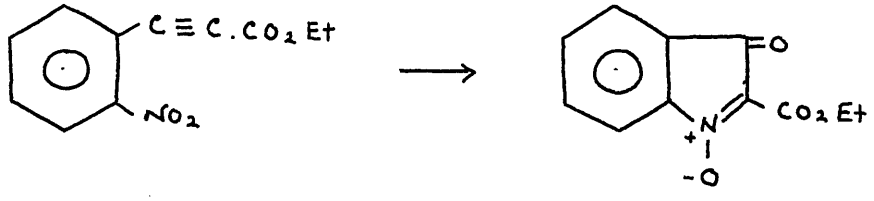


VII



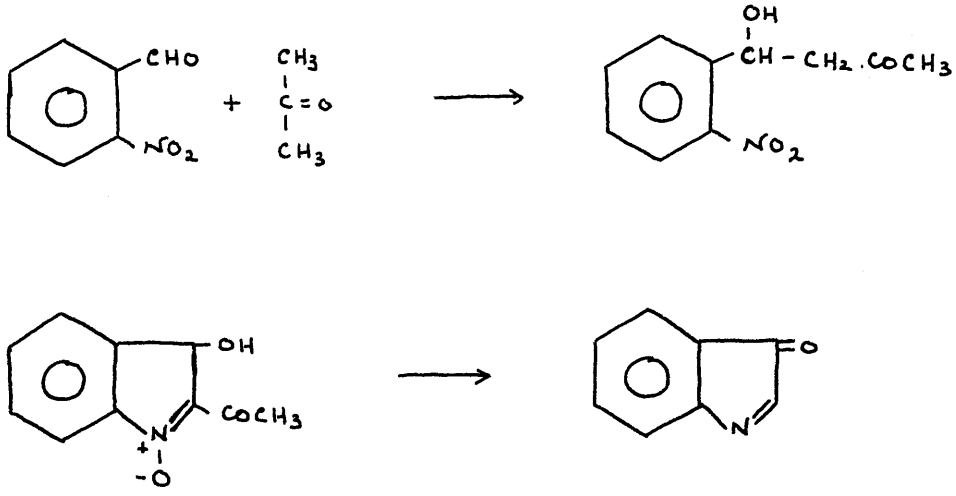
VIII

A similar cyclisation, but effected in acid conditions, takes place with o-nitrophenylacetylenes of type (IX) to give the isotogens[6](X)

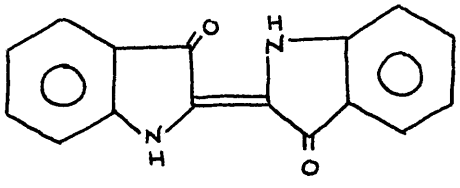


IX X

The Bayer[7] synthesis of indigo (XII), from o-nitrobenzaldehyde and acetone in warm alkali, is believed, by Sumpter and Miller[8], to take place by the mechanism described below, in which the N-oxide (XI) is an intermediate.



XI

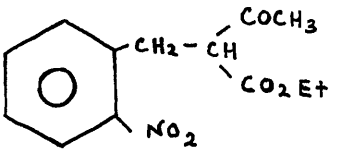


XII

Cyclic N-hydroxy compounds form another group of products which can result from this type of interaction. Again the N = O bond of the nitro-group acts like a carbonyl compound undergoing an addition type of reaction. Thus o-nitrophenylhydrazines (XIII) are converted into 1-hydroxy-benzotriazoles (XIV) by alkali[9]

XIII XIV

Ethyl o-nitrobenzylideneacetoacetate[10] (XV) and diethyl o-nitrobenzylidenemalonate[11] (XVI) are cyclised to the same 1-hydroxy-2-carboxyindole (XVII, R = H) or its ethyl ester (XVII, R = Et), by warming in dilute alkali.



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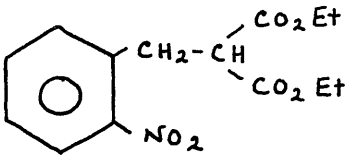
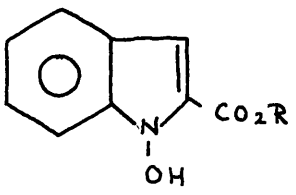
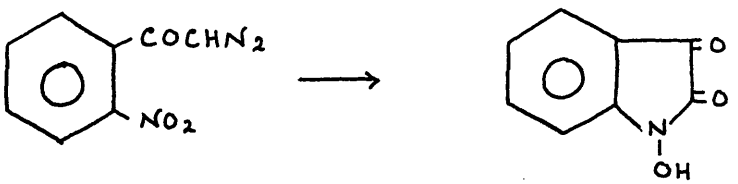


XVI



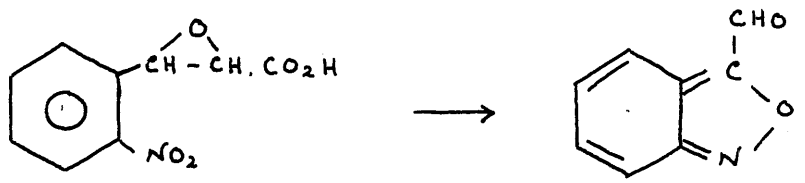
XVII

Acid catalysed interaction of the nitro-group with the ortho-side chain is involved in the formation of 1-hydroxyisatin [12] (XIX) by treatment of o-nitrobenzoyl-diazomethane (XVIII) with 2N-sulphuric acid.



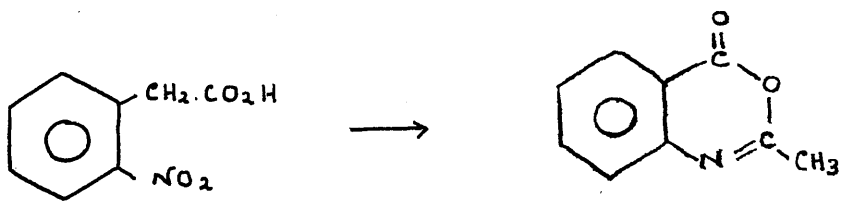
XVIII XIX

Anthranil formation, from o-nitrobenzene derivatives, provides examples of cyclisations in which the nitrogen atom and an oxygen atom of the nitro-group are retained in the heterocyclic ring. β-(2-nitrophenyl)-glycidic acid[13] (XX) is cyclised to 3-formylanthranil (XXI) by treatment with acetic acid.

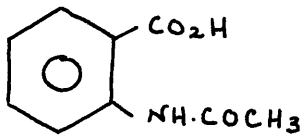


XX XXI

Acetylanthranil (XXIII) has been proposed by Walker[14] as an intermediate in the rearrangement of o-nitrophenylacetic acid (XXII) to N-acetylanthranilic acid (XXIV), with acetic anhydride



XXII XXIII



XXIV

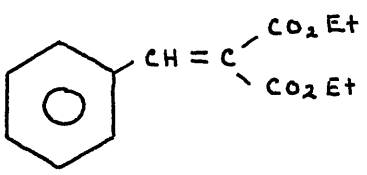
As these examples show the condensative interaction of a nitro-group and (ortho) side-chain, under the influence of acid or alkali, can lead to a variety of product types, although the precise courses of the reactions are by no means always clear.

DISCUSSION

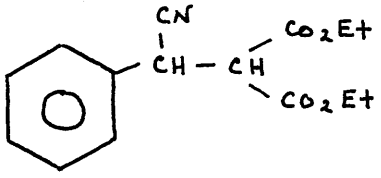
SECTION I

A Novel Synthesis of a Cyclic Hydroxamic Acid

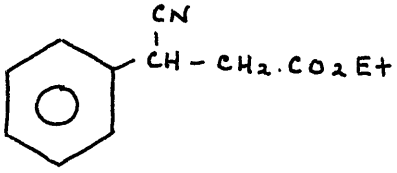
Addition of hydrogen cyanide to the activated double bond of diethyl benzylidenemalonate (I), is known to afford two different products depending on reaction conditions[15]. When the diester (I) is treated, at room temperature, with potassium cyanide in ethanolic hydrochloric acid, diethyl (α-cyanobenzyl)-malonate (II) is formed. The same diester, however, reacts with potassium cyanide in warm aqueous ethanol to yield ethyl β-cyano-β-phenylpropionate (III)



I

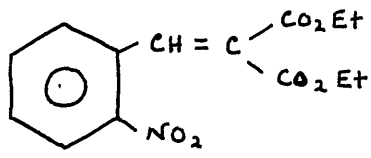


II

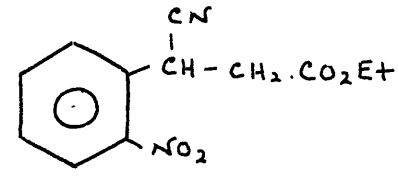


III

It therefore seemed reasonable to expect that diethyl o-nitrobenzylidenemalonate (IV), on treatment with potassium cyanide in warm aqueous ethanol, would afford ethyl β-cyano-β-o-nitrophenylpropionate (V). This product would be a useful starting material for oxindole synthesis.



IV



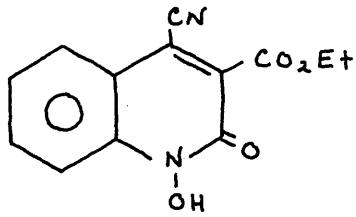
V

Synthesis of the diester (IV) was achieved by condensing o-nitrobenzaldehyde with diethyl malonate in acetic anhydride/potassium bicarbonate, after more standard condensing agents had failed. The same diester (IV) was originally obtained by Stuart[16] as a product of the nitration of (I).

When the diester (IV) was warmed with potassium cyanide in aqueous ethanol, the reaction mixture underwent a startling transition from an almost homogeneous solution to a solid mass of orange-red crystals. The product,

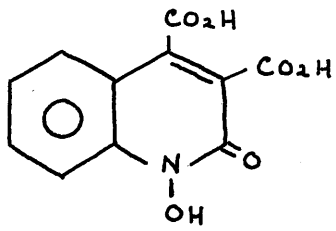
a water soluble potassium salt, was treated with acid affording a yellow compound ($C_{13}H_{10}N_2O_4$), which had infra-red bands at 3130, 2200 and 1745 cm^{-1}, attributable to an hydroxyl, a nitrile and an ester-carbonyl group respectively. The infra-red bands characteristic of a nitro-group were absent.

The evidence from this rather surprising spectrum, together with the yellow colour and high melting point (158°C), suggested that ($C_{13}H_{10}N_2O_4$) was a cyclic compound. Further investigation showed that it had the remarkable structure of a cyclic hydroxamic acid, ethyl 4-cyano-1-hydroxy-2-oxo-1:2-dihydroquinoline-3-carboxylate (VI).



VI

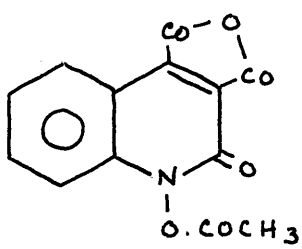
Chemical evidence for this structure was obtained from a series of reactions which began with acid hydrolysis of the nitrile-ester (VI) to the dicarboxylic acid (VII), which had infra-red bands at 3480 and 1720 cm^{-1}, due to an hydroxyl and an acid-carbonyl group respectively.



VII

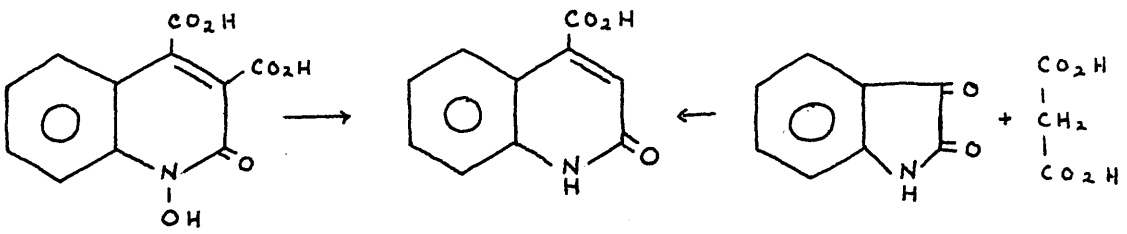
The presence of the hydroxamic acid grouping $-\underset{\underset{OH}{|}}{N}-\overset{\overset{O}{\|}}{C}-$ in (VI) and(VII)was confirmed by the ferric chloride test, viz. the formation of a blood-red colour.

On being warmed with acetic anhydride the diacid (VII) formed the acetylated inner anhydride (VIII), showing that the nitrile and ethoxycarbonyl groups were on adjacent carbon atoms. The infra-red spectrum of the anhydride (VIII) contained twin bands at 1860 and 1790 cm^{-1}, attributable to the anhydride grouping and also a band at 1825 cm^{-1} which has been shown to be characteristic of the C = O stretching frequency of N-acetates.



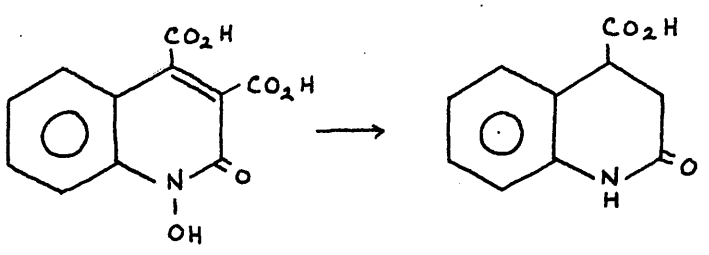
VIII

Two methods of degradation were used to relate the diacid (VII) to known derivatives. When this diacid was heated for several hours in a sealed tube with diluate sulphuric acid, quinolone-4-carboxylic acid (IX) was obtained and was identical with an authentic specimen prepared from isatin and malonic acid[17].



VII IX

Reduction of the diacid (VII) with zinc dust and acetic acid/concentrated hydrochloric acid gave the known 3:4-dihydroquinolone-4-carboxylic acid (X)[18].



VII X

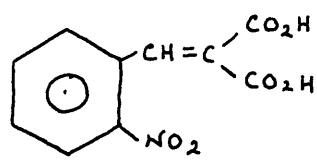
Physical evidence for the structures of (VI) and (VII) was furnished from ultra-violet and infra-red studies of these and other related compounds. Table I, below, summarises the ultra-violet data and infra-red data are shown in Table II (See page 36a).

TABLE I

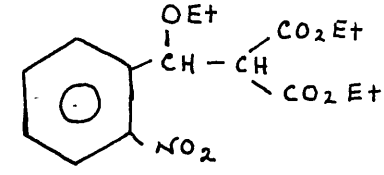
Ultra-violet Data

Compound	λ	ε
Quinol-2-one-3-carboxylic acid[19]	230 290 350	42,700 10,000 5,500
3-Carboxy-1-hydroxy-2-oxo-1:2-dihydroquinoline[20]	235 295 360	42,700 12,000 6,000
Ethyl 1-hydroxy-2-oxo-1:2-dihydroquinoline-3-carboxylate	240 290 360	37,000 8,500 4,500
Quinol-2-one-4-carboxylic acid[17]	230 280 340	23,400 4,700 4,700
3:4-Dihydroquinol-2-one-4-carboxylic acid[18]	250	10,000
3:4-Dicarboxy-1-hydroxy-2-oxo-1:2-dihydroquinoline	235 295 360	27,000 7,000 4,000
1-Hydroxyquinol-2-one[21]	235 275 335	40,000 5,200 5,200
1-Hydroxypyrid-2-one[22]	230 305	7,200 4,800

Attempts to form derivatives of the cyclic ester (VI), by treating diethyl o-nitrobenzylidenemalonate (IV) with other alkaline reagents, were unsuccessful. o-Nitrobenzylidenemalonic acid (XI) was the only product formed on warming the diester (IV) in aqueous-ethanolic sodium hydroxide. On treatment with sodium ethoxide, the diester (IV) gave the sodium salt of diethyl (α-ethoxy-o-nitrobenzyl)-malonate (XII) which afforded (XII) on acidification with dilute acetic acid.

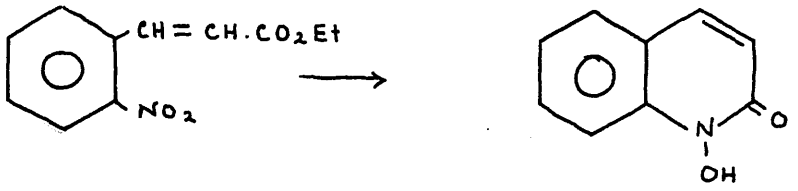


XI



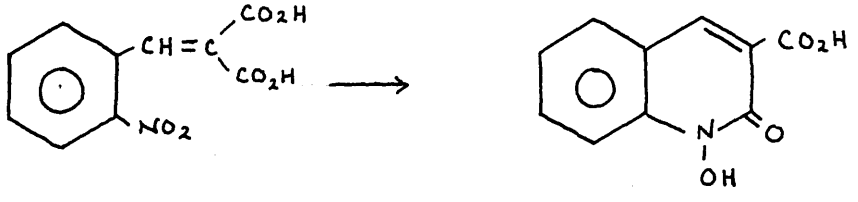
XII

To date only two hydroxamic acids of the quinoline type have been described in the literature. The first was prepared by Friedländer and Ostermaier[21] in 1881. These workers isolated a small quantity of "oxycarbostyril" (XIII) as a byproduct from ferrous ammonium sulphate reduction of ethyl o-nitrocinnamate.



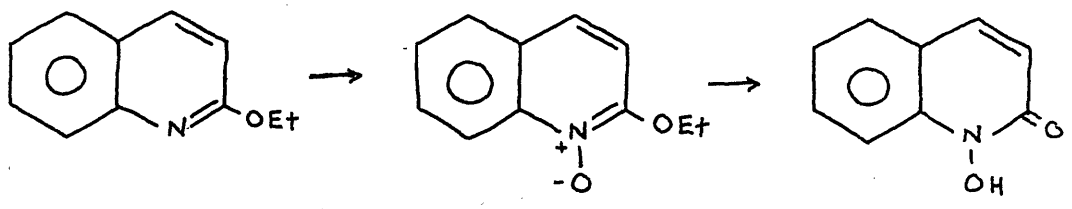
XIII

More than thirty years later, in 1914, Heller and Wunderlich[20] prepared the related carboxylic acid, 3-carboxy-1-hydroxy-2-oxo-1:2-dihydroquinoline (XIV), by reduction of o-nitrobenzylidenemalonic acid (XI) with zinc dust and dilute acetic acid.



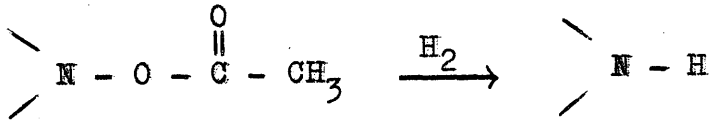
XI XIV

In 1948, Newbold and Spring[23] described the synthesis of (XIII) from 2-ethoxyquinoline (XV). Treatment of (XV) with peracetic acid afforded 2-ethoxyquinoline-1-oxide (XVI) which was converted to (XIII) by hydrolysis with dilute hydrochloric acid.

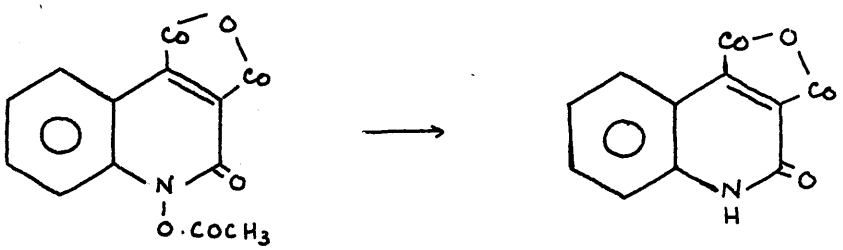


XV XVI XIII

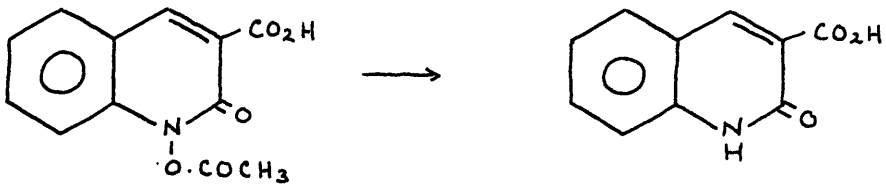
Methods for reducing the N-hydroxyl group in cyclic hydroxamic acids of the above type were investigated in some detail. Although reduction with zinc dust in acetic acid is known to convert the N-OH group to N-H[20], catalytic hydrogenation at normal temperature and pressure leaves it unchanged. Acetylation of the hydroxyl group, however, affords an N-acetate which undergoes hydrogenolysis to the N-H derivative on hydrogenation over a palladium-charcoal catalyst.



Two examples of this hydrogenolysis were provided by hydrogenation of the N-acetates (VIII) and (XVIII).



VIII XVII



XVIII XIX

The structure of the anhydride (XVII) was confirmed by hydrolysis to the known diacid* [24] (XX), followed

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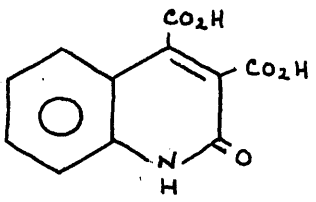
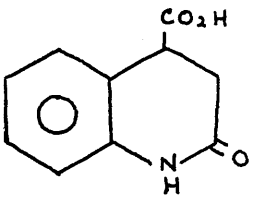
* Previous mention of the diacid (XX) in the literature is rather confusing, as values varying from 304°C to greater than 340°C have been reported for its melting point. A pure analytical sample of this diacid was found to melt at 358°C with decomposition.

by zinc dust reduction to 3:4-dihydroquinol-2-one-4-carboxylic acid[18] (X).

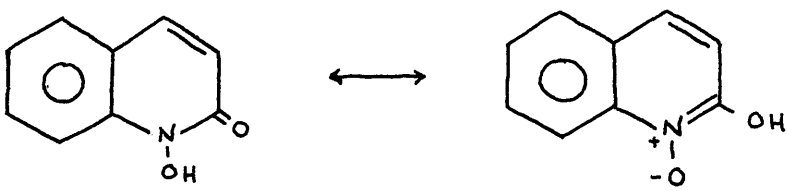


XX



X

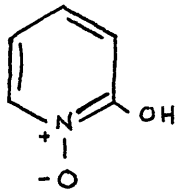
Cyclic hydroxamic acids of the quinoline type can exist in two tautomeric forms. Thus the simplest member, 1-hydroxy-quinol-2-one (XIII), may be written as the N-oxide (XXI).



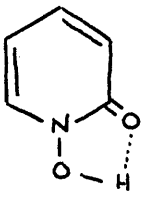
XIII XXI

In the pyridine series the corresponding 2-hydroxy-pyridine-1-oxide (XXII) was investigated in some detail

by Katritzky and Gardner[22]. They showed from extensive physical measurements, including ultra-violet and infra-red data, that (XXII) existed mainly as the strongly hydrogen banded 1-hydroxypyrid-2-one (XXIII).



XXII



XXIII

The ultra-violet and infra-red spectra of hydroxamic acids of the quinoline type support the view that the compounds exist in the N-hydroxyl form. All the hydroxamic acids examined show absorption in the ultra-violet at 275-295 mu (ε = 5,000 - 12,000) characteristic of 2-quinolones[5], and in the infra-red strong amide-carbonyl absorption occurs at 1620-1640 cm^{-1}. Furthermore the infra-red bands at 1255-1300 cm^{-1} and at 847-872 cm^{-1} assigned to the N - O stretching frequency of N-oxides[26] are absent in the spectra of these hydroxamic acids.

From the data recorded in Table II, it is possible to suggest that the broad absorption in the region 3,500-2,300 cm^{-1} may be characteristic of the -O-H stretching frequency of the N-hydroxyl group. This

observation is supported by spectra of 1-hydroxyindoles (See Section II) and of 1-hydroxyquinol-4-ones (See Chapter III).

The quinol-2-one-N-acetates show a strong absorption band at 1800-1825 cm^{-1}, which is attributed to the C=O stretching frequency of the N-acetate group. This band is also found in the spectra of indole-N-acetates (see Section II) and quinol-4-one-N-acetates (see Chapter III).

TABLE II

Infra-red Data

Compound	cm^{-1}	intensity[+]	mode
Ethyl 4-cyano-1-hydroxy-2-oxo-1:2-dihydroquinoline-3-carboxylate	3130(br)	S	O-H
	2200	W	C≡N
	1745	V.S.	C=O of ester.
	1640	V.S.	C=O of amide.
3:4-Dicarboxy-1-hydroxy-2-oxo-1:2-dihydroquinoline	3480(br)	S	-O-H
	1720	V.S	C=O of acid.
3:4-Dicarboxy-2-oxo-1:2 dihydroquinoline anhydride-N-acetate	1862 } 1790 }	V.S.	C=O of anhydride.
	1825	V.S.	C=O of acetate.
	1640	V.S.	C=O of amide.
3-Carboxy-1-hydroxy-2-oxo-1:2-dihydroquinoline[20]	3220(br)	S	-O-H
	1740	V.S.	C=O of acid
	1630	V.S.	C=O of amide.
3-Carboxy-2-oxo-1:2-dihydroquinoline-N-acetate	1805	S	C=O of acetate
	1750	S	C=O of acid.
	1640	S	C=O of amide.
Ethyl 1-hydroxy-2-oxo-1:2-dihydroquinoline-3-carboxylate	3000-2690(br)	M	-O-H
	1740	V.S.	C=O of ester.
	1620	V.S.	C=O of amide.

TABLE II (contd.)

Compound	cm^{-1}	intensity+	mode
* 1-Hydroxyquinol-2-one[21]	3000-2480(br)	M	-O-H
	1635	V.S.	C=O of amide.
1-Hydroxypyrid-2-one[22]	3200-2200(br)	S	-O-H
Acetophenone oxime	3200(br)	S	-O-H

* We are indebted to Dr. G.T. Newbold of The Royal College of Science and Technology, Glasgow, for a specimen of this compound.

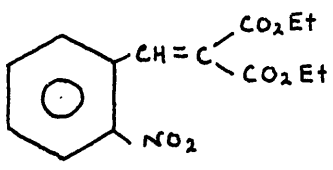
+ Abbreviations used are:- M = medium
S = strong
V.S. = very strong
W = weak

All spectra were measured in nujol mulls.

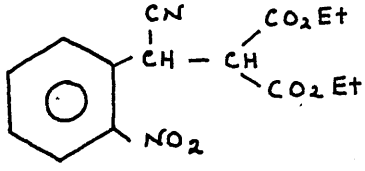
SECTION II

Studies of some 1-Hydroxyindoles

Addition of hydrogen cyanide to the activated double bond of diethyl o-nitrobenzylidenemalonate (I) was finally achieved by careful control of pH conditions during the reaction. A suspension of the diester (I) was shaken for two hours at room temperature with a solution of potassium cyanide in acetic acid and ethanol, to yield diethyl (α-cyano-o-nitrobenzyl)-malonate (II).

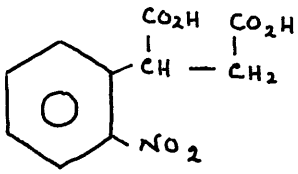


I



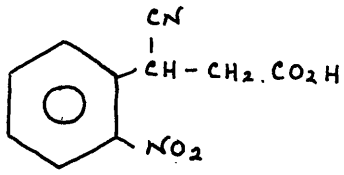
II

Horner and his co-workers[27] have reported the synthesis of the dimethyl ester of (II), but failed in their attempts to prepare (II) by the addition of hydrogen cyanide to (I). The structure of the nitrile-ester (II) was confirmed by acid hydrolysis to the known o-nitrophenylsuccinic acid[18] (III).

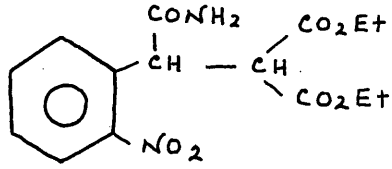


III

In an effort to hydrolyse the nitrile-ester (II) to β-cyano-β-o-nitrophenylpropionic acid (IV), it was dissolved in concentrated sulphuric acid and the resulting solution poured into water. The product, however, was the amide (V).



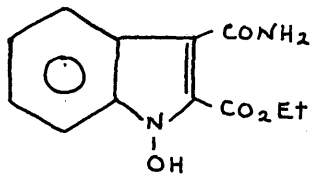
IV



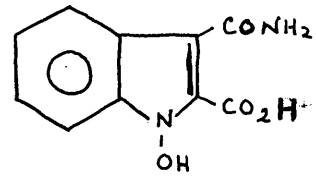
V

During the working up of (V), it was found to form a yellow solution in warm dilute sodium carbonate, which afforded a cream coloured product ($C_{12}H_{12}N_2O_4$) on acidification. This compound had infra-red bands at 3350, 3150 and 1590 cm^{-1} due to an amide group and at 1700 cm^{-1} due to an ester-carbonyl group. The bands characteristic of a nitro-group were absent.

The data from this rather unusual spectrum and the high melting point (207°C with decomposition), again suggested that ($C_{12}H_{12}N_2O_4$) was the product of an internal cyclisation between the nitro-group and the side chain ortho to it. Further experimental work showed that it had the structure of a 1-hydroxyindole, *viz.* 1-hydroxy-2-carbethoxyindole-3-carboxyamide (VI).

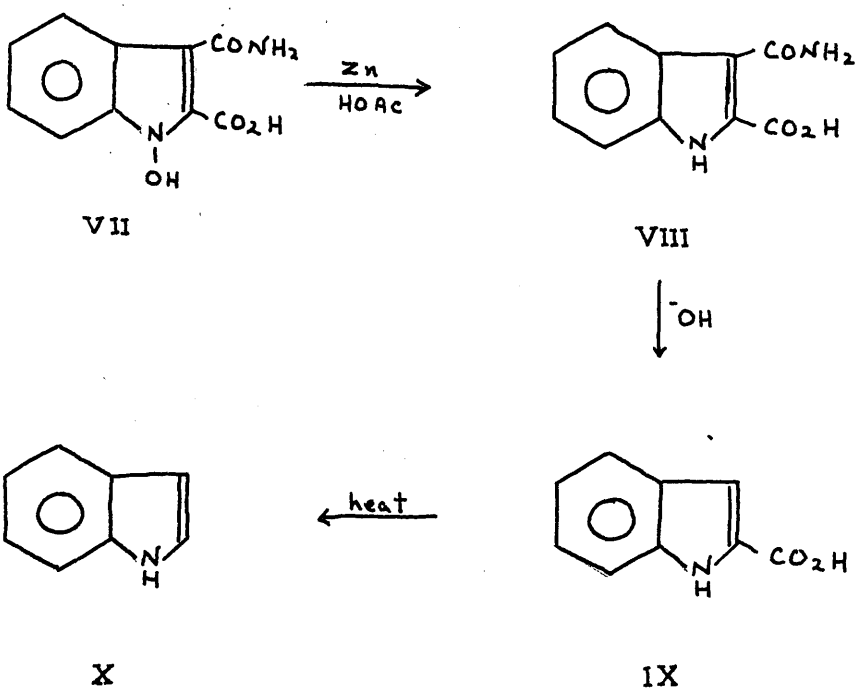


VI



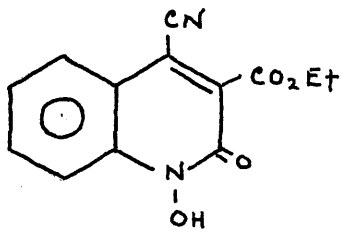
VII

When the amide-ester (V) was warmed with dilute sodium hydroxide instead of sodium carbonate, the corresponding carboxylic acid (VII) was formed. The structure of the 1-hydroxyindole (VII) was established by stepwise degradation to indole (X) in the following manner:-

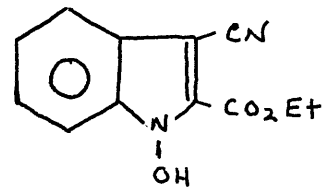


Further experiments, designed to hydrolyse the nitrile-ester (II) to the nitrile-acid (IV), were carried out under alkaline conditions. In practice it was found that treatment of (II) with strong alkali, e.g. alcoholic potassium hydroxide, afforded the cyclic hydroxamic acid (XI) described in Section I; whereas mild alkali, e.g. alcoholic sodium carbonate, converted

(II) to ethyl 3-cyano-1-hydroxyindole-2-carboxylate (XII).



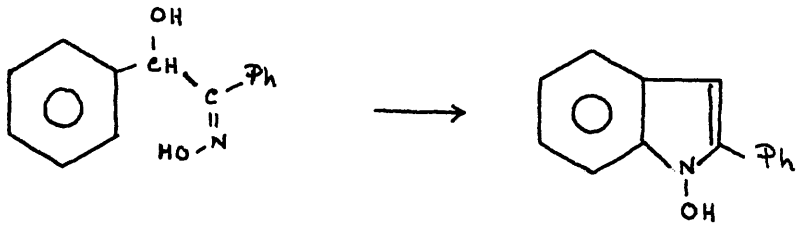
XI



XII

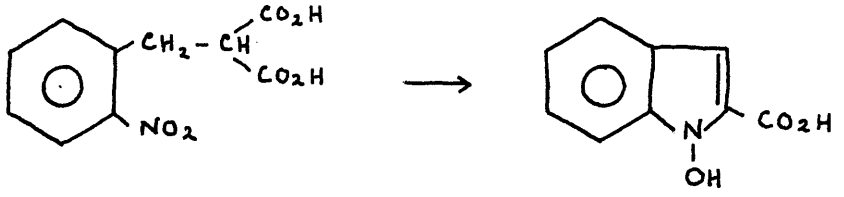
The structure of (XII) was proved by acid hydrolysis to 1-hydroxy-2-carboxyindole-3-carboxyamide (VII). All the 1-hydroxyindoles described give a dark green colour in alcoholic ferric chloride solution. This serves as a simple chemical test for distinguishing them from cyclic hydroxamic acids, which give a blood-red colour with the same reagent.

The first preparation of a 1-hydroxyindole was described by Fisher and Hutz[28] in 1895. They dissolved α-benzoinoxime (XIII) in concentrated sulphuric acid and allowed the solution to stand for several hours. On pouring this solution into water a precipitate of 1-hydroxy-2-phenylindole (XIV) was formed.



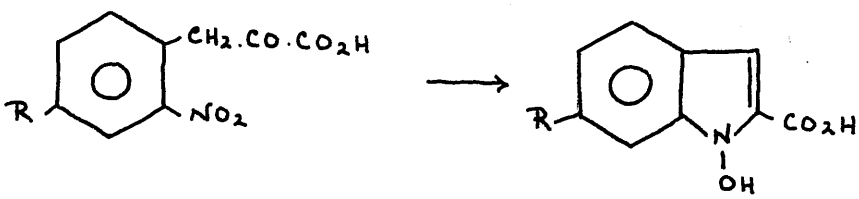
XIII XIV

A rather different synthesis of this type of compound was reported by Reissert[11] in the following year. He prepared 1-hydroxy-2-carboxyindole (XVI) by treating o-nitrobenzylmalonic acid (XV) with aqueous sodium hydroxide.



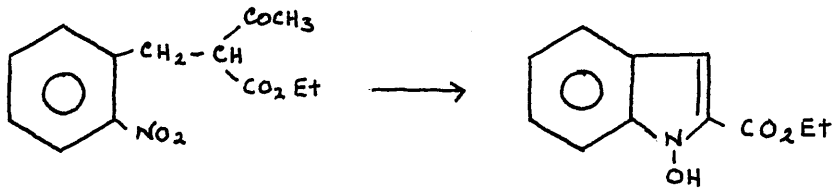
XV XVI

In 1897 he obtained the 1-hydroxyindoles (XVIII, R = H or CH_3) by reduction of the corresponding o-nitrophenylpyruvic acids (XVII, R = H or CH_3) with sodium amalgam[29].



XVII XVIII

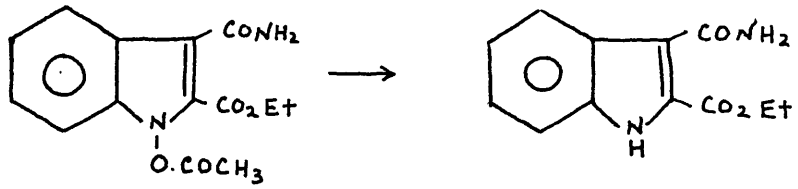
Gabriel and co-workers[10], in 1923, prepared ethyl 1-hydroxyindole-2-carboxylate (XX) by warming ethyl o-nitrobenzylacetoacetate (XIX) in dilute sodium hydroxide.



XIX XX

As in the case of the cyclic hydroxamic acids of Section I, zinc dust in acetic acid reduces the N-hydroxyl group of the 1-hydroxyindoles to N-H[28], but catalytic hydrogenation leaves it unchanged. The hydroxyl-group is readily acetylated to afford indole-N-acetates which are hydrogenalysed to the N-H derivative by catalytic hydrogenation. Thus hydrogenation of 2-carbethoxindole-3-carboxyamide-N-acetate (XXI) afforded the indole derivative,

2-carbethoxyindole-3-carboxyamide (XXII). The formation of 2-carboxyindole-3-carboxyamide (VIII) from the corresponding N-acetate provided another example of this hydrogenalysis.



XXI XXII

The infra-red measurements recorded in Table I below, supplement those described in Section I, Table II. They provide further evidence for assigning the broad absorption band at 3,200-2,300 cm^{-1} to the -O-H stretching frequency of the N-hydroxyl group. The two N-acetates, present in Table I, show the strong band at 1800 cm^{-1} associated with the C=O stretching frequency of the N-acetate group.

TABLE I

Infra-red Data

Compound	cm^{-1}	intensity[+]	mode
Acetophenone oxime	3200(br)	S	-O-H
Ethyl 3-cyano-1-hydroxyindole-2-carboxylate	3260(br)	M	-O-H
	2200	M	C≡N
	1685	V.S.	C=O of ester.
1-Hydroxy-2-phenylindole[28]	2400(br)	M	-O-H
1-Hydroxy-2-carboxyindole-3-carboxyamide	3260(br)	S	-O-H
	1680	M	C=O of acid.
	3250	S	N-H of amide.
	3180	S	" "
1-Acetoxy-2-carboxyindole-3-carboxyamide	1800	M	C=O of acetate
1-Hydroxy-2-carbethoxyindole-3-carboxyamide	1700	V.S.	C=O of ester.
	3350	S	N-H of amide.
	3150	S	" " "

TABLE I (contd.)

Compound	cm^{-1}	intensity+	mode
1-Acetoxy-2-carbethoxyindole-3-carboxyamide	1800	V.S.	C=O of acetate.

+ Abbreviations used are:- M = medium.
S = strong.
V.S = very strong.
W = weak.

All spectra were measured in nujol mulls.

EXPERIMENTAL

SECTION I

Diethyl o-nitrobenzylidenemalonate[16] (IV)

o-Nitrobenzaldehyde (1.5 g.), diethyl malonate (1.6 g.) and potassium bicarbonate (1.5 g.) were warmed together in acetic anhydride for two hours. The mixture was cooled, poured into water and the resulting oil extracted with ether. The ether extract was washed with dilute sodium carbonate and concentrated to give the diester (2.2 g.), m.p. 53 C (from ethanol).

(Found: C, 57.4; H, 5.0; N, 4.9%. Calculated for $C_{14}H_{15}NO_6$; C, 57.3; H, 4.8; N, 4.7%).

Ethyl 4-cyano-1-hydroxy-2-oxo-1:2-dihydroquinoline-3-carboxylate (VI)

A solution of potassium cyanide (2.64 g.) in water (4 c.c.) was added slowly to a stirred solution of diethyl o-nitrobenzylidenemalonate (2.9 g.) in ethanol (30 c.c.) and the mixture warmed for fifteen minutes. On cooling the solid product was filtered, washed with ether and dissolved in water (100 c.c.). This solution was acidified with dilute hydrochloric acid (5 c.c.) affording a precipitate

which was filtered off and redissolved in hot water (50 c.c.). Acidification of the hot solution with dilute hydrochloric acid gave (VI) as yellow needles (0.63 g.) m.p. 157-8°C (from acetic acid).

(Found; C, 60.5; H, 3.9; N, 10.9%. $C_{13}H_{10}N_2O_4$ requires C, 60.4; H, 3.9; N, 10.9%).

3:4-Dicarboxy-1-hydroxy-2-oxo-1:2-dihydroquinoline (VII)

The ester (VI) (1.3 g.) was refluxed for two hours with a solution of water (16 c.c.), glacial acetic acid (8 c.c.) and concentrated sulphuric acid (1.2 c.c.) to yield the diacid (1.1 g.) m.p. 294°C with decomposition (from dilute acetic acid).

(Found: C, 49.8; H, 3.6; N, 5.5%. $C_{11}H_7NO_6H_2O$ requires C, 49.5; H, 3.4; N, 5.2%).

1-Acetoxy-2-oxo-1:2-dihydroquinoline-3:4-dicarboxylic anhydride (VIII)

The diacid (VII) (0.7 g.) was heated for five minutes in acetic anhydride (2 c.c.) to give the acetyl derivative (0.7 g.) m.p. 232°C with decomposition (from acetic anhydride).

(Found; C, 57.0; H, 2.7; N, 5.3%. $C_{13}H_7NO_6$ requires C, 57.1; H, 2.6; N, 5.1%).

Quinol-2-one-4-carboxylic acid (IX) [17]

The diacid (VII) (1 g.) was heated with water (50 c.c.) and concentrated sulphuric acid (4 c.c.) in a sealed tube at 270°C for five hours. The solid product was dissolved in dilute sodium carbonate and the filtered solution acidified to yield (IX) m.p. and mixed m.p. with an authentic sample of (IX) 343°C. with decomposition (from acetic acid).
(Found: C, 63.3; H, 3.9; N, 7.5%. Calculated for $C_{10}H_7NO_3$ C, 63.5; H, 3.7; N, 7.4%).

3:4-Dihydroquinol-2-one-4-carboxylic acid (X) [18]

The diacid (VII) (0.3 g.) was refluxed for one hour with zinc dust (1.0 g.) in a solution of glacial acetic acid (8 c.c.) and 5 N hydrochloric acid (2 c.c.). Concentration of the reaction mixture gave (X) m.p. and mixed m.p. with an authentic specimen 221°C (from water).
(Found; C, 62.9; H, 4.6; N, 7.4%. Calculated for $C_{10}H_9NO_3$ C, 62.8; H, 4.7; N, 7.3%).

3-Carboxy-1-hydroxy-2-oxo-1:2-dihydroquinoline (XIV) [20]

Zinc dust (1 g.) was added in small portions to a refluxing solution of diethyl o-nitrobenzylidenemalonate (5 g.) in glacial acetic acid (16 c.c.) and water (4 c.c.). After the addition of zinc dust, heating was continued for fifteen minutes. The cooled solution was poured into

water (100 c.c.) affording the acid (2.1 g.) m.p. and mixed m.p. with an authentic specimen 261°C.
(Found; C, 58.5; H, 3.4; N, 6.8%. Calculated for $C_{10}H_7NO_4$ C, 58.7; H, 3.6; N, 6.8%).

Ethyl 1-hydroxy-2-oxo-1:2-dihydroquinoline-3-carboxylate

The acid (XIV) (0.5 g.) was refluxed for two hours with ethanol (15 c.c.) and concentrated sulphuric acid (0.2 c.c.). Concentration of the reaction solution gave the ester (0.5 g.) m.p. 168°C (from ethanol).
(Found; C, 62.0; H, 4.9; N, 6.2%. $C_{12}H_{11}NO_4$ requires C, 61.8; H, 4.7; N, 6.0%).

1-Acetoxy-3-carboxy-2-oxo-1:2-dihydroquinoline (XVIII)

The acid (XIV) (0.2 g.) was heated for five minutes in acetic anhydride (1 c.c.) to yield the acetyl derivative (0.23 g.) m.p. 203°C (from acetic anhydride).
(Found; C, 58.2; H, 3.3; N, 5.8%. $C_{12}H_9NO_5$ requires C, 58.4; H, 3.6; N, 5.7%).

Quinol-2-one-3-carboxylic acid [16] (XIX)

The N-acetate (XVIII) (0.3 g.) was hydrogenated in acetic acid (10 c.c.) over 5% palladium/charcoal catalyst (0.2 g.).

After the uptake of one mole of hydrogen (25 c.c.) the catalyst was filtered off and the solution concentrated to give (XIX) m.p. 330°C (from acetic acid).
(Found; C, 63.5; H, 3.9; N, 7.5%. Calculated for $C_{10}H_7NO_3$ C, 63.5; H, 3.7; N, 7.4%).

Quinol-2-one-3:4-dicarboxylic anhydride (XVII)

The N-acetate (VIII) was hydrogenated in the same manner as above to yield the anhydride (XVII) m.p. 349°C with decomposition (from acetic anhydride).
(Found; C, 61.5; H, 2.6; N, 6.45%. $C_{11}H_5NO_4$ requires C, 61.5; H, 2.3; N, 6.5%).

Quinol-2-one-3:4-dicarboxylic acid [24] (XX)

The anhydride (XVII) was warmed with dilute hydrochloric acid to afford the dicarboxylic acid (XX) m.p. 358°C with decomposition (from water).
(Found; C, 56.8; H, 3.0; N, 6.0%. Calculated for $C_{11}H_7NO_5$ C, 56.7; H, 3.0; N, 6.0%).
This dicarboxylic acid was reduced with zinc in acetic acid to the acid (X) m.pt. and mixed m.pt. with an authentic specimen 221°C.

SECTION II

Diethyl (α-cyano-o-nitrobenzyl)-malonate (II)

To a solution of potassium cyanide (7.0 g.) in water (25 c.c.) and ethanol (200 c.c.) were added in turn, aqueous acetic acid (50 c.c. of 10% by weight) with cooling and finely powdered diethyl o-nitrobenzylidenemalonate (25 g.). This solution was shaken for two hours giving a crystalline precipitate of the nitrile-ester (II). More nitrile-ester was obtained by pouring the filtrate from this reaction into water, extracting with ether, and evaporating off the ether in vacuo. The total yield of nitrile-ester was 21 gm. [77%] m.p. 46°C (from ethanol). (Found; C, 56.2; H, 4.8; N, 8.9% $C_{15}H_{16}N_2O_6$ requires C, 56.2; H, 5.0; N, 8.7%).

Ethyl 3-cyano-1-hydroxyindole-2-carboxylate (XII)

The nitrile-ester (II) (3.2 g.) was refluxed for two hours with a solution of sodium carbonate (3.2 g.) in water (8 c.c.) and ethanol (24 c.c.). The solution was then concentrated and poured into excess dilute sulphuric acid giving the 1-hydroxyindole (1.5 g.) m.p. 116°C (from benzene/petroleum ether 40-60°C; 1:3)
(Found; C, 62.3; H, 4.4; N, 11.8%. $C_{12}H_{10}N_2O_3$ requires C, 62.6; H, 4.4; N, 12.1%).

2-Carboxy-3-cyano-1-hydroxyindole

The nitrile-ester (II) (3.2 g.) was refluxed for two hours with a solution of potassium hydroxide (2.3 g.) in water (16 c.c.) and ethanol (16 c.c.). The solution was concentrated and poured into excess dilute sulphuric acid yielding the 1-hydroxyindole (1.3 g.) m.p. 211°C (from water).

(Found; C, 59.5; H, 2.9; N, 13.6%. $C_{10}H_6N_2O_3$ requires C, 59.4; H, 2.9; N, 13.8%).

Both the above 1-hydroxyindoles were hydrolysed with alkali to 2-carboxy-1-hydroxyindole-3-carboxyamide (VII) m.p. and mixed m.p. 245°C with decomposition.

Diethyl (α-amido-o-nitrobenzyl)-malonate (V)

The nitrile-ester (II) (0.64 g.) was dissolved in concentrated sulphuric acid and the solution poured into excess water to afford the amide (0.67 g.) m.p. 165°C (from ethanol).

(Found: C, 53.5; H, 5.2; N, 8.5%. $C_{15}H_{18}N_2O_7$ requires C, 53.3; H, 5.4; N, 8.3%).

o-Nitrophenylsuccinic acid[18] (III)

The amide (V) (3.4 g.) was refluxed for three hours with concentrated hydrochloric acid (150 c.c.) and glacial acetic acid (15 c.c.). Concentration of this solution

to a small volume gave the acid (1.9 g.) m.p. 188°C (from water; with charcoal)
(Found; C, 50.0; H, 4.0; N, 6.2%. Calculated for $C_{10}H_9NO_6$ C, 50.2; H, 3.8; N, 5.9%).

o-Nitrophenylsuccinic anhydride[27]

o-Nitrophenylsuccinic acid (0.24 g.) was refluxed for one hour with acetyl chloride (4 c.c.) to yield the anhydride (0.2 g.) m.p. 128°C (from acetic anhydride)
(Found: C, 54.4; H, 3.0; N, 6.4%. Calculated for $C_{10}H_7NO_5$ C, 54.3; H, 3.2; N, 6.3%).

1-Hydroxy-2-carbethoxyindole-3-carboxyamide (VI)

The amide (V) (3.4 g.) was warmed with dilute sodium carbonate (50 c.c.) for ten minutes giving a clear yellow solution. Acidification of this solution gave the 1-hydroxyindole (2 g.) m.p. 207 °C with decomposition (from dilute acetic acid)
(Found; C, 58.3; H, 4.8; N, 11.4%. $C_{12}H_{12}N_2O_4$ requires C, 58.1; H, 4.9; N, 11.3%).

1-Acetoxy-2-carbethoxyindole-3-carboxyamide (XXI)

The 1-hydroxyindole (VI) was warmed with acetic anhydride

for five minutes affording the acetyl derivative (XXI) m.p. 168°C (from ethanol).

(Found: C, 58.1; H, 5.0; N, 9.6%. $C_{14}H_{14}N_2O_5$ requires C, 58.0; H, 4.8; N, 9.6%).

2-Carboxy-1-hydroxyindole-3-carboxyamide (VII)

The amide (V) (3.4 g.) was warmed with dilute sodium hydroxide (50 c.c.) for ten minutes and the resulting solution acidified to give (VII) (1.9 g.) m.p. 245°C with decomposition (from glacial acetic acid). This compound may also be prepared by alkaline hydrolysis of the ester (VI).

(Found: C, 54.8; H, 3.6; N, 12.8%. $C_{10}H_8N_2O_4$ requires C, 54.6; H, 3.7; N, 12.7%).

1-Acetoxy-2-carboxyindole-3-carboxyamide

The 1-hydroxyindole (VII) was warmed for five minutes in acetic anhydride to yield the acetyl derivative, m.p. 187°C (from acetic anhydride)

(Found; C, 55.2; H, 3.7; N, 10.4%. $C_{12}H_{10}N_2O_5$ requires C, 55.0; H, 3.8; N, 10.7%).

2-Carboxyindole-3-carboxyamide (VIII)

The 1-hydroxyindole (VII) (0.5 g.) was reduced by dissolving in acetic acid (30 c.c.) and treated with

zinc dust (1.5 g.), added in small portions to the boiling solution. After addition of the zinc dust the solution was refluxed for one hour and concentrated to give the indole (0.4 g.) m.pt. 284°C with decomposition (from acetic acid).

(Found; C, 58.6; H, 4.0; N, 13.6%. $C_{10}H_8N_2O_3$ requires C, 58.8; H, 3.9; N, 13.7%).

Indole-2-carboxylic acid (IX)

The indole (VIII) (1 g.) was refluxed for two hours with dilute sodium hydroxide (40 c.c.). The solution was acidified to give indole-2-carboxylic acid (0.65 g.) m.p. 204°C (from water).

(Found; C, 67.2; H, 4.6; N, 8.6%. Calculated for $C_9H_7NO_2$ C, 67.1; H, 4.4; N, 8.7%).

Picrate of Indole

Indole-2-carboxylic acid (0.2 g.) was ground up with soda lime (0.6 g.) and heated at 220°C for one minute. The residue, on cooling, was extracted with ethanol and filtered. The filtrate was treated with a solution of picric acid in ethanol to give the picrate of indole, m.p. 182°C (from ethanol). Mixed m.p. with an authentic specimen of picrate of indole 182°C.

Hydrogenation Experiments

(a) 2-Carbethoxyindole-3-carboxyamide (XXII)

The N-acetate (XXI) (1 g.) was hydrogenated in acetic acid with 5% palladium/charcoal catalyst to yield the indole (0.7 g.) m.p. 200°C (from ethanol).

(Found: C, 62.0; H, 5.4; N, 12.3%. $C_{12}H_{12}N_2O_3$ requires C, 62.1; H, 5.2; N, 12.1%).

This ester gave the acid (VIII) on acid hydrolysis, m.p. and mixed m.p. with an authentic specimen 284°C with decomposition.

(b) A similar hydrogenation of the N-acetate of (VII) afforded the indole derivative (VIII) m.p. and mixed m.p. with an authentic specimen 284°C with decomposition.

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CHAPTER III

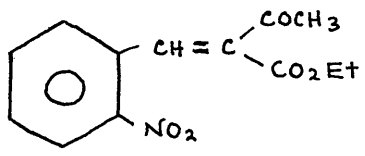
A Novel Synthesis of

6-Chloro-1-hydroxyquinol-4-ones.

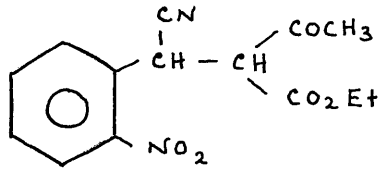
CONTENTS

DISCUSSION

The well established ease of removal of the acetyl-group from substituted acetoacetic esters, suggested that ethyl o-nitrobenzylideneacetoacetate (I) would be a useful compound to prepare and examine. It was proposed to add hydrogen cyanide to the activated double bond to obtain the nitrile-ester (II), which, if it did not afford the desired ethyl β-cyano-β-o-nitrophenylpropionate (III) on hydrolysis, could be used to extend the type of cyclisation described in Chapter II.



I



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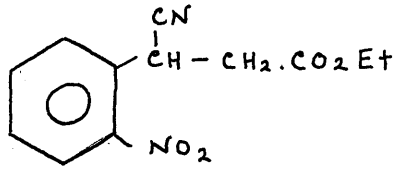
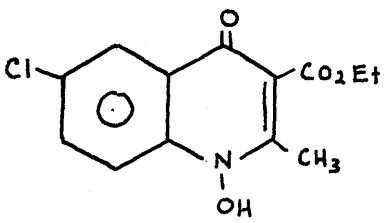


III

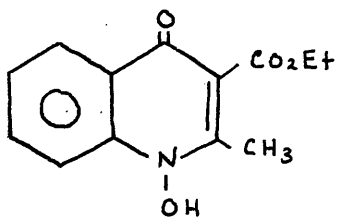
The m- and p-nitro-isomers of the keto-ester (1) are described in the literature[1], but the o-nitro-compound is not mentioned. One method of preparing the m- and p-isomers is to pass hydrogen chloride into an ether solution of the nitrobenzaldehyde and ethyl acetoacetate. When o-nitrobenzaldehyde and ethyl acetoacetate were treated in this way, a high-melting, yellow compound ($C_{13}H_{12}NO_4Cl$) was obtained. The infra-red spectrum of this product showed a broad band at 3000-2300 cm^{-1} attributable to an N-hydroxyl group, and a strong band at 1730 cm^{-1} due to an ester-carbonyl group. The bands characteristic of a nitro-group were absent.

The chlorine atom present in the molecule was found to be unionised, since warming the product with silver nitrate in acetonitrile gave no precipitate of silver chloride. However, on warming the chloro-compound in concentrated nitric acid containing silver nitrate, a precipitate of silver chloride was formed showing the presence of a replaceable chlorine atom. This was further demonstrated by hydrogenation of the compound ($C_{13}H_{12}NO_4Cl$) over a palladium-charcoal catalyst to yield a dechlorinated derivative ($C_{13}H_{13}NO_4$), whose infra-red spectrum was almost identical with that of the parent chloro-compound.

The general properties of these compounds, e.g. high melting point, colour, and infra-red spectra, suggested that an unusual cyclisation had taken place. Further investigation showed that the compound ($C_{13}H_{12}NO_4Cl$) is ethyl 6-chloro-1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline-3-carboxylate (IV), and the corresponding dechloro-derivative ($C_{13}H_{13}NO_4$) is (V).

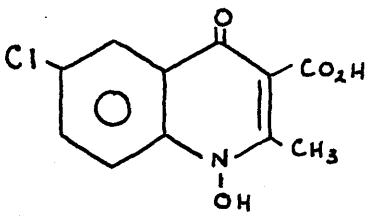


IV



V

Chemical evidence for the structure of the chloro-ester (IV) was provided by series of degradations to products of known structure. Acid hydrolysis of the ester (IV) afforded the acid (VI), which lost carbon dioxide readily on heating above its melting point to give (VII).



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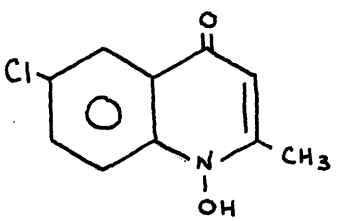
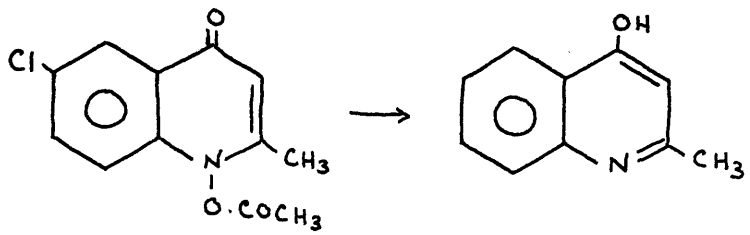


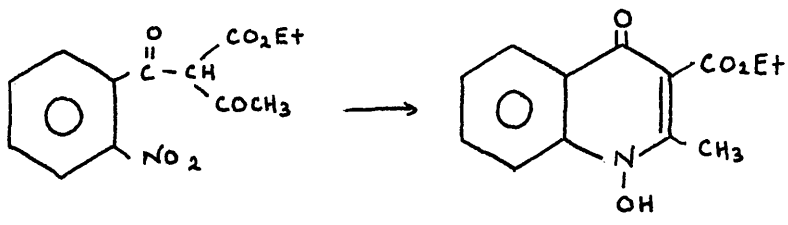
VII

Since the infra-red spectra of these products indicated the presence of an N-hydroxyl group, it was proposed to acetylate the hydroxyl and remove the acetate group by hydrogenolysis. This step was suggested by analogy with the earlier work on hydrogenolysis of N-acetates of 1-hydroxyindoles and 1-hydroxyquinol-2-ones described in Chapter II. In the event, hydrogenation of the N-acetate (VIII) took place with the uptake of two moles of hydrogen, instead of the expected one mole. The product was found to have lost not only the acetate grouping but also the chlorine atom from the parent chloro-N-acetate (VIII), and was shown to be 4-hydroxyquinaldine[2] (IX).



VIII IX

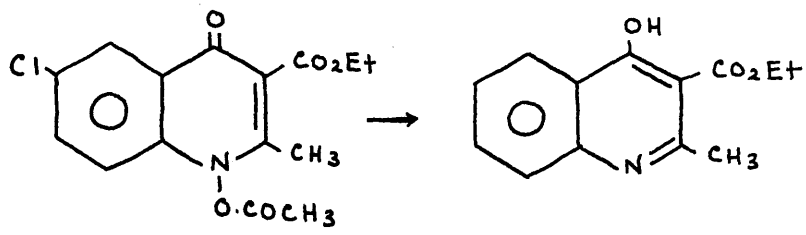
The discovery, demonstrated above, that the chlorine atom could be removed by catalytic hydrogenation led to the preparation of the ester (V) from the chloro-ester (IV). The ester (V) was shown to be identical with an authentic specimen of ethyl 1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline-3-carboxylate. This was originally prepared by McClusky[3] in 1922, who obtained it by passing hydrogen chloride into an acetic acid solution of ethyl o-nitrobenzoylacetoacetate (X) and stannous chloride.



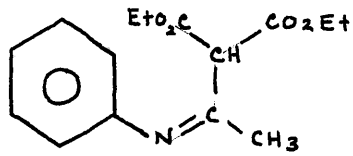
X V

To provide further evidence for the structure of the chloro-ester (IV), it was decided to hydrogenate its N-acetate (XI) to obtain ethyl 4-hydroxy-2-methyl-quinoline-3-carboxylate (XII). The ester (XII) was originally prepared by Jacobs and Gould[4], who reported its melting point as 104-7°C which is suspiciously low for a compound of its type. The product obtained from the hydrogenation of the N-acetate (XI), however, had a much higher melting point (232°C) and yet analysed correctly for the quinoline derivative (XII).

In order to solve this problem the synthesis of the ester (XII), as described by Jacobs and Gould, was repeated. Aniline was condensed with diethyl acetylmalonate to give the anil (XIII) which was cyclised in boiling diphenyl ether to a product whose melting point and mixed melting point with the hydrogenation product was 232°C.



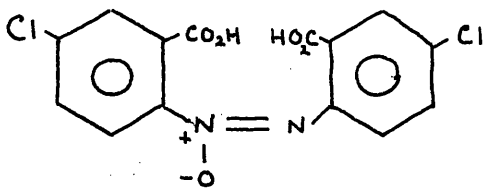
XI XII



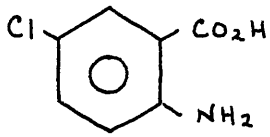
XIII

In an effort to determine the position of the chlorine atom present in the molecule, the chloro-ester (IV) was oxidised with sodium dichromate in dilute acetic acid. No o-nitrobenzoic or chloro-o-nitrobenzoic acid could be isolated from the oxidation, but a high-melting, orange product ($C_{14}H_8N_2O_5Cl$) was formed in reasonable yield. The orange colour and empirical formula suggested that it was an azoxybenzene (XIV), and this was supported by reduction of (XIV) with zinc dust and acetic acid/concentrated hydrochloric acid to give

2-amino-5-chlorobenzoic acid (XV). The acid (XV) was shown to be identical with an authentic specimen of 2-amino-5-chlorobenzoic acid prepared by reduction of 5-chloro-2-nitrobenzoic acid.

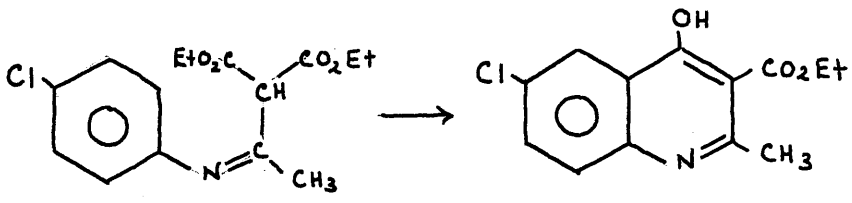


XIV



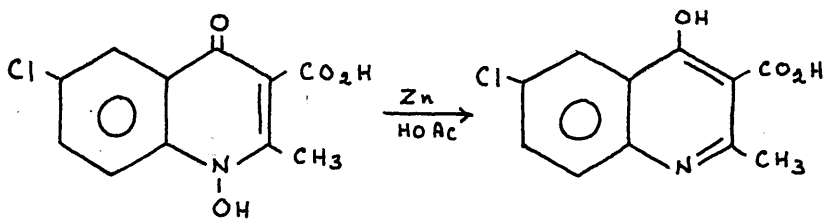
XV

Further evidence for the position of the chlorine atom in the chloro-ester (IV) was provided by synthesis of 3-carboxy-6-chloro-4-hydroxy-2-methylquinoline (XVIII). p-Chloroaniline was condensed with diethyl acetylmalonate, and the resulting anil (XVI) cyclised in diphenyl ether to the ester (XVII).



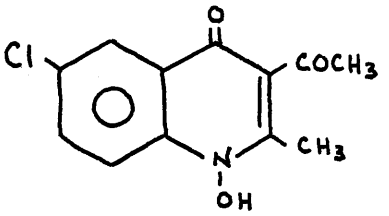
XVI XVII

Acid hydrolysis of the ester (XVII) afforded the acid (XVIII) which was shown to be identical with the product obtained by reduction of the acid (VI) with zinc dust and acetic acid.

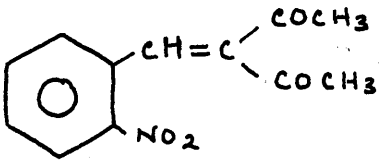


VI XVIII

Another example of this unusual condensation and cyclisation was provided by using acetylacetone in place of ethyl acetoacetate. Thus when hydrogen chloride was passed into an ether solution of o-nitrobenzaldehyde and acetylacetone, 3-acetyl-6-chloro-2-methyl-4-oxo-1:4-dihydroquinoline (XIX) was formed, along with some o-nitrobenzylideneacetylacetone (XX). It is interesting to note that the benzylidene derivative (XX) may be converted to the cyclic chloro-ketone (XIX) on treatment with hydrogen chloride. This was the only case in which the intermediate benzylidene compound could be isolated.

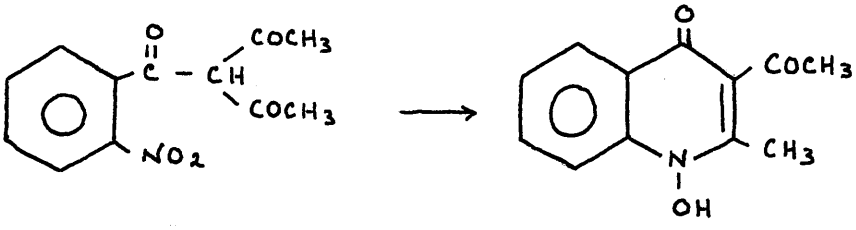


XIX



XX

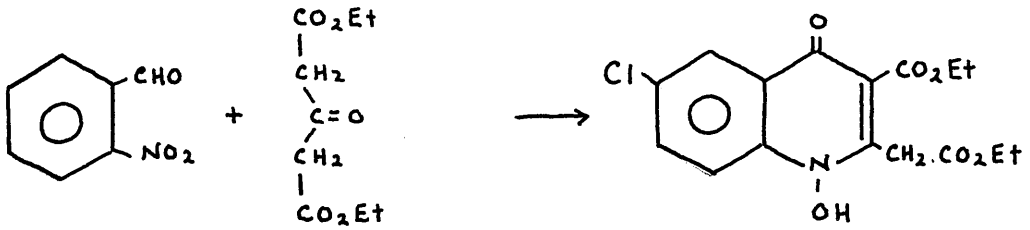
The structure of the chloro-ketone (XIX) was established by catalytic hydrogenation to the dechlorinated derivative (XXI). The ketone (XXI) was shown to be identical with an authentic specimen of 3-acetyl-1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline prepared by passing dry hydrogen chloride into an acetic acid solution of o-nitrobenzoylacetylacetone (XXII) and stannous chloride.



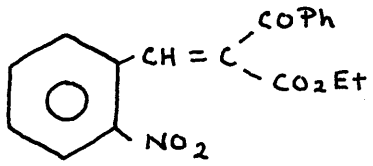
XXII XXI

The position of the chlorine atom in the chloro-ketone (XIX) was determined by oxidation to the same azoxybenzene (XIV) as obtained from the chloro-ester (IV), followed by reduction to 2-amino-5-chlorobenzoic acid (XV).

Two other keto-esters, diethyl acetonedicarboxylate and ethyl benzoylacetate, were reacted with hydrogen chloride and o-nitrobenzaldehyde in an effort to find more examples of cyclisations to 1-hydroxyquinol-4-ones. Of these, diethyl acetonedicarboxylate afforded the cyclic chloro-diester (XXIII), whose structure was assigned by analogy with the previous chlorine-containing cyclic products. Rather surprisingly, ethyl benzoylacetate gave only the benzylidene derivative (XXIV), and no cyclic products were isolated.



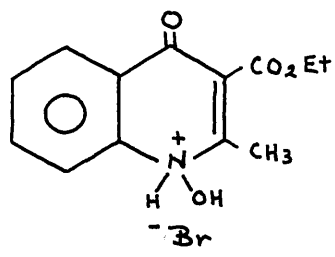
XXIII



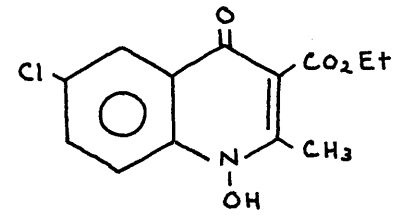
XXIV

An interesting extension of this work was carried out by G. Tennant, who used hydrogen bromide as the condensing agent in place of hydrogen chloride. When hydrogen bromide was passed into an ether solution of o-nitrobenzaldehyde and ethyl acetoacetate, the hydrobromide (XXV) of the ester (V) was formed.

It has not been possible to explain why the hydrobromide (XXV) should be formed in one case, and the chloro-ester (IV) in the other, as very little is known of the mechanism of this type of cyclisation. Two other major points which require to be explained by any future mechanism are 1. The occurrence of an oxygen atom at the 4-position in the quinolone ring. 2. The introduction of a chlorine atom in the 6-position of the quinolone ring.



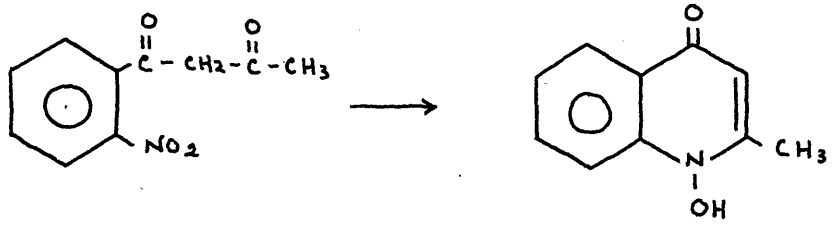
XXV



IV

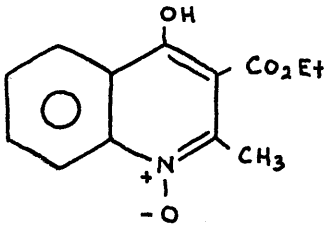
All the 1-hydroxyquinol-4-ones described give a red brown colour with alcoholic ferric chloride, which serves as a simple chemical test for these compounds. Many of these cyclic products are amphoteric in their properties and several form picrates, which have the unusual property of melting at a lower temperature than the parent compound.

The earliest synthesis of a 1-hydroxyquinol-4-one was by Gabriel and Gerhard[5] in 1921. These workers prepared 1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline (XXVII) by treating o-nitrobenzoylacetone (XXVI) with ~~zinc~~ stannous chloride in hydrochloric acid.

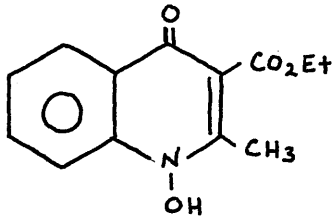


XXVI XXVII

In the following year, McClusky[3] prepared the 3-ethoxycarbonyl-analogue of (XXVII), which she formulated as the N-oxide (XXVIII). This form is a tautomer of the ester (V) described earlier.

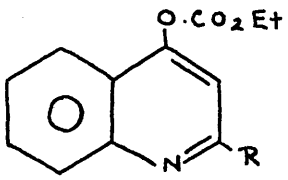


XXVIII

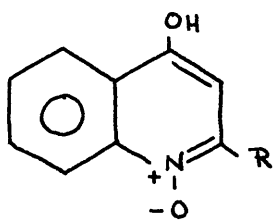


V

In 1956, Cornforth and James[6] prepared 2-n-heptyl-4-hydroxyquinoline N-oxide [XXX, R = $(CH_2)_6CH_3$] by perbenzoic acid oxidation of the O-ethoxycarbonyl derivative [XXIX, R = $(CH_2)_6CH_3$] of 2-n-heptyl-4-hydroxyquinoline.



XXIX

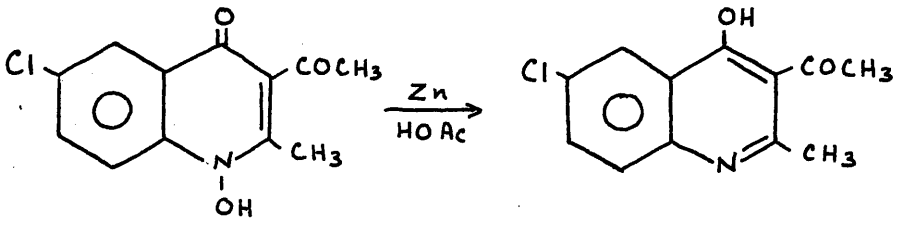


XXX

These workers also prepared 2-n-heptyl-, 2-n-nonyl- and 2-n-undecyl-4-hydroxyquinoline N-oxides by McClusky's method.

As in the case of the N-hydroxy compounds described in Chapter II, zinc dust and acetic acid reduces the N-OH

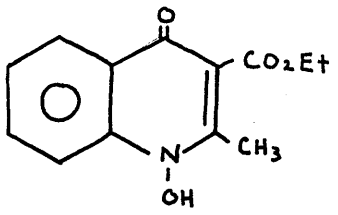
group of 1-hydroxyquinol-4-ones to N-H, and catalytic hydrogenation leaves it unchanged. An instance of the zinc dust reduction was the conversion of the chloro-ketone (XIX) to 3-acetyl-6-chloro-4-hydroxy-2-methylquinoline (XXXI).



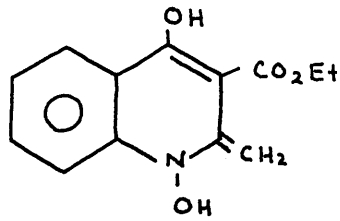
XIX XXXI

Several examples of hydrogenolysis of N-acetates to N-H derivatives have been described above. This is the most effective method of removing an hydroxyl group from an heterocyclic nitrogen atom.

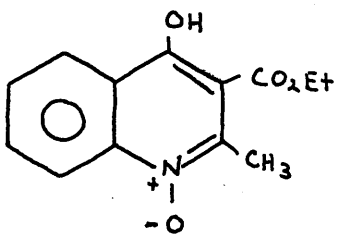
In this discussion the cyclic products have been written as 1-hydroxyquinol-4-ones, but other tautomeric forms are not excluded. The ester (V) may also be written in the form (XXXII) or as the N-oxides (XXXIII) and (XXXIV).



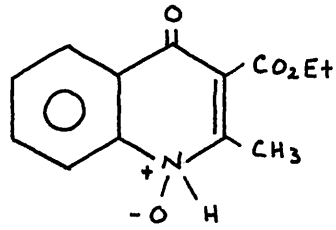
V



XXXII

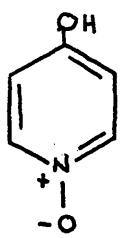


XXXIII

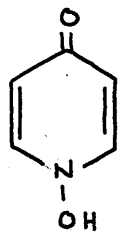


XXXIV

In the pyridine series, 4-hydroxypyridine-1-oxide was investigated by Katritzky and Gardner[7], who showed that it is a mixture of comparable amounts of N-oxide (XXXV) and pyridone (XXXVI) in aqueous solution.

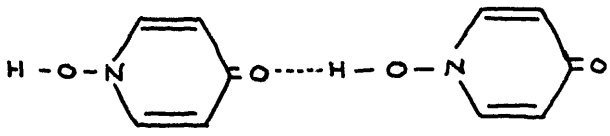


XXXV



XXXVI

In the solid state, however, evidence supports the view that the pyridone (XXXVI) is present in the strongly intermolecularly hydrogen bonded form(XXXVII)



XXXVII

All the infra-red measurements of the 1-hydroxyquinol-4-ones, in the solid state, show the broad absorption in the region 3000-2,300 cm^{-1} believed to be characteristic of the -O-H stretching frequency of a hydrogen-bonded N-hydroxyl group [See Table II, Chapter II, p 36a]. Furthermore the infra-red bands at 1255-1300 cm^{-1} and at 847-872 cm^{-1}, assigned to the N-O stretching frequency of N-oxides[8], are absent.

This spectral data, and the fact that these compounds form only mono-acetyl derivatives, suggests that they exist mainly as intermolecularly hydrogen bonded 1-hydroxyquinol-4-ones (as V). The ultra-violet spectra of these compounds do not contribute much useful structural evidence, but those in Table II are given for reference.

The quinol-4-one N-acetates, in Table I below, show the strong absorption band at 1795-1800 cm^{-1} now attributed to the C=O stretching frequency of the N-acetate group. This absorption band may be compared with that of indole N-acetates and quinol-2-one N-acetates which occurs at 1800-1825 cm^{-1}.

Table I

Infra-red Data

Compound	cm^{-1}	Intensity[+]	Mode
Ethyl 6-chloro-1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline-3-carboxylate	2400(br)	M	-O-H
		V.S.	C=O of ester.
Ethyl 1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline-3-carboxylate	2300(br)	M	-O-H
	1720	V.S.	C=O of ester
3-Carboxy-6-chloro-1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline	2400(br)	M	-O-H
	1670	S	C=O of acid.
6-Chloro-1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline	2300(br)	M	-O-H
3-Acetyl-6-chloro-1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline	2500(br)	S	-O-H
	1670	S	C=O of ketone.
3-Acetyl-1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline	2500(br)	S	-O-H
	1670	V.S.	C=O of ketone.
6-Chloro-3-ethoxycarbonyl-1-hydroxy-2-methyleneethoxy-carbonyl-4-oxo-1:4-dihydroquinoline	2600(br)	M	-O-H
	1725	V.S.	C=O of ester.

Table I (contd.)

Compound	cm^{-1}	Intensity+	Mode
Ethyl 1-acetoxy-6-chloro-2-methyl-4-oxo-1:4-dihydroquinoline-3-carboxylate	1800	V.S.	C=O of acetate
	1715	V.S.	C=O of ester
1-Acetoxy-6-chloro-2-methyl-4-oxo-1:4-dihydroquinoline	1795	V.S.	C=O of acetate.
1-Acetoxy-3-acetyl-6-chloro-2-methyl-4-oxo-1:4-dihydroquinoline	1795	V.S.	C=O of acetate
	1680	V.S.	C=O of ketone.

All spectra were measured in nujal mulls.

+ Abbreviations used M = medium
S = strong
V. S = very strong.

Table II

Ultra-violet Data

Compound		
Ethyl 6-chloro-1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline-3-carboxylate	220	31,000
	265	11,000
	330	10,000
Ethyl 1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline-3-carboxylate [3]	217	30,000
	250(shoulder)	14,000
	330	10,000
3-Acetyl-6-chloro-1-hydroxy-2-methyl-4-oxo-1:4-dihycroquinoline	220	40,000
	270	16,000
	330	12,000

All spectra were measured in ethanol.

EXPERIMENTAL

Ethyl 6-chloro-1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline-3-carboxylate (IV)

A solution of o-nitrobenzaldehyde (3.02 g.) and ethyl acetoacetate (2.6 c.c.) in dry ether (50 c.c.) was saturated with hydrogen chloride at room temperature. After standing for 12-24 hours, crystals of the cyclic ester (IV) were deposited, filtered off and the filtrate resaturated with hydrogen chloride. In this way 3.7 g. (66%) of (IV) were obtained, m.p. 226°C with decomposition (from ethanol) (Found; C, 55.5; H, 4.2; N, 4.9% $C_{13}H_{12}NO_4Cl$ requires C, 55,45; H, 4.25; N, 4.95%). λ max. 220, 265, 330 mu (log ε 4.50, 4.05, 4.00) in ethanol.

The N-acetate of (IV) was formed by warming (IV) in acetic anhydride, m.p. 155°C (from ethanol) (Found; C, 55.7; H, 4.4; N, 4.5%. $C_{15}H_{14}NO_5Cl$ requires C, 55.7; H, 4.3; N, 4.35%).

3-Carboxy-6-chloro-1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline (VI)

The ester (IV) (1.4 g.) was refluxed for three hours

with a solution of acetic acid (8 c.c.), water (16 c.c.) and concentrated sulphuric acid (2 c.c.). Concentration of the solution gave the carboxylic acid (1.0 g.) m.p. 236°C with decomposition (from dimethylformamide). After melting, the material resolidifies and melts again at 285°C, the melting point of the decarboxylated product (VII). (Found: C, 51.9; H, 3.2; N, 5.5%. $C_{11}H_8NO_4Cl$ requires C,52.1; H, 3.2; N, 5.5%).

The N-acetate of (VI) was prepared by warming this acid in acetic anhydride, m.p. 190°C (from acetic anhydride). (Found; C, 52.6; H, 3.6; N, 5.0%. $C_{13}H_{10}No_5Cl$ requires C, 52.8; H, 3.4; N, 4.75%).

6-Chloro-1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline (VII)

The acid (VI) (0.6 g.) was heated at 220°C for ten minutes on a metal bath, giving the decarboxylated product (0.35 g.), m.p. 285°C with decomposition (from dimethylformamide) (Found: C, 57.0; H, 3.8; N, 6.8%. $C_{10}H_8NO_2Cl$ requires C, 57.2; H, 3.8; N, 6.7%).

The N-acetate of (VII) was prepared by warming (VII) in acetic anhydride, m.p. 164°C [from benzene: petroleum ether (b.p. 60-80°C)]

(Found: C, 57.3; H, 4.0; N, 6.0%. $C_{12}H_{10}NO_3Cl$ requires C, 57.4; H, 4.0; N, 5.7%).

The picrate of (VII) was formed by treating (VII) with an ethanolic solution of picric acid, m.p. 185°C (from ethanol).

(Found: C, 44.1; H, 2.8; N, 12.6%. $C_{16}H_{11}N_4O_9Cl$ requires C, 43.9; H, 2.5; N, 12.8%).

4-Hydroxyquinaldine[2] (IX)

The N-acetate of (VII) was hydrogenated over a 5% palladium-charcoal catalyst in ethanol. Two moles of hydrogen were taken up, then the solution was filtered and concentrated to give a solid residue. An ethanolic picric acid solution was added to the residue and warmed to give yellow needles of the picrate of (IX), m.p. 202°C (from ethanol)

(Found: C, 49.8; H, 3.2; N, 14.4% calculated for $C_{16}H_{14}N_4O_8$ C, 49.6; H, 3.1; N, 14.4%). Mixed m.p. with an authentic specimen of the picrate of 4-hydroxyquinaldine, 201-2°C.

Ethyl 1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline-3-carboxylate[3] (V)

The chloro-ester (IV) (1.2 g.) was hydrogenated in ethanol (150 c.c.) over a 5% palladium-charcoal catalyst (0.8 g.). After the uptake of one mole of hydrogen (90 c.c.), the solution was filtered and concentrated to give (V) (0.7 g.), m.p. 176°C (from ethanol) (Found: C, 63.2; H, 5.1; N, 5.8%. Calculated for $C_{13}H_{13}NO_4$. C, 63.2; H, 5.3; N, 5.7%). Mixed m.p. with an authentic specimen of (V) 175-6°C. The infra-red spectra of the two products were also identical.

The picrate of (V) was formed by treating (V) with ethanolic picric acid, m.p. and mixed m.p. with an authentic specimen 132°C (from ethanol). (Found: C, 48.0; H, 3.6; N, 11.6%. $C_{19}H_{16}N_4O_{11}$ requires C, 47.95; H, 3.4; N, 11.7%).

Ethyl 4-hydroxy-2-methylquinoline-3-carboxylate (XII)

The N-acetate of the chloro-ester (IV) was hydrogenated in ethanol over a 5% palladium-charcoal catalyst. After the uptake of two moles of hydrogen, the solution was filtered and concentrated to give (XII) m.p. 232°C

(from ethanol)
(Found; C, 67.5; H, 5.5; N, 6.2%. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.6; N, 6.1%). Mixed m.p. with an authentic specimen of (XII) 232°C.

The picrate of (XII) was formed by treating (XII) with ethanolic picric acid, m.p. and mixed m.p. with an authentic specimen 156°C (from ethanol)
(Found; C, 49.8; H, 3.3; N, 12.2%. $C_{19}H_{16}N_4O_{40}$ requires C, 49.6; H, 3.5; N, 12.15%).

The authentic specimen of ethyl 4-hydroxy-2-methyl-quinoline-3-carboxylate (XII) was prepared by condensing diethyl acetylmalonate[9] with aniline in the presence of a crystal of iodine. The reaction mixture was allowed to stand at room temperature for eight hours, then the resulting crude anil (XIII) was cyclised in boiling diphenyl ether to the quinoline (XII) m.p. 232°C (from ethanol).

2:2'-Dicarboxy-4:4'-dichloroazoxybenzene (XIV)

A solution of sodium dichromate (12 g.) in water (30 c.c.) was added slowly to a boiling solution of the chloro-ester (IV) (2 g.) in acetic acid (40 c.c.), water (25 c.c.)

and concentrated sulphuric acid (10 c.c.). The reaction mixture was refluxed for one hour after the addition of the sodium dichromate solution. On cooling orange crystals of (XIV) were deposited, m.p. 264°C with decomposition (from acetic acid).

(Found: C, 47.3; H, 2.25; N, 7.7; Cl, 20.4%.
$C_{14}H_8N_2O_5Cl_2$ requires C, 47.3; H, 2.25; N, 7.9; Cl, 20.0%).

2-Amino-5-chlorobenzoic acid (XV)

Zinc dust (2.5 g.) was added in small portions to a refluxing solution of the azoxybenzene (XIV) (1 g.) in acetic acid (40 c.c.) and concentrated hydrochloric acid (5 c.c.). After refluxing for one hour the solution was cooled and concentrated to give a solid product, which was filtered off and dissolved in dilute sodium hydroxide. This alkaline solution was made almost neutral with dilute hydrochloric acid, then made acid by the addition of glacial acetic acid. The precipitate of chloroanthranilic acid (XV) was recrystallised from ethanol m.p. 206°C. Mixed m.p. with an authentic specimen of (XV), prepared by reduction of 5-chloro-2-nitrobenzoic acid, 206°C. The infra-red spectra of these two specimens were identical.

Diethyl p-chloroanilidomethylmethylenemalonate (XVI)

Diethyl acetymalonate[9] (10.1 g.) and p-chloroaniline (6.4 g.) were allowed to stand for eight hours at room temperature with a crystal of iodine, to give the anil (13 g.), m.p. 63°C (from petroleum ether 40-60°) (Found; C, 58.1; H, 5.9; N, 4.7%. $C_{15}H_{18}NO_4Cl$ requires C, 58.0; H, 5.8; N, 4.5%).

Ethyl 6-chloro-4-hydroxy-2-methylquinoline-3-carboxylate (XVII)

The anil (XVI) (3 g.) was added slowly to ~~a~~ boiling ~~solution of~~ diphenyl ether (50 c.c.) and the mixture refluxed for thirty minutes. On cooling, the diphenyl ether was removed from the quinoline ester by washing the crude solid product with petroleum ether (b.p. 60-80°C) (200 c.c.). The ester (2 g.) was recrystallised from dimethylformamide, m.p. 275°C with decomposition. (Found; C, 58.6; H, 4.4; N, 5.4%. $C_{13}H_{12}NO_3Cl$ requires C, 58.7; H, 4.5; N, 5.3%).

3-Carboxy-6-chloro-4-hydroxy-2-methylquinoline (XVIII)

The chloro-acid (VI) (0.6 g.) was refluxed for one hour with zinc dust (1.5 g.) in glacial acetic acid (20 c.c.). Concentration of the reaction mixture gave (XVIII)

(0.36 g.) m.p. 315°C with decomposition (from dimethylformamide).

(Found; C, 55.5; H, 3.2; N, 6.2%. $C_{11}H_8NO_3Cl$ requires C, 55.6; H, 3.4; N, 5.9%). Mixed m.p. with an authentic specimen of (XVIII) 315°C.

The authentic specimen of 3-carboxy-6-chloro-4-hydroxy-2-methylquinoline (XVIII) was prepared by alkaline hydrolysis of the ester (XVII) m.p. 315°C (from dimethylformamide).

(Found; C, 55.8; H, 3.5; N, 6.2%. $C_{11}H_8NO_3Cl$ requires C, 55.6; H, 3.4; N, 5.9%).

The infra-red spectra of these two specimens were identical.

3-Acetyl-6-chloro-1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline (XIX)

A solution of o-nitrobenzaldehyde (3.02 g.) and acetylacetone (2.06 c.c.) in dry ether (50 c.c.) was saturated with hydrogen chloride at room temperature. After standing for eight hours, crystals of the cyclic chloro-ketone were formed (4.5 g.) m.p. 286°C with decomposition (from dimethylformamide).

(Found; C, 57.0; H, 3.9; N, 5.8%. $C_{12}H_{10}NO_3Cl$ requires C, 57.2; H, 4.0; N, 5.6%).

The N-acetate of (XIX) was formed by warming (XIX) in acetic

anhydride, m.p. 166°C (from acetic anhydride)
(Found; C, 57.3; H, 4.1; N, 5.1%. $C_{14}H_{12}NO_4Cl$ requires C, 57.25; H, 4.1; N, 4.8%).

The N-methoxy derivative of (XIX) was prepared by warming (XIX) in dimethyl sulphate and alkali, m.p. 172°C (from methanol).
(Found; C, 58.7; H, 4.5; N, 5.4%. $C_{13}H_{12}NO_3Cl$ requires C, 58.8; H, 4.5; N, 5.3%).

3-Acetyl-6-chloro-4-hydroxy-2-methylquinoline (XXXI)

The chloro-ketone (XIX) (1 g.) was refluxed for one hour with zinc dust (3 g.) in glacial acetic acid (40 c.c.). Concentration of the reaction mixture gave (XXXI) (0.6 g.) m.p. 310°C with decomposition (from acetic acid)
(Found; C, 61.7; H, 4.3; N, 6.1%. $C_{12}H_{10}NO_2Cl$ requires C, 61.5; H, 4.25; N, 5.9%).

o-Nitrobenzylideneacetylacetone (XX)

A solution of o-nitrobenzaldehyde (3.02 g.) and acetylacetone (2.06 c.c.) in dry ether was saturated with hydrogen chloride at room temperature. After standing for ten minutes, the ether was removed under reduced pressure to

afford a residual oil. The residue was dissolved in the minimum of ethanol, and the solution cooled in ice to give large crystals of the benzylidene product (4.0 g.). A small quantity of the cyclic chloro-ketone (XIX) was also obtained. The benzylidene derivative (XX) had m.p. 76°C (from ethanol).

(Found; C, 61.8; H, 4.9; N, 6.2%. $C_{12}H_{11}NO_4$ requires C, 61.8; H, 4.7; N, 6.0%).

o-Nitrobenzoylacetylacetone (XXII)

Sodium (3.1 g.) was dissolved in ethanol (32 c.c.) and the solution made up to 50 c.c. by the addition of more ethanol. Acetylacetone (5.6 g.) was dissolved in 25 c.c. of the sodium ethoxide solution, the whole cooled to 0°C and o-nitrobenzoyl chloride (5.6 g.) added in small portions with stirring, the temperature being kept below 5°C.

After thirty minutes, 12.5 c.c. of sodium ethoxide solution were added and, after mixing, 2.8 g. of acid chloride run in slowly. Thirty minutes later the rest of the sodium ethoxide solution (12.5 c.c.) and acid chloride (2.8 g.) were added. After stirring for a further four hours, the yellow product was filtered off, washed with ethanol and then ether. The yellow solid

was added to an excess of dilute hydrochloric acid containing ice, affording a solid precipitate of o-nitrobenzoylacetylacetone (10.2 g.) m.p. 72°C (from ethanol).

(Found; C, 57.8; H, 4.2; N, 5.5%. $C_{12}H_{11}NO_5$ requires C, 57.8; H, 4.4; N, 5.6%).

3-Acetyl-1-hydroxy-2-methyl-4-oxo-1:4-dihydroquinoline (XXI)

The chloro-ketone (XIX) (1.0 g.) was hydrogenated in acetic acid (100 c.c.) over a 5% palladium-charcoal catalyst (0.8 g.). After the uptake of one mole of hydrogen (90 c.c.), the solution was filtered and concentrated under reduced pressure to give (XXI) (0.6 g.) m.p. 259-60°C with decomposition (from dimethylformamide).

(Found; C, 66.4; H, 4.8; N, 6.6%. $C_{12}H_{11}NO_3$ requires C, 66.5; H, 5.1; N, 6.45%).

An authentic specimen of (XXI) was prepared in the following manner:- Stannous chloride (71 g.) was added to glacial acetic acid (225 c.c.) and hydrogen chloride passed through the solution until it became clear. o-Nitrobenzoylacetylacetone (12 g.) was added to this stirred solution and hydrogen chloride continued to be

passed. After thirty minutes, white crystals of (XXI) began to separate m.p. 259°C with decomposition (from dimethylformamide).

(Found; C, 66.6; H, 5.0; N, 6.4%. $C_{12}H_{11}NO_3$ requires C, 66.5; H, 5.1; N, 6.45%). Mixed m.p. with the hydrogenation product from the chloro-ketone (XIX) 258-9°C with decomposition.

6-Chloro-3-ethoxycarbonyl-1-hydroxy-2-methylene-ethoxycarbonyl-4-oxo-1:4-dihydroquinoline (XXIII)

A solution of o-nitrobenzaldehyde (3.02 g.) and diethyl acetonedicarboxylate (4 g.) in dry ether was saturated with hydrogen chloride at room temperature.

After standing for 48 hours, the ether was removed under reduced pressure to afford a residual oil. This residue was dissolved in warm glacial acetic acid (10 c.c.) and the resulting solution poured into water (100 c.c.) to give the chloro-diester (2 g.) m.p. 202°C with decomposition (from ethanol).

(Found; C, 54.4; H, 4.4; N, 4.2%. $C_{16}H_{16}NO_6Cl$ requires C, 54.2; H, 4.5; N, 4.0%).

Ethyl o-nitrobenzylidene~~aceto~~benzoylacetate (XXIV)

A solution of o-nitrobenzaldehyde (3.02 g.) and ethyl benzoylacetate (3.24 g.) in dry ether (50 c.c.) was saturated with hydrogen chloride at room temperature. After standing for 24 hours, the ether was removed under reduced pressure to yield an oily residue. The residue was dissolved in the minimum of ethanol and cooled in ice water, to give crystals of (XXIV) (4 g.), m.p. 107°C. (from ethanol).

(Found; C, 66.4; H, 4.8; N, 4.4%. $C_{18}H_{15}NO_5$ requires C, 66.5; H, 4.6; N, 4.3%).

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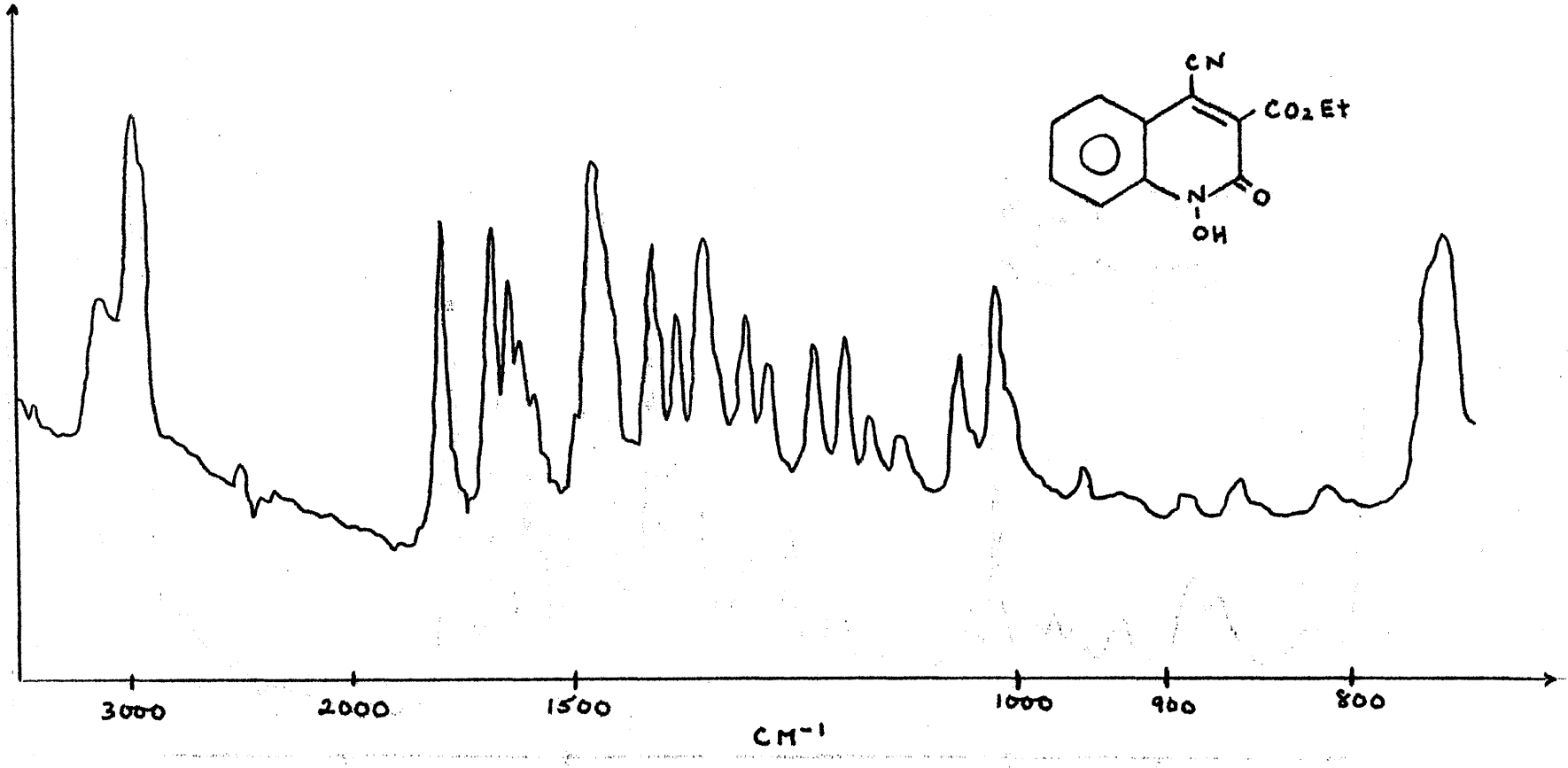
Infra-red Spectra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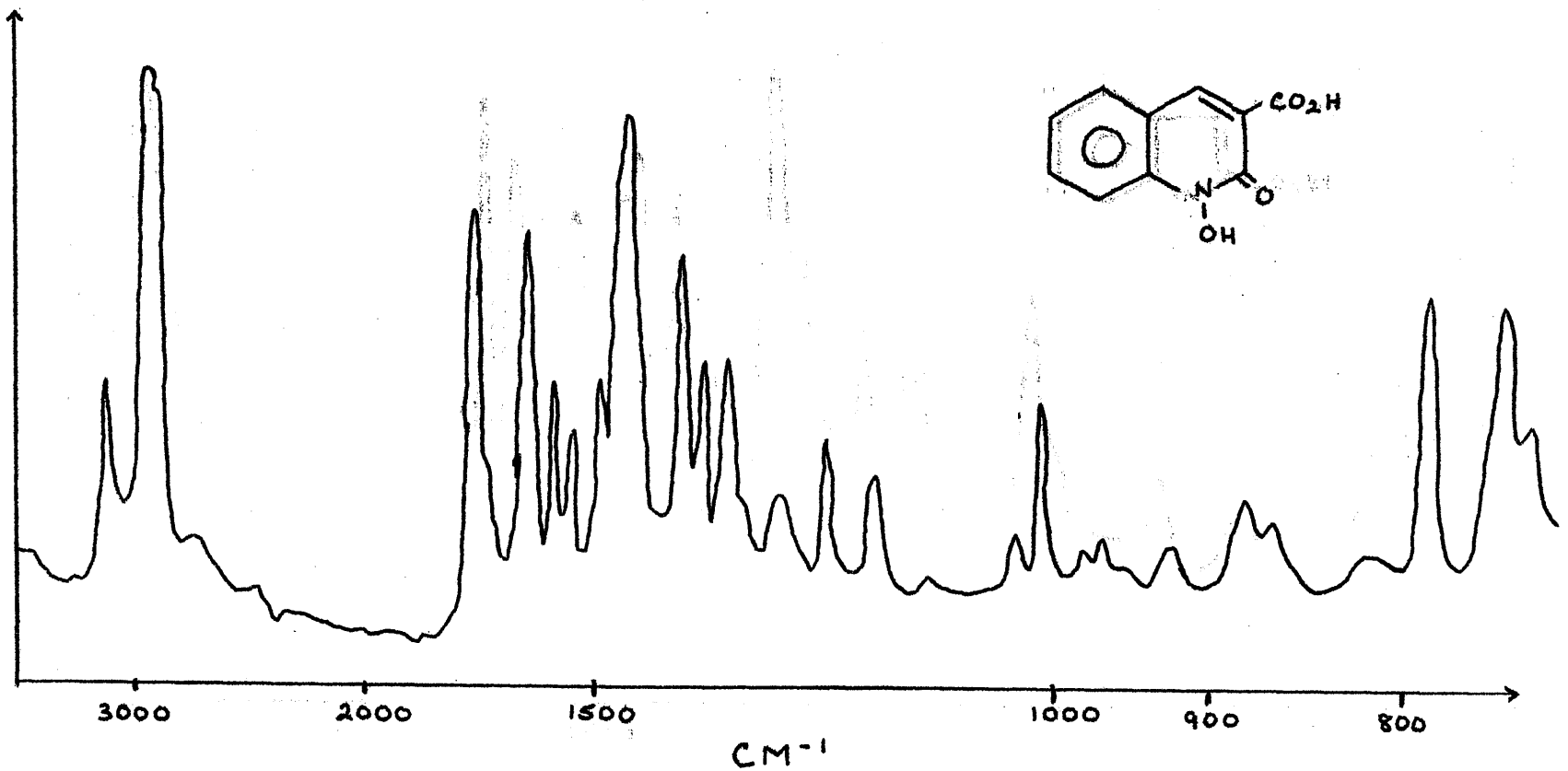
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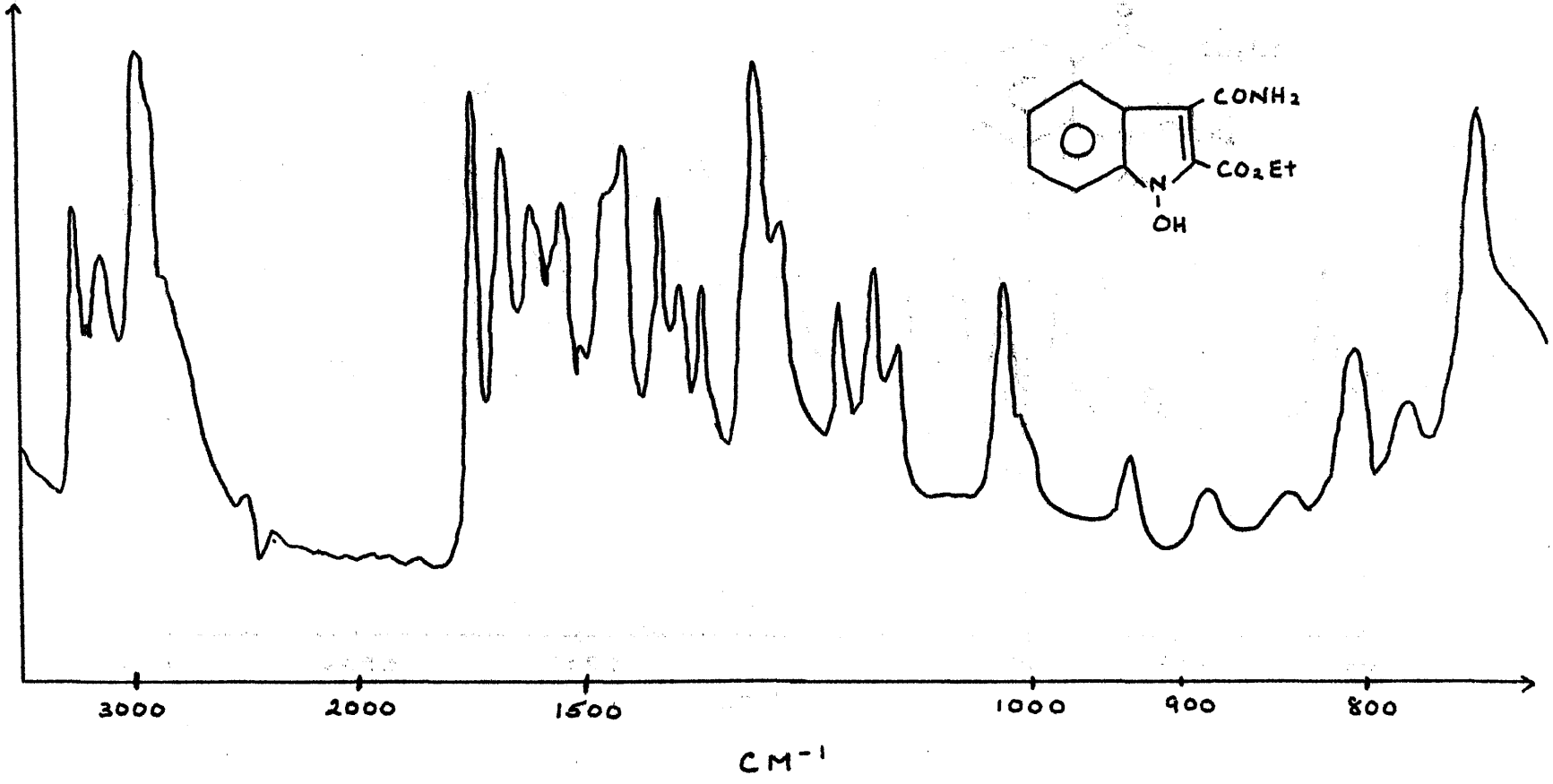
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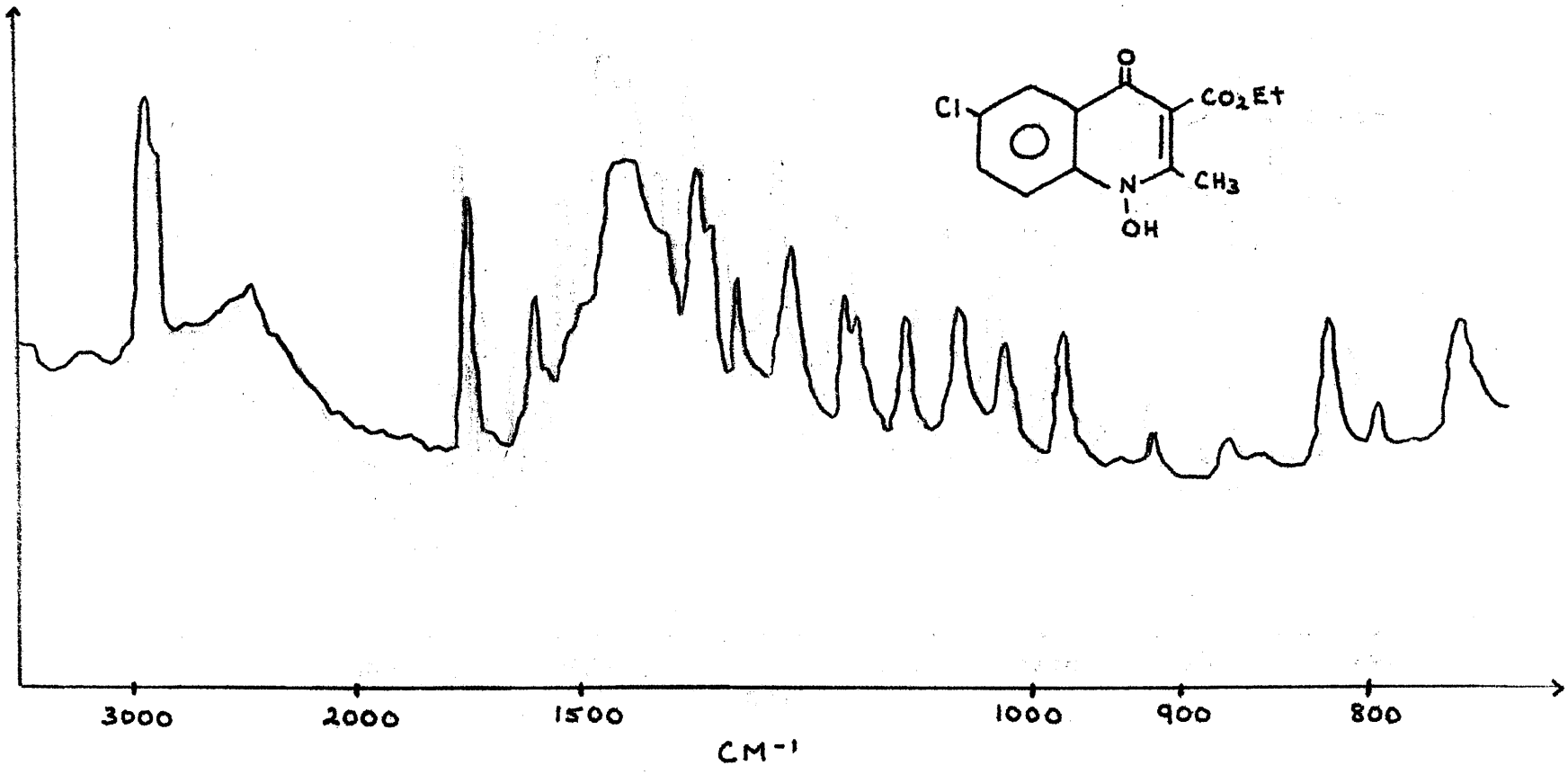
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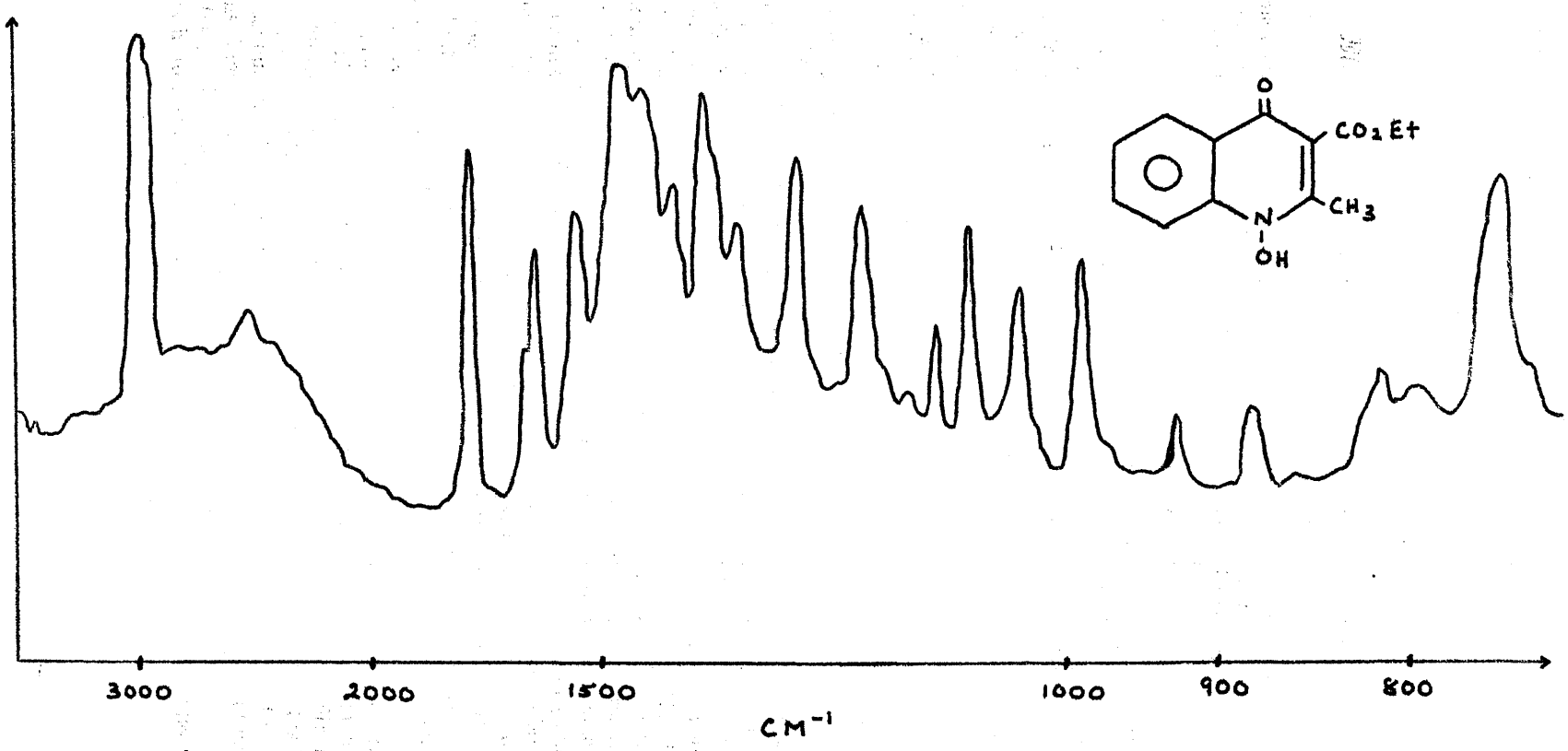
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