STUDIES OF NEIGHBOURING GROUP INTERACTION IN ORTHO-SUBSTITUTED NITROBENZENES

by

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SUMMARY

The scope and mechanisms of interaction between ortho nitro-groups and side-chains on the benzene nucleus were studied. Interactions of this type can be acid or base-catalysed, and can lead to acyclic or cyclic products, notably aza-heterocycles, often of novel structure.

Base-catalysed Interactions A number of N,N-disubstituted o-nitrobenzamides were synthesised from o-nitrobenzoyl chloride and the appropriate amine. Treated with base, N-methyl-, N-benzyl- and (N-o-nitrobenzoyl-N-phenyl)amino-acetonitrile underwent intramolecular aldol condensations involving the nitro-group, to give the corresponding 2,4-dioxo-1-hydroxy-3-substituted-1,2,3,4-tetrahydroquinazolines, in good yield. Similar treatment of ethyl α-(N-o-nitrobenzoyl-N-phenyl)aminoacetate, ω-(N-o-nitrobenzoyl-N-phenyl)aminoaceto-phenone, α-(N-o-nitrobenzoyl-N-phenyl) and α-(N-benzyl-N-o-nitrobenzoyl)amino-propionitrile gave the corresponding 2-substituted 3-indazolones, again presumably by base-catalysed aldol condensation involving the nitro-group, followed by ring cleavage and reclosure. In contrast, reaction of α-(N-o-nitrobenzoyl-N-phenyl), α-(N-benzyl-N-o-nitrobenzoyl) and α-(N-methyl-N-o-nitrobenzoyl)aminophenylacetonitrile in basic media, afforded mainly the corresponding 2-substituted 3-cyano-3-phenylphthalimidines, indicating that the main mode of interaction was intramolecular nucleophilic aromatic displace-ment of the nitro-group by the carbanion generated in the side-chain.

Acid-catalysed Interactions When trans 1-benzoyl-2-(o-nitrophenyl)ethylene oxide and its 1-acetyl analogue were treated with dry hydrogen chloride, the corresponding 6-chloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-substituted quinolines were obtained in moderate yield, by a reaction mechanism probably involving initial transfer of oxygen from the nitro-group, to the side-chain, followed

by external reduction of the resultant nitrosophenylketone to the hydroxylamino compound by insertion of chloride, and cyclisation. The use of hydrogen bromide, or hydrogen chloride in the presence of quinol, yielded the corresponding unhalogenated 1,3-dihydroxy-2-substituted quinolines. In contrast with the trans isomer, cis 1-benzoyl-2-(o-nitrophenyl)ethylene oxide, treated with hydrogen chloride, afforded a quantitative yield of the 6-chloro-1,3-dihydroxyquinoline, suggesting the possibility of a concerted cyclisation mechanism, where the situation is sterically favourable. 1,1-Diacetyl- and 1-acetyl-1-benzoyl-2-(o-nitrophenyl)ethylene oxides, treated similarly, both gave very high yields of 6-chloro-1,4-dihydro-1,3-dihydroxy-2-methyl-4-oxoquinoline, also illustrating the effect of the stereochemistry of the epoxide on the reaction.

Trans 1-benzoyl-2-(o-nitrophenyl)ethylene oxide, treated with stannic chloride, gave N-(α-hydroxyphenacyl)-2,1-benzisoxazolone, while with boron trifluoride etherate, it yielded a mixture of the former and N-phenylglyoxyloylanthranilic acid. N-Desyl-2,1-benzisoxazolone was isolated when the reaction was repeated in the presence of acetic anhydride, using stannic chloride. 1-Acetyl-2-(o-nitrophenyl)ethylene oxide, treated with boron trifluoride etherate, gave a product assigned the structure ω-acetyl-ω-hydroxy-o-nitrosoacetophenone, while with added acetic anhydride, ω-acetoxy-ω-acetyl-o-nitrosoacetophenone was obtained. o-Nitrophenylethylene oxide itself gave only methylene-bis-2,1-benzisoxazolone, when treated with Lewis acids.

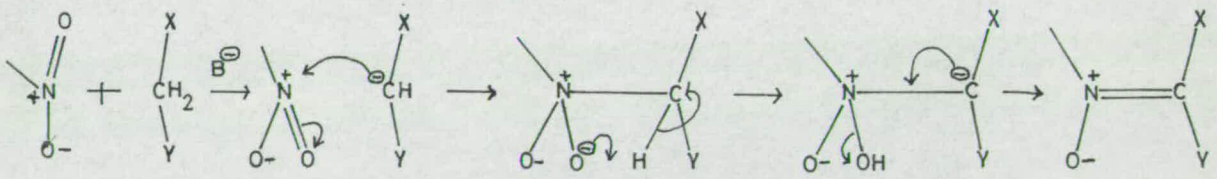
1-Benzoyl-2-(o-nitrophenyl)ethylene oxide, refluxed in glacial acetic acid, afforded 1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinoline, whereas, refluxed in formic acid, it gave N-phenylglyoxyloylanthranilic acid.

CONTENTS

GENERAL INTRODUCTION

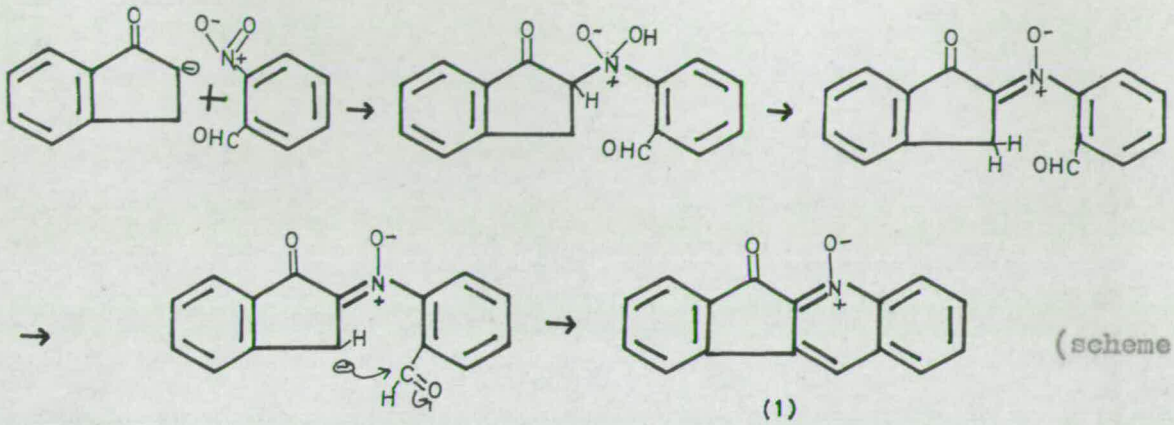
Due to the proximity of aromatic nitro-groups to ortho-side-chains, there is the possibility of chemical interaction, if there is a suitably activated centre present in the side-chain. The most common type of interaction involves prior reduction of the nitro-group by an external reagent, followed by cyclisation of the resulting hydroxylamine or amine to give a nitrogen-containing heterocycle. This is a common method of heterocyclic synthesis. However a number of reactions are known which appear to involve direct interaction between the side-chain and the intact nitro-group. The scope and mechanism of interactions of this type are summarised in a recent review[1].

Two types of interaction are possible involving reaction across space. The first of these occurs by attack at nitrogen by a nucleophilic centre in the side-chain, the second, by attack at oxygen by an electrophilic centre in the side-chain. The former process is the simplest to envisage, and may be considered to take place via a base-catalysed aldol type of mechanism, as shown in scheme 1.



(scheme 1)

There are few recorded examples in the literature of intermolecular condensations of the aldol type involving the nitro-group. Recently, however, it has been suggested that the reaction of o-nitrobenzaldehyde with indanone, to give an indanoquinoline-1-oxide (1), involves such a condensation.[2]



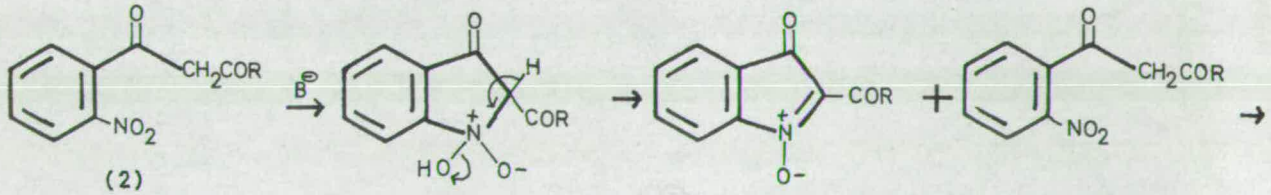
(scheme 2)

(1)

However, it is difficult to accept that as implied by the proposed mechanism (scheme 2), a nitro-group can compete successfully with an aldehyde group in an aldol type condensation.

Intramolecular interactions of this type, howevever, are much more common, presumably because the nitro-group is held in a sterically favoured position for reaction to take place. The most clear-cut examples occur in systems where the benzylic position is blocked, e.g. in o-nitrobenzoyl derivatives.

Thus methyl or ethyl o-nitrobenzoylacetate (2; R=OMe or OEt) or o-nitrobenzoylacetone (2; R=Me) react in the cold with aqueous sodium bicarbonate[3], giving products later identified[4] as the orange isatogens (3) and the purple indogenides (4).



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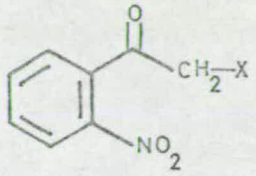

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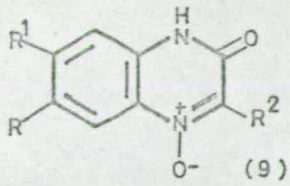

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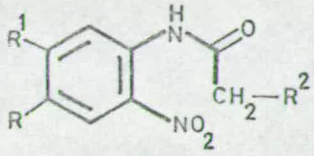

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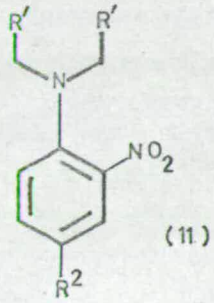

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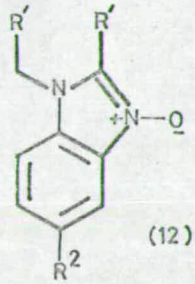

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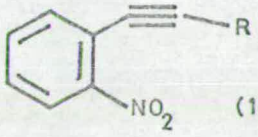

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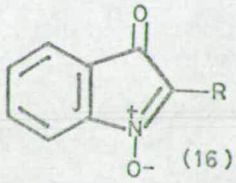

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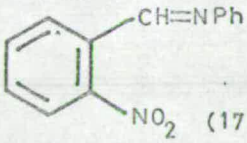

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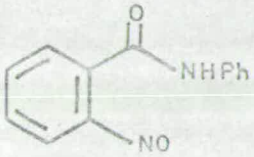

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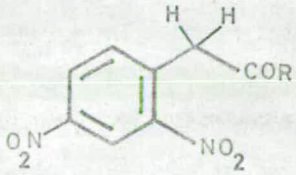

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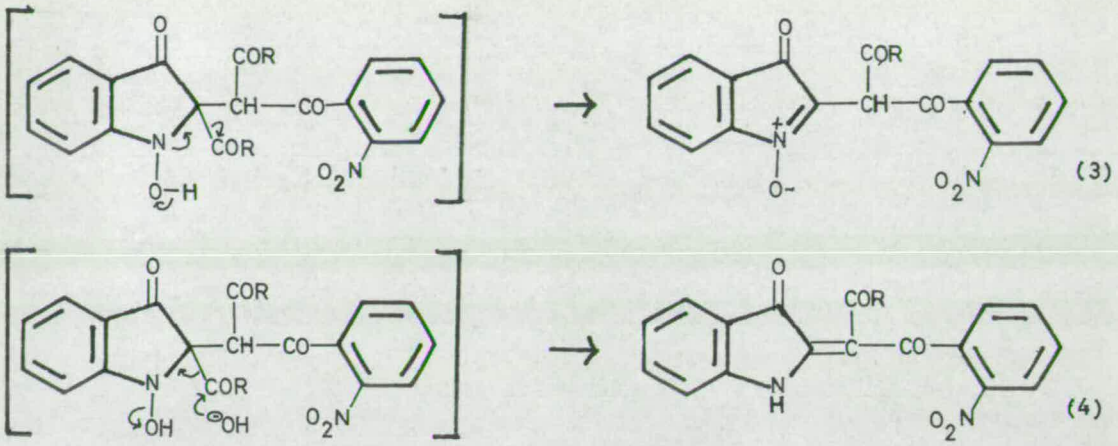


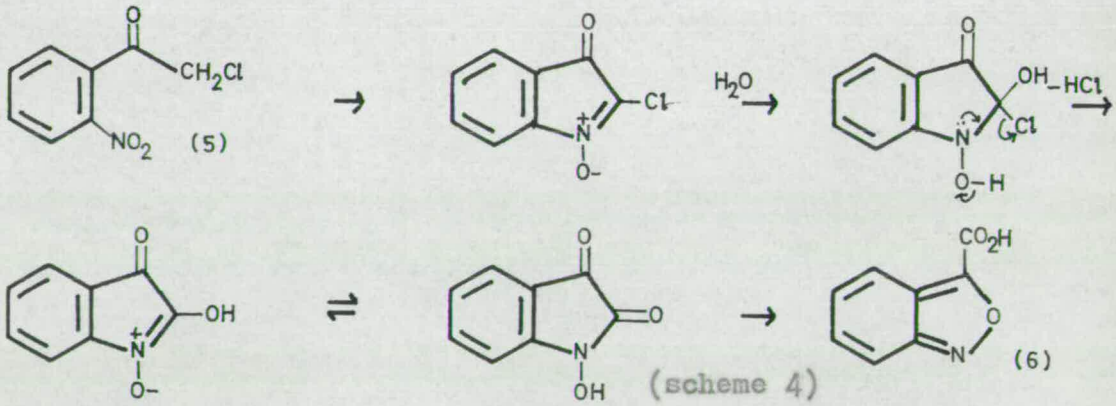
(3)

(4)

(scheme 3)

Presumably the common intermediate can lead to both products, as in scheme 3.

o-Nitroacetophenone derivatives may also interact by this direct aldol type of process. Thus the chloro-ketone (5) has been shown to yield anthranil-3-carboxylic acid (6) when heated with aqueous ethanolic potassium hydroxide, the suggested intermediates being the chloroisatogen and 1-hydroxyisatin[5].

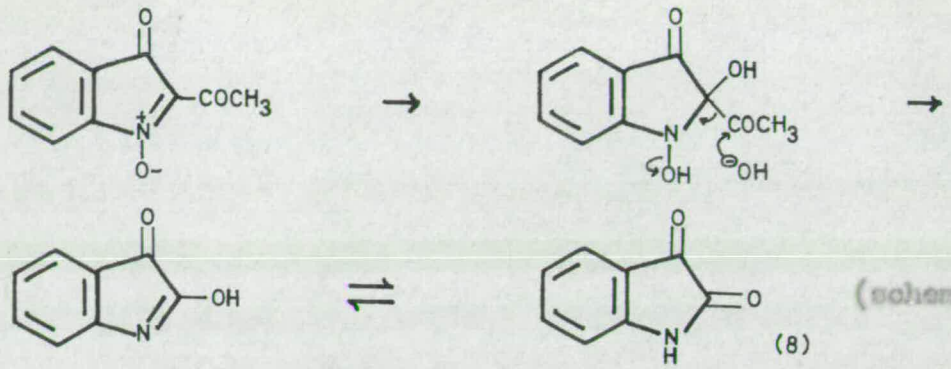


(5)

(6)

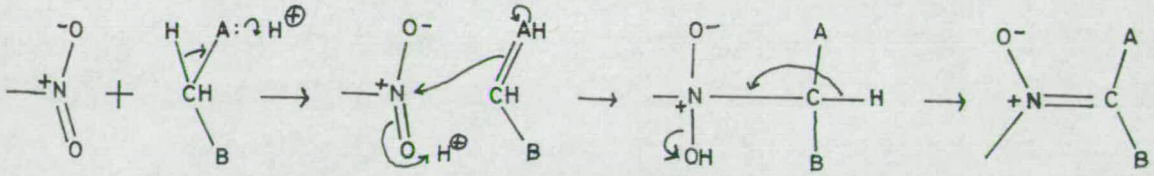
(scheme 4)

Similarly,[5] o-nitrobenzoylacetone (7; X=$COCH_3$) gives isatin (8), possibly by hydroxide attack on the hydrated form of 2-acetylisatogen, formed by an initial aldol-type condensation.



(scheme 5)

The formation of quinoxaline-1-oxides[6] (9; R^2=Bz or Ac) when the substituted o- nitroacetanilides e.g. (10; R^2=Bz or Ac) are treated with base, further illustrate nucleophilic interactions in which the side-chain nucleophile is a carbanion. Other examples[7,8,9] demonstrate the generality of this type of cyclisation. N-Methylation of the o-nitroacetanilide appears to enhance both yield and rate of cyclisation[9]. In theory, the nitro-group could also interact with the side-chain by an acid-catalysed aldol type of reaction (scheme 6).

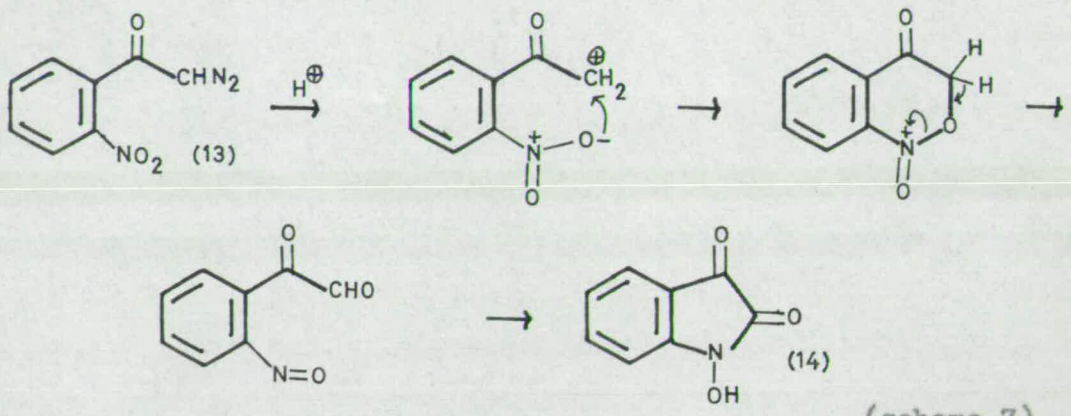


(scheme 6)

The recently reported[10] acid-catalysed cyclisation of N,N-dialkyl-o-nitroanilines (11) to benzimidazole N-oxides (12) may take place by this type of mechanism.

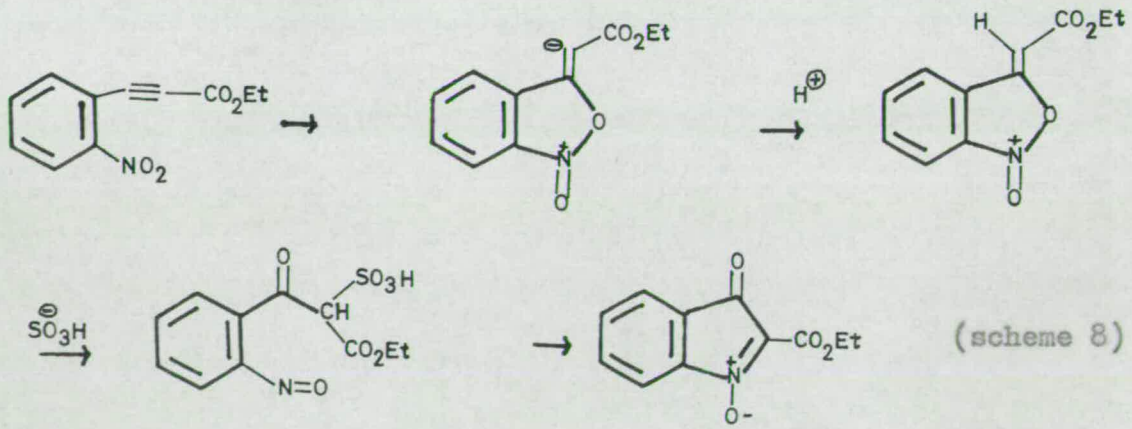
Examples of electrophilic attack by the side-chain on oxygen of the nitro-group are rarer, and not so clearly defined as the aldol type. However, the transformation of o-nitrobenzoyldiazomethane (13) into 1-hydroxy-isatin[11] (14) by mixed formic and acetic acids illustrates this

type of mechanism (scheme 7).



(scheme 7)

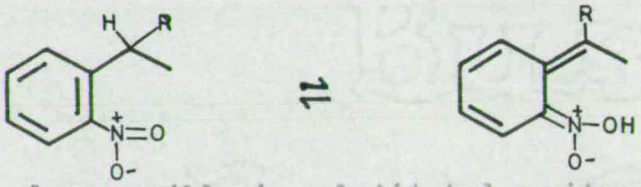
The treatment of acetylene derivatives (15; R=CO_2H or CO_2Et) with concentrated sulphuric acid leads to cyclisation giving isatogens, or products obtainable from them by further reaction; i.e. the ester (15; R=CO_2Et) gives ethyl isatogenate (16; R=CO_2Et), while the acid (15;R=COOH) gives the isatin (8), probably through the initial formation and further reaction of the unstable isatogenic acid (16; R=COOH).[12] Hydration of the acetylene does not appear to be a significant step in forming the isatogenic ester, since ethyl-o -nitrobenzoylacetate is hydrolysed rather than cyclised in concentrated sulphuric acid.[13] It follows that the nitro-group must interact directly with the triple bond.



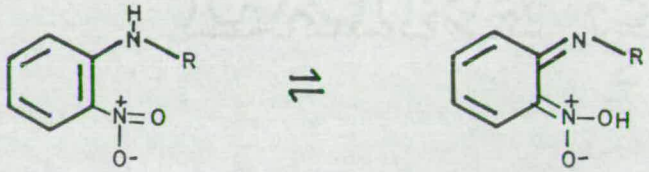
(scheme 8)

An electrophilic type of interaction may also be involved in some photochemical processes, e.g. in the conversion of o-nitrobenzylidene-aniline (17)[14] into 2-nitrosobenzanilide (18) and the tolane (15; R=Ph)[15] into the isatogen (16; R=Ph) in the presence of light, in pyridine.

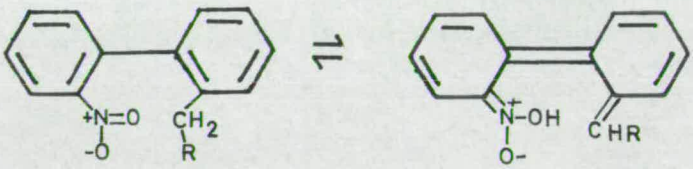
Demonstration of these direct types of interaction between the side-chain and the nitro-group across space, is often complicated by the possible modification of the nitro-group prior to interaction, by initial conversion into the aci-nitro tautomer, as shown.



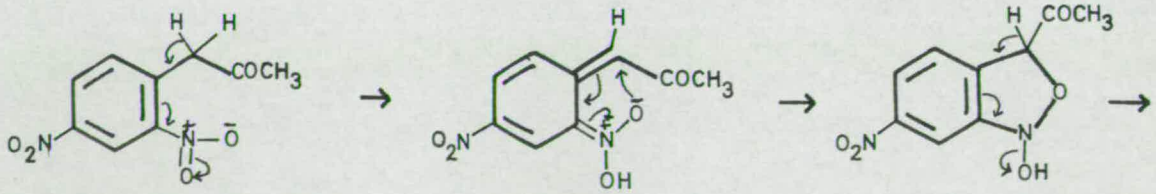
This is also possible in substituted o-nitroanilines,

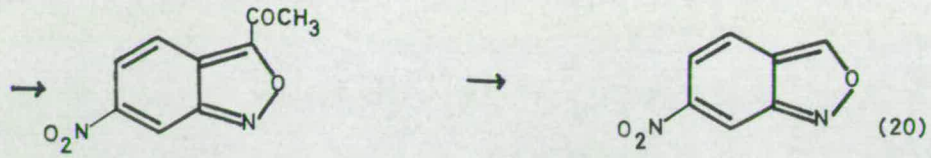


or even in the case of nitrobiphenyl derivatives.



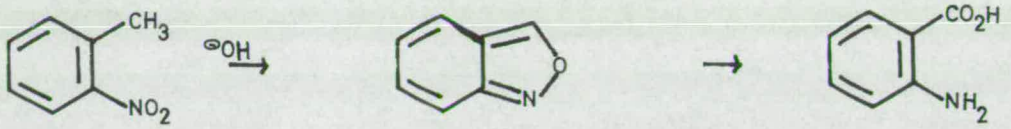
There are a number of reactions known in which this type of interaction appears to be involved, e.g. when 2,4-dinitrophenylacetone (19; R=Me)[16] or 2,4-dinitrophenylacetic acid (19; R=OH)[17] is heated with concentrated sulphuric acid, the product obtained is 6-nitroanthranil (20),





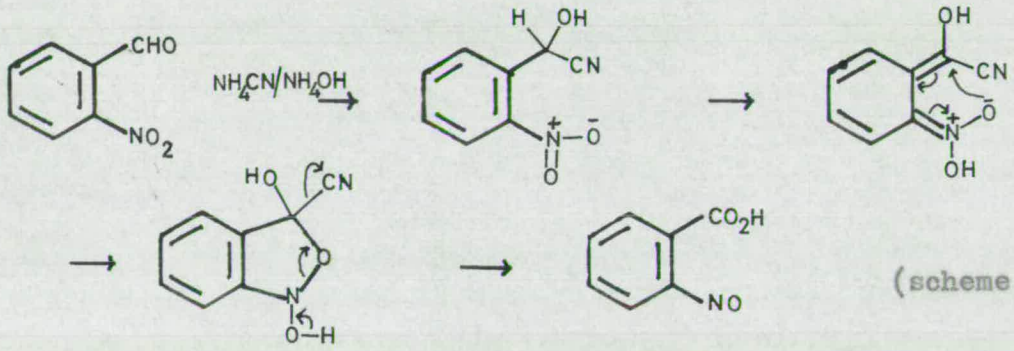
(20) (scheme 9)

while o-nitrotoluene is converted by base into anthranilic acid[18]



(scheme 10)

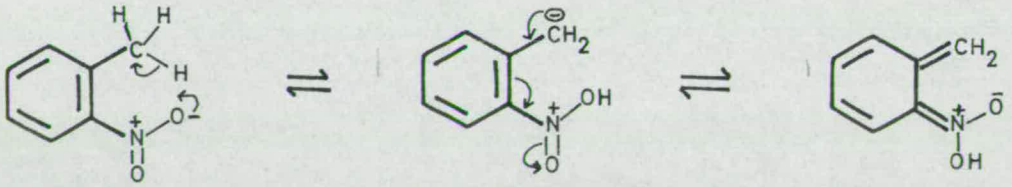
and o-nitrobenzaldehyde into o-nitrosobenzoic acid,[19] probably through the cyanohydrin, in the presence of a mixture of ammonium cyanide and hydroxide.



(scheme 11)

As can be seen from the examples cited, this type of interaction can be acid or base-catalysed.

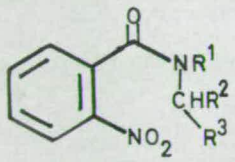
However, even interactions involving the aci-nitro tautomer may at least in the base-catalysed examples proceed by initial hydrogen abstraction from the side-chain by the nitro group(cf. scheme 10).



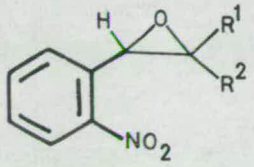
The present research was undertaken in an attempt to gain further information on the scope and mechanism of certain of these types of interaction. As the examples discussed above demonstrate, reactions involving nitro-group side-chain interaction are both mechanistically

interesting and synthetically important, often providing novel routes to otherwise inaccessible products.

Two types of ortho-substituted nitrobenzene derivative were chosen for study. The first (type 1) contains a substituted amide side-chain and the second (type 2), a substituted epoxide side-chain.



(type 1)



(type 2)

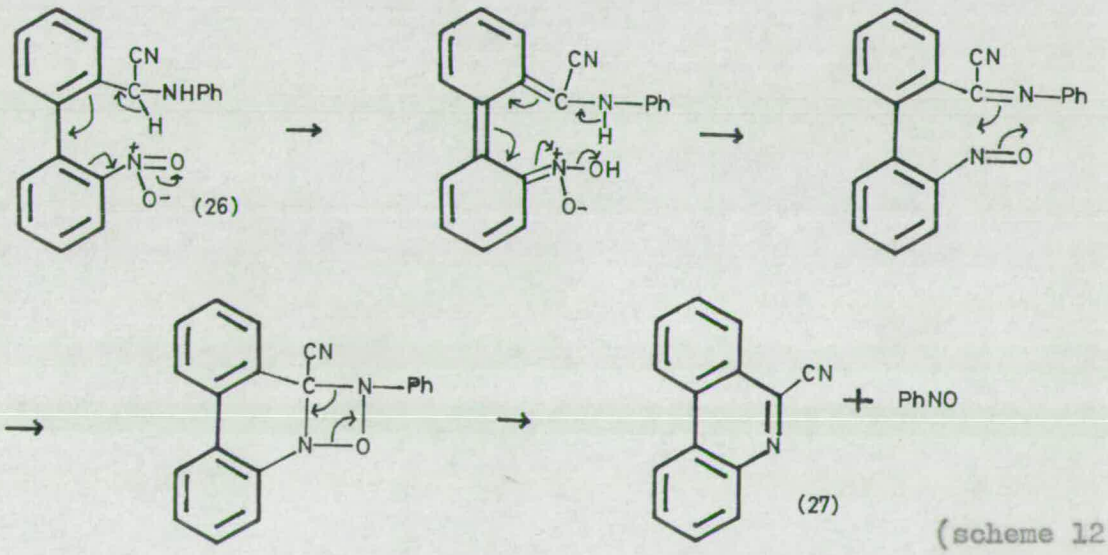
As it turned out, interaction occurring with the type 1 nitro-compounds was of the base-catalysed nucleophilic type, whereas that observed in the type 2 nitro-compounds was of the acid catalysed electrophilic type. On the basis of this differentiation the subject material of the thesis is divided into two main sections.

Base Catalysed Interactions

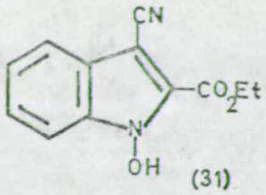
Introduction

(a) o-Nitrobiphenyl Derivatives. Base catalysed cyclisations of the biphenyls [21(a-c)] were observed by Muth[20,21] to give phenanthridine-N-oxides [22(a-c)] as the simple aldol-type dehydration products. An aldol-type of mechanism for these reactions is supported by the observations that the rate of cyclisation increases with increasing electron withdrawal in the substituent (R) in (21) and that cyclisation fails when R=CO_2H, H, OH, and Br. Similar treatment of [21(d-e)] gave products [22(d-e)] obtained as a result of hydrolysis of the initially formed oxides (22; R= COPh or SO_2Ph). 2-Amino-2'-nitrodiphenyl (21; NH_2 for CH_2R) gave the benzocinnoline-4-oxide (23). This type of reactivity is also demonstrated in the quinoxalines (24) which are cyclised by base to the quinoxaline-1-oxides (25)[22].

On the other hand the o-nitrobiphenyl (26)[23] can be converted by treatment with base, or irradiation, into the phenanthridine (27), the mechanism probably being one involving an aci-nitro tautomer.



(scheme 12)



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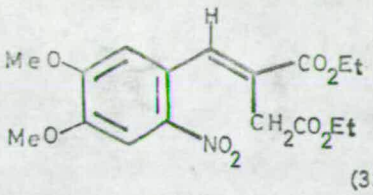

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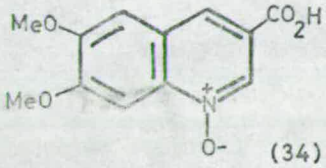

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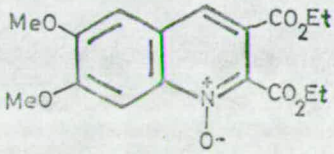

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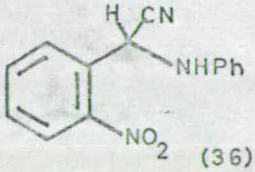

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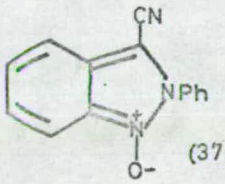

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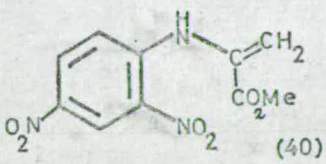

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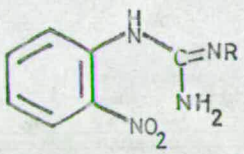

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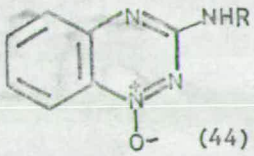

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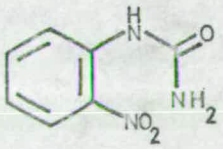

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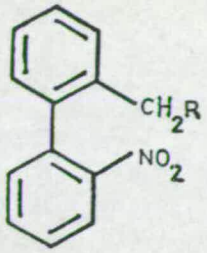
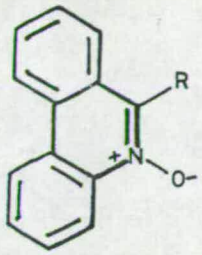


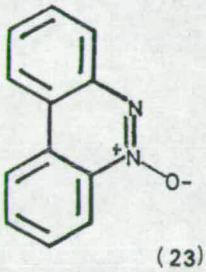
(21)

	R
a	CO_2Me
b	$CONH_2$
c	CN
d	COPh
e	SO_2Ph



(22)

	R
a	CO_2Me
b	$CONH_2$
c	CN
d	H + $PhCO_2H$
e	OH + $PhSO_3H$



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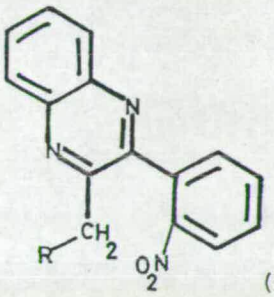

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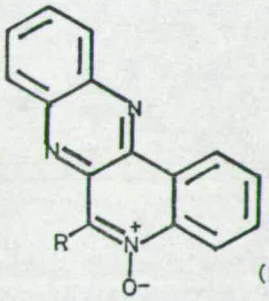

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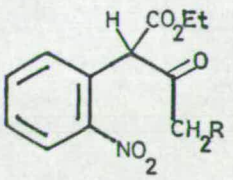

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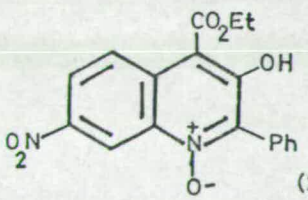

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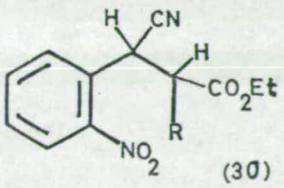
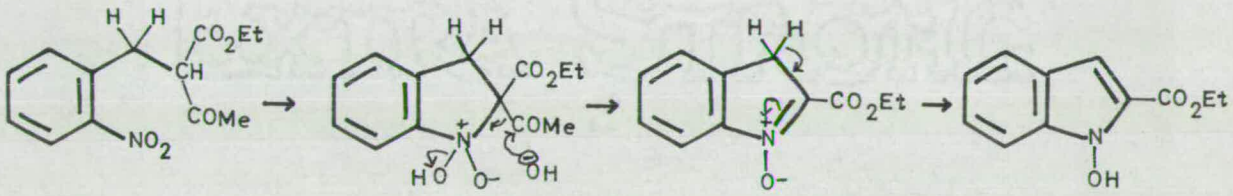


(30)

(b) o-Nitrobenzyl Derivatives. o-Nitrophenylacetone and the 2,4-dinitrophenylacetoacetic acid ester (28; R=H) are not cyclised by base, presumably because the doubly activated proton on the sterically hindered ∝-carbon is removed instead of the relatively unactivated methyl proton. However, a very similar compound (28; R=Ph)[24] is cyclised to the quinoline derivative (29)[25].

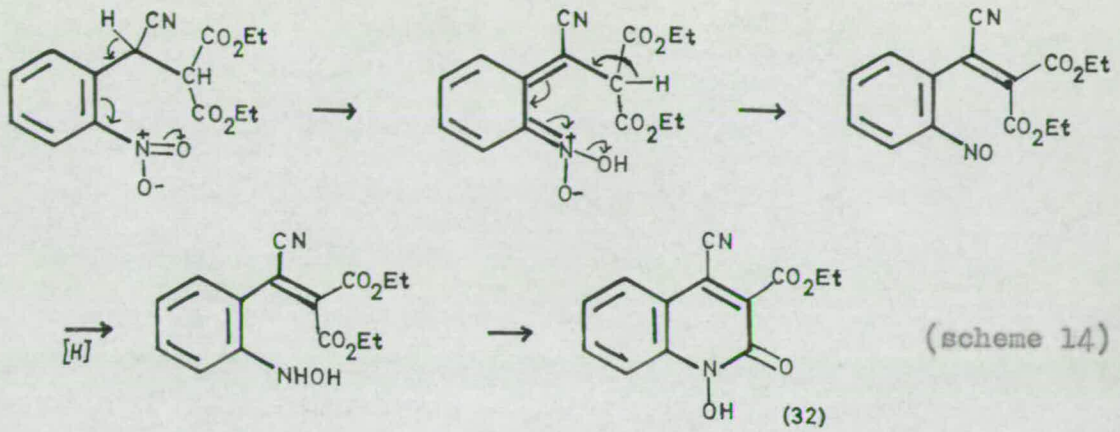
When there are ∝ and β carbons carrying protons capable of ionisation, as in the ester (30; R=COMe, H for CN)[26], then the product obtained is the indole (31; H for CN). An aldol type of condensation provides a convenient explanation for this interaction (scheme 13), although the possibility of aci-nitro intermediates cannot be ruled out.



(scheme 13)

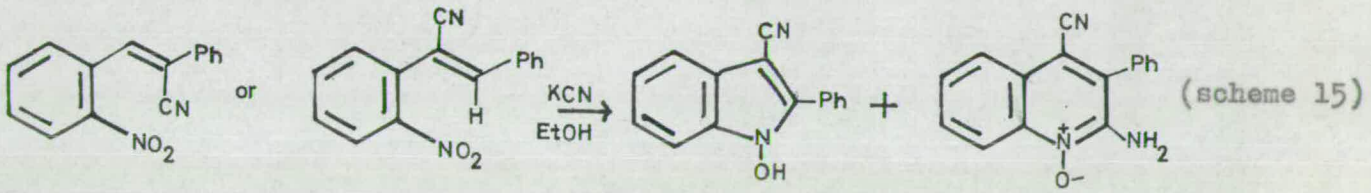
The ability of this type of compound to undergo base catalysed cyclisation to indoles seems to be quite general. Thus o-nitrobenzylmalonic acid affords the indole (31; CO_2H for CO_2Et, H for CN)[27], while the nitrile (30; R=CO_2Et) and amide (30; R=CO_2Et, $CONH_2$ for CN) are respectively converted to the indoles (31) and (31; $CONH_2$ for CN) by the action of sodium carbonate[28].

However, when the diester (30; R=CO_2Et) is treated with hot ethanolic potassium hydroxide, reduction by the reaction medium results in the formation of the quinoline derivative (32) as shown in scheme 14.

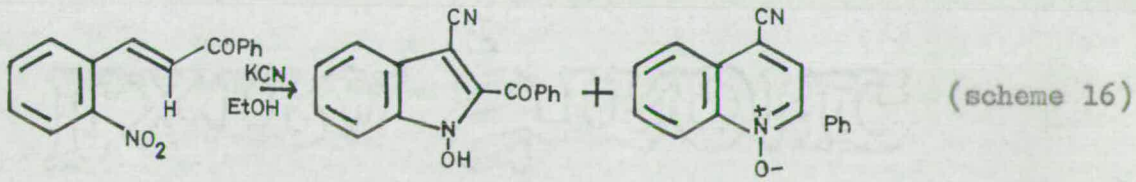


(scheme 14)

The quinoline (32) may also be obtained directly by reacting diethyl o-nitrobenzylidenemalonate with potassium cyanide, in ethanol. Also, as shown in the reactions below[29,30] (schemes 15, 16),



(scheme 15)



(scheme 16)

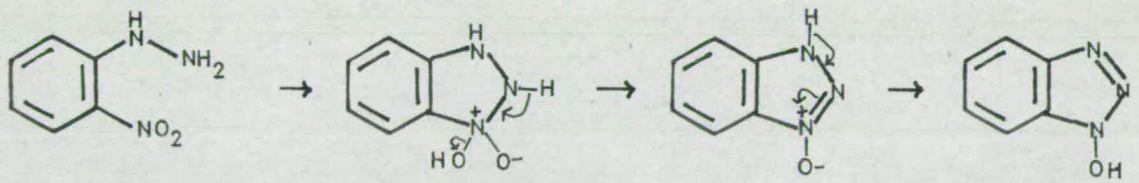
where the initial adducts (cf. 30) are not isolated, the reactions are found to yield mixtures of the indoles and quinolines, as shown, thereby demonstrating the simultaneous operation of the two mechanisms.

On the other hand, the succinate (33) cyclises smoothly in 20% aqueous potassium hydroxide, to give 3-carboxyquinoline-N-oxide (34),[31] presumably by an aldol type of condensation initially, giving the diester (35), followed by hydrolysis to the diacid (35; CO_2H for CO_2Et) and decarboxylation of the 2-carboxyl-group.

o-Nitrobenzylamine does not cyclise, presumably because the side-

chain is not sufficiently activated. However, many of its derivatives do so readily, providing valuable routes to indazole derivatives. Thus, the o-nitrobenzylamine derivative (36) is converted by warming with ethanolic sodium carbonate into the indazole-1-oxide (37)[32]. Behr[33] has shown that indazole-1-oxides are formed directly by heating a mixture of the amine and o-nitrobenzaldehyde with potassium cyanide in the presence of acetic acid. An aldol type of condensation provides an explanation for these interactions, although again the possibility of aci-nitro intermediates cannot be ruled out. However, the products formed in the cyclisation of 2-nitrobenzylideneanilines could in fact be the corresponding 2-nitroso-benzanilides[1], rather than the indazole N-oxides as formulated[34].

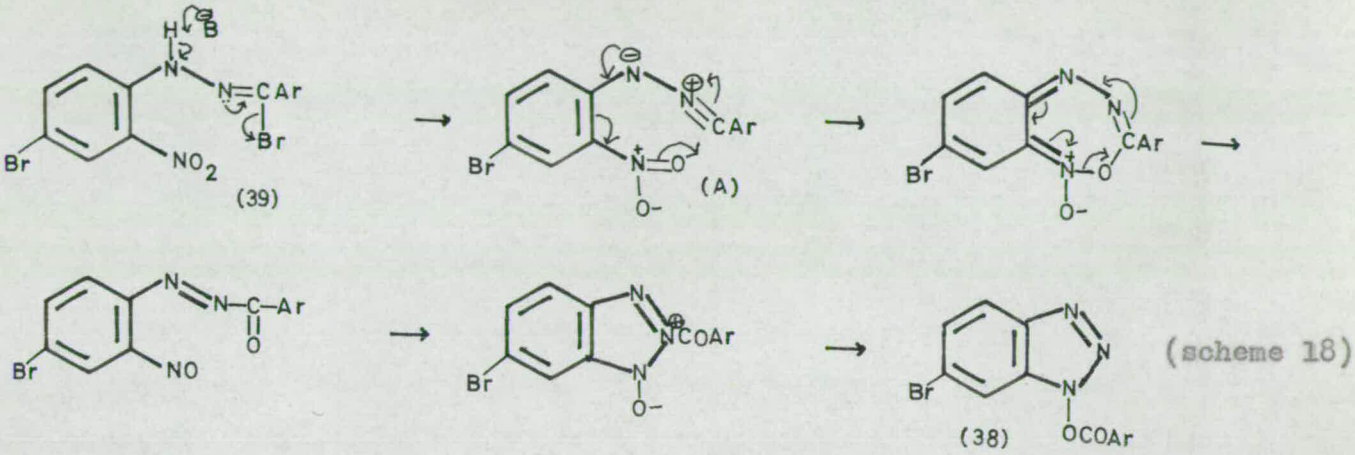
(c) o-Nitroaniline Derivatives. o-Nitrophenylhydrazine was found by Nietzki and Braunschweig[35] not to give hydrazine, when treated with alkali, but instead, to give 1-hydroxybenzotriazole (scheme 17). This reaction constitutes a general method for the synthesis of 1-hydroxybenzo-triazoles.[36,37,38] The aldol mechanism offers an attractively simple explanation for the formation of these products, but again aci-nitro intermediates could be involved.



(scheme 17)

The reducing properties of hydrazines are also in evidence in cyclisations of this type. Thus 2,4-dinitrophenylhydrazine yields[39] 3,3'-dinitro-azoxybenzene, m-dinitrobenzene and 1-hydroxy-6-nitrobenzotriazole in proportions which vary with the pH of the medium, and are minimal for the heterocycle at low concentrations of basic condensing agent.

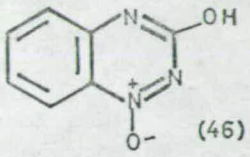
Hydrazidic halides (39; Ar=Ph or p-$CH_3C_6H_4$) treated with a weak base, such as triethylamine, are smoothly dehydrohalogenated and cyclised to the corresponding benzotriazoles (38; Ar=Ph or p-$CH_3C_6H_4$)[40]. The mechanism proposed involves oxygen transfer, as shown.



(scheme 18)

A similar result has been reported by Huisgen and Weberndorfer[41], who have also obtained evidence for intermediates of type A (scheme 18), in the form of a 1:1 adduct with methyl acrylate.

When methyl-α-(2,4-dinitrophenylamino)acrylate (40) is treated with sodium methoxide, or ammonia, in methanol, the products obtained are the benzimidazoles (41; $X=NO_2$, $R^2=CO_2Me$ or $CONH_2$)[42]. Likewise[43], α-(2,4-dinitrophenylamino)-αβ unsaturated acyl derivatives, e.g. (42; $X=NO_2$, R^1=H, Me or Ph, $R^2=CO_2Me$) are cyclised by a variety of bases, e.g. diethylamine, sodium carbonate, sodium methoxide or sodium hydroxide, in protonic or aprotic solvents, to yield the 6-nitrobenzimidazole-1-oxide (41; $X=NO_2$, $R^2=CO_2Me$). The mechanism proposed[43] is one involving oxygen transfer. A simpler and equally plausible course for these reactions involves hydrolytic fission of the double bond, followed by an aldol type of condensation, as shown in scheme 19.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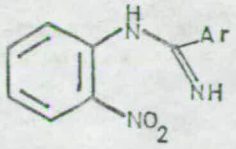
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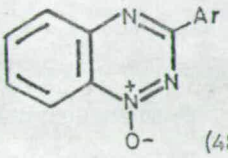
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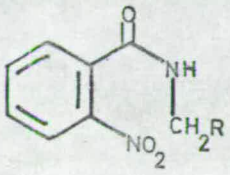
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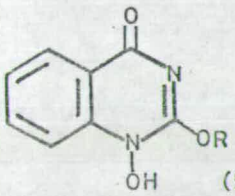
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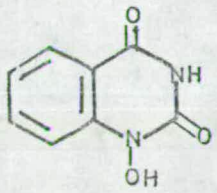
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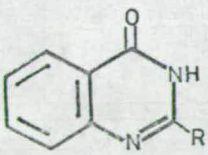
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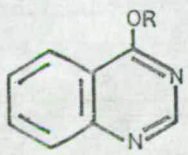
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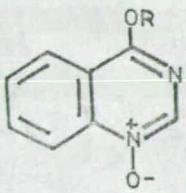
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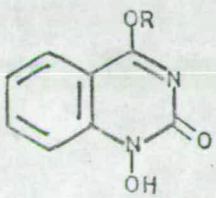
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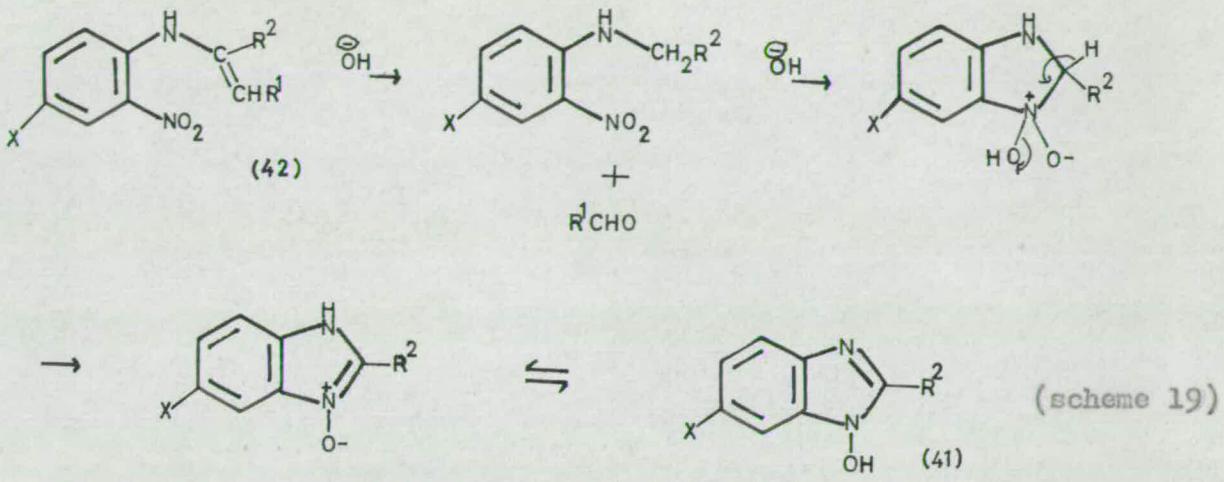


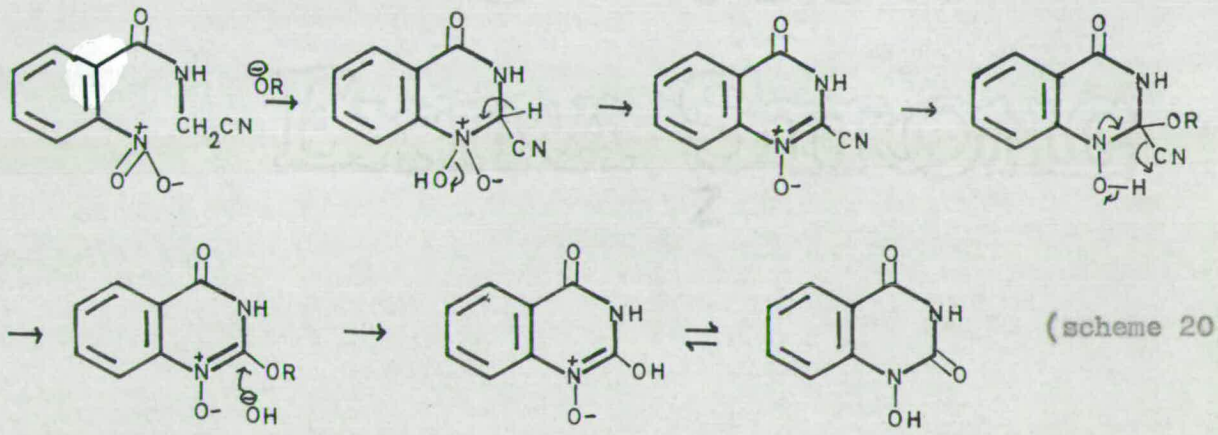
(scheme 19)

o-Nitrophenylguanidine (43; R=H) is cyclised to 3-aminobenzotriazine 1-oxide (44; R=H) when warmed with dilute alkali, and the analogous urea derivative (45) to the corresponding 3-hydroxybenzotriazine 1-oxide (46) by 10% aqueous potassium hydroxide.[44] Extensions of this type of reaction include cyclisations of the guanidine (43; R=Ph), the o-nitrophenylthiourea (45; S for O),[45] and various aryl-substituted guanidines[46] (as 43; R=H). Many other variations have been recorded, such as the cyclisation of o-nitrophenylbenzamidines[47] (47) to 3-arylbenzotriazine 1-oxides (48). The already discussed cyclisations of o-nitroacetanilides (10; R^2=Bz or Ac) to the quinoxaline-1-oxides[6] (9; R=R^1=R^3=H, R^2=Bz or Ac), illustrate the extension of these cyclisations to cases where the side-chain provides the nucleophile in the form of carbanion.

(d) <u>o-Nitrobenzoyl Derivatives.</u> Several examples of this type of interaction involving o-nitrobenzoyl derivatives have already been discussed in the general introduction (see previously).

When o-nitrobenzamidoacetonitrile[49] (49; R=CN) was warmed with

alcoholic solutions of sodium alkoxides, products identified as 1-hydroxy-quinazolines (50; R=Me or Et) were obtained, as well as the dioxo-compound (51) and benzoic acid. The ketone ω -(o-nitrobenzamido)acetophenone (49; R=Bz) warmed in aqueous alkali, afforded 2-benzoyl-3,4-dihydro-4-oxoquinazoline (52; R=Bz), and refluxed in ethanolic sodium ethoxide, gave the N-hydroxy-compound, 1,4-dihydro-1-hydroxy-4-oxoquinazoline (50; H for OR). The mechanism operative here must be the aldol type, presumably involving cyclisation to the nitrile (50; CN for OR), followed by displacement of the cyano-group by alkoxide, or hydroxide ion, to give the observed products (scheme 20).

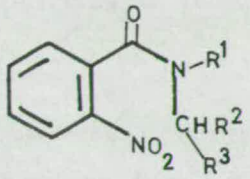


(scheme 20)

The formation of benzoic acid from the nitrile (49; R=CN) is unexpected and is explicable only if the NH group in the side-chain competes with the adjacent CH_2 for attack on the nitro-group. In the case of the ketone (49; R=Bz), the formation of (52; R=Bz) suggests that the N-hydroxy-2-benzoyl derivative (50; Bz for OR) is probably an intermediate which can either yield the quinazoline (50; H for OR), by loss of the benzoyl group, or the ketone (52; R=Bz) by reduction in the alkaline

medium.

As an extension of these reactions, it was decided to examine the scope and mechanism of base catalysed interactions in the o-nitrobenzamide derivatives of general formula



where R^1=H, alkyl or aryl; R^2=H, alkyl or aryl and R^3=CN, Bz or CO_2Et. These molecules are of interest because (a) variation of R^2 and R^3 will affect the acidity of the proton, thereby increasing or decreasing the nucleophilic character of the reactive centre in the side-chain, (b) replacement of the proton on the nitrogen by R^1 (alkyl or aryl) will have the effect of reducing the influence of a competing nucleophilic centre in the side-chain, (c) if these amides cyclise in a manner analogous to the compound (49; R=CN or Bz), then they will provide a useful synthetic route to otherwise inaccessible 2 and 3-substituted quinazoline-1-oxides.

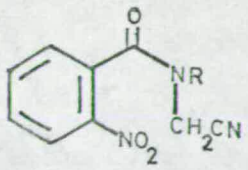
Quinazoline-N-oxides were almost totally unknown until about a decade ago, when products formulated as 1-acylindazoles by Auwers and Mayenburg[50] were shown by Sternbach and co-workers[51] to be quinazoline-3-oxides.

Quinazoline-1-oxide itself is unknown, but 4-substituted derivatives are available by peracid oxidation of the parent quinazoline. This can sometimes lead to ambiguity of structure in the product (i.e. position of the N-oxide group), or side-reactions such as oxidative degradation of side-chains, or destruction of the ring system. Thus, oxidation of 4-alkoxyquinazolines (53) with hydrogen peroxide in acetic acid[52], yields 3,4-dihydro-4-oxoquinazoline (52; R=H), probably as a result of hydrolysis. On the other hand, perphthalic acid in ether oxidises various 4-alkoxyquinazolines

to the respective 1-oxides (54) in acceptable yields[52]. The 4-alkoxy-1,2-dihydro-1-hydroxy-2-oxoquinazolines (55) were also formed, but in lower yield.

Peracetic acid can be used when the group in the 4-position is less sensitive to oxidation. Sternbach and his co-workers[51] oxidised 2-chloromethyl- and 2-methyl-6-chloro-4-phenoxy-quinazoline in this manner to the respective 1-oxides, while Toyoshima[53] has similarly prepared the 1-oxides of 3-aryl-3,4-dihydro-2-methyl-4-oxoquinazolines. However, in the latter reactions, the corresponding N-aryl-o-nitrobenzamides are obtained as byproducts.

Quinazoline-3-oxides are generally synthesised by the dehydration of o-acylaminoarylketoximes[51,54]. Quinazoline-3-oxide itself was first prepared[55] in 1957 by treating o-aminobenzaldoxime with ethylorthoformate. This type of reaction has been extended to the synthesis of quinazoline-3-oxides with a variety of substituents on the benzene ring.[56]



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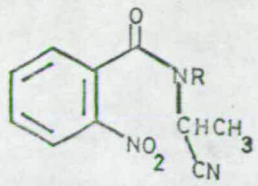

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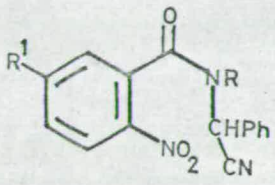

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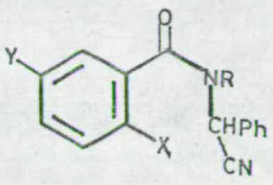

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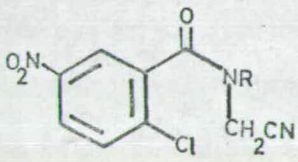

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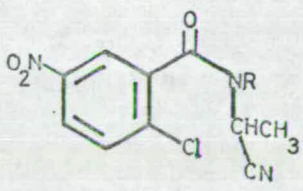

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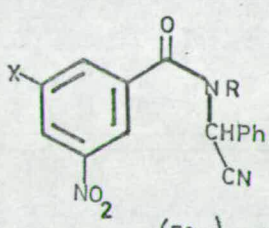
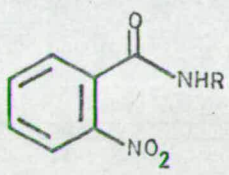


(59c)



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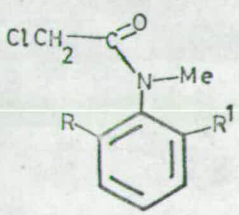
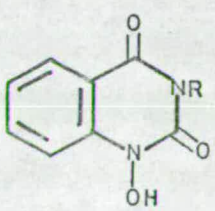


(61)

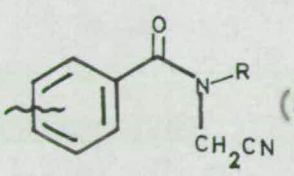


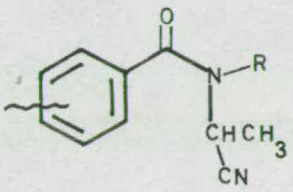
(62)

DISCUSSION OF BASE CATALYSED INTERACTIONS

Preparation of the Amides. The amides were all prepared by one of three general methods already recorded in the literature. The amines required were either available commercially, or were prepared by standard methods, as were the acid chlorides.

For convenience, the amides are divided into three general types according to their chemical structures.



(a)


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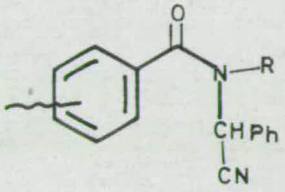


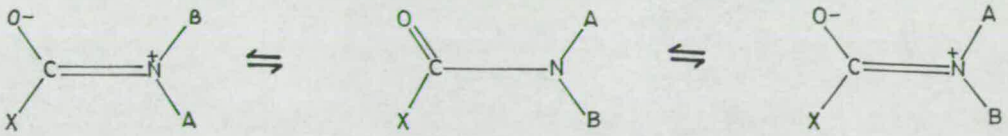
(c)

Amides (56a; R=Me or $PhCH_2$, and R=Ph, Bz or CO_2Et for CN) were prepared by condensing the appropriate amine or amine hydrochloride with o-nitrobenzoyl chloride in glacial acetic acid, in the presence of an excess of fused sodium acetate. In the case of the compound (56a; R=Ph), the method was modified by carrying out the reaction in refluxing benzene. Although successful for the preparation of the amides mentioned, this method failed in all attempts to prepare amides having substituents other than hydrogen on the carbon adjacent to the amido-nitrogen, the products being intractable tars. The other amides required for study were, however, readily prepared by two alternative methods. In the first of these, the amides (56b; R=Me or Ph) and (56c; R=Me or $PhCH_2$, R^1=H) were prepared by reacting the acid chloride at room temperature in the absence of a solvent, with twice the theoretical amount of amine. In the second method, used in the preparation of amides (56b; R=H or $PhCH_2$), (56c; R=H or Ph, R^1=H and R=Ph, R^1=Me), (57c; X=Cl or OMe, Y=H and X=Cl, Y=NO_2), (58a; R=Ph), (58b; R=Ph), (59c; R=Ph, X=H or NO_2) and (60; R=Ph or $PhCH_2$), the amine, (two moles), in dry

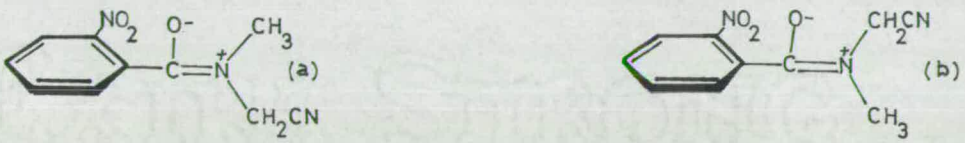
benzene, was treated with the acid chloride (one mole), also in benzene, at room temperature, and stirred until reaction was complete. All the amides contained a carbonyl band in the infra-red, in the range 1670-1630 cm^{-1}, expected for tertiary amides, but lacked a band in the region expected for a cyano group. This is not unusual since the nitrile vibration can vary widely in its intensity and may be completely absent.[57] The presence of the nitro-group was indicated by bands at 1530 and 1350 $cm.^{-1}$

The chemical shift of the methylene or methine proton(s) in the nuclear magnetic resonance spectra of the amides is of interest, in giving some indication of the acidity of the nucleophilic centre in the side-chain and hence (as will be discussed later) having a bearing on the product formed. In the type (a) amides (56a; R=Me, Ph or $PhCH_2$), the absorptions fall within the range τ = 5.2-5.5. The methylene protons of the amide (56a; R=Ph, COPh for CN) absorb at somewhat lower field (τ = 4.55). When the amide is methyl substituted (type b) (56b; R=Me, Ph or $PhCH_2$) the methine proton absorbs at τ = 4.0-4.6, with the exception of the compound (56b; R=H), which contains a methine absorption at τ = 5.1. Finally, when the amide is phenyl substituted, the absorption of the methine proton is shifted well downfield to τ = 2.0-3.15, the exception again being the N-unsubstituted amide (56c; R=H, R^1=H) which absorbs somewhat higher at τ = 3.9. With the exception of the unexpected relative downfield shift of the methine proton in the methyl-substituted amides, these variations in chemical shift follow the expected differences in the acidity of the methylene or methine protons. The n.m.r. spectra of the amides (56a; R=Me or $PhCH_2$) indicate that there is restricted rotation about the N-C=O bond in these molecules. The features of the n.m.r. spectra and the

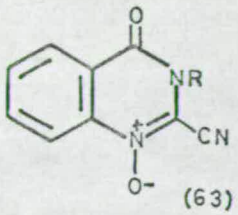
presence of restricted rotation may be explained by the existence of the amide in geometrically isomeric zwitterionic forms.



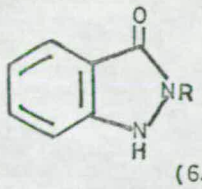
These isomers are reasonably stable, and can be separated in certain cases by slow crystallisation in the cold. Clupp[58] has isolated the individual isomers by this method from a series of amides (61), where R^1 and R are unlike bulky groups, and has shown by n.m.r. that they slowly equilibrate in solution, at room temperature. By analogy, the n.m.r. spectrum of the amide (56a; R=Me) indicates that the molecule exists as an equilibrium mixture of cis and trans zwitterionic forms (a) and (b) as shown,



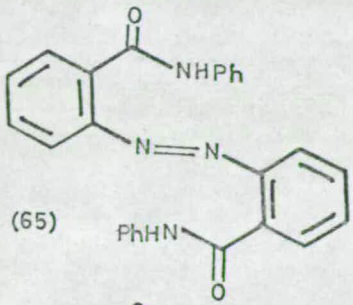
the o-nitrophenyl group lying perpendicular to the plane of the double bond in the least crowded position. In form (a), the methyl group will be further from the nitro-group and less deshielded, while the methylene is closer, and so more deshielded. In form (b) the situation is reversed, resulting in the methyl group being more deshielded, while the methylene is comparatively less deshielded. Hence the spectrum obtained shows four peaks, corresponding to the two possible situations. From peak integration, the isomer ratio is determined as a:b, 1;0.2. Similarly, in amide (56a; R=$PhCH_2$) the a:b ratio is found to be exactly 1:1, however, it is not possible here to assign structures. In the case of amide (56a; R=Ph) consideration of a model shows that there will be considerable steric hindrance to the formation of the structure corres-



(63)



(64)



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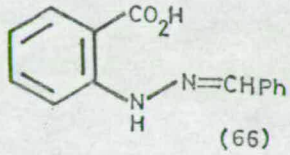

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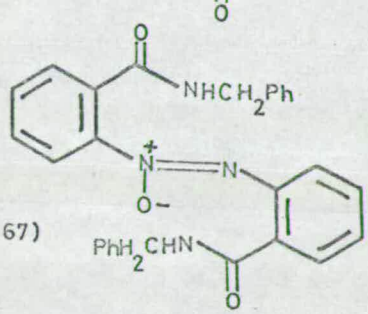

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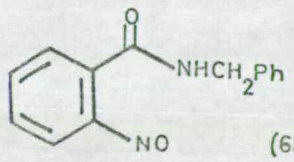

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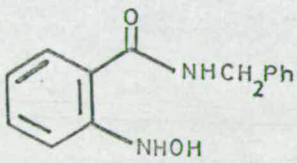
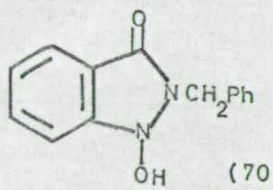


(69)



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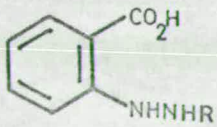

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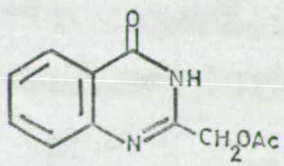


(72)

ponding to (b), due to the size of the phenyl-group. Thus, as indicated by its n.m.r. spectrum, the molecule probably exists exclusively in the form corresponding to (a) above.

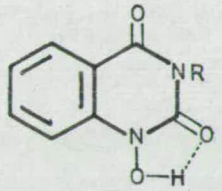
Base-Catalysed Reactions of Type (a) Amides.

When the nitriles (56a; R=Me, $PhCH_2$ or Ph) were warmed with ethanolic sodium ethoxide a smooth and rapid reaction occurred, affording high yields of 2,4-dioxo-1-hydroxyquinazolines (62; R=Ph, Me or $PhCH_2$). The N-hydroxyquinazolones (62; R=Me or $PhCH_2$) were also formed in high yield by warming the amides (56a; R=Me or $PhCH_2$) with ethanolic potassium hydroxide or 10% aqueous sodium hydroxide, or by stirring in ethanolic sodium ethoxide at room temperature. As in the case of the N-unsubstituted compounds studied by Tennant and Vaughan,[49] none of the expected cyanoquinazoline 1-oxides (63; R=Ph, Me or $PhCH_2$) could be detected.

The 1-hydroxyquinazoline diones were colourless, high-melting solids which decomposed at their melting-points. They dissolved readily in aqueous alkali and were recovered unchanged on acidification. In contrast to the yields obtained from the N-unsubstituted amides,[49] the N-hydroxyquinazolones (62; R=Me, Ph or $PhCH_2$) were obtained in > 90% yield. This may be due partly to a more favourable disposition of the side-chain brought about by the presence of the N-substituent and partly to the absence of the N-H group, thereby excluding possible side-reactions due to the presence of an alternative nucleophilic centre in the side-chain (i.e. N-H). The existence of the side-chain in a preferred conformation is supported by n.m.r. evidence (see previously). The ability of amide N-H to function as a nucleophile in nitro-group side-chain interactions of this type is supported by the cyclisation of N-benzyl-o-

nitrobenzamide to 2-benzylindazolone (64; R=$PhCH_2$) on treatment with ethanolic alkali[59], though the precise course of this reaction is not clear. Similar enhancement in yield has been observed in the base catalysed cyclisations of substituted o-nitroacetanilides when the proton on the amide nitrogen atom is replaced by an alkyl group[48]. In this case, however, effects other than steric may be involved.

The i.r. spectra of the 1-hydroxyquinazolinediones contain two carbonyl bands at ~1700 and ~1650 $cm.^{-1}$ The higher frequency band is assigned to the C_4 carbonyl group and that at lower frequency to the C_2 carbonyl, which will be lowered due to hydrogen bonding.

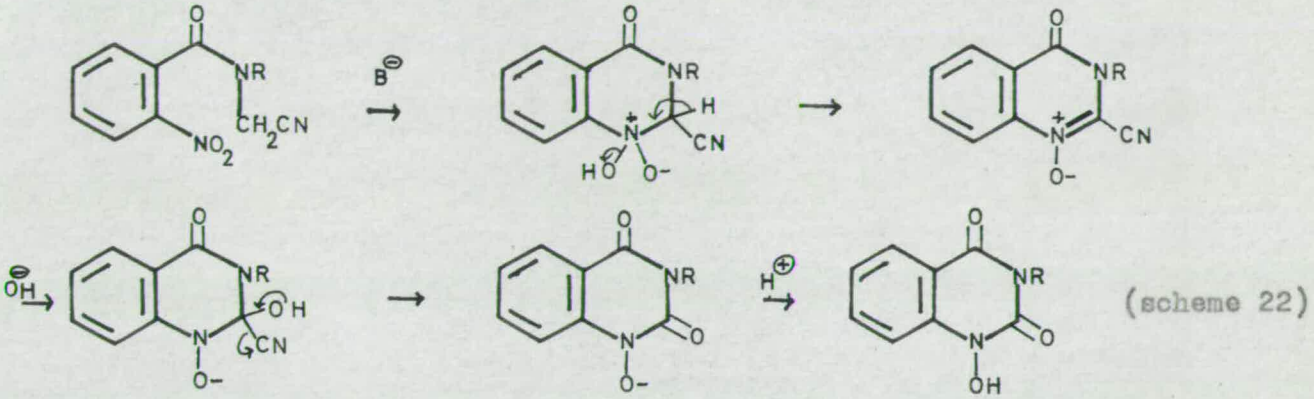


Like 4-alkoxy-1-hydroxy-2-oxoquinazolines, the 1-hydroxyquinazolinediones gave a red or violet colour with alcoholic ferric chloride[60]. Warmed in acetic anhydride, they afforded acetoxy-derivatives (62; R=Me, Ph or $PhCH_2$, Ac for H) having an i.r. band just below 1800 $cm.^{-1}$, characteristic of cyclic N-acetoxy-derivatives[28]. Hydrogenolysis of these acetoxy-compounds gave the known quinazolones (62; R=Me, Ph or $PhCH_2$, H for OH), which were also obtained by the reduction of the N-hydroxyquinazolinediones (62; R=Me, Ph or $PhCH_2$) with sodium dithionite in aqueous ethanol.

The structures of the quinazolones (62; R=Me, Ph or $PhCH_2$ H for OH) were established by their unambiguous synthesis, by heating the appropriate substituted anthranilamides with urea, a standard literature method for the synthesis of such compounds[61,62,63].

A plausible course for the formation of the N-hydroxyquinazoline-

diones is one involving initial cyclisation to the corresponding 2-cyano-quinazoline-1-oxide (63; R=Me, Ph or $PhCH_2$) as shown in scheme 22.

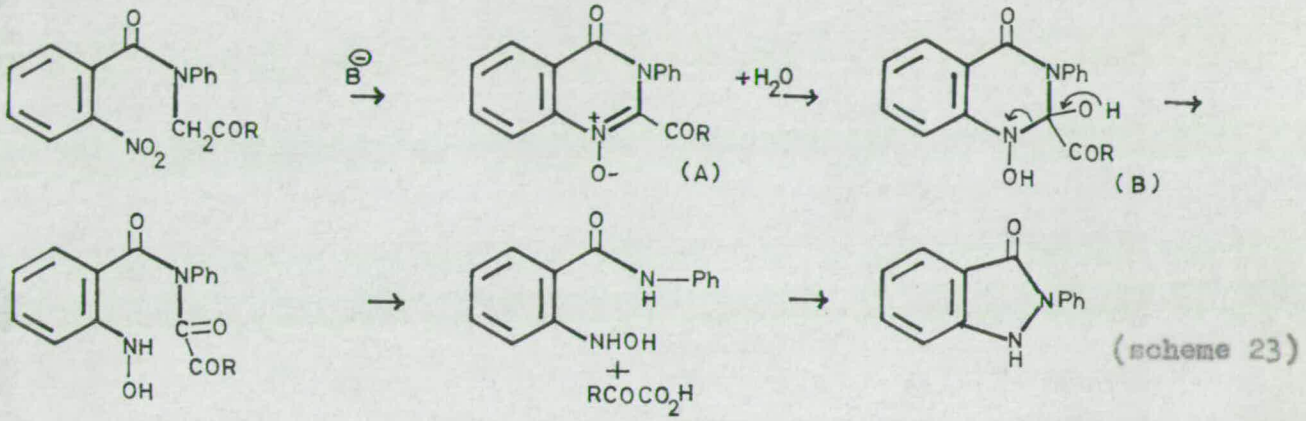


(scheme 22)

Conversion of the cyano N-oxide into the observed products may occur by direct replacement of the cyano-group by the hydroxyl ions liberated during the initial condensation, or by initial formation of the ether (63; OEt for CN) which would be quickly hydrolysed during the work up. The instability of the cyano N-oxides proposed as intermediates is not unexpected since the enhanced electrophilic character of the 2-position in such a structure (63; R=Me, Ph or $PhCH_2$) will promote rapid reaction with hydroxide or ethoxide ion, followed by ejection of the cyano-group. This instability is in accord with the known behaviour of 2-cyanoquinazolines. Hayashi and Higashino[64] report that in 2-cyanoquinazolines the cyano-group is readily displaced by nucleophiles such as methoxide or ethoxide ion.

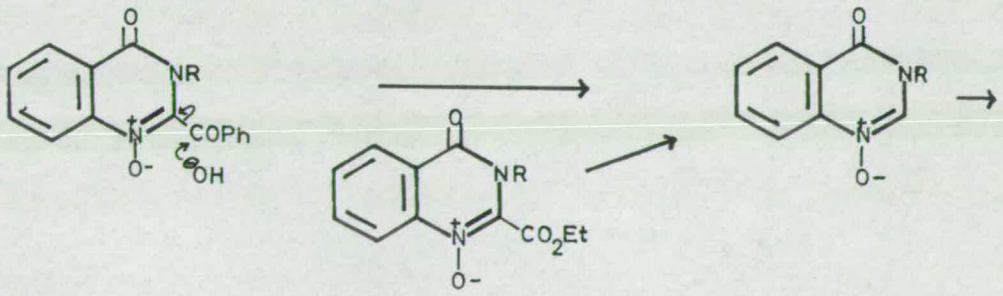
When the amides (56a; R=Ph, Bz for CN and R=Ph, CO_2Et for CN) were warmed with ethanolic sodium ethoxide, or in the case of the ester, with aqueous ethanolic alkali, the expected quinazoline-1-oxides (63; R=Ph, Bz or CO_2Et for CN) were not obtained. In both cases 2-phenylindazolone (64; R=Ph) was the only product identified, though unidentified oils were also formed. In the case of the ketone (56a; R=Ph, Bz for CN) the indazolone was obtained in 40% yield, and in the case of the ester (56a; R=Ph, CO_2Et

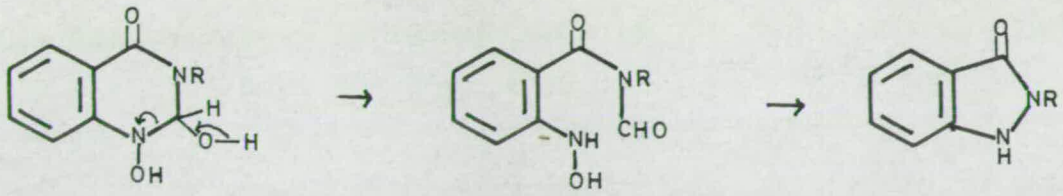
for CN), in 52% yield. The structure of 2-phenylindazolone was established by unambiguous synthesis from N-phenyl-o-nitrobenzamide. A possible mechanism for the formation of 2-phenylindazolone in these reactions is shown in scheme 23.



(scheme 23)

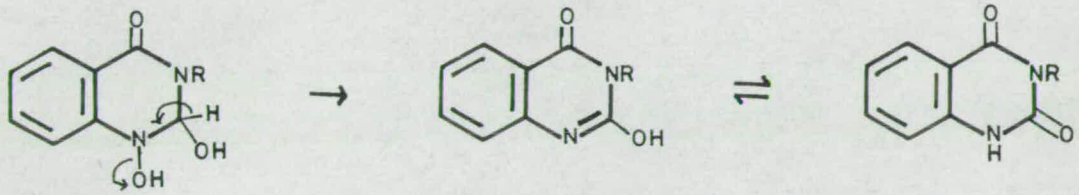
It is assumed that the intermediate is a 2-benzoyl or 2-carbethoxyquinazoline-1-oxide (A), which then hydrates (B) and ring opens, as shown. This type of behaviour is well known in the case of acyclic nitrones[65], and has also been reported in cyclic systems[5]. The hydroxylamine derivative formed then recyclises with the loss of benzoylformic or monoethyloxalic acid. The benzoic acid obtained as a by-product in the cyclisation of the benzoyl-compound is probably derived by decomposition of the benzoylformic acid produced initially. An alternative pathway would involve hydrolysis of the initial benzoyl or carbethoxyl group, followed by hydration of the double bond in the common intermediate N-oxide formed, as shown in scheme 24.





(scheme 24)

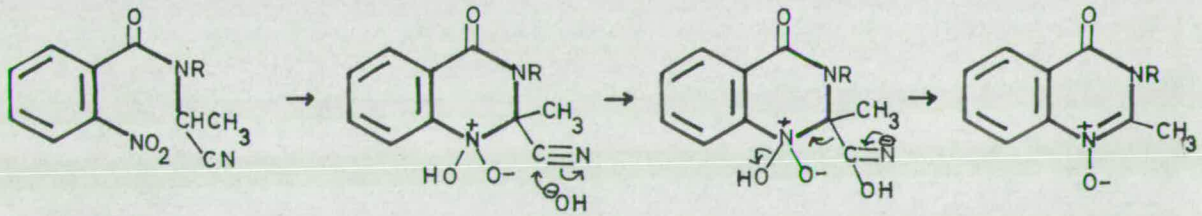
Subsequent ring opening and recyclisation would then yield the indazolone. However the intermediate hydrate could also dehydrate to the parent quinazolinedione,



which, being stable under the conditions of the reaction, might be expected among the products. Failure to isolate this compound, though not conclusive, makes the first route more likely.

Base-Catalysed Reactions of Type (b) Amides

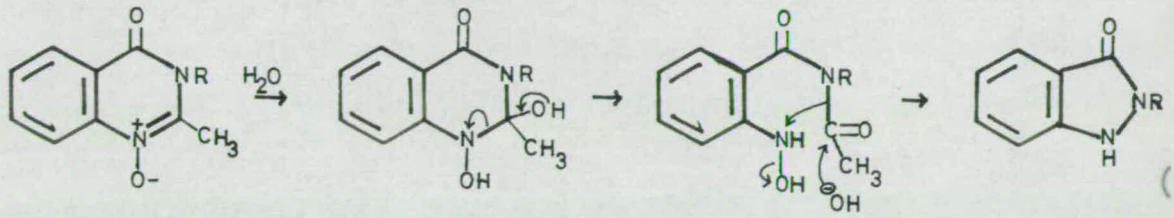
When the amides (56b; R=Ph or $PhCH_2$) were refluxed with ethanolic sodium ethoxide, the products isolated were the 2-substituted indazolones (64; R=Ph or $PhCH_2$), identical with samples synthesised by reduction of N-phenyl and N-benzyl-o-nitrobenzamide (60; R=Ph or $PhCH_2$). The route through to the indazolones probably involves intermediate formation of 2,3-disubstituted quinazoline-1-oxides, as shown in scheme 25.



(scheme 25)

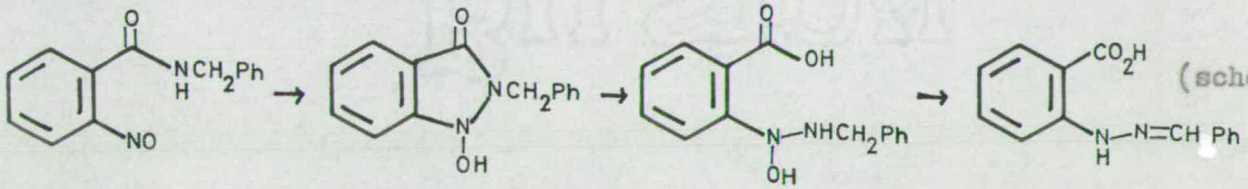
This is supported by the fact that the amide (56b; R=H) is cyclised to the quinazoline-1-oxide(63; R=H, CH_3 for CN) under similar conditions (see below).

The N-oxides (63; R=Ph or $PhCH_2$, CH_3 for CN) are then probably hydrated, after which ring cleavage occurs, giving hydroxylamino intermediates, which cyclise to the corresponding indazolones (64; R=Ph or $PhCH_2$)(scheme 26).



(scheme 26)

The presence of hydroxylamino intermediates in these reactions may be inferred from the formation of a mixture of the indazolone (64; R=Ph) and the azo-compound (65) when the amide (56b; R=Ph) was refluxed in aqueous ethanolic sodium carbonate. On the other hand, when the amide (56b; R=$PhCH_2$) was treated similarly, a mixture of the hydrazone (66) and the azoxy-compound (67) was obtained, suggesting the presence of the nitroso-compound (68), which could arise by mild oxidation of the hydroxylamine (69) in the alkaline medium[66]. The formation of the hydrazone (66) can be explained as occurring by ring opening of the 1-hydroxyindazolone (70), formed by cyclisation of the nitroso-compound (68)(scheme 27).



(scheme 27)

In support of this mechanism, o-nitrosobenzanilide[14] warmed with ethanolic sodium carbonate yields azobenzene 2-carboxylic acid in good yield. Likewise, ring opening of the 1-hydroxyindazolone intermediate is analogous to the known[67] conversion of 1-hydroxyindolinones into N-acylanthranilic acids.

In contrast to the reactions of the amides (56b; R=Ph or $PhCH_2$), the amide (56b; R=Me) afforded unidentifiable gums, when treated with

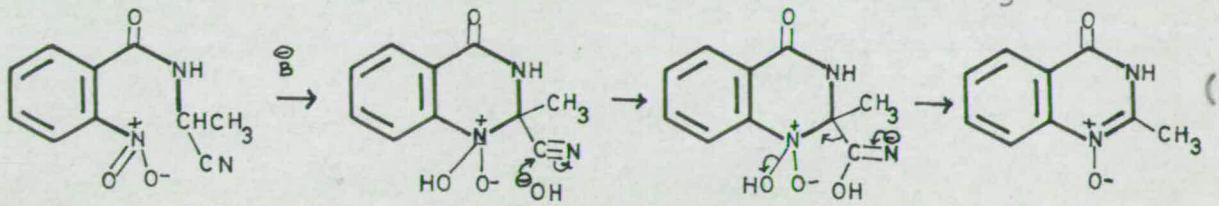
ethanolic sodium ethoxide, or aqueous ethanolic sodium carbonate.

3-Indazolones are usually obtained by heating the appropriate hydrazinobenzoic acid with mineral acid. Thus, 3-indazolone itself is prepared[68] by treating o-hydrazinobenzoic acid (71; R=H) with phosphoryl chloride or hydrochloric acid, or by the action of heat alone. Analogues substituted in the benzene ring are prepared similarly.[69]

2-Substituted 3-indazolones are likewise obtained from the appropriate N-substituted o-hydrazinobenzoic acids (71). Thus, the acids (71; R=Ph or $PhCH_2$), on warming with phosphoryl chloride, acetic anhydride, or alcoholic acetic or hydrochloric acids, yield 2-phenylindazolone or 2-benzylindazolone (64; R=Ph or $PhCH_2$)[70]. A recent method used to synthesise 2-substituted 3-indazolones involves reaction of the appropriate azobenzene derivative with carbon monoxide at high pressure, in the presence of a transition metal catalyst. Thus, Murahashi and Horiie[71] have prepared 2-phenylindazolone by the reaction of azobenzene and carbon monoxide, at 150 atmospheres, using cobalt octacarbonyl as catalyst. It is of interest that depending upon the reaction conditions and the catalyst used, varying amounts of 2,4-dioxo-3-phenyl-1,2,3,4-tetrahydroquinazoline (62; R=Ph, H for OH) can be obtained as a by-product in this reaction. 2-Benzyl and 2-phenylindazolone (64; R=Ph or $PhCH_2$) are also obtained by reductive cyclisation of N-benzyl and N-phenyl-o-nitrobenzamide (60; R=$PhCH_2$ or Ph), using zinc and sodium hydroxide (see experimental section). N-Benzyl-o-nitrobenzamide however is also converted into 2-benzylindazolone on treatment with 20% ethanolic potassium hydroxide.[72] The detailed course of this cyclisation is not clear, but appears to require reduction by the reaction medium at some stage.

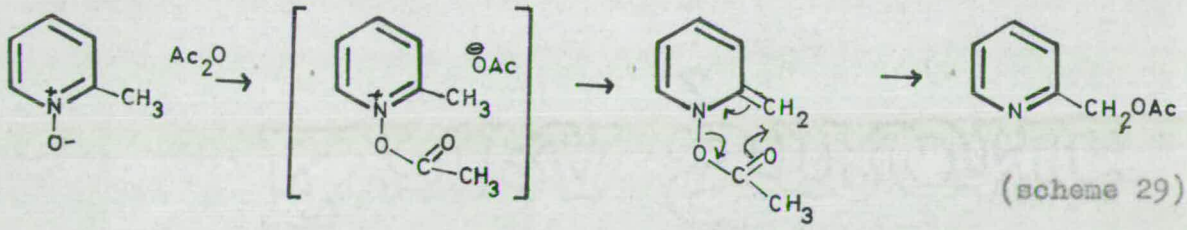
When the amide (56b; R=H) was treated with base (ethanolic sodium

hydroxide), the product obtained in good yield was the expected (scheme 28) 3,4-dihydro-2-methyl-4-oxoquinazoline-1-oxide (63; R=H, CH_3 for CN).



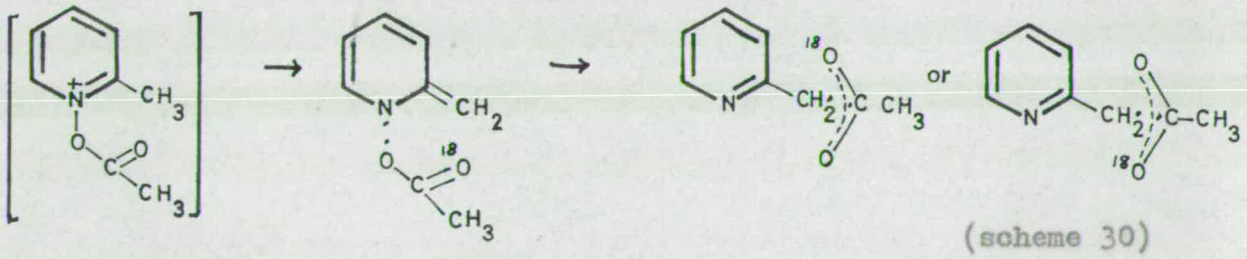
(scheme 28)

The structure of this product was established by its conversion on warming with acetic anhydride into 2-acetoxymethylquinazoline (72). This reaction is analogous to the conversion of 2-methylpyridine-1-oxides and 2-methylquinoline-1-oxides by acetic anhydride into 2-acetoxymethylpyridines and 2-acetoxymethylquinolines. For a long time the accepted mechanism of this type of reaction was that suggested by Pachter[73] (scheme 29).



(scheme 29)

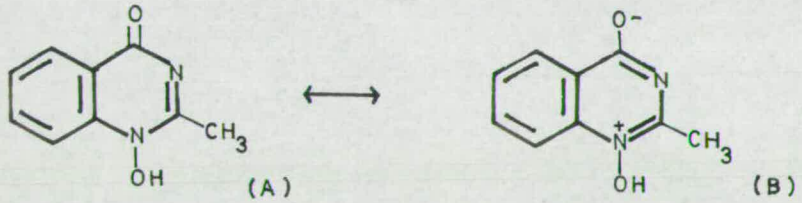
However, the issue became complicated when Boekelheide and Harrington[74] found that the reaction displayed certain characteristics of a free-radical process, while Traynelis and Martello[75] obtained evidence which tended to support the original mechanism. The mechanism was clarified by the use of ^{18}O tracers[76]. Based on the results obtained a "radical pair" mechanism has been suggested[76] (scheme 30).



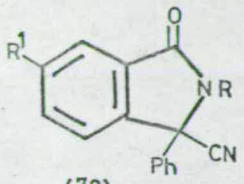
(scheme 30)

Since the reaction is not affected by radical scavengers, it must take place in a "solvent cage". Further work[77] with tracers has shown that this type of mechanism is also operative in similar reactions of acetic anhydride and benzoyl chloride with N,N-dimethylaniline-N-oxide and quinaldine-1-oxide.

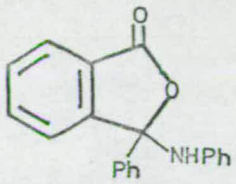
The i.r. spectrum of the crystalline 3,4-dihydro-2-methyl-4-oxo-quinazoline-1-oxide (63; R=H, CH_3 for CN) is very similar to those of the ethers (63; R=H, OEt or OMe for CN),[49] in that it shows no absorption above 1625 $cm.^{-1}$, attributable to a carbonyl group. It also contains a broad band of low intensity in the region 2100-2400 $cm.^{-1}$ as is also observed [49] in the i.r. spectra of the ethers (63; R=H, OEt or OMe for CN). By analogy with the structure[49] proposed for the ethers (63; R=H, OEt or OMe for CN), it is probable that 3,4-dihydro-2-methyl-4-oxoquinoline-1-oxide (63; R=H, Me for CN) does not exist in N-oxide form in the solid state, but rather as the N-hydroxy-betaine structure shown.



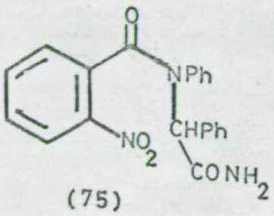
The broad absorption at 2100-2400 $cm.^{-1}$ can then be attributed to inter-molecular hydrogen bonding between the N-hydroxy- and 4-oxo-groups in the above structure. Likewise hydrogen bonding and the possibility of mesomerism (A ↔ B) explains the absence of carbonyl absorption above 1625 $cm.^{-1}$



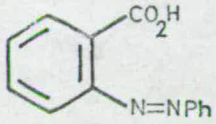
(73)



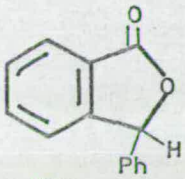
(74)



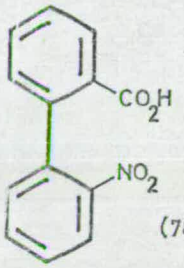
(75)



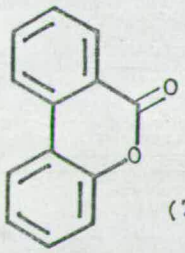
(76)



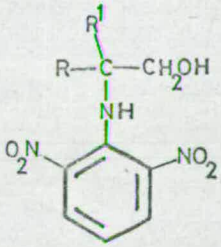
(77)



(78)



(79)



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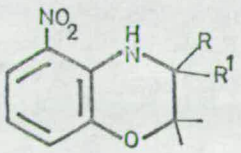

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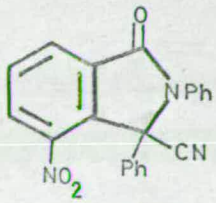
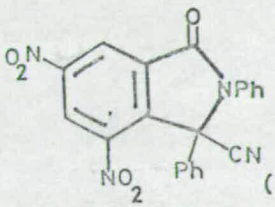


(136)



(137)

Base-Catalysed Reactions of Type (c) Amides.

Initially, the reactivity of the amides (56c; R=Ph, $PhCH_2$ or Me, R^1=H) towards ethanolic sodium ethoxide was studied. However, the results were not entirely satisfactory, since the products formed initially tended to react further, yielding mixtures. Higher yields of single products were obtained, however, using aqueous sodium carbonate as the base.

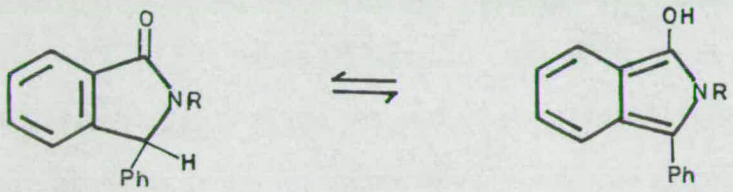
When the amide (56c; R=Ph, R^1=H) was treated with sodium ethoxide, a mixture of 3-cyano-2,3-diphenylphthalimidine (73; R=Ph, R^1=H) and the parent compound, 2,3-diphenylphthalimidine (73; R=Ph, R^1=H, H for CN) was obtained, together with a quantity of 3-N-phenylamino-3-phenylphthalide (74). In contrast, when the same amide was refluxed in aqueous ethanolic sodium carbonate solution, 3-cyano-2,3-diphenylphthalimidine (73; R=Ph, R^1=H) was obtained in 51% yield, together with a small amount of the amide (75) and azobenzene-2-carboxylic acid (76).

Similarly, treatment of the amide (56c; R=$PhCH_2$, R^1=H) with ethanolic sodium ethoxide yielded 2-benzyl-3-cyano-3-phenylphthalimidine (73; R=$PhCH_2$, R^1=H), together with 2-benzyl-3-phenylphthalimidine (73; R=$PhCH_2$, R^1=H, H for CN) and a quantity of the corresponding amide (73; R=$PhCH_2$, R^1=H, $CONH_2$ for CN). Using aqueous ethanolic sodium carbonate, on the other hand, gave the cyanophthalimidine (73; R=$PhCH_2$, R^1=H) and benzaldehyde-2-carboxyphenylhydrazone (66).

Likewise, the amide (56c; R=Me, R^1=H) treated with ethanolic sodium ethoxide yielded 3-carbamoyl-2-methyl-3-phenylphthalimidine (73; R=Me, R^1=H, $CONH_2$ for CN) as the sole product isolated. Aqueous ethanolic sodium carbonate, on the other hand, converted the amide (56c; R=Me, R^1=H) into a mixture of the cyanophthalimidine (73; R=Me, R^1=H), the amide (73;

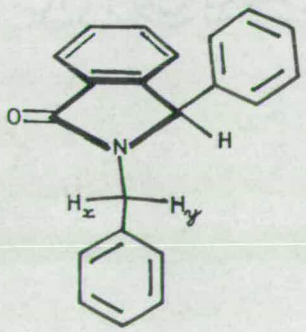
R=Me, R^1=H, $CONH_2$ for CN) and benzoic and azidobenzoic acids.

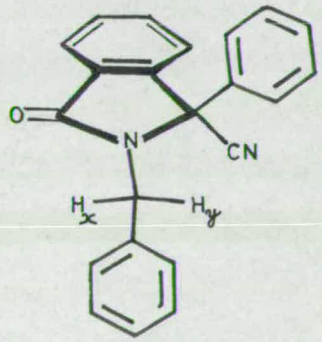
The 3-cyano-2-phenylphthalimidines (73; R=Ph, $PhCH_2$ or Me, R^1=H) were obtained as colourless solids. Their i.r. spectra contained carbonyl absorption at 1700-1720 $cm.^{-1}$, in the range expected for lactams. In contrast, the carbonyl absorption in the parent 3-phenylphthalimidines (73; R= Ph, $PhCH_2$, or Me, R^1=H, H for CN) is centred at ~ 1680 $cm.^{-1}$ The lower carbonyl stretching frequency in the latter compounds is presumably a measure of keto/enol tautomerism,



which is not possible in the cyanophthalimidines.

In the n.m.r. spectra of the benzylcyanophthalimidine (73; R=$PhCH_2$, R^1=H) and its parent[78] (73; R=$PhCH_2$, R^1=H, H for CN) the methylene protons appear as two doublets, indicating that rotation about the N-C (methylene) bond is restricted. Study of a molecular model gives the preferred conformations, shown-

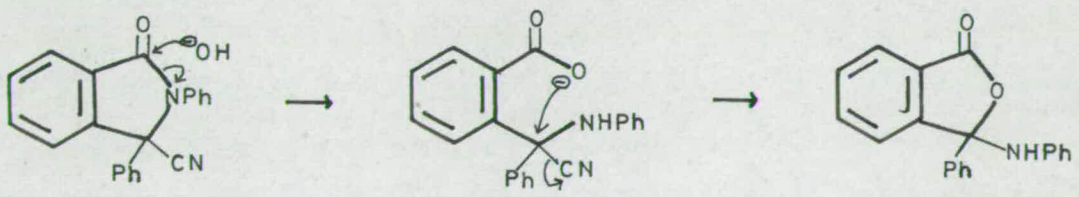




The plane of the N-C-C atoms of the benzyl-group is at approximately 90° to the plane of the 5-membered ring and the phenyl-group on C_3 is also perpendicular to the 5-membered ring. Since the molecule does not have a plane of symmetry bisecting the H_x-C-H_y angle, the two protons H_x and H_y have different average environments and hence different chemical shifts.

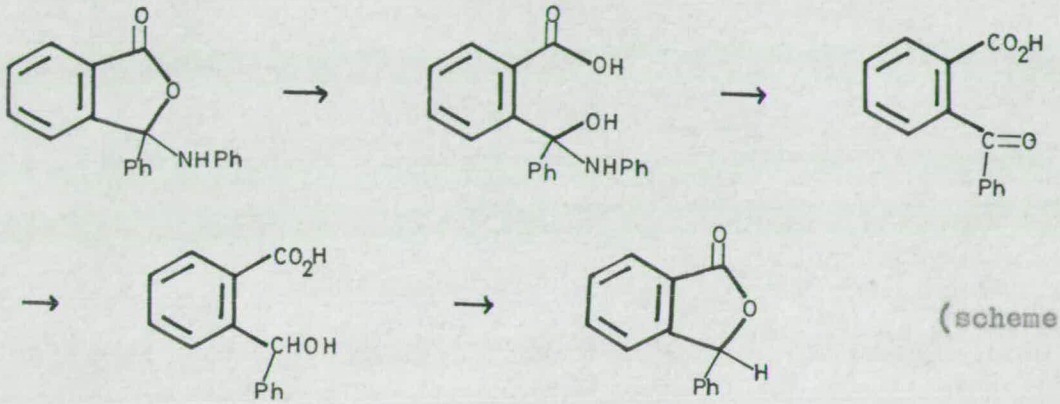
The difference in chemical shift of the two protons is less in the cyanophthalimidine case, since the full effect of shielding on H_y by the phenyl-group on C_3 is counteracted somewhat by the deshielding effect of the cyano-group, hence its absorption moves downfield from $\tau = 6.3$ in the parent to $\tau = 5.72$ in the cyanophthalimidine.

Though unaffected by dilute sulphuric acid, the cyanophthalimidine (73; R=Ph, R^1=H) was converted into the 3-carbamoyl-derivative (73; R=Ph, R^1= H, $CONH_2$ for CN) by treatment with concentrated sulphuric acid. This method of hydrolysis was unsuccessful in the case of the nitriles (73; R=$PhCH_2$ and Me, R^1=H) which were hydrolysed to the amides by prolonged refluxing with N aqueous sodium carbonate solution. The amides were in turn converted into the parent phthalimidines (73; R=Ph, $PhCH_2$ or Me, R^1=H, H for CN) by refluxing them with 20% aqueous potassium hydroxide. Heating the cyanophthalimidines (73; R=Ph, $PhCH_2$ or Me, R^1=H) with potassium hydroxide in trigol, afforded the parent phthalimidines directly. In the case of the nitrile (73; R=Ph, R^1=H) an acidic by-product subsequently identified as 3-N-phenylamino-3-phenyl-phthalide (74) was also obtained. This compound presumably arises by hydrolysis of the cyanophthalimidine, followsd by cyclisation of the amino-acid formed (scheme 31).



(scheme 31)

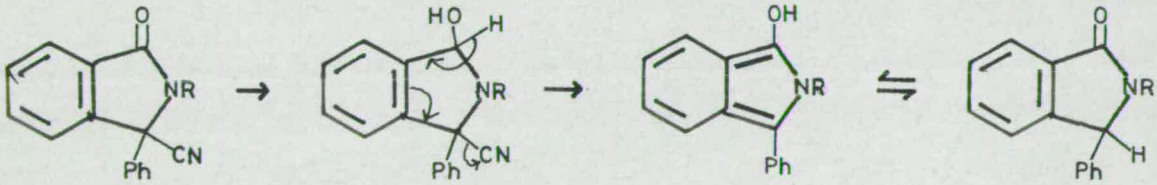
When the phthalide derivative (74) was further refluxed with 6% W/V potassium hydroxide in trigol, it gave 3-phenylphthalide (77) in good yield. The mechanism of this latter reaction is of interest since it would appear to involve the intermediate formation and reduction of o-benzoylbenzoic acid, followed by cyclisation of the alcohol formed (scheme 32).



(scheme 32)

Such a course is supported by the observation that o-benzoylbenzoic acid refluxed with 10% W/V potassium hydroxide in trigol, affords 3-phenylphthalide in good yield.

Lithium aluminium hydride reduction of the cyanophthalimidines (73; R=Ph, $PhCH_2$ or Me, R^1=H) resulted in their conversion into the parent compounds (73; R=Ph, $PhCH_2$ or Me, R^1=H, H for CN), presumably by initial reduction to hydroxy-derivatives, followed by loss of hydrogen cyanide.



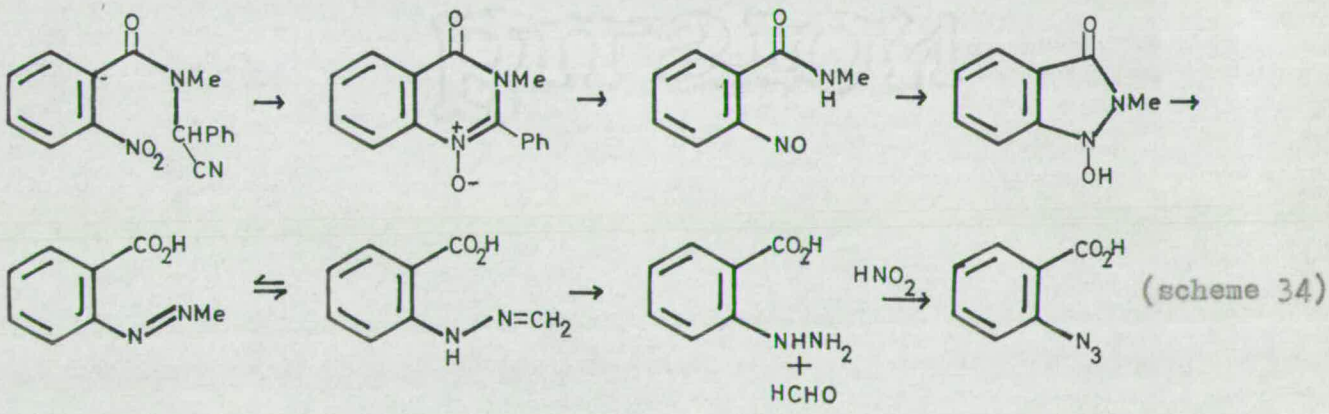
(scheme 33)

The structures of the parent phthalimidines (73; R=Ph or $PhCH_2$, R^1=H, H for CN) were established by unambiguous synthesis and the structure of the phthalimidine (73; R=Me, R^1=H, H for CN) assigned by analogy.

Cyanophthalimidines are almost unknown in the literature, the only

example being the parent compound (73; R=H, R^1=H), which was prepared by Pfeiffer and Jaensch[79], by reacting o-benzoylbenzoic acid with ammonium carbonate and potassium cyanide. Thus, the described cyclisations of the amides (56c; R=Ph, $PhCH_2$ or Me, R^1=H) provide a novel route to the corresponding 2-substituted 3-cyanophthalimidines.

The main mode of interaction of the amides (56c; R=Ph, $PhCH_2$ or Me, R^1=H) would seem to involve displacement of the nitro-group in a nucleophilic fashion. This is supported by the detection of nitrite ion in the mother-liquors. However, the presence of the acidic compounds azobenzene 2-carboxylic acid (76), the phenylhydrazone (66) and 2-azidobenzoic acid, indicates that interaction also occurs between the nitro-group and the side-chain. Thus the acid (76) and the hydrazone (66) have already been isolated as products of the base-catalysed reactions of the amides (56b; R=Ph or $PhCH_2$). The isolation of 2-azidobenzoic acid is in accord with the general pattern. Its presence can be explained in terms of the reaction sequence shown,

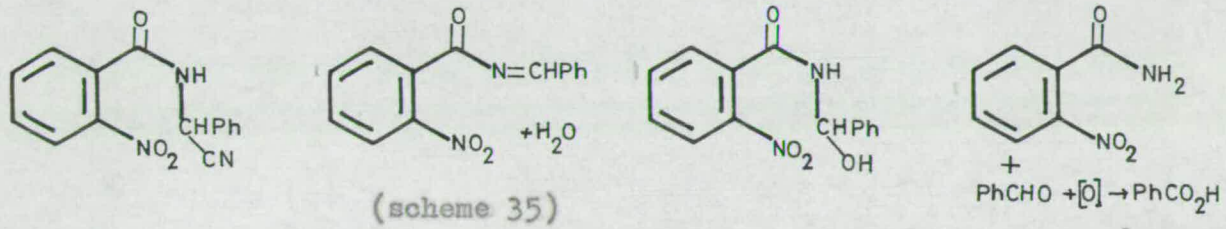


(scheme 34)

since it is known that hydrazinobenzoic acids can be converted into azidobenzoic acids by the action of nitrous acid. In the cyclisations of the amides (56c; R=Ph, $PhCH_2$ or Me, R^1=H), nitrite ions are provided by nucleophilic displacement of the nitro-group, hence the conversion of the

intermediates to 2-azidobenzoic acid can occur in the alkaline medium, or upon acidification in the work up.

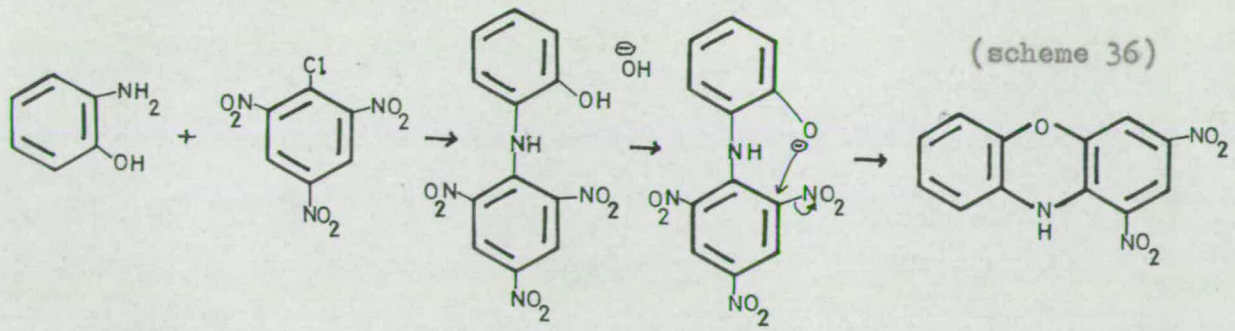
On the other hand, when the amide (56c; $R=R^1=H$) was refluxed with ethanolic sodium ethoxide or aqueous ethanolic sodium carbonate, cyclisation did not take place, the only identified products being o-nitrobenzamide and benzoic acid. A plausible mechanism involving initial loss of hydrogen cyanide is shown in scheme 35.



(scheme 35)

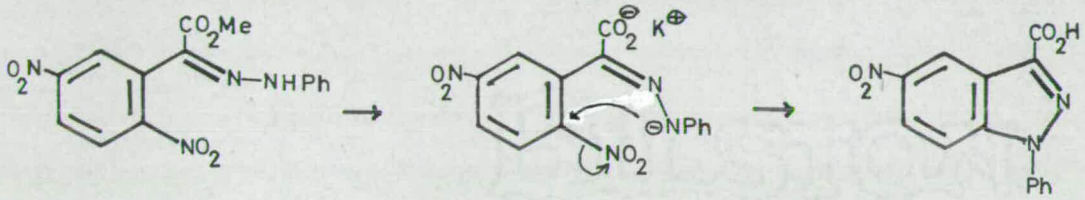
The cyclisations of the amides (56c; R=Ph, $PhCH_2$ or Me, $R^1=H$) to the cyanophthalimidines (73; R=Ph, $PhCH_2$ or Me, $R^1=H$) constitute examples of intramolecular nucleophilic displacement of the nitro-group. Although intermolecular nucleophilic substitution reactions are well documented, e.g. in the reviews by Bunnett[80], Bunnett and Zahler[81] and Ross[82], intramolecular nucleophilic substitution reactions of aromatic nitro-compounds, involving direct replacement of the nitro-group are rare. Hey, Leonard and Rees[83] have shown that the biphenyl carboxylic acid (78) is converted into the tricyclic compound (79), when the salt of the acid is heated, or when the free acid is heated in an inert solvent, with piperidine, or quinoline.

Phenoxide ion can displace the nitro-group in a similar fashion, as in the base-catalysed reaction between o-aminophenol and picryl chloride, to give a morpholine derivative,[84] as shown in scheme 36. Kehrmann[85] has extended this reaction to include analogous thiophenols. A recent example of the same type of reaction has been demonstrated by



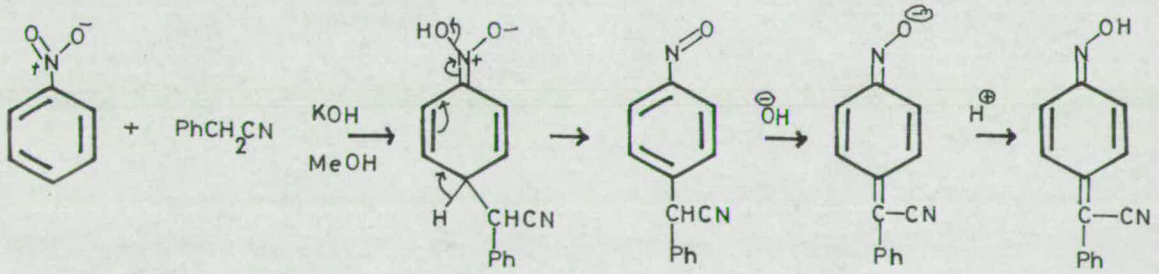
(scheme 36)

Jurgens et al.[86], who report that sodium methoxide catalyses the cyclisation of the alcohols (80) to the morpholine derivatives (81). The nitro-group is displaced similarly in the formation of indazoles by base-catalysed cyclisation of o-nitrophenylhydrazones,[87] as shown in scheme 37.



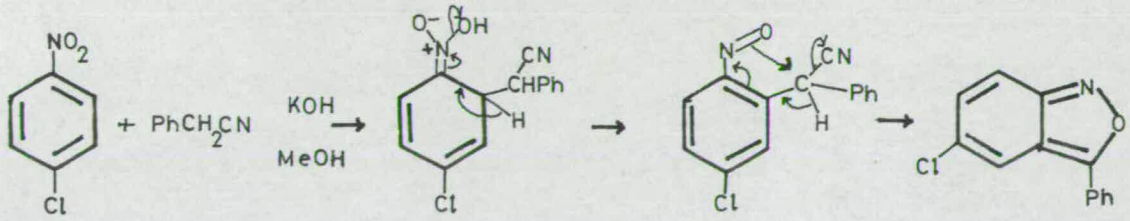
(scheme 37)

Intermolecular nucleophilic substitution reactions of aromatic nitro-compounds, involving carbanions are also rare. Davis et al.,[88] have reacted nitrobenzene with arylacetonitriles, obtaining substituted methylene-quinone oximes (scheme 38).



(scheme 38)

Similarly, when the para-position is blocked, (scheme 39), nucleophilic attack is found to occur in the ortho position, leading to the formation of 3-arylanthranils.[89]



(scheme 39)

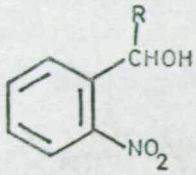
The base-catalysed condensations of 2-chloro-nitrobenzene with ethylcyanoacetate or diethylmalonate, affording ethyl o-nitrophenylcyano-acetate and malonate[90] respectively, also illustrate nucleophilic attack by carbanions, leading to substitution, with displacement of halogen.

In order to further investigate the scope of these intramolecular nucleophilic substitution reactions, a number of similar amides containing groups other than nitro in the ortho-position were treated with base, as before. When the amide (56c; R=Ph, R^1=Me) was refluxed with aqueous ethanolic sodium carbonate, no reaction took place. However, similar treatment with ethanolic sodium ethoxide gave the corresponding cyanophthalimidine (73; R=Ph, R^1=Me), demonstrating the retarding effect of the electron-donating methyl-group on the rate of nucleophilic attack.

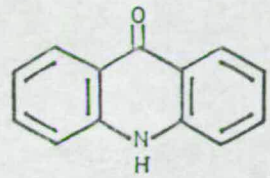
Amides (57c; R=Ph, X=Cl or OMe, Y=H) also did not react with sodium carbonate, thus illustrating the requirement of a fair degree of electron deficiency at the ortho-position, for nucleophilic displacement to take place. However, when the chlorine atom in the ortho-position was made more active by incorporating a p-nitro-group, as in the amide (57c; R=Ph, X=Cl, Y=NO_2), a rapid reaction took place, giving the cyanophthalimidine (73; R=Ph, R^1=NO_2) as the sole product, thereby illustrating once more the effect of enhancing the electron deficiency at the ortho-position. Amides (58a; R=Ph) and (58b; R=Ph) on the other hand did not react with aqueous

ethanolic sodium carbonate, presumably due to the lower stability of the side-chain carbanion derived from these amides.

Treatment of the amide (59c; R=Ph, X=H) in the cold with aqueous ethanolic sodium carbonate, gave a mixture which was separated by chromatography into three components, one of which was identified as the cyanophthalimidine (73; $R^1=NO_2$, R=Ph). The second was shown to be an isomer, having an identical analysis and molecular weight, and was therefore assigned the cyanophthalimidine structure (136). The remainder of the recovered material was not identified, being an amorphous yellow solid, which was not obtained pure. In an attempt to overcome the problem of isomeric products due to possible cyclisation into two positions, the amide (59c; R=Ph, $X=NO_2$) was also treated with aqueous ethanolic sodium carbonate. However, the reaction was very rapid, with immediate darkening of the solution, to deep magenta. Only a very low yield of the cyanophthalimidine (137) was obtained, the rest of the recovered material being an amorphous solid, which was again shown by thin-layer chromatography to be a mixture. This reaction, however, coupled with that of the amide (59c; R=Ph, X=H), illustrates the somewhat unusual displacement of hydride ion by a carbanion, under very mild conditions.



(82)



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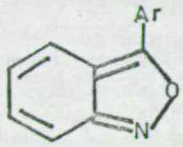

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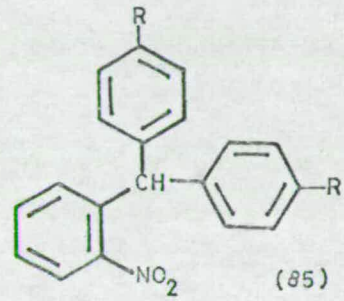

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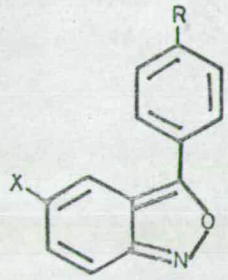

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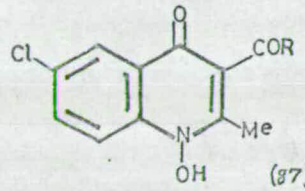

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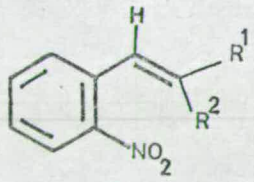

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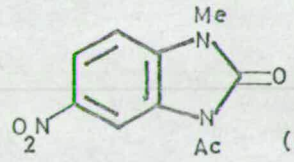

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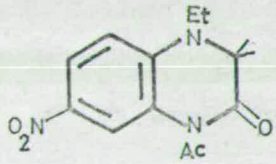

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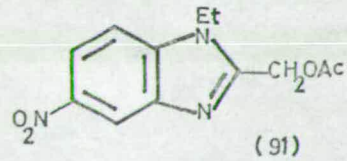


(91)

Acid-Catalysed Interactions.

Introduction.

As described earlier, anthranils are sometimes found as products in acid-catalysed cyclisations of o-nitrobenzyl compounds. o-Nitrobenzaldehyde reacts with aromatic compounds giving products such as triarylmethanes, 3-arylanthranils, or acridones, depending on the acid used and the reactivity of the aromatic compound involved. 2-Nitrodiarylmethanols appear to be intermediates being converted by oxidation into 2-nitrobenzophenones which are isolated as by-products. Silberg[91] has in fact demonstrated that o-nitrobenzhydrol (82; R=Ph) treated with concentrated sulphuric acid, in the presence of sodium nitrite, yields acridone (83) and N-hydroxyacridone (83; OH for H). In the absence of nitrite, the product is the 3-arylanthranil (84), which in turn may be converted to the acridone, by treatment with concentrated sulphuric acid and sodium nitrite.

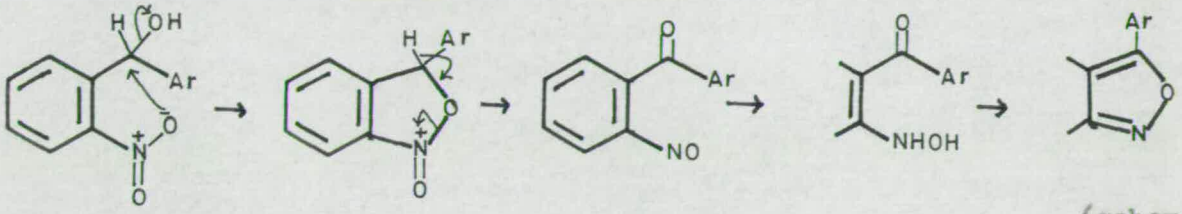
However, when o-nitrobenzaldehyde condenses with the more reactive type of aromatic compound, the products are almost exclusively anthranils. Thus zinc chloride[92] catalyses the reaction of o-nitrobenzaldehyde with aniline, to give a mixture of the triarylmethane (85; R=R=NH_2) and the 3-arylanthranil (86; X=H; R=NH_2), while using acetic and hydrochloric acids as the catalyst, a mixture of the anthranil (86; X=H, R=NH_2) as well as the 5-chloro-derivative (86; R^1=NH_2, X=Cl) is obtained.[93]

Phenols behave in a similar fashion. Phenol and o-nitrobenzaldehyde condense at room temperature in the presence of sulphuric acid, to yield the triarylmethane (85; R=OH),[94] and in the presence of hydrogen chloride to give 5-chloro-3-p-hydroxyphenylanthranil (86; X=Cl, R=OH).[95] The use of hydrogen bromide as catalyst gives a mixture of the unhalogen-

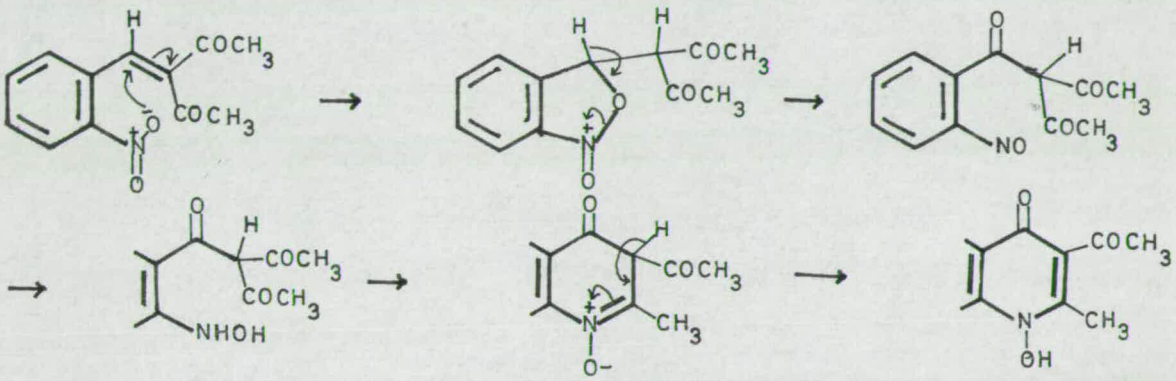
ated anthranil and its 5-bromo-derivative.[96] The difference between hydrogen chloride and hydrogen bromide is illustrated more clearly, however, when phenol is condensed with 5-bromo or 5-chloro-2-nitrobenzaldehyde. Using hydrogen chloride, the product is the 5,7-dihalogenated anthranil, while hydrogen bromide gives only the 5-halogenoanthranil, without insertion of bromine. It is perhaps significant that when quinol, which is a reducing phenol, is used, cyclisation to the anthranil occurs, using hydrogen chloride, without insertion of chlorine. A carbinol intermediate is indicated by the observation that the benzhydrol derivatives (82; R=Ph or p-C_6H_4OH) can be cyclised to the corresponding anthranils, using hydrogen chloride.[97] Likewise, thionyl chloride is reported[98] to cyclise the hydroxy-compound (82; R=Ph) to 5-chloro-3-phenylanthranil. On the other hand, a second intermediate, 2-nitrosobenzophenone is obtained on treatment with formic acid or toluene-p-sulphonyl chloride.

The 6-chloro-1,4-dihydro-1-hydroxy-4-oxoquinolines (87; R=Me, Ph or OEt) are obtained when mixtures of o-nitrobenzaldehyde and acetylacetone, benzoylacetone or ethyl acetoacetate are treated with hydrogen chloride.[96,99] o-Nitrobenzylidene derivatives, e.g. (88; R^1=R^2=Ac) have been shown to act as intermediates in this reaction. However, those formed from o-nitrobenzaldehyde and acetone, desoxybenzoin or ethyl benzoylacetate fail to cyclise. The use of hydrogen bromide or hydrogen chloride in the presence of quinol, leads to cyclisation as before, to the appropriate 1-hydroxy-4-oxoquinolines, but without insertion of halogen.[96] The reactions are thus similar to those of o-nitrobenzaldehyde and phenols, with hydrogen halides, to give anthranils. The mechanisms of formation of both the anthranils and the quinolines appear to involve oxygen transfer from the

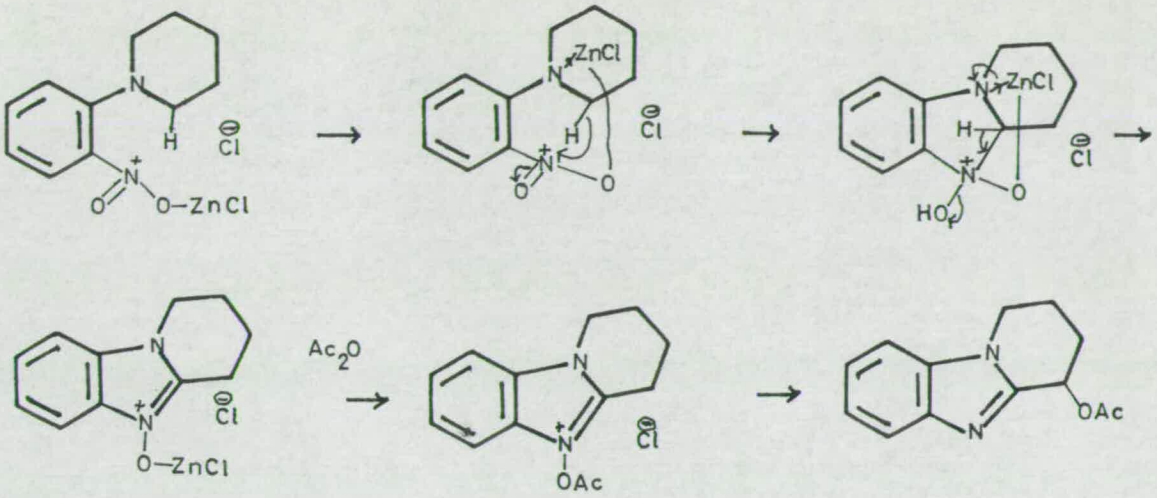
nitro-group to the side-chain, presumably followed by reduction and cyclisation as shown in scheme 40.



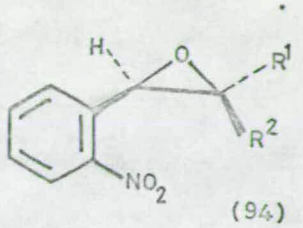
(scheme 40)



Derivatives of o-nitroaniline have also been cyclised under acidic conditions, the products being benzimidazoles. Van Romburgh[100] found that 2,4-dinitro-N,N-dimethylaniline refluxed with zinc chloride in acetic anhydride, gave the benzimidazole (89). He further suggested that the diethyl analogue gave the quinoxaline (90), however, in a reappraisal of his work, Grantham and Meth-Cohn[101] found that the product was in fact the benzimidazole (91). The mechanism suggested[101] incorporates the facts that no reaction took place in the absence of zinc chloride, together with the provision that the product isolated is derivable by reaction of an intermediate benzimidazole-N-oxide with acetic anhydride (scheme 41).



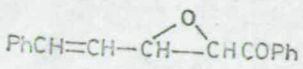
(scheme 41)



(94)

PhCH=CH−CH=CHCOPh

(96)



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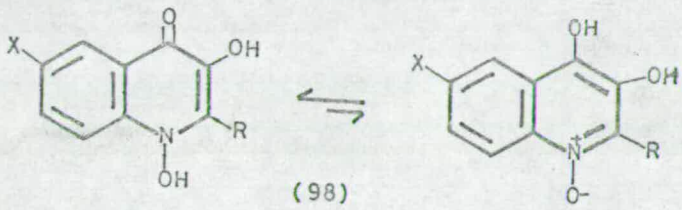

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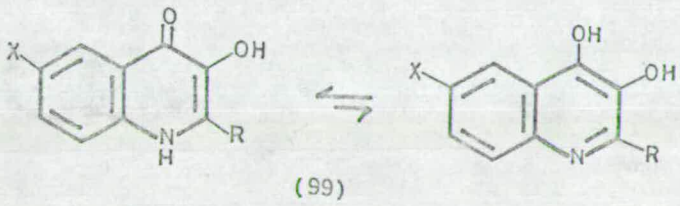

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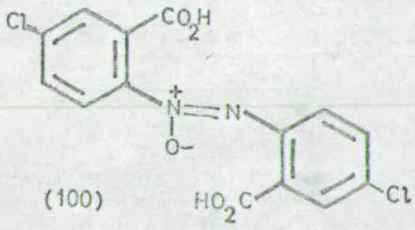

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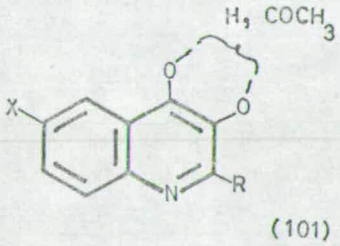

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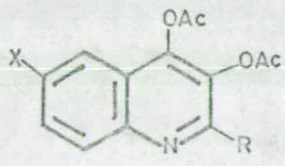

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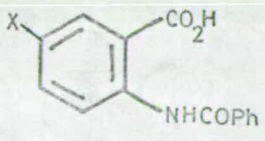
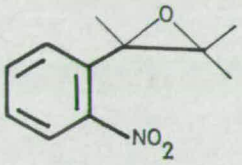


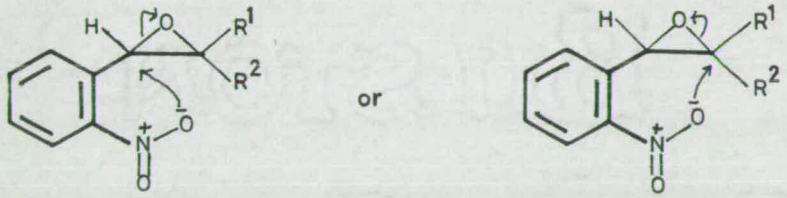
(103)

DISCUSSION OF ACID-CATALYSED INTERACTIONS.

In order to further examine the scope and mechanism of acid-catalysed interactions, it was decided to investigate neighbouring group interaction between an ortho-nitro-group and an epoxide side-chain.



The epoxide group provides potentially electrophilic centres at two points, which can be attacked by the oxygen of the nitro-group,

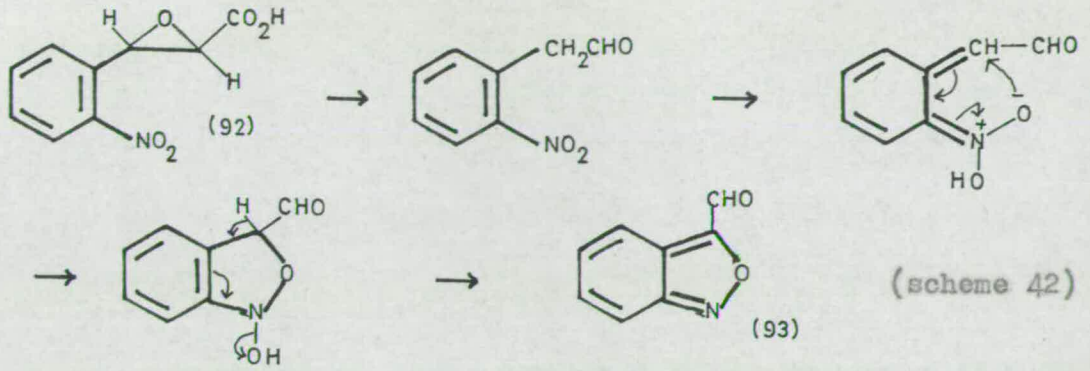


leading to oxygen transfer, and the possibility of cyclisation.

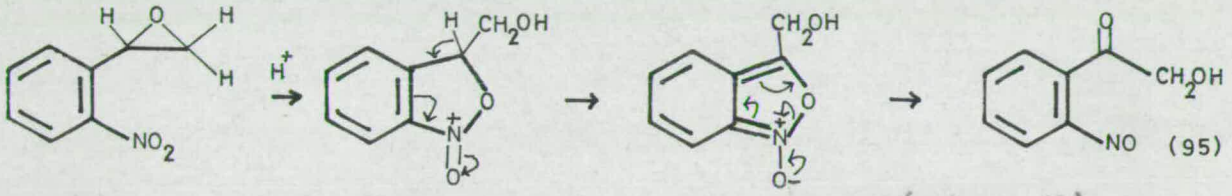
There is very little information available in the literature regarding the interactions of a nitro-group with an adjacent epoxide system. o-Nitrophenylglycidic acid (92) is reported[102] to yield a mixture of anthranil and its aldehyde (93) when it is heated in acetic acid, or steam-distilled. o-Nitrophenylacetaldehyde is a possible intermediate in this reaction (scheme 42).

On the other hand, o-nitrophenylethylene oxide (94; R^1=R^2=H) can be converted into o-nitrosobenzoylcarbinol (95) when heated carefully with formic acid (scheme 43).[103] Treatment of the epoxide (94; R^1=R^2=H) with acetic anhydride yields the acetate of the alcohol (95; OAc for OH).

The epoxides (94; R^1=Bz or Ac, R^2=H) were prepared in good yield by the Darzens reaction, using sodium methoxide[104] or potassium carbonate as

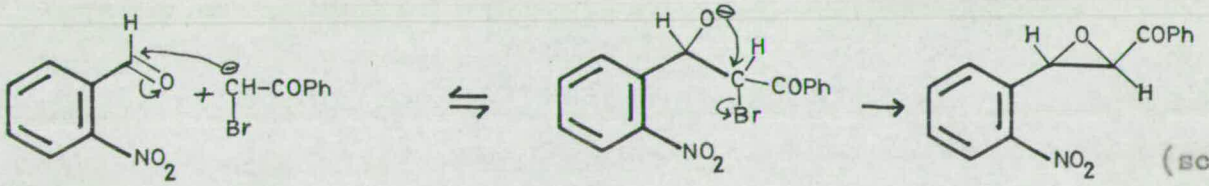


(scheme 42)



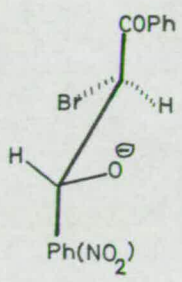
(scheme 43)

the base. This reaction is essentially an aldol condensation. The base first of all forms the enolate anion, which then attacks the carbonyl group of the aldehyde or ketone, forming the halohydrin anion, which cyclises to form the epoxide ring by an intramolecular displacement of halide ion (scheme 44).

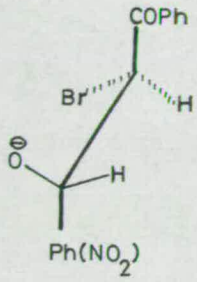


(scheme 44)

Consideration of the steric requirements of the intermediate explains why the reaction generally gives products having the trans configuration

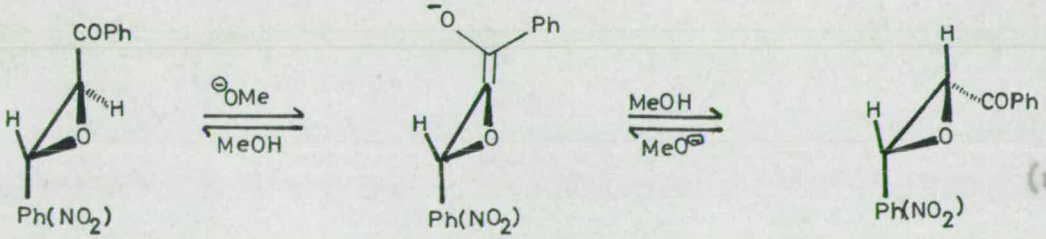


(dl erytho)



(dl threo)

To eliminate halide ion by an Sn 2 process, the oxygen must come in from behind. The dl erythro isomer is already set up for displacement, whereas the dl threo isomer must rotate through 180°, thereby causing eclipsing of the benzoyl and o-nitrophenyl groups, and hence an energetically less favourable situation. Since the formation of the aldol anion is reversible, any dl threo anion formed may revert to the components which can then recombine to give the anion in which epoxide formation occurs more readily. The fact that prolonged contact with methoxide converts the trans-epoxide (94; R^1=Bz, R^2=H) into the cis isomer (94; R^1=H, R^2=Bz) is explained[104] by the fact that the two forms have different solubilities in methanol. In the presence of base, the epoxide can enolise, as shown in scheme 45.



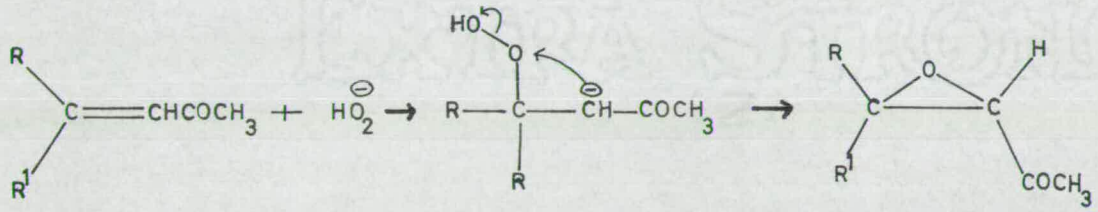
(scheme 45)

The cis form comes out of solution, leading to the enolisation of further quantities of the trans form, to restore equilibrium.

Epoxides (94; R^1=R^2=Ac) and (94; R^1=Bz, R^2=Ac) were prepared by the reaction of the benzylidene compounds (88; R^1=R^2=Ac) and (88; R^1=Bz, R^2=Ac)

with hydrogen peroxide in the presence of base. However, o-nitrobenzylidenedesoxybenzoin (88; R^1=Bz, R^2=Ph) was not epoxidised by this method, even under forcing conditions. This method of epoxide formation is synthetically important in that it is selective for double bonds linked to electron withdrawing substituents, a fact that is clearly demonstrated by the base-catalysed epoxidation of (96) yielding (97).[105] Attack only occurs at the double bond in (96) which is conjugated with the carbonyl group. Another notable feature of this reaction is the fact that it will often epoxidise heavily substituted and sterically inaccessible double bonds.

The mechanism of base-catalysed epoxidation is considered to involve attack by the hydroperoxy anion, as shown in scheme 46.



(scheme 46)

When isomeric products are possible, the trans configuration is normally the one obtained. However, if barriers to free rotation in the intermediate anion are high, the formation of cis and trans mixtures can result.

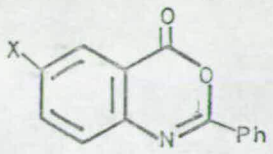
(a) Reactions of Substituted o-Nitrophenylethylene Oxides With Halogen Acids.

Treatment of the epoxides (94; R^1=Ac or Bz, R^2=H) with dry hydrogen chloride in ether, at room temperature, gave products, in lowish yields (43 or 19%). These analysed for $C_{15}H_{10}ClNO_3$ and $C_{10}H_8ClNO_3$ respectively, and had properties and transformations consistent with the 1,4-dihydro-1,3-dihydroxy-4-oxoquinoline structures (98; R=Ph or Me, X=Cl). They dissolved

unchanged in sodium hydroxide, and gave intense blue colours with ferric chloride in ethanol. These colours contrast with the red colour developed by 1-hydroxy-4-oxoquinolines in contact with ferric chloride.[99] Reduced with sodium dithionite in 70% aqueous ethanol, the N-hydroxy-compounds (98; R=Ph or Me, X=Cl) gave the corresponding 1,4-dihydro-3-hydroxy-4-oxoquinolines (99; R=Ph or Me, X=Cl). Oxidation of the compound (98; R=Ph, X=Cl) using potassium dichromate, afforded 4,4'-dichloroazoxybenzene-2,2'-dicarboxylic acid[99] (100), thus proving the position of the chlorine atom. The position of the chlorine atom in the methyl compound (98; R=Me, X=Cl) was assigned by analogy.

Briefly heated with acetic anhydride, the 4-oxoquinolines (99; R=Ph or Me, X=Cl) gave monoacetylation products (101; R=Ph or Me, X=Cl). There are two points of attack possible in these molecules, and hence the exact structures of the mono-acetoxy derivatives are not known. The products are however, o-acetyl and not N-acetyl derivatives, as shown by the carbonyl absorption at 1740-1745 $cm.^{-1}$ in their i.r. spectra. When heated for a much longer time with acetic anhydride, the 4-oxoquinolines (99; R=Ph or Me, X=Cl) gave diacetoxy-derivatives (102; R=Ph or Me, X=Cl), their i.r. spectra showing only one strong absorption at 1760 $cm.^{-1}$ Hydrolyis with dilute sodium hydroxide reconverted the compound (102; R=Ph, X=Cl) into the 4-oxoquinoline (99; R=Ph, X=Cl).

Acetylation of the 6-chloro-1,4-dihydro-1,3-dihydroxyquinolines (98; R=Ph or Me, X=Cl) on the other hand, gave low yields of the monoacetylation products (101; R=Ph or Me, X=Cl) previously obtained. A possible mechanism may involve initial dehydration to the diketone, followed by



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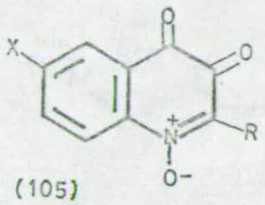

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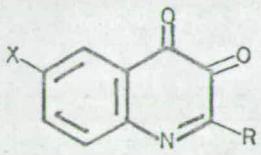

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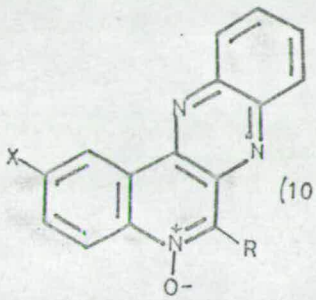

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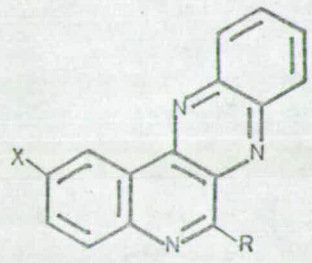

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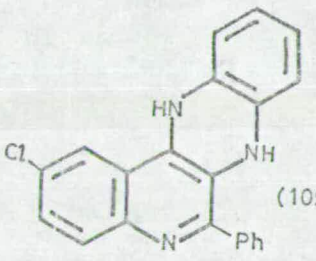

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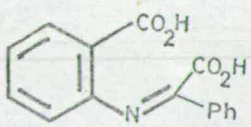

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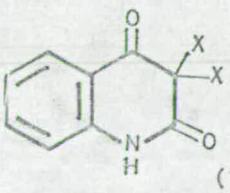

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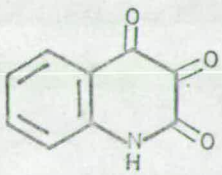

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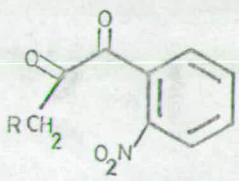


(113)

reduction and acetylation.

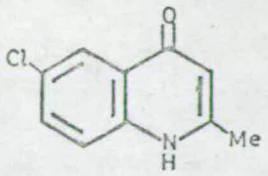
Oxidised with chromium trioxide in glacial acetic acid, the 1,4-dihydro-3-hydroxy-4-oxoquinoline (99; R=Ph, X=Cl) gave a compound whose elemental analysis and molecular weight corresponded to the structure (103; X=Cl). Warmed in acetic anhydride, the oxidation product gave a compound assigned the 3,1-benzoxazine structure (104; X=Cl), on the basis of its elemental analysis, molecular weight (mass spectrum) and the similarity of its i.r. spectrum to that of the compound (104; X=H) discussed below.

In contrast, oxidation of the 1,3-dihydroxy-4-oxoquinolines (98; R=Ph or Me) X=Cl) and the 1,4-dihydro-3-hydroxy-4-oxoquinoline (99; R=Ph, X=Cl) with manganese dioxide in anhydrous acetone, gave the expected quinoline quinones (105; R=Ph or Me, X=Cl) and (106; R=Ph, X=Cl) as red solids. The activity of the manganese dioxide and the length of exposure to the reagent were important factors in determining the yields of the quinones. The difficulties were overcome by following the reaction by thin-layer chromatography. Attempts to oxidise the methyl compound (99; R=Me, X=Cl) to the quinone (106; R=Me, X=Cl) were unsuccessful. The ease of reduction of the ortho-quinone system in these products was demonstrated by shaking a portion of the quinone (105; R=Ph, X=Cl) with sodium dithionite in 70% aqueous ethanol. Reduction occurred smoothly in the cold, the red colour being rapidly discharged, giving the 1,3-dihydroxyquinoline (98; R=Ph, X=Cl). Refluxing the reaction mixture caused further reduction of the N-hydroxy-group, yielding the hydroxyquinoline (99; R=Ph, X=Cl).

When heated in ethanol with an equivalent quantity of o-phenylene-diamine, the quinoline quinones (105; R=Ph, X=Cl) and (106; R=Ph, X=Cl) gave the corresponding quinolino[3,4-b]quinoxalines (107; R=Ph, X=Cl) and

(108; R=Ph, X=Cl) as somewhat insoluble, high-melting yellow solids. On the other hand, attempts to prepare the quinolinoquinoxaline (107; R=Me, X=Cl) from the quinone (105; R=Me, X=Cl) were unsuccessful. Reduction of the quinolinoquinoxaline-N-oxide (107; R=Ph, X=Cl) using sodium dithionite in aqueous ethanol, gave at first a deep-purple compound, which rapidly reverted to its initial yellow colour, on standing in air or when heated in ethanol. On the basis of its molecular weight (mass spectrum) and its i.r. spectrum, the purple compound is assigned the dihydro structure (109). When shaken with manganese dioxide, it rapidly afforded the quinolinoquinoxaline (108; R=Ph, X=Cl).

Although the 2,3-, 2,4- and 6,8-dihydroxyquinoline systems are reasonably well known, 3,4-dihydroxyquinolines are not. 3,4-Dihydroxyquinoline itself is reported to have been synthesised from 4-hydroxyquinoline-2-carboxylic acid by bromination first of all in the three position, followed by nucleophilic replacement of the bromine by hydroxyl. This latter step leads to simultaneous decarboxylation, giving the required product.[106] A more recent route to this compound and 3,4-dihydroxy-2-methylquinoline involves Dakin oxidation of the appropriate 3-formyl-4-hydroxyquinoline.[107] In contrast, attempted Dakin oxidation of the 2-phenyl analogue resulted not in the 3,4-dihydroxy-2-phenylquinoline but instead in the anthranil of phenylglyoxylic acid (110),[107] indicating that the method lacks generality. Hence it can be seen that acid catalysed cyclisation of the epoxides described above provides a novel route to substituted 1,4-dihydro-1,3-dihydroxy-4-oxoquinolines, and the parent 1,4-dihydro-3-hydroxy-4-oxoquinolines. Likewise, oxidation of the hydroxyquinolines provides a route to quinoline-3,4-quinones. In this work the catalyst used



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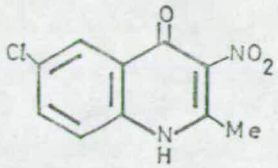

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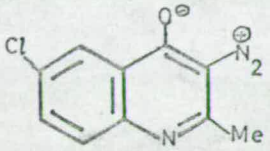

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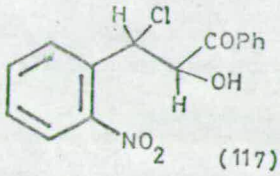

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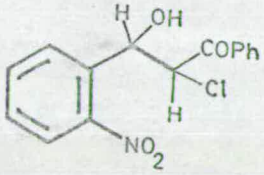

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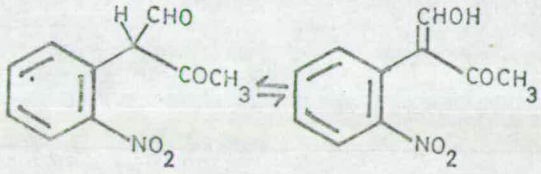

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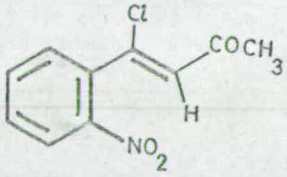

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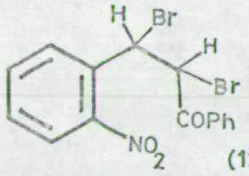

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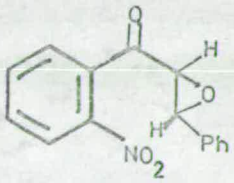

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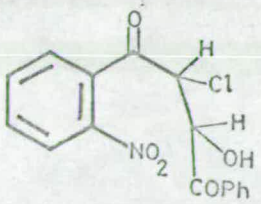


(123)

was slightly activated manganese dioxide, although a silver oxide/sodium sulphate slurry in methanol has also been used.[107] Another route to quinoline-3,4-quinones involves hydrolysis of a gem-dihalide. Thus hydrolysis of the compound (111; X=Cl or Br) is reported to give the triketone (112).[108] Other quinolinequinones are also known. 5-Amino-8-hydroxyquinoline, oxidised with chromic acid, gave[109] quinoline-5,8-quinone, while 5-amino-6-hydroxyquinoline, treated with ferric chloride yielded[110] quinoline-5,6-quinone.

Quinoline-ortho-quinone systems provide very convenient routes to to quinolinoquinoxalines, by reaction with o-phenylenediamine. Examples of this ring system are rare, presumably because of the difficulty in obtaining the appropriate quinolinoquinones. Examples include the hydroxy-compound (108; R=OH, X=H) although the structure of this product has not been firmly established.[108]

In another approach used by Barnes et al.,[22] benzyl-o-nitrophenylglyoxals (113) are reacted with o-phenylenediamine, giving the quinoxalines (24), which are then cyclised by a base-catalysed aldol type of reaction, to give the quinoxalinoquinolines (107). In this way these authors prepared the compound (107; R=Ph, X=H).

In order to demonstrate the presence of the quinoline nucleus in the compounds (98) an attempt was made to synthesise 6-chloro-1,4-dihydro-3-hydroxy-2-methyl-4-oxoquinoline by an unambiguous route. 6-Chloro-1,4-dihydro-2-methyl-4-oxoquinoline (114) was first of all nitrated to give the 3-nitro compound (115) which was then reduced to the 3-amino compound (115; NH_2 for NO_2). It was hoped that diazotisation, followed by hydrolysis would give the required compound, however the quinone diazide (116) formed

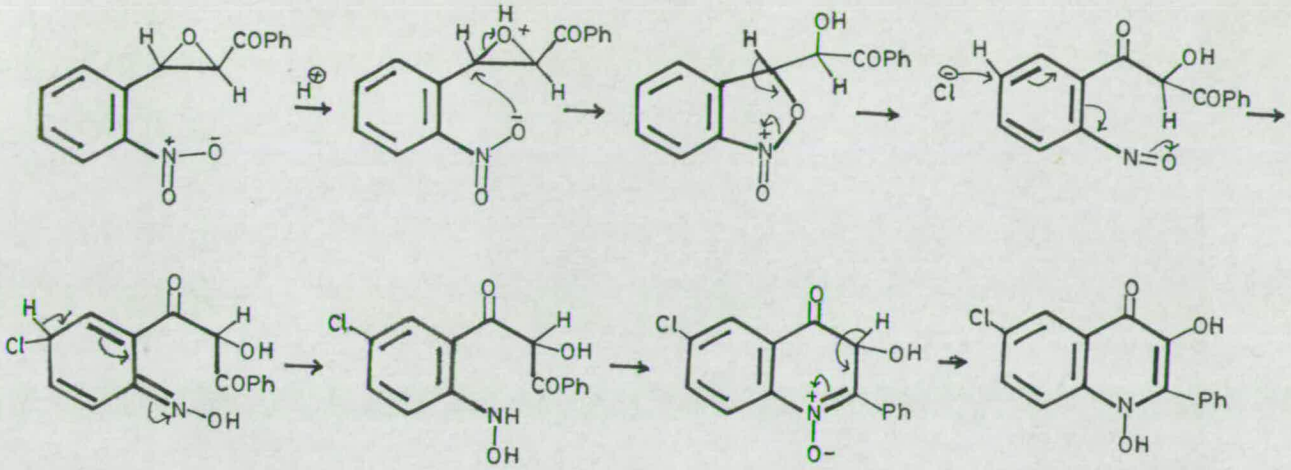
could not be decomposed except under very forcing conditions, when no identifiable material was isolated.

As well as the 3-hydroxy-4-oxoquinolines (98; R=Ph or Me, X=Cl) isolated when the epoxides (94; R^1=Bz or Ac, R^2=H) were treated with hydrogen chloride in ether, products were also obtained from the ethereal mother liquors. Working up of the ethereal mother liquors from the reaction of the epoxide (94; R^1=Bz, R^2=H) with hydrogen chloride, gave a solid whose n.m.r., i.r. spectra and analysis were consistent with the chlorohydrin structure (117). Treatment with sodium ethoxide reconverted it into the original epoxide (94; R^1=Bz, R^2=H), while reductive cyclisation afforded 2-phenylquinoline, which was identified as the picrate. The compound failed to give an α-haloketone test, hence it was assigned structure (117) rather than the alternative (118). This formulation is in accord with the report[105] that the epoxide (94; R^1=Bz, H for NO_2) ring opens, when treated with hydrogen chloride in ether, to give the chlorohydrin (117; H for NO_2), thus demonstrating the greater ability of the phenyl-group to stabilise an adjacent positive centre in the transition state.[105]

The mother liquors obtained from the reaction of the epoxide (94; R^1=Ac, R^2=H) with hydrogen chloride gave an oil, which was separated into two low-melting components by means of washing with sodium bisulphite, suggesting that the soluble fraction might be an aldehyde (119), formed as a result of acid-catalysed Tiffeneau rearrangement[168] of the epoxide. The assigned structure (119) for this by-product is in agreement with the analysis and molecular weight (mass spectrum) of its dinitrophenylhydrazone. However, the n.m.r. spectrum of the oil did not contain a signal attributable to a normal aldehyde proton in the region (τ =0-0.7), but it did have bands in its i.r. spectrum, corresponding to a hydroxyl group and one or

more carbonyl groups. This suggests that the molecule probably exists in the enol form, in which case the lower of the absorption bands in the carbonyl region is probably due to the double bond. The n.m.r. spectra of similar enols, e.g. (119; H for NO_2) show the aldehyde protons occurring at higher fields (τ =0.8–2.7) than those in ordinary aldehydes.[111] The bisulphite insoluble material was found to contain chlorine. Analysis, as the dinitrophenylhydrazone, suggested the formula $C_{16}H_{12}ClN_5O_6$ which was confirmed by the mass spectrum (M+=405). On this basis, the bisulphite insoluble fraction is tentatively assigned the structure (120), arising as a result of dehydration of the initially formed chlorohydrin (117; Ac for Bz). The n.m.r. spectrum of the bisulphite insoluble oil contains no signal due to an olefinic proton. This is possibly due to enhanced deshielding by the adjacent carbonyl group, causing the signal due to the olefinic hydrogen to become merged with the aromatic region.

The halogen acid catalysed transformations of the epoxides (94; R^1=Bz or Ac, R^2=H) into the 6-chloro-1,4-dihydro-1,3-dihydroxyquinolines (98; R=Ph or Me, X=Cl) are similar to the acid-catalysed cyclisations of the o-nitrobenzylidene derivatives (88; R^1=Ac, R^2=CO_2Et) and (88; R^1=R^2=Ac) to N-hydroxyquinolines.[1] Thus, by analogy with these reactions, the products may be regarded as being derived by cyclisation of the corresponding o-hydroxylaminophenylketones (cf. scheme 40). Formation of these intermediates requires first of all the creation of an electron deficient benzylic centre in the side-chain, to facilitate nucleophilic attack by the oxygen atom of the nitro-group, followed by external reduction of the resultant nitrosophenylketone, by insertion of chloride, as in the conversion of nitrosobenzene into p-chlorophenylhydroxylamine by hydrogen chloride.[112] (scheme 47).



(scheme 47)

Analogy can also be drawn between the reactions leading to the hydroxyquinolines (98; R=Ph or Me, X=C_2) and that between phenol and o-nitrobenzaldehyde, in the presence of hydrogen chloride, which affords 5-chloro-3-p-hydroxyphenylanthranil (86; X=Cl, R=OH).[95] Again, the latter compound can be regarded as a dehydration product of the appropriate o-hydroxylaminophenylketone.[1]

In the reactions of o-nitrobenzaldehyde (a) with phenols, to give anthranils, and (b) with active methylene compounds to give quinolines, it was found that hydrogen bromide or hydrogen chloride in the presence of quinol effected cyclisation without insertion of halogen. To further investigate the possible analogy with these reactions, therefore, the epoxides (94; R^1=Bz, R^2=H) and (94; R^1=Ac, R^2=H) were treated similarly.

The epoxide (94; R^1=Bz, R^2=H) in ether, treated with hydrogen bromide, yielded a solid, which was shown after crystallisation from aqueous ethanol, not to contain halogen. It was identified as 1,4-dihydro-1,3-dihydroxy-2-phenylquinoline (98; R=Ph, X=H). As in the case of the hydroxyquinoline (98; R=Ph, X=Cl), the compound gave an intense blue colour

with ethanolic ferric chloride, and was reduced by aqueous ethanolic sodium dithionite to the 1,4-dihydro-3-hydroxy-4-oxoquinoline (99; R=Ph, X=H). Concentration of the ethereal mother-liquors gave a good yield of a bromine-containing compound, which was identified by i.r. and n.m.r. spectra and unambiguous synthesis as 2,3-dibromo-3-o-nitrophenyl-1-phenyl-propan-1-one (121). This compound is probably formed as a result of dehydration of the initially formed bromohydrin (117; Br for Cl) followed by the addition of hydrogen bromide.

On the other hand, the epoxide (94; R^1=Ac, R^2=H) treated similarly with hydrogen bromide, gave only unidentifiable tars.

Also the epoxides (94; R^1=Ac or Bz, R^2=H) treated with hydrogen chloride in the presence of quinol afforded the appropriate dehalogenated 1,4-dihydro-1,3-dihydroxy-4-oxoquinolines (98; R=Ph or Me, X=H), the former being identical with the product obtained by hydrogen bromide treatment of the epoxide (94; R^1=Bz, R^2=H).

The properties and transformations of the 1,4-dihydro-1,3-dihydroxy-4-oxoquinolines (98; R=Ph or Me, X=H) were analogous to those of their halogenated counterparts. Reduced with 70% aqueous ethanolic sodium dithionite, the N-hydroxy-compounds (98; R=Ph or Me, X=H) gave the corresponding 1,4-dihydro-3-hydroxy-4-oxoquinolines (99; R=Ph or Me, X=H), and oxidised with manganese dioxide, the quinoline derivatives (98; R=Ph or Me, X=H) and (99; R=Ph, X=H) yielded the corresponding quinones (105; R=Ph or Me, X=H) and (106; R=Ph, X=H). Attempts to oxidise the hydroxyquinoline (99; R=Me, X=H) to the quinone (106; R=Me, X=H) using manganese dioxide or silver oxide as the oxidising agent were unsuccessful. However, oxidation of the hydroxyquinoline (99; R=Me, X=H) may be complicated by attack on the

methyl group. Thus, the manganese dioxide oxidation of quinaldine affords the manganese salt of quinoline-2-carboxylic acid.[113] The quinones (105; R=Ph, X=H) and (106; R=Ph, X=H) reacted with o-phenylenediamine to give the quinolinoquinoxalines (107; R=Ph, X=H) and (108; R=Ph, X=H). However, the quinone (105; R=Me, X=H) failed to yield the corresponding quinolinoquinoxaline, thus behaving in a similar way to the chloro-compound (105; R=Me, X=Cl).

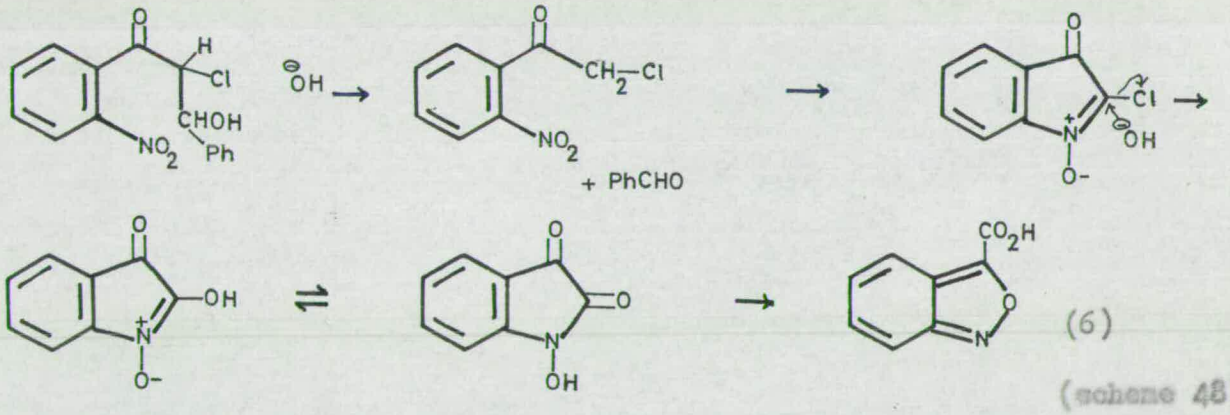
Oxidation of 1,4-dihydro-3-hydroxy-2-phenylquinoline (99; R=Ph, X=H) with chromium trioxide in glacial acetic acid, gave a product with similar properties to the compound obtained by the chromium trioxide oxidation of the chloro-compound (99; R=Ph, X=Cl). Its analysis and mass spectrum suggested the molecular formula $C_{14}H_{11}NO_3$ and it was subsequently shown to be identical with an authentic sample of N-benzoylanthranilic acid. In support of this structure it was converted by warm acetic anhydride into the 3,1-benzoxazine (104; X=H), which was identical with a sample prepared by heating authentic N-benzoylanthranilic acid with acetic anhydride.

Acetylation of the compound (99; R=Ph, X=H) gave both mono and diacetoxy-derivatives, whereas only the monoacetoxy-derivative could be isolated from the hydroxyquinoline (99; R=Me, X=H) even after refluxing for 2 hours in acetic anhydride.

The mother-liquors from the hydrogen chloride/quinol treatment of the epoxide (94; R^1=Bz, R^2=H) were columned on alumina, giving a chlorine containing compound which had a molecular weight of 287 and analysed for $C_{15}H_{10}ClNO_3$. This is consistent with the structure (120; Bz for Ac) derived by dehydration of the initially formed chlorohydrin (117). On the other hand, the mother-liquors from (94; R^1=Ac, R^2=H) treated with hydrogen chloride in the presence of quinol, yielded an intractable tar, which could

not be identified.

In the formation of the 1-hydroxyquinolines (98; R=Ph or Me, X=Cl or H) the first step appears to be interaction between one of the oxygen atoms of the nitro-group with an electron deficient centre in the side-chain. The epoxide system can furnish two such centres. In the mechanism proposed, interaction is thought to occur at the benzylic carbon atom but it might also conceivably occur at the β position. In an attempt to clarify this point the epoxide (122) in which attack at the α position is blocked, was studied. Treatment with hydrogen chloride yielded the chlorohydrin (123). The structure of this compound was verified by treating it with dilute sodium hydroxide to yield a mixture of benzaldehyde, and anthoxanic acid (6). This reaction is explicable by retroaldol reaction of the chlorohydrin (123),



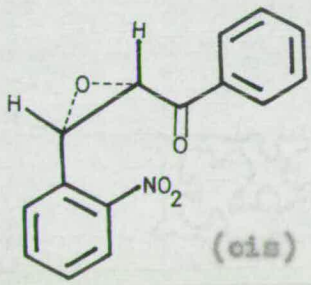
(6)

(scheme 48)

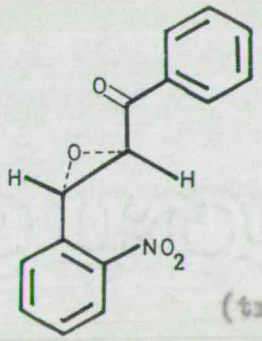
to give benzaldehyde and ω-chloro-o-nitroacetophenone, which is known[5] to give anthranil-3-carboxylic acid in presence of alkali. The failure of the epoxide (122) to undergo cyclisation supports a mechanism involving attack by the nitro-group at the benzylic position.

Steric requirements of the reaction were further investigated by studying the reaction of the epoxides (94; R^1=H, R^2=Bz) and (94; R^1=Ac or

Bz, R^2=Ac) with hydrogen chloride. In contrast to the trans epoxide (94; R^1=Bz, R^2=H) the cis isomer (94; R^1=H, R^2=Bz) gave a quantitative yield of the 1-hydroxyquinoline (98; R=Ph, X=Cl), while epoxides (94; R^1=R^2=Ac) and (94; R^1=Bz, R^2=Ac) also gave high yields of the compound (98; R=Me, X=Cl) without the formation of detectable amounts of the by-products previously obtained. The marked difference in yield of the 1-hydroxyquinoline (98; R=Ph, X=Cl) obtained from the cis and trans chalcone epoxides can only be due to the different stereochemistry of the molecules since electronic effects should be the same in both. Consideration of molecular models shows that in the trans configuration the benzoyl group is held away from the nitro-group, whereas, in the cis form, the groups are close to each other.

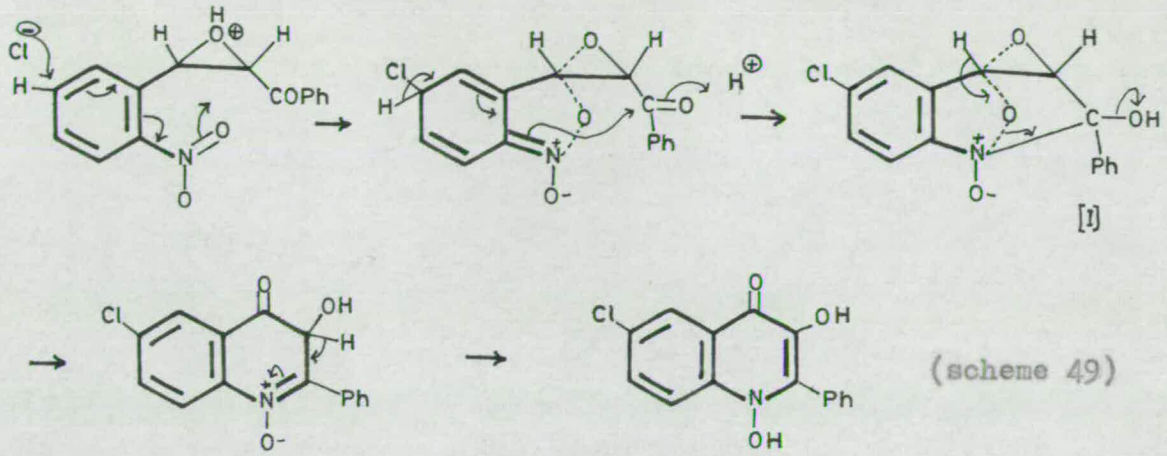


(cis)



(trans)

When the cis epoxide ring opens, the molecule should be able to rotate to a more stable conformation, with the bulky groups far from each other. This does not occur, suggesting that the reaction in the case of the cis isomer must occur via a fast, concerted mechanism, through an intermediate species which does not allow free rotation (scheme 49).

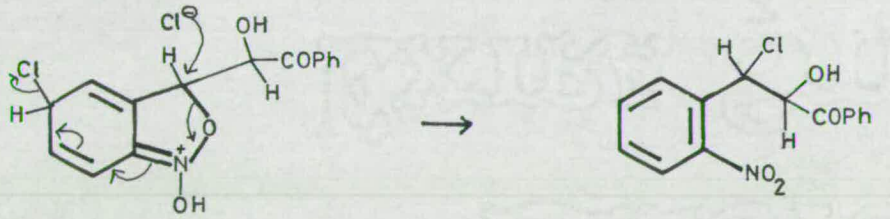


[I]

(scheme 49)

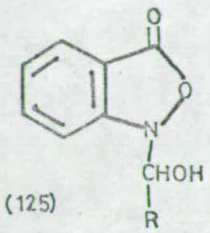
The oxygen bridge in species I (scheme 49) would appear to remain intact throughout, since, if it does not, the side-chain would again be free to rotate.

On the other hand, the intermediate for the trans isomer has to overcome a considerable energy barrier to rotation in order to attain a conformation suitable for interaction. Hence the rate of rotation will be slow, as will be the rate of cyclisation, allowing time for chloride ion to attack the intermediate, with formation of the chlorohydrin.



(scheme 50)

The high yields of the 1-hydroxyquinoline (98; R=Me, X=Cl) formed from the epoxides (94; R^1=Ac or Bz, R^2=Ac) can be explained similarly, since in each case the nitro-group is close to one of the carbonyl groups. The fact that the product from the hydrogen chloride catalysed cyclisation of (94; R^1=Bz, R^2=Ac) is (98; R=Me, X=Cl) and not (98; R=Ph, X=Cl) is probably best explained in terms of the configuration of the original epoxide, which



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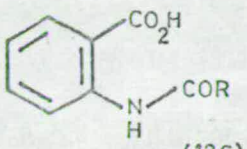

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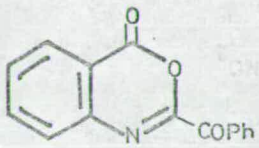

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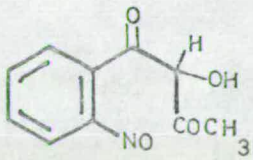

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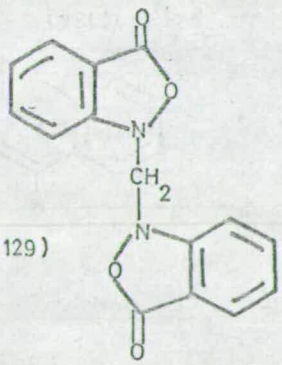

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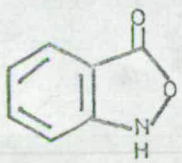
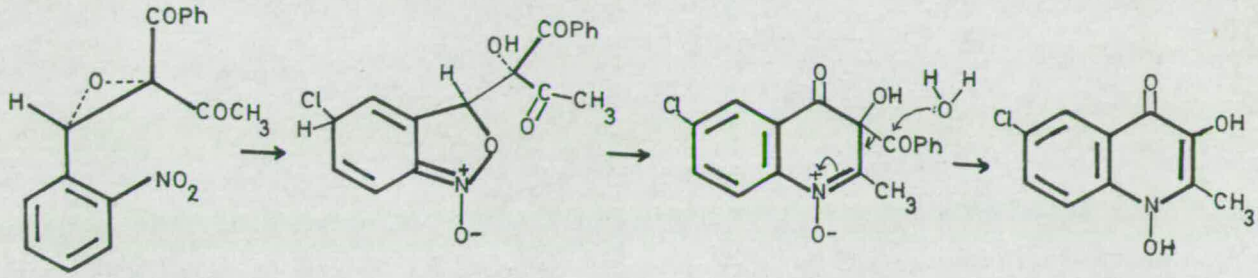


(130)

will almost certainly be trans with respect to the bulkiest groups, as discussed earlier.



(scheme 51)

(b) Reactions of Substituted o-Nitrophenylethylene Oxides With Lewis Acids.

In an early attempt to prepare the chlorohydrin (117), the chalcone epoxide (94; R^1=Bz, R^2=H) in benzene, was treated with stannic chloride. However, the product obtained in good yield was not the expected chlorohydrin. Its i.r. spectrum contained absorptions corresponding to two carbonyl groups and one hydroxyl group, while those corresponding to the nitro-group were absent. The n.m.r. spectrum showed only two non-aromatic peaks, one being broad, and each corresponding to a single proton. Elemental analysis and molecular weight data were in agreement with a formula $C_{15}H_{11}NO_4$.

When the reaction was repeated using boron trifluoride etherate, in benzene, a mixture of the same neutral product (125; R=Bz) and an isomeric acidic material were obtained. The acidic compound was subsequently identified by unambiguous synthesis as N-phenylglyoxyloylanthranilic acid (126; R=Bz). In contrast, treated with stannic chloride in ether, the chalcone epoxide (94; R^1=Bz, R^2=H) gave only the acid (126; R=Bz).

The neutral compound (125; R=Bz) could be converted under a variety

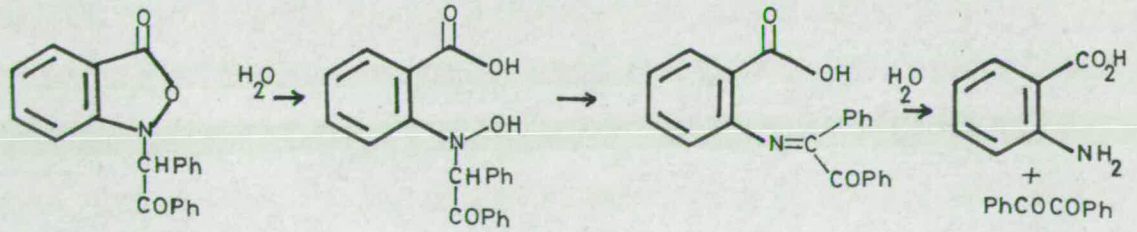
of conditions into N-phenylglyoxyloylanthranilic acid (126; R=Bz), in particular by treating it in the cold with aqueous sodium hydroxide, or concentrated sulphuric acid. When it was heated with acetic anhydride and sodium acetate, or stirred at room temperature in acetic anhydride, containing a trace of concentrated sulphuric acid, it yielded a product identical with that obtained by heating the acid (126; R=Bz) with sodium acetate in acetic anhydride. This compound is assigned the benzoxazine structure (127) on the basis of its mode of formation, elemental analysis, molecular weight and i.r. spectrum, which contains a band at 1760 $cm.^{-1}$ attributable to the lactonic carbonyl group. The structure (125; R=Bz) for the neutral compound was finally verified by its unambiguous synthesis from 2,1-benzisoxazolone and phenylglyoxal.

In contrast to the chalcone epoxide (94; R^1=Bz, R^2=H), reaction of the epoxide (94; R^1=Ac, R^2=H) with stannic chloride, in benzene, gave only intractable rars which left residues on burning. All attempts to isolate identifiable material from these products were unsuccessful. However, when the epoxide (94; R^1=Ac, R^2=H) was treated with boron trifluoride in benzene, a product was obtained which, by analogy with compound (125; R=Bz), was at first assigned the structure (125; R=Ac) on the basis of its analysis, molecular weight and spectroscopic evidence. Its n.m.r. spectrum showed three peaks. The two more deshielded peaks were not completely resolved, but consisted of a sharp singlet, superimposed upon a broad peak. The i.r. spectrum was similar to that of (125; R=Bz), having an absorption band at 3200 $cm.^{-1}$ corresponding to the presence of a hydroxyl group, and two carbonyl bands, at 1700 and 1650 $cm.^{-1}$ Warmed in acetic anhydride, it formed a monoacetyl derivative. However, the compound was not identical with the

benzisoxazolone (125; R^1=Ac) prepared by unambiguous synthesis from 2,1-benzisoxazolone and methyl glyoxal. The structure of this compound and its acetyl derivative have not been established with certainty but it is possible that they have the structures (128) and (128; OAc for OH) which would also fit the available information. Further work is necessary to confirm this suggestion.

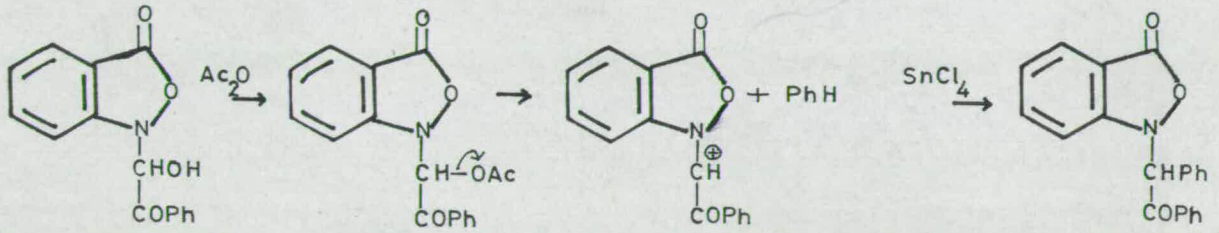
The reactions of the epoxides (94; R=Ac or Bz) with Lewis acids appear to be analogous to the conversion of o-nitrophenylethylene oxide (94; R^1=R^2=H) by the action of formic acid into a mixture of the methylene-bis-benzisoxazolone (129) and o-nitrosobenzoylmethanol (95).[103] Thus, treatment of the epoxide (94; R^1=R^2=H) with Lewis acids (stannic chloride or boron trifluoride) was found to yield the methylene-bis-benzisoxazolone (129)

With a view to trapping possible intermediates, the reactions of the epoxides (94; R^1=Ac or Bz, R^2=H) with Lewis acids were studied in the presence of an excess of acetic anhydride. The chalcone epoxide (94; R^1=Bz, R^2=H) treated in benzene with stannic chloride and acetic anhydride, gave a product formulated as N-desyl-2,1-benzisoxazolone (125; R=Bz, Ph for OH). Its i.r. spectrum was similar to that of (125; R=Bz), having carbonyl absorptions at 1730 and 1685 $cm.^{-1}$, while the n.m.r. spectrum showed only one peak outside the aromatic region. It was transformed by mild hydrolysis into anthranilic acid and benzil (scheme 52).



(scheme 52)

N-Desyl-2,1-benzisoxazolone (125; R=Bz, Ph for OH) was also obtained when the compound (125; R=Bz) and acetic anhydride, in benzene, were treated with stannic chloride. The formation of the compound (125; R=Bz, Ph for OH) therefore probably involves the benzisoxazolone (125; R=Bz, OA for OH) as an intermediate (scheme 53).

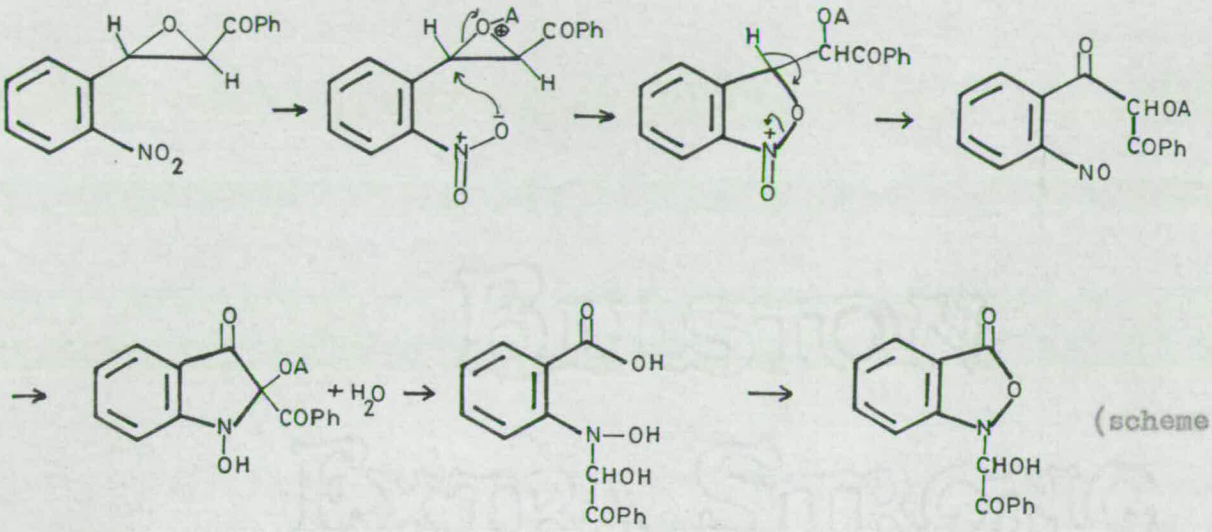


(scheme 53)

Ionisation of the acetoxy-group yields a carbonium ion, which can then attack the benzene in an electrophilic substitution reaction. The acetoxy group appears to provide a better leaving group than hydroxyl, since there is no evidence for attack on the solvent in the absence of acetic anhydride. The epoxide (94; R^1=Ac, R^2=H) and acetic anhydride in benzene, treated as before, with boron trifluoride etherate, gave the acetate tentatively formulated above as the nitroso compound (128; OAc for OH). o-Nitrophenylethylene oxide, on the other hand, when treated with acetic anhydride and boron trifluoride in benzene, gave only the methylene-bis-benzisoxazolone (129).

The mechanism of these Lewis acid catalysed cyclisations all appear to follow a similar course to that proposed for the reaction of o-nitrophenylethylene oxide with formic acid, to give o-nitrosobenzoylcarbinol (95) and thence N-hydroxymethyl-2,1-benzisoxazolone (125; R=H) and the methylene-bis-benzisoxazolone (129).[103] In the case of the epoxide (94; R^1=Ac, R^2=H) the analogous nitroso-compound (128) does not react further, and in the

presence of acetic anhydride gives the acetyl derivative (128; OAc for OH). The chalcone epoxide, on the other hand, gives the 2,1-benzisoxazolone (125; R=Bz). A possible route is shown in scheme 54.



(scheme 54)

Since N-phenylglyoxyloylanthranilic acid (126; R=Bz) is not converted into the benzisoxazolone (125; R=Bz), when treated with stannic chloride, it cannot act as an intermediate in the formation of (125; R=Bz) from the epoxide (94; R^1=Bz, R^2=H). 2,1-Benzisoxazolone (130) and phenylglyoxal could possibly act as precursors, since they condense in the presence of stannic chloride, to give the 2,1-benzisoxazolone (125; R=Bz), however the demonstration of the presence of 2,1-benzisoxazolone (130) by trapping it as its acetyl derivative (130; Ac for H) would not be reliable, since compound (125; R=Bz), treated with stannic chloride and acetic anhydride, yields N-desyl-2,1-benzisoxazolone (125; R=Bz, Ph for OH) and N-acetyl-2,1-benzisoxazolone (130; Ac for H).

The epoxide (122) was treated with stannic chloride, to determine whether interaction would occur at any other centre in the molecule when the benzylic carbon was blocked. Again, only the chlorohydrin (123) was obtained.

(c) Reactions of Substituted o-Nitrophenylethylene Oxides With Acetic Acid and Formic Acid.

The study of the acid-catalysed interaction of a nitro-group with an adjacent epoxide group was extended to the reactions of the epoxides (94; R^1=Ac or Bz, R^2=H) with acetic and formic acids.

When the trans chalcone epoxide (94; R^1=Bz, R^2=H) was stirred in the cold with glacial acetic acid, no reaction occurred. However, on refluxing, reaction occurred readily, yielding 1,4-dihydro-3-hydroxy-4-oxo-2-phenyl-quinoline (99; R=Ph, X=H) identical with a sample obtained by reducing the N-hydroxyquinoline (98; R=Ph, X=H). A small quantity of an unidentifiable red solid was also obtained. Its molecular weight (mass spectrum) suggests that it may be dimeric, while the colour could indicate the presence of an azo-linkage.

The mechanism of interaction is presumably broadly similar to that followed in the halogen-acid cyclisations already mentioned, however, not a great deal can be deduced, since only a very limited amount of identifiable material was isolated.

Formic acid, on the other hand, converted the epoxide (94; R^1=Bz, R^2=H) into the acid (126; R=Bz), indicating that this reaction appears to take a course similar to that which occurs when the chalcone epoxide (94; R^1=Bz, R^2=H) is treated with Lewis acids, as discussed earlier. Treatment of the epoxide (94; R^1=Ac, R^2=H) with acetic or formic acid yielded only intractable tars.

Experimental Procedure.

Melting points were determined on a Kofler block and are uncorrected. Unless otherwise stated, infra-red spectra were recorded as nujol mulls, using a Unicam SP 200 instrument. Ultraviolet spectra were recorded for ethanol solutions using an SP 800 instrument. Nuclear magnetic resonance spectra were obtained for deuteriochloroform solutions, with tetramethylsilane as internal standard, using Perkin Elmer R 10 and Varian HA 100 spectrometers. Mass spectra were measured with an A.E.I. MS 902 instrument. Thin-layer chromatograms were run on Merck silica-gel G, or Merck alumina G, and colourless compounds detected with iodine vapour. Column chromatography was carried out using Spence alumina type H or silica-gel M.F.G.

Unless otherwise stated, light petroleum refers to the fraction b.p. 60-80°. Chloroform and ether extracts were dried over anhydrous sodium or magnesium sulphate.

Synthesis of N,N -Disubstituted o-Nitrobenzamides.

Preparation of the acid chlorides. The acid chlorides were all prepared by the method used for o-nitrobenzoyl chloride.[114]

o-Nitrobenzoyl chloride was obtained as a pale yellow liquid (yield 95%), b.p. 110-125°/0.4-0.6 mm., (lit.,[114] 139-141°/0.7 mm.).

3-Methyl-6-nitrobenzoyl chloride[115] was obtained as a pale yellow liquid (yield 82%), b.p. 165-168°/10-12 mm.

m-Nitrobenzoyl chloride was obtained as a pale yellow liquid (yield 34%), b.p. 106-110/0.5-1 mm., (lit.,[116] 154-155°/18 mm.).

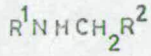
o-Chlorobenzoyl chloride was commercially available from Koch-Light Laboratories.

ø-Methoxybenzoyl chloride was obtained as a colourless liquid (yield 90%), b.p. 125-127°/10 mm. (lit.,[117] 136-138°/17 mm.).

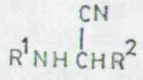
3,5-Dinitrobenzoyl chloride. 3,5-Dinitrobenzoic acid was heated with thionyl chloride for 5 days, with the gradual addition of a further 10 ml. of reagent. The product was obtained as a yellow oil (yield 27%), b.p. 190-196°/11 mm. (lit.,[118] 196°/10-12 mm.). It solidified upon cooling. Unreacted acid (14 g.) was recovered from the distillation flask.

2-Chloro-5-nitrobenzoic acid was prepared from 2-chlorobenzoic acid, as described by Lemstedt.[119] It crystallised as yellow needles, m.p. 160-165° (from aqueous ethanol) (lit.,[119] 165°).

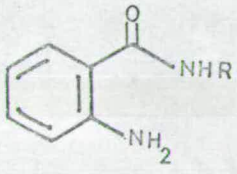
2-Chloro-5-nitrobenzoyl chloride was obtained as a pale yellow oil which solidified upon cooling. It was washed with petrol ether, and used without further purification, m.p. 54-59° (lit.,[120] 59°).



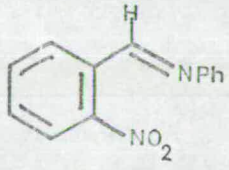
(131)



(132)



(133)



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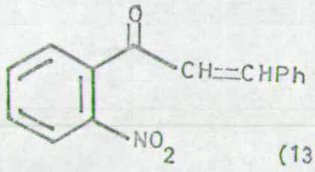

(135)

Preparation of the Amines. The amines used are all known compounds, and unless otherwise stated, were prepared as described in the literature.

ω-N-phenylaminoacetophenone[121] (131; R^1=Ph, R^2=Bz) (yield 79%) was obtained as yellow needles, m.p. 98-99° (lit.,[122] 93°), and was found to decompose on attempted crystallisation from ethanol.

N-Benzylaminoacetonitrile. (131; R^1=$PhCH_2$, R^2=CN) was obtained as its hydrochloride (yield 14%). It formed colourless needles, m.p. 163-168° (from ethanol) (lit.,[123] 170°). The crude product melted at 130°, being contaminated with benzylamine hydrochloride, which was removed by filtration during two recrystallisations from ethanol.

N-Phenylaminoacetonitrile (131; R^1=Ph, R^2=CN) (yield 40%) formed colourless needles, m.p. 44-45° (from ether/light petroleum) (lit.,[124,125] 45°).

Ethyl-N-Phenylaminoacetate (131; R^1=Ph; R^2=CO_2Et) was prepared by the method of Eade and Earl[128] (yield 68%) m.p. 52-57° (lit.,[126,127] 58°).

α-N-Phenylamino-α-phenylacetonitrile (132; R^1=R^2=Ph) (yield 59%) formed colourless needles, m.p. 84-85° (from aqueous ethanol) (lit.,[124,125] 85°).

α-N-Phenylaminopropionitrile (132; R^1=Ph, R^2=Me) was prepared by the method of Bucherer and Schwalbe[125] (yield 83%) m.p. 88-90° (from aqueous ethanol) (lit.,[129] 92°).

α-Aminopropionitrile (132; R^1=H, R^2=Me) was prepared according to the method of Kendall and McKenzie.[130] Having been shaken for 4 hrs. the reaction mixture was extracted with ether and the extract (containing 16 g. of amine in 450 ml. ether) separated, dried, and stored in a refrigerator. It was concentrated under reduced pressure at room temperature with dry

benzene and used directly in the preparation of the amide.

∝-Aminophenylacetonitrile[131] (132; R^1=H, R^2=Ph) was extracted into ether after the stated reaction time, separated from the aqueous phase, washed with saturated aqueous sodium bisulphite solution, then with water and dried. Removal of the solvent in vacuo gave the crude product (yield 76%), which was dissolved in dry benzene, and used directly in the preparation of the amide.

∝-N-Methylamino-∝-phenylacetonitrile[132] (132; R^1=Me, R^2=Ph), ∝-N-benzylamino-∝-phenylacetonitrile[133] (132; R^1=$PhCH_2$, R^2=Ph) and ∝-N-benzylamino-propionitrile[134,135] (132; R^1=$PhCH_2$ R^2=Me) were prepared by the following general method.

The aldehyde (0.2 mole) was added slowly to a solution of sodium bisulphite (0.2 mole, 21 g.) in water (200 ml.) and the mixture stirred until homogeneous. The amine (0.2 mole) was then added slowly and stirring continued for 2 hrs., at room temperature. Finally, potassium cyanide (0.2 mole, 14 g.) was added and the stirring continued for a further 0.5-1 hr., at room temperature. The oil was then extracted into chloroform, and the organic layer separated, dried and evaporated, to yield the crude product.

∝-N-Methylamino-∝-phenylacetonitrile so obtained (yield 54%), was used without further purification in the preparation of the amide. It was characterised as the hydrochloride, which formed colourless needles, m.p. 116-118° (lit.,[136] 110-112°).

∝-N-Benzylamino-∝-phenylacetonitrile was obtained as an oil (yield 78%) and was used without further purification. Upon standing it crystallised to give colourless plates, m.p. 28-32° (lit.,[133] 33°).

∝-N-Benzylaminopropionitrile was obtained as an oil (26.1 g., 82%), b.p. 115-120°/15 mm., (lit.,[135] 131-137°/18 mm.).

∝-N-Methylaminopropionitrile[137] (132; R^1=R^2=Me). Acetaldehyde (0.25 mole, 11 g.) was slowly added to a solution of sodium bisulphite (0.25 mole, 26 g.) in water (200 ml.), with stirring. After 30 minutes, 27.5% aqueous methylamine solution (0.25 mole, 28 g.) was stirred in slowly and the contents of the flask left at room temperature overnight. The stirred solution was warmed to 65° on a water bath and treated with potassium cyanide (0.25 mole, 18 g.). After 30 minutes, the homogeneous solution was cooled and extracted with chloroform. Evaporation of the dried chloroform extract afforded the product as a light oil (9.9 g., 47%), b.p. 70-74°/36 mm. (lit.,[137] 70-78°/34 mm.).

N,N-Disubstituted o-nitrobenzamides

Method A

A slurry of fused sodium acetate (9 g.), in glacial acetic acid (54 ml.), was treated in one portion with the amine, or amine hydrochloride (0.024 mole), and then dropwise with stirring, with o-nitrobenzoyl chloride (0.024 mole). The mixture was stirred at room temperature for three hours, concentrated under reduced pressure, and the residue treated with water, to give the solid amide, which was collected, dried and crystallised.

N-Methyl-N-o-nitrobenzoylaminoacetonitrile (56a; R=Me) crystallised as colourless prisms (yield 75%), m.p. 111-113° (from ethanol), $\nu_{max.}$ 1640, 1535 and 1355 $cm.^{-1}$, n.m.r: τ=1.7-2.65 (multiplet, aromatic, 4H); 5.45, 5.88, 6.74, 7.0 (complex amide system, 5H). (Found: C, 54.7; H, 4.2; N, 19.3. $C_{10}H_9N_3O_3$ requires C, 54.8; H, 4.1; N, 19.2%).

N-Benzyl-N-o-nitrobenzoylaminoacetonitrile (56a; R=$PhCH_2$) crystallised as colourless prisms (yield 72%), m.p. 111-113° (from ethanol), $\nu_{max.}$ 1655, 1540 and 1360 $cm.^{-1}$, n.m.r.: τ=1.8-2.75 (multiplet, aromatic, 9H); 5.12, 5.58, 5.68, 6.08 (complex amide system, 4H). (Found: C, 64.6; H, 4.6; N, 14.2. $C_{16}H_{13}N_3O_3$ requires C, 65.1; H, 4.4; N, 14.2%).

Ethyl α-(N-o-nitrobenzoyl-N-phenyl)aminoacetate (56a; R=Ph, CO_2Et for CN) crystallised as colourless prisms (yield 66%), m.p. 107-108° (from ethanol), $\nu_{max.}$ 1730, 1660, 1535 and 1350 $cm.^{-1}$ n.m.r: τ=2-2.5 (multiplet, aromatic, 9H); 5.39 (singlet, CH_2, 2H); 5.73 (quartet, J=7Hz, CH_2, 2H); 8.7 (triplet, J=7Hz; CH_3, 3H). (Found: C, 62.4; H, 4.9; N, 8.9. $C_{17}H_{16}N_2O_5$ requires C, 62.6; H, 4.9; N, 8.5%).

ω-(N-o-nitrobenzoyl-N-phenyl)aminoacetophenone (56a; R=Ph, Bz for CN) crystallised as colourless cubes (yield 54%), m.p. 122-124° (from ethanol) $\nu_{max.}$ 1680, 1650, 1530 and 1360 $cm.^{-1}$, n.m.r: τ=1.87-2.96 (multiplet, aromatic, 14H); 4.63 (singlet, methylene, 2H). (Found: C, 69.5; H, 4.6; N, 7.9. $C_{21}H_{16}N_2O_4$ requires C, 70.0; H, 4.5; N, 7.8%).

(N-o-nitrobenzoyl-N-phenyl)aminoacetonitrile (56a; R=Ph) could not be prepared by the general method, as an uncrystallisable gum was obtained. Chromatography on alumina failed to effect purification. This amide was eventually obtained as follows-

A slurry of freshly fused sodium acetate (19 g.) in dry benzene (113 ml.) was treated with anilinoacetonitrile (6.6 g.), and o-nitrobenzoyl chloride (9.28 g.), and the mixture refluxed with stirring, for 2 hrs. The benzene was then removed under reduced pressure, and the residue triturated with water. The oil obtained was extracted into chloroform, and the separated

chloroform layer washed with saturated aqueous sodium bicarbonate. Evaporation of the dried extract left an oil (13.2 g.) which crystallised in contact with light petroleum. Filtration gave the amide (9.8 g., 69%), as colourless prisms, m.p. 99-101° (from methanol), $\nu_{max.}$ 1660, 1530 and 1350 $cm.^{-1}$, n.m.r: τ=2-2.9 (multiplet, aromatic, 5H); 5.17 (singlet, CH_2). (Found: C, 63.6; H, 4.1; N, 15.5. $C_{15}H_{11}N_3O_3$ requires C, 64.1; H, 3.9; N, 14.9%).

Method B.

The amine (0.02 mole) was cooled on an ice bath and stirred while o-nitrobenzoyl chloride (0.01 mole) was added dropwise. The flask was then fitted with a drying tube and heated at 100° for 30 minutes, during which time the contents of the flask darkened to a deep red. After cooling, the gum was treated with water and chloroform, and the chloroform layer washed with saturated aqueous sodium bicarbonate, dried and evaporated to yield the crude amide, which was then crystallised.

α-(N-methyl-N-o-nitrobenzoyl)aminopropionitrile (56b; R=Me) (yield 74%) formed colourless needles, m.p. 156-158° (from methanol), $\nu_{max.}$ 1640, 1535 and 1345 $cm.^{-1}$, n.m.r: τ=1.68-2.71 (multiplet, aromatic, 4H); 4.13 (quartet, CH, 1H,); 7.1 (singlet, $N-CH_3$, 3H); 8.34 (doublet, $C-CH_3$, 3H). (Found: C, 56.5; H, 5.1; N, 18.2. $C_{11}H_{11}N_3O_3$ requires C, 56.7; H, 4.8; N, 18.0%).

α-(N-o-nitrobenzoyl-N-phenyl)aminopropionitrile (56b; R=Ph) (yield 68%) formed colourless needles, m.p. 133-136° (from methanol), $\nu_{max.}$ 1660, 1530 and 1350 $cm.^{-1}$, n.m.r: τ=2.0-2.8 (multiplet, aromatic, 9H); 4.0 (quartet J= 8 Hz, CH, 1H); 8.4 (doublet, J=8 Hz, CH_3, 3H). (Found: C, 65.2; H, 5.1; N, 14.2. $C_{16}H_{13}N_3O_3$ requires C, 65.1; H, 4.4; N, 14.2%).

α-(N-Methyl-N-o-nitrobenzoyl)aminophenylacetonitrile (56c; R=Me, R^1=H) (yield 75%) formed colourless platelets, m.p. 110-112° (from ethanol), $\nu_{max.}$ 1650, 1535 and 1350 $cm.^{-1}$, n.m.r: τ=1.70-2.60 (multiplet, aromatic, 9H); 2.80 (singlet, CH, 1H); 7.32 (singlet, CH_3, 3H). (Found: C, 64.6; H, 4.4; N, 14.0. $C_{16}H_{13}N_3O_3$ requires C, 65.1; H, 4.4; N, 14.0%).

α-(N-Benzyl-N-o-nitrobenzoyl)aminophenylacetonitrile (56c; R=$PhCH_2$, R^1=H) (yield 91%) formed colourless needles, m.p. 179-181° (from benzene), $\nu_{max.}$ 1650, 1530 and 1355 $cm.^{-1}$, n.m.r: τ=1.76-3.30 (multiplet, aromatic, +CH, 15H); 5.73 (singlet, CH_2, 2H). (Found: C, 71.2; H, 4.6; N, 11.2. $C_{22}H_{17}N_3O_3$ requires C, 71.2; H, 4.6; N, 11.3%).

Method C

The amine (0.02 mole), in dry benzene (100 ml.) was treated slowly with o-nitrobenzoyl chloride (0.01 mole) in dry benzene (60 ml.) and the reaction mixture stirred at room temperature for 24 hrs., with the exclusion of moisture. The amine hydrochloride was then filtered off, and the filtrate evaporated to dryness, to yield the crude amide, which was purified by crystallisation.

α-(N-o-Nitrobenzoyl-N-phenyl)aminophenylacetonitrile (56c; R=Ph, R^1=H) (yield 76%) formed colourless prisms, m.p. 179-181° (from methanol), $\nu_{max.}$ 1655, 1535 and 1345 $cm.^{-1}$, n.m.r: all aromatic. (Found: C, 70.8; H, 3.9; N, 11.9. $C_{21}H_{15}N_3O_3$ requires C, 70.6; H, 4.2; N, 11.8%).

α-(N-Benzyl-N-o-nitrobenzoyl)aminopropionitrile (56b; R=$PhCH_2$) (yield 58%) was purified by chromatography on 10% deactivated alumina, eluting with benzene/light petroleum. It formed colourless needles, m.p. 90-92° (from ethanol), $\nu_{max.}$ 1650, 1530 and 1350 $cm.^{-1}$, n.m.r: τ=1.7-2.93 (multiplet,

aromatic, 9H); 4.7 (quartet, J=6 Hz, CH, 1H); 5.6 (singlet, CH_2, 2H); 8.35 (doublet, J=6 Hz, CH_3, 3H). (Found: C, 65.7; H, 4.7; N, 13.8. $C_{17}H_{15}N_3O_3$ requires C, 66.0; H, 4.9; N, 13.6%).

∝-(N-m-nitrobenzoyl-N-phenyl)aminophenylacetonitrile (59c; R=Ph, X=H) (yield 59%) formed colourless needles, m.p. 119–122° (from ethanol/light petroleum), $\nu_{max.}$ 1660, 1540, 1355 $cm.^{-1}$ (Found: C, 70.5; H, 4.4; N, 11.6, $C_{21}H_{15}N_3O_3$ requires C, 70.6; H, 4.2; N, 11.8%).

∝-(N-3,5-Dinitrobenzoyl-N-phenyl)aminophenylacetonitrile (59c; R=Ph, X=NO_2) (yield 82%) formed colourless needles, m.p. 164–166° (from glacial acetic acid), $\nu_{max.}$ 1655, 1540 and 1340 $cm.^{-1}$ (Found: C, 61.3; H, 3.5; N, 14.1. $C_{21}H_{14}N_4O_5$ requires C, 62.7; H, 3.5; N, 13.9%).

∝-(N-2-Chloro-5-nitrobenzoyl-N-phenyl)aminophenylacetonitrile (57c; R=Ph, X=Cl, Y=NO_2) (yield 80%), formed colourless needles, m.p. 189–191° (from glacial acetic acid), $\nu_{max.}$ 1660, 1540 and 1360 $cm.^{-1}$ (Found: C, 64.3; H, 3.9; N, 11.1. $C_{21}H_{14}ClN_3O_3$ requires C, 64.3; H, 3.6; N, 11.7%).

N-(2-Chloro-5-nitrobenzoyl)-N-phenylaminoacetonitrile (58a; R=Ph) (yield 95%) formed colourless needles, m.p. 170–172° (from glacial acetic acid), $\nu_{max.}$ 1655, 1530 and 1345 $cm.^{-1}$, n.m.r: τ=1.92–2.71 (multiplet, aromatic, 8H); 5.18 (singlet, CH_2, 2H). (Found: C, 56.6; H, 3.4; N, 13.3. $C_{15}H_{10}ClN_3O_3$ requires C, 57.1; H, 3.2; N, 13.3%).

∝-(N-2-Chloro-5-nitrobenzoyl-N-phenyl)aminopropionitrile (58b; R=Ph) (yield 66%), formed colourless prisms, m.p. 176–178° (from ethanol), $\nu_{max.}$ 1660, 1540 and 1365 $cm.^{-1}$, n.m.r: τ=1.98–2.70 (multiplet, aromatic, 8H); 4.03 (quartet, J=7 Hz, CH, 1H); 8.43 (doublet, J=7 Hz, CH_3, 3H). (Found: C, 57.9; H, 3.7; N, 13.1. $C_{16}H_{12}ClN_3O_3$ requires C, 58.3; H, 3.7; N, 12.7%).

α-(N-5-Methyl-2-nitrobenzoyl-N-phenyl)aminophenylacetonitrile (56c; R=Ph, R^1=Me) (yield 51%) formed colourless needles, m.p. 154-155° (from ethanol), $\nu_{max.}$ 1660, 1530 and 1350 $cm.^{-1}$ (Found: C, 70.6; H, 4.6; N, 11.1. $C_{22}H_{17}N_3O_3$ requires C, 71.1; H, 4.6; N, 11.3%).

α-(N-o-Methoxybenzoyl-N-phenyl)aminophenylacetonitrile (57c; R=Ph, X=OMe, Y=H) (yield 61%) formed colourless needles, m.p. 122-124° (from ethanol /light petroleum), $\nu_{max.}$ 1655 $cm.^{-1}$ (Found: C, 77.1; H, 5.4; N, 8.1. $C_{22}H_{18}N_2O_2$ requires C, 77.2; H, 5.3; N, 8.2%).

α-(N-o-Chlorobenzoyl-N-phenyl)aminophenylacetonitrile (57c; R=Ph, X=Cl, Y=H) (yield 60%) formed colourless prisms, m.p. 143-146° (from ethanol), $\nu_{max.}$ 1660 $cm.^{-1}$ (Found: C, 73.2; H, 4.6; N, 8.1. $C_{21}H_{15}ClN_2O$ requires C, 72.8; H, 4.3; N, 8.1%).

N-Phenyl-o-nitrobenzamide (60; R=Ph) (yield 98%), formed colourless needles m.p. 153-155° (from ethanol) (lit.,[138] 155°), $\nu_{max.}$ 3200, 1660, 1540 and 1355 $cm.^{-1}$

N-Benzyl-o-nitrobenzamide (60; R=$PhCH_2$) (yield 94%), formed colourless needles, m.p. 118-121° (from aqueous ethanol) (lit.,[139] 122°), $\nu_{max.}$ 3200, 1640, 1540 and 1360 $cm.^{-1}$

Preparation of α-(N-o-nitrobenzoyl)aminopropionitrile (56b; R=H).

α-Aminopropionitrile (2.3 g.) in dry benzene (30 ml.) was added to a solution of o-nitrobenzoyl chloride (3 g.) in dry benzene (20 ml.) and the mixture stirred with exclusion of moisture for 48 hrs. The benzene was then removed under reduced pressure, the resultant oil shaken with chloroform and water, and the chloroform layer separated, washed with saturated aqueous sodium bicarbonate, dried and evaporated. The oil obtained (4.4 g.)

yielded the amide (56b; R=H) (1.0 g., 28%), on standing overnight in ether/light petroleum. The amide crystallised as colourless needles, m.p. 103-110° (from ethanol), $\nu_{max.}$ 3225, 1640, 1540 and 1360 $cm.^{-1}$, n.m.r: τ=2.0-2.9 (multiplet, aromatic +NH, 5H); 5.15 (quartet, CH, 1H); 8.5 (doublet, CH_3, 3H). (Found: C, 55.0; H, 4.2; N, 19.1. $C_{10}H_9N_3O_3$ requires C, 54.8; H, 4.1; N, 19.2%). Concentration of the ethereal mother liquors yielded no further identifiable material.

Preparation of ∝-(N-o-nitrobenzoyl)aminophenylacetonitrile (56c; R=R^1=H). ∝-Aminophenylacetonitrile (20 g.) in dry benzene (120 ml.) was added dropwise at room temperature, to a solution of o-nitrobenzoyl chloride (14 g.) in dry benzene (150 ml.) and the mixture stirred with the exclusion of moisture for 48 hrs. The precipitate which formed was filtered off and washed with chloroform, leaving the amine hydrochloride (2.3 g.) m.p. 166-170° (lit,[140] 178°). The amide (5.6 g., 22%) was obtained by evaporation of the chloroform washings, and crystallised to yield colourless needles, m.p. 154-156° (from ethanol), $\nu_{max.}$ 3200, 1650, 1540 and 1360 $cm.^{-1}$, n.m.r: τ= 1.65-2.47 (multiplet, aromatic +NH, 10H); 3.95 (doublet, CH, 1H). (Found: C, 63.7; H, 4.2; N, 15.4; $C_{15}H_{11}N_3O_3$ requires C, 64.1; H, 3.9; N, 14.9%).

The benzene mother liquors, washed with dilute sulphuric acid, saturated aqueous sodium bicarbonate and water, then dried and concentrated under reduced pressure, afforded an oil which solidified in contact with ether and methanol to give an unidentified yellow solid which formed yellow needles (4.8 g.), m.p. 156-158° (from ethanol), $\nu_{max.}$ 3400 (broad, w), 1560 (sh., w) and 1540 $cm.^{-1}$ (Found: C, 71.4; H, 4.6; N, 11.7%).

Base Catalysed Reactions of Amides.

Unless otherwise stated, the amide cyclisation reactions were worked up according to the following general procedure.

After the reaction had proceeded for the required period of time, the solvent was removed under reduced pressure, the residue shaken with water and chloroform, and the layers separated.

Evaporation of the chloroform extract (extract A) gave any neutral or basic material formed in the reaction. The basic aqueous layer was then acidified (2N aqueous sulphuric acid) and extracted with chloroform, the aqueous part being retained. After being washed with saturated aqueous sodium bicarbonate, the chloroform layer (extract B) was evaporated, yielding any enolic material. Acidification of the sodium bicarbonate washings, followed by chloroform extraction (extract C) yielded acid material. The initial aqueous phase was then rebasified by careful addition of solid sodium bicarbonate, reacidified (Ph 6) with a few drops of glacial acetic acid, and extracted into chloroform (extract D). Evaporation of the solvent then yielded any amphoteric material.

1-Hydroxyquinazolinediones (62; R=Me, $PhCH_2$ or Ph). The amides (56a; R=Me, $PhCH_2$ or Ph) (0.01 mole), in dry ethanol (25 ml.) were treated in one portion with a solution of sodium (0.92 g.) dissolved in dry ethanol (25 ml.). An immediate reaction took place, the contents of the flask becoming deeply coloured. After being refluxed for 1 hr., the reaction mixture was concentrated under reduced pressure, and the residue treated with water and chloroform. Acidification of the aqueous layer afforded the crude 1-hydroxyquinazolinedione, which was purified by crystallisation.

2,4-Dioxo-1-hydroxy-3-methyl-1,2,3,4-tetrahydroquinazoline (62; R=Me) gave a violet colour with ferric chloride in ethanol, and crystallised as colourless needles (yield 91%), m.p. 238-240° (decomp.)(from methanol),(lit.,[48] 245°), $\nu_{max.}$ 3100 (w), 1700, 1670, 1630 and 1605 $cm.^{-1}$ (Found: C, 56.5; H, 4.6; N, 14.6. $C_9H_8N_2O_3$ requires C, 56.3; H, 4.2; N, 14.6%).

3-Benzyl-2,4-dioxo-1-hydroxy-1,2,3,4-tetrahydroquinazoline (62; R=$PhCH_2$) crystallised as colourless needles or prisms, (yield quantitative), m.p. 235-237° (decomp.)(from glacial acetic acid), $\nu_{max.}$ 3100 (w), 1700, 1640 and 1610 (sh) $cm.^{-1}$ (Found: C, 67.4; H, 4.7; N, 10.4. $C_{15}H_{12}N_2O_3$ requires C, 67.2; H, 4.5; N, 10.4%). It gave an olive green colour with ferric chloride in ethanol.

2,4-Dioxo-1-hydroxy-3-phenyl-1,2,3,4-tetrahydroquinazoline (62; R=Ph) crystallised as colourless needles (yield 73%), m.p. 177-180° (decomp.) (from methanol), $\nu_{max.}$ 3150 (w), 1700, 1650 and 1610 $cm.^{-1}$ (Found: C, 65.8; H, 4.1; N, 11.3; $C_{14}H_{10}N_2O_3$ requires C, 66.1; H, 4.0; N, 11.0%). It gave a deep violet colour with ferric chloride in ethanol.

1-Acetoxyquinazolinediones (62; R=Me, $PhCH_2$ or Ph, Ac for H). The N-hydroxyquinazolinediones (62; R=Me, $PhCH_2$ or Ph), (0.001 mole) were gently refluxed with acetic anhydride (0.5 g.) for 0.5 hr. Excess acetic anhydride was then removed under reduced pressure, and the residue triturated with ether or water, to yield the crude product, which was collected and dried.

1-Acetoxy-2,4-dioxo-3-methyl-1,2,3,4-tetrahydroquinazoline (62; R=Me, Ac for H) crystallised as colourless needles (yield 97%), m.p. 130-132° (from benzene/light petroleum), $\nu_{max.}$ 1790, 1720, 1680 and 1610 $cm.^{-1}$ (Found: C, 56.5; H, 4.6; N, 11.8. $C_{11}H_{10}N_2O_4$ requires C, 56.4; H, 4.3; N, 11.9%).

1-Acetoxy-3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (62; R=$PhCH_2$, Ac for H) (yield 99%) crystallised as colourless needles, m.p. 149-151° (from benzene/light petroleum), $\nu_{max.}$ 1825, 1730, 1690 and 1630 $cm.^{-1}$ (Found: C, 65.1; H, 4.4; N, 9.3. $C_{17}H_{14}N_2O_4$ requires C, 65.8; H, 4.6; N, 9.0%)

1-Acetoxy-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydroquinazoline (62; R=Ph, Ac for H) (yield 93%) crystallised as colourless needles, m.p. 201-204° (from ethanol), $\nu_{max.}$ 1800, 1720, 1660 and 1610 $cm.^{-1}$ (Found: C, 65.0; H, 4.0; N, 9.6. $C_{16}H_{12}N_2O_4$ requires C, 64.9; H, 4.1; N, 9.5%).

Quinazolinediones (62; R=Me, $PhCH_2$ or Ph, H for OH).

(a) By hydrogenolysis of the 1-acetoxyquinazolinediones.

The 1-acetoxy-compounds (62; R=Me, $PhCH_2$ or Ph, Ac for H) (0.06 g.) in ethanol (20 ml.) were hydrogenated at room temperature and pressure, over 10% palladium on charcoal (0.02 g.). After filtration, removal of the solvent yielded the corresponding 2,4-dioxo-3-substituted-1,2,3,4-tetrahydroquinazoline (yield: N-Me, quantitative; N-CH_2Ph, 58%; N-Ph, 78%).

(b) By dithionite reduction of the 1-hydroxyquinazolinediones.

The 1-hydroxyquinazolinediones (62; R=Me, $PhCH_2$ or Ph) (0.001 mole) were heated under reflux with an equal weight of sodium dithionite, in 70% v/v aqueous ethanol (10-20 ml.) for 30 minutes. A fresh portion of sodium dithionite was then added and refluxing continued for a further 30 minutes. After filtration to remove inorganic material, concentration under reduced pressure and dilution with water, gave the product.

2,4-Dioxo-3-methyl-1,2,3,4-tetrahydroquinazoline (62; R=Me, H for OH) crystallised as colourless needles (yield 77%) m.p. 237-239° (from methanol) $\nu_{max.}$ 1710, 1660, 1640 (sh) and 1620 (sh) $cm.^{-1}$

3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (62; R=$PhCH_2$, H for OH) crystallised as colourless needles (yield 83%), m.p. 226-229° (from methanol), $\nu_{max.}$ 1725, 1670 and 1610 (sh) $cm.^{-1}$

2,4-Dioxo-3-phenyl-1,2,3,4-tetrahydroquinazoline(62; R=Ph, H for OH) crystallised as colourless needles (yield 70%), m.p. 280-282° (from methanol), $\nu_{max.}$ 3150, 1730, 1650 and 1610 (sh) $cm.^{-1}$

The melting points, mixed melting points and i.r. spectra of the quinazolinediones (62; R=Me, $PhCH_2$ or Ph, H for OH) were those of authentic samples, prepared as described below.

Unambiguous synthesis of the 2,4-dioxo-3-substituted-1,2,3,4-tetrahydroquinazolines.

The substituted amides of anthranilic acid were readily prepared by methods adequately described in the literature.

o-Amino-N-methylbenzamide (133; R=Me) (yield 83%) crystallised as colourless needles, m.p. 80-82° (from benzene/light petroleum) (lit.,[141] 79-80°).

o-Amino-N-phenylbenzamide (133; R=Ph) (yield 95%) crystallised as colourless needles, m.p. 122-124° (from benzene) (lit.,[142] 125°).

o-Amino-N-benzylbenzamide (133; R=$PhCH_2$) (yield 50%) crystallised as colourless needles, m.p. 120-122° (from benzene) (lit.,[63] 123°).

2,4-Dioxo-3-substituted-1,2,3,4-tetrahydroquinazolines (62; R=Me, $PhCH_2$ or Ph, H for OH). The substituted anthranilamide (0.01 mole) and urea (0.01

mole) were ground together to give an intimate mixture which was heated for 1-1.5 hrs. at 200° (oil bath) until ammonia ceased to be liberated. The dark melt was then cooled and crystallised. The 3-Benzyl compound (62; R=$PhCH_2$, H for OH) was obtained in 52% yield, m.p. 227-229° (from methanol) (lit.,[62,143] 226-228°). The 3-Phenyl compound (62; R=Ph, H for OH) was obtained in 77% yield, m.p. 280-282° (from methanol) (lit.,[144] 280-282°). The 3-Methyl compound (62; R=Me, H for OH) was obtained in 34% yield, m.p. 233-235° (from methanol) (lit.,[145] 234°).

Reaction of N-Methyl-o-nitrobenzoylaminoacetonitrile (56a; R=Me) with 10% ethanolic potassium hydroxide, 10% aqueous potassium hydroxide or 10% aqueous sodium hydroxide in ethanol.

(a) The amide (56a; R=Me) (0.22 g.) was refluxed in a solution of potassium hydroxide (0.5 g.) in ethanol (4.5 ml.) for 10 minutes. The solid which separated was filtered off, and acidified (2N aqueous sulphuric acid), to yield 2,4-dioxo-1-hydroxy-3-methyl-1,2,3,4-tetrahydroquinazoline (62; R=Me,) (0.14 g.), m.p. 237-239° (from methanol). The filtrate was concentrated under reduced pressure, diluted with water, and acidified, to yield a further crop of the 1-hydroxy-compound (62; R=Me), m.p. 238-240° (from methanol), giving a total yield of 90%.

(b) The amide (56a; R=Me) (0.22 g.) was treated with 10% potassium hydroxide (5 ml.) and refluxed for 15 minutes. The clear solution, cooled and acidified, afforded the 1-hydroxyquinazoline (62; R=Me) (0.08 g., 38%), m.p. 238-240° (from methanol). The filtrate was extracted with chloroform. Evaporation of the dried extract yielded a red gum (0.09 g.) which could not be induced to crystallise. Acetylation of the red gum afforded no identifiable product.

(c) The amide (56a; R=Me) (0.22 g.), in ethanol (5 ml.) was treated with 10% aqueous sodium hydroxide (2.5 ml.) and refluxed for 30 minutes. The ethanol was removed under reduced pressure, and the residue treated with 2N aqueous sulphuric acid, yielding the N-hydroxyquinazolinedione (62; R=Me) (0.15 g., 80%), m.p. 238-240° (from methanol).

Reaction of N-Methyl-N-o-nitrobenzoylaminoacetonitrile (56a; R=Me) with potassium cyanide in aqueous ethanol.

The amide (56a; R=Me) (0.44 g., 0.002 mole) in ethanol (15 ml.) was treated with a solution of potassium cyanide (0.52 g., 0.008 mole) in water (0.5 ml.) and refluxed for 1 hr. The ethanol was then removed under reduced pressure and the residue treated with water and chloroform. Evaporation of the dried chloroform extract gave a light brown oil (0.24 g.) which could not be obtained crystalline. Acidification of the aqueous layer gave a solid which was taken into chloroform, washed with aqueous sodium bicarbonate, dried and freed from solvent yielding the N-hydroxyquinazolinedione (62; R=Me) (0.07 g.) m.p. 237-241° (from methanol). A further yield of this product (0.07 g.) was obtained by acidification of the bicarbonate washings and filtration of the resultant solid, m.p. 238-240° (from methanol).

Reaction of N-Benzyl-o-nitrobenzoylaminoacetonitrile (56a; R=$PhCH_2$) with ethanolic sodium ethoxide at room temperature.

The amide (56a; R=$PhCH_2$) (0.3 g., 0.001 mole), dissolved in dry ethanol (15 ml.) was treated slowly with ice cooling with a solution of sodium (0.09 g.) in ethanol (5 ml.) and the reaction mixture stirred for 0.5 hr. The ethanol was then removed under reduced pressure at room temperature and the residue treated with water. Acidification of the yellowish solution

with 2N aqueous sulphuric acid afforded the N-hydroxyquinazolinedione (62; R=$PhCH_2$) (0.25 g., 93%) m.p. 236-238° (from methanol), i.r. spectrum identical with that of the sample obtained above.

Reaction of ω-(N-o-nitrobenzoyl-N-phenyl)aminoacetophenone (56a; R=Ph, Bz for CN) with ethanolic sodium ethoxide.

ω-(N-o-nitrobenzoyl-N-phenyl)aminoacetophenone (2.5 g.), dissolved in hot ethanol (30 ml.) was treated with a solution of sodium (1.1 g.) dissolved in ethanol (50 ml.). The mixture became red immediately, and a precipitate formed. After refluxing for 1 hr. the solution was cooled, and the solid filtered off. Treatment of the solid with 2N aqueous sulphuric acid gave a white precipitate, which was collected and dissolved in saturated aqueous sodium bicarbonate solution. Acidification of the washed (chloroform) solution gave a white solid (0.69 g.) m.p. 118-120°, i.r. spectrum identical to that of authentic benzoic acid.

The filtrate was concentrated in vacuo and diluted with water. Acidification with 2N aqueous sulphuric acid yielded 2-phenylindazolone (64; R=Ph) (0.58 g.), m.p. 204-206° (from benzene), lit.,[146] 204°, $\nu_{max.}$ 1650 $cm.^{-1}$ (Found: C, 74.2; H, 5.1; N, 13.2 calculated for $C_{13}H_{10}N_2O$: C, 74.3; H, 4.8; N, 13.3%), which was further characterised as the acetyl derivative (64; R=Ph, Ac for H) m.p. 87-89° (from light petroleum) (lit.,[147] 91°), $\nu_{max.}$ 1695 $cm.^{-1}$

Reaction of Ethyl α-(N-o-nitrobenzoyl-N-phenyl)aminoacetate (56a; R=Ph, CO_2Et for CN) with sodium ethoxide.

The amide (56a; R=Ph, CO_2Et for CN) (0.5 g.), in absolute ethanol (5 ml.) was treated in one portion with a solution of sodium (0.22 g.), in absolute ethanol (5 ml.), and the mixture refluxed for one hour. The reaction mixture

was then worked up by the standard method. Extract (B) yielded 2-phenylindazolone (64; R=Ph) (0.15 g., 52%), as colourless needles, m.p. 203-206° (from benzene), mixed m.p. and i.r. spectrum identical with those of an authentic sample prepared below. Extract (C) gave a red oil (0.21 g.) which was not identified.

Base Catalysed Reactions of ∝-(N-o-nitrobenzoyl)aminopropionitrile (56b; R=H).

(a) The amide (56b; R=H) (0.002 mole, 0.44 g.) in absolute ethanol (30 ml.) was treated with a solution of sodium (0.18 g.), dissolved in absolute ethanol (10 ml.) and the mixture refluxed for 1 hr., then worked up as described above. Extract (A) gave an oil (0.07 g.) which was not identified. Extract (B) yielded an oil (0.11 g.) which solidified when rubbed with ether, giving starting material (0.05 g.), identified by its i.r. spectrum and m.p. 105-108°. Extract (D) gave 3,4-dihydro-2-methyl-4-oxoquinazoline-1-oxide (63; R=H, CH_3 for CN) (0.14 g.), as colourless platelets, m.p. 245-247° (decomp.) (from dimethylformamide), $\nu_{max.}$ 2600 (w), 2150 (w, broad), 1615 and 1600 $cm.^{-1}$ (Found: C, 61.4; H, 4.5; N, 16.6. $C_9H_8N_2O_2$ requires C,61.4; H, 4.5; N, 15.9%). The oxide (63; R=H, CH_3 for CN) gave a deep magenta colour with ethanolic ferric chloride, and warmed with acetic anhydride, it afforded 2-acetoxymethyl-3,4-dihydro-4-oxoquinazoline (72) as colourless needles, m.p. 192-196° (from aqueous methanol), $\nu_{max.}$ 1750 and 1680 $cm.^{-1}$, identical with those of an authentic sample.[148]

(b) The amide (56b; R=H) (0.002 mole, 0.44 g.) in ethanol (30 ml.) was refluxed for 1 hr. with 10% aqueous sodium hydroxide (3.2 ml.), then worked up by the general procedure described above. Extract (B) yielded starting material (0.02 g.), identified by m.p. and i.r. spectrum. Extract (C) gave

benzoic acid (0.01 g.), identical (m.p., mixed m.p. and i.r. spectrum)with an authentic sample. Extract (D) afforded a sticky solid (0.24 g.) which crystallised from methanol, yielding 3,4-dihydro-2-methyl-4-oxoquinazoline-1-oxide (63; R=H, CH_3 for CN) (0.14 g.), m.p. 245-247° (from dimethylformamide), i.r. spectrum identical with the sample obtained in (a) above.

Base Catalysed Reactions of ∝-(N-o-nitrobenzoyl)aminophenylacetonitrile (56c; $R=R^1=H$).

(a) The amide (56c; $R=R^1=H$) (0.002 mole, 0.56 g.) in absolute ethanol (25 ml.) was refluxed with a solution of sodium (0.008 mole, 0.18 g.) in absolute ethanol (25 ml.) for 1 hr., and the reaction mixture worked up in the usual way. Extract (A) gave an oily solid (0.12 g.), which crystallised as colourless needles, m.p. 174° (from ethanol), identical (mixed m.p. 174° and i.r. spectrum with an authentic sample of o-nitrobenzamide. Extract (B) yielded an oil (0.04 g.) which did not crystallise. Extract (C) afforded benzoic acid (0.14 g.) as colourless needles, m.p. 120-122° (from water), identical (mixed m.p. and i.r. spectrum) with an authentic sample. Extract (D) gave a further crop of o-nitrobenzamide (0.02 g.), m.p. and i.r. spectrum identical with those of the first crop.

(b) The amide (56c; $R=R^1=H$) (0.002 mole, 0.56 g.) in ethanol (40 ml.) was refluxed for 1 hr. with N aqueous sodium carbonate (8 ml.), then worked up as above. Extract (A) gave o-nitrobenzamide (0.08 g.), which crystallised as colourless needles, m.p. 173-175° (from ethanol) (lit.,[149] 176°), identical i.r. spectrum with that of an authentic sample. Extract (B) yielded an oil which was not identified. Extract (C) afforded benzoic acid (0.1 g.), identical i.r. spectrum with that of an authentic sample. Extract (D) gave an oil (0.09 g.) which was not identified.

Base Catalysed Reactions of ∝-(N-o-nitrobenzoyl-N-phenyl)aminopropionitrile (56b; R=Ph).

(a) The amide (56b; R=Ph) (0.002 mole, 0.59 g.) in dry ethanol (15 ml.) was treated with a solution of sodium (0.008 mole, 0.18 g.) in dry ethanol (10 ml.) and refluxed for 1 hr., then worked up as above. Extract (B) yielded 2-phenylindazolone (64; R=Ph) (0.32 g. 76%) which crystallised as colourless needles, m.p. 208–211° (from aqueous ethanol) identified with an authentic sample by mixed m.p. 211° and i.r. spectrum. Extracts (A), (C) and (D) contained negligible quantities of unidentified gums.

(b) The amide (56b; R=Ph) (0.001 mole, 0.3 g.), in ethanol (20 ml.) was refluxed with 10% sodium hydroxide (4 ml.) for 30 minutes, then worked up by the general procedure. Extract (B) gave 2-phenylindazolone (64; R=Ph) (0.14 g., 65%) m.p. 200–204° (from benzene) (lit.,[146] 204°), identical i.r. spectrum with that of an authentic sample prepared below. Extracts (A), (C) and (D) contained negligible quantities of unidentified gums.

(c) The amide (56b; R=Ph) (0.009 mole, 2.68 g.), in ethanol (130 ml.) was refluxed for 1 hr. with N aqueous sodium carbonate (70 ml.), then worked up by the general procedure described above. Extract (A) gave a reddish semi-solid (2.36 g.) which was chromatographed on alumina. Elution with benzene /25% ether gave starting material (0.86 g.), m.p. 128–132°, (identical i.r. spectrum). Further elution with benzene/50% ether gave a crude red solid which crystallised from glacial acetic acid to give 2,2'-di-(N-phenylcarbamoyl)azobenzene (65) (0.2 g.), m.p. and mixed m.p. 260–262°, identical i.r. spectrum with a sample synthesised below.

Evaporation of the crystallisation liquors yielded a further crop

(0.16 g.) of starting material, m.p. 128-132°. Further elution of the column with ether/25% chloroform yielded 2-phenylindazolone (64; R=Ph) (0.21 g.), as colourless needles, m.p. 204-205° (from benzene), identical (mixed m.p. and i.r. spectrum) with a sample synthesised as described later.

Extract (B) gave a gum (0.07 g.) which was not obtained solid and was not identified. Extract (C) also yielded a gum (0.16 g.) which could not be obtained crystalline, and was not identified.

2,2'-Di-(N-phenylcarbamoyl)azobenzene (65).

2-Nitrosobenzanilide (0.23 g.) and 2-aminobenzanilide (0.21 g.) in glacial acetic acid (15 ml.) were stirred at room temperature for two days. The solution darkened and an orange precipitate appeared. The solid (0.13 g.) was filtered off and crystallised from glacial acetic acid to give orange needles, m.p. 258-262°, $\nu_{max.}$ 3300 and 1640 $cm.^{-1}$, n.m.r: τ=0.36 (singlet, NH, 1H), 2.15-2.74 (multiplet, 9H) (in DMSO). (Found: C, 73.8; H, 5.0; N, 13.7. $C_{26}H_{20}N_4O_2$ requires C, 74.3; H, 4.8; N, 13.3%). Dilution of the mother-liquors with water gave a dark solid (0.17 g.). Thin-layer chromatography on silica gel, with benzene/25% ether elution showed three spots. Crystallisation from glacial acetic acid yielded a further crop (0.03 g.) of the azo-compound (65), m.p. 256-260°.

Base Catalysed Reactions of α-(N-Benzyl-o-nitrobenzoyl)aminopropionitrile (56b; R=$PhCH_2$).

(a) The amide (56b; R=$PhCH_2$) (0.002 mole, 0.62 g.) in absolute ethanol (15 ml.) was treated with a solution of sodium (0.008 mole, 0.18 g.) in absolute ethanol (7 ml.) and the mixture refluxed gently for 1 hr., then worked up as described above. Extract (A) gave a brown oil (0.31 g.). Thin-layer chromatography (elution with benzene/25% ether) showed four spots.

Chromatography on alumina failed to separate the mixture. Extract (B) yielded a gum (0.3 g.) which solidified when triturated with benzene, giving 2-benzylindazolone (64; R=$PhCH_2$) (0.2 g.), m.p. 140-150° (from ethanol/light petroleum). After elution with chloroform through a short column of alumina, it crystallised as colourless needles, m.p. 175-178° (from ethanol/light petroleum) (lit.,[70] 180°), i.r. spectrum identical with a synthetic sample, prepared below.

(b) The amide (56b; R=$PhCH_2$) (0.002 mole, 0.62 g.), in ethanol (50 ml.) was treated with N aqueous sodium carbonate (8 ml.), and the mixture refluxed for 1 hr. The reaction mixture was then worked up by the general procedure described above. Extract (A) yielded a light brown oil (0.45 g.) which was chromatographed on alumina. Elution with benzene/50% chloroform afforded initially starting material (0.09 g.) identified by i.r. spectrum and m.p. 90-92° (from methanol). Further elution with the same solvent mixture gave 2,2'-di-(N-benzylcarbamoyl)azobenzene (67) (0.22 g.), as yellow needles, m.p. 170-172° (from methanol), identical (mixed m.p. and i.r. spectrum) with a synthetic sample, prepared below. Extracts (B) and (C) afforded benzaldehyde 2-carboxyphenylhydrazone (66) (0.16 g.) as colourless platelets, m.p. 226-228° (from benzene) (lit.,[70] 227-228°) identical (mixed m.p. and i.r. spectrum with an authentic sample).

2,2'-Di-(N-benzylcarbamoyl)azobenzene (65; $PhCH_2$ for Ph).

N-Benzyl-o-nitrobenzamide (0.02 mole, 5.04 g.), in methanol (50 ml.), was refluxed with zinc dust (2.65 g.) and sodium hydroxide (0.081 mole, 3.25 g.) in water (75 ml.), for 13 hrs. The contents of the flask were then filtered hot, removing zinc residues, and the filtrate concentrated under reduced pressure. Dilution with cold water (100 ml.) and ice-cooling yielded a

precipitate (0.74 g.) which was filtered off and sucked dry. Crystallisation from aqueous ethanol gave the red azo-compound (0.14 g.) m.p. 195-200° as first crop, and upon cooling and further dilution with water, starting material (0.47 g.), m.p. 117-121°, (identical i.r. spectrum.) The azo-compound crystallised as orange needles, m.p. 207-209° (from ethanol), $\nu_{max.}$ 3200 and 1630 $cm.^{-1}$ (Found: C, 74.9; H, 5.3; N, 12.8. $C_{28}H_{24}N_4O_2$ requires C, 75.0; H, 5.4; N, 12.5%).

The aqueous mother-liquors were acidified with 2N aqueous sulphuric acid and extracted with chloroform. Evaporation of the dried extract gave a brown oil (3.64 g.) which crystallised from benzene. The crude product m.p. 155-160° was purified by passing its chloroform solution through a short column of alumina. Evaporation of the solvent yielded 2-benzylindazolone (64; R=$PhCH_2$) (2.0 g.), m.p. 176-179° (lit.,[70] 180°). A deep red band at the top of the column was removed by elution with methanol. Evaporation of the solvent gave a deep red oil (0.5 g.) which could not be obtained crystalline.

Synthesis of 2,2'-di-(N-benzylcarbamoyl)azoxybenzene (67).

2,2'-Di-(N-benzylcarbamoyl)azobenzene (0.1 g.), in glacial acetic acid (40 ml.) was treated dropwise with 30% hydrogen peroxide (8 ml.) over a period of 6 hrs. The red colour gradually faded, giving a pale yellow solution. Dilution with water (75 ml.) yielded the azoxy-compound (0.05 g.), which formed yellow needles, m.p. 170-172° (from ethanol), $\nu_{max.}$ 3200 and 1640 $cm.^{-1}$ (Found: C, 72.3; H, 5.4; N, 12.5. $C_{28}H_{24}N_4O_3$ requires C, 72.4; H, 5.2; N, 12.1%).

2-Phenylindazolone (64; R=Ph).

N-Phenyl-o-nitrobenzamide (0.02 mole, 4.76 g.), in methanol (50 ml.) was

treated with zinc dust (2.65 g.) and a solution of sodium hydroxide (3.25 g.) in water (7.5 ml) and refluxed for 13 hrs. The contents of the flask were then filtered hot, removing zinc residues, and the filtrate concentrated under reduced pressure, giving a brown oil. Dilution with water (100 ml.) and ice-cooling yielded a sticky precipitate (0.76 g.) which was collected. Crystallisation from ethanol gave starting material (0.6 g.), m.p. 148–153° i.r. spectrum identical with an authentic sample.

The aqueous filtrate was acidified (2N H_2SO_4) and extracted with chloroform. Evaporation of the dried extract yielded 2-phenylindazolone (64; R=Ph) (1.56 g.), m.p. 200–203° (from benzene) (lit.,[146] 204°).

The aqueous layer from the extraction was neutralised with sodium bicarbonate, reacidified with glacial acetic acid, and extracted again with chloroform. Evaporation of the dried extract yielded a gum (0.3 g.) which was not identified.

Base Catalysed Reactions of ∝-(N-methyl-N-o-nitrobenzoyl)aminopropionitrile

(a) The amide (0.47 g., 0.002 mole), in dry ethanol (25 ml.) was treated with a solution of sodium (0.18 g.) in ethanol (5 ml.), and left at room temperature for 1 hr. The reaction was then worked up in the usual fashion. Extract (A) yielded an oil (0.02 g.) which was not identified. Similarly, extracts (B) and (C) also yielded unidentifiable oils (0.15 g.) and (0.06 g.).

(b) The amide (56b; R=Me) (0.47 g., 0.002 mole) in ethanol (25 ml.) was refluxed for 1 hr. with N aqueous sodium carbonate (8 ml.), then worked up by the general procedure. Extracts (A), (B) and (C) afforded only negligible quantities of dark, unidentifiable gums.

Base Catalysed Reactions of α-(N-o-nitrobenzoyl-N-phenyl)aminophenylacetonitrile (56c; R=Ph, R^1=H).

(a) The amide (56c; R=Ph, R^1=H) (0.01 mole, 3.57 g.) in absolute ethanol (25 ml.) was treated with a solution of sodium (0.04 mole, 0.9 g.) in absolute ethanol (25 ml.), and the mixture heated under reflux for 30 minutes. The mixture was then worked up as described above. Extract (A) yielded a gum (2.57 g.) which gave a solid (0.53 g.), m.p. 170-189° in contact with methanol. The i.r. spectrum indicated this to be a mixture of 3-cyano-2,3-diphenylphthalimidine (73; R=Ph, R^1=H) and 2,3-diphenylphthalimidine (73; R=Ph, R^1=H, H for CN), the latter forming the greater part. Crystallisation from benzene or methanol did not effect a separation. Elution from a column of alumina with benzene/25% light petroleum gave a solid (0.2 g.) identified by its m.p. 193° and i.r. spectrum as 2,3-diphenylphthalimidine (73; R=Ph, R^1=H, H for CN).

The mother-liquors, freed of methanol, gave a gum, which left in contact with light petroleum for a few days, afforded a solid (0.2 g.). This crystallised as colourless needles, m.p. 200-209°, identified by its i.r. spectrum as slightly impure 3-phenylamino-3-phenylphthalide (74).

Extract (B) yielded a gum (0.88 g.) which gave a solid (0.72 g.) on standing in contact with benzene/light petroleum. Crystallised from methanol, the solid formed colourless needles, m.p. 216-218°, no depression in m.p. on admixture with an authentic sample of 3-N-phenylamino-3-phenylphthalide, its i.r. spectrum being identical.

Extract (C) yielded benzoic acid (0.16 g.), m.p. 115°, identified by comparison of its i.r. spectrum with that of an authentic sample.

(b) The amide (56c; R=Ph, R^1=H) (0.014 mole, 5 g.) in ethanol (280 ml.)

was refluxed with N aqueous sodium carbonate (56 ml.) for 1 hr., and worked up as above. Extract (A) gave a semi-solid (4.29 g.) which was purified by chromatography on alumina. Elution with benzene/25% light petroleum gave 3-cyano-2,3-diphenylphthalimidine (73; R=Ph, R^1=H) (1.7 g.) as colourless needles, m.p. 186-188° (from ethanol), $\nu_{max.}$ 1715 $cm.^{-1}$, n.m.r: only aromatic protons. (Found: C, 81.1; H, 4.5; N, 8.9. $C_{21}H_{14}N_2O$ requires C, 81.3; H, 4.5; N, 9.0%).

Further elution with benzene/ 10% chloroform yielded starting material (1.7 g.) identified by its m.p. 171-172°, and i.r. spectrum. Finally, elution with chloroform/10% methanol gave α-(N-o-nitrobenzoyl-N-phenyl)aminophenylacetamide (75) as colourless prisms, m.p. 226-228° (from ethanol), $\nu_{max.}$ 3375, 3150, 1700, 1635, 1530 and 1345 $cm.^{-1}$ (Found: C, 66.2; H, 4.6; N, 11.2. $C_{21}H_{17}N_3O_4$ requires C, 67.2; H, 4.5; N, 11.2%).

Extract (C) afforded azobenzene-2-carboxylic acid (76) (0.25 g.) as orange needles, m.p. 88-89° (from benzene/light petroleum), no depression in m.p. on admixture with an authentic sample, identical i.r. spectrum.

Base Catalysed Reactions of α-(N-benzyl-N-o-nitrobenzoyl)aminophenylacetonitrile (56c; R=$PhCH_2$, R^1=H).

(a) The amide (56c; R=$PhCH_2$, R^1=H) (0.002 mole, 0.74 g.) in absolute ethanol (40 ml.) was refluxed for ½ hr. with a solution of sodium (0.008 mole, 0.2 g.) in dry ethanol (10 ml.) and worked up as above. Extract (A) yielded a gum (0.57 g.) which was chromatographed on alumina. Elution with benzene gave 2-benzyl-3-cyano-3-phenylphthalimidine (73; R=$PhCH_2$, R^1=H) (0.01 g.), which crystallised as colourless needles, m.p. 115-118° (from 40-60° b.p. light petroleum), identical (mixed m.p. and i.r. spectrum) with that of a sample prepared below. Elution with benzene/25% ether gave

2-benzyl-3-phenylphthalimidine (73; R=$PhCH_2$, R^1=H, H for CN) (0.14 g.) which formed colourless needles, m.p. 118-120° (from benzene/light petroleum), identical (mixed m.p. and i.r. spectrum) with a sample synthesised as described below. Finally, elution of the column with ether/75% chloroform afforded 2-benzyl-3-carbamoyl-3-phenylphthalimidine (73; R=$PhCH_2$, R^1=H, $CONH_2$ for CN) (0.03 g.), as colourless needles, m.p. 200-202° (from aqueous ethanol), identified by mixed m.p. and i.r. spectrum with a sample synthesised below.

Extract (B) gave a gum (0.08 g.) which solidified on trituration with ether. This product was not identified.

Extract (C) yielded benzoic acid (0.06 g.) as colourless needles, m.p. 122° (from water), i.r. spectrum identical with that of an authentic sample.

(b) The amide (56c; R=$PhCH_2$, R^1=H) (0.002 mole, 0.74 g.), in ethanol (40 ml.) was refluxed with N aqueous sodium carbonate, (8 ml.) for 1 hour, then worked up by the general method. Extract (A) gave an oil (0.6 g.) which yielded 3-cyano-2-benzyl-3-phenylphthalimidine (73; R=$PhCH_2$, R^1=H) (0.32 g.) as colourless needles, m.p. 115-118° (from ethanol), $\nu_{max.}$ 1710 $cm.^{-1}$, n.m.r: τ =1.97-2.86 (multiplet, aromatic, 14H); 5.06 (doublet, J=16 Hz, CH, 1H); 5.72 (doublet, J=16 Hz, CH, 1H). (Found: C, 81.2; H, 5.0; N, 9.1. $C_{22}H_{16}N_2O$ requires C, 81.5; H, 4.9; N, 8.7%).

Extract (C) yielded an oily orange precipitate (0.1 g.). Sublimation of the crude product at 100° (water-bath) onto a "cold finger" in an evacuated flask, afforded benzoic acid (0.02 g.), m.p. 118-120°, i.r. spectrum identical with that of an authentic sample. The residue, benzaldehyde-2-carboxyphenylhydrazone (66) (0.05 g.), crystallised as colourless platelets, m.p. 228-230° (from benzene) (lit.,[70] 227-228°), and was identified with an

authentic sample by mixed m.p. and comparison of i.r. spectra.

3-Carbamoyl-2,3-diphenylphthalimidine (73; R=Ph, R^1=H, $CONH_2$ for CN). The cyanophthalimidine (73; R=Ph, R^1=H) (0.15 g.) was stirred at room temperature for 30 minutes with concentrated sulphuric acid (6 ml.). The solution was then poured into water and the product (0.1 g.) collected and crystallised. 3-Carbamoyl-2,3-diphenylphthalimidine (73; R=Ph, R^1=H, $CONH_2$ for CN) formed colourless platelets m.p. 245° (from ethanol), $\nu_{max.}$ 3350, 3175 and 1680 $cm.^{-1}$ (Found: C, 76.9; H, 4.9; N, 8.8. $C_{21}H_{16}N_2O_2$ requires C, 76.8; H, 4.9; N, 8.5%).

2-Benzyl-3-carbamoyl-3-phenylphthalimidine (73; R=$PhCH_2$, R^1=H, $CONH_2$ for CN). The cyanophthalimidine (73; R=$PhCH_2$, R^1=H) (0.2 g.) in ethanol (10 ml.) was refluxed for 6 hrs. with N aqueous sodium carbonate (4 ml.), then concentrated under reduced pressure and extracted with chloroform. Removal of the solvent from the dried chloroform extract left an oil, which crystallised on being rubbed with ethanol, to give 2-benzyl-3-carbamoyl-3-phenylphthalimidine (73; R=$PhCH_2$, R^1=H, $CONH_2$ for CN) (0.07 g.) as colourless needles, m.p. 200-202° (from aqueous ethanol), $\nu_{max.}$ 3250, 3100 and 1670 $cm.^{-1}$ (Found: C, 77.4; H, 5.2; N, 8.2. $C_{22}H_{18}N_2O_2$ requires C, 77.2; H, 5.3; N, 8.2%).

Evaporation of the original mother-liquors afforded an oil (0.12 g.) which was purified by chromatography on alumina. Benzene eluted starting material (0.02 g.), m.p. 113-115° (identical i.r. spectrum.) Further elution with benzene/25% ether gave 2-benzyl-3-phenylphthalimidine (73; R=$PhCH_2$, R^1=H, H for CN) (0.02 g.), m.p. and mixed m.p. 119-121°, i.r. spectrum identical with an authentic sample.[150] Finally, washing the column with chloroform gave a further crop (0.01 g.) of the amide, m.p. 196-198°.

Base Catalysed Reactions of α-(N-methyl-N-o-nitrobenzoyl)aminophenylaceto-nitrile (56c; R=Me, R^1=H).

(a) The amide (56c; R=Me, R^1=H) (0.003 mole, 1.2 g.) in absolute ethanol (30 ml.) was treated with a solution of sodium (0.012 mole, 0.28 g.) in absolute ethanol (16 ml.) and refluxed for 1 hr., then worked up in the usual fashion. Extract (A) yielded a semi-solid, which completely solidified (0.034 g.) when triturated with ether, and was identified as 3-carbamoyl-2-methyl-3-phenylphthalimidine (73; R=Me, R^1=H, $CONH_2$ for CN), m.p. 268-272°, i.r. spectrum identical with that of a sample prepared below. Removal of the ether left a gum which could not be made to crystallise and was not further characterised.

Extract (B) gave a brown gum, which yielded a semi-solid (0.07 g.) when triturated with ether. This also was not further characterised.

Extract (C) afforded benzoic acid (0.13 g.), m.p. 120-122° (from water) i.r. spectrum identical with that of an authentic sample.

(b) The amide (56c; R=Me, R^1=H) (0.02 mole, 5.9 g.) in ethanol (250 ml.) was refluxed for 2.5 hrs., with N aqueous sodium carbonate (80 ml.), then worked up in the usual way. Extract (A) gave an oil (3.4 g.) which, when triturated with ethanol, yielded 3-carbamoyl-2-methyl-3-phenylphthalimidine (73; R=Me, R^1=H, $CONH_2$ for CN) (0.12 g.) m.p. 295-297° (from glacial acetic acid), i.r. spectrum identical with that of a sample prepared below. The ethanol mother-liquors were evaporated and the residual oil triturated with ether, to yield 3-cyano-2-methyl-3-phenylphthalimidine (73; R=Me, R^1=H) as colourless platelets, m.p. 101-103° (from aqueous ethanol), $\nu_{max.}$ 1700 $cm.^{-1}$, n.m.r: τ=1.97-2.73 (multiplet, aromatic, 9H); 6.99 (singlet, CH_3, 3H). (Found: C,77.4; H, 4.9; N, 11.3. $C_{16}H_{12}N_2O$ requires C, 77.3; H, 4.8; N, 11.3%).

The residue (1.2 g.) from the dried ethereal filtrate was chromatographed on alumina. Elution with benzene/50% ether, yielded a further crop (0.23 g.) of the cyanophthalimidine (73; R=Me, R^1=H), identified by m.p. 101-103° and i.r. spectrum with the first crop. Elution with chloroform yielded a red oil (0.25 g.), which could not be made to crystallise and was not further characterised.

Extract (C) yielded an impure red solid (1.3 g.) which was leached several times with light petroleum, leaving an insoluble red gum (0.1 g.). Evaporation of the petroleum extract yielded a white solid (1.2 g.). Sublimation on to a "cold-finger" under reduced pressure, at 100° removed benzoic acid (0.55 g.), m.p. 118-120°, i.r. spectrum identical with an authentic sample. The residue (0.51 g.), m.p. 136-140°, $\nu_{max.}$ 2600 (sh), 2160 and 1690 $cm.^{-1}$, n.m.r: τ=1.06 (broad singlet, acidic H, 1H); 1.87-2.85 (multiplet, 4H), was identified as o-azidobenzoic acid m.p. 136-140° (lit.,[151] 145°) by mixed m.p. 138-141° and comparison of its i.r. spectrum with that of an authentic sample.

3-Carbamoyl-2-methyl-3-phenylphthalimidine (73; R=Me, R^1=H, $CONH_2$ for CN)
The cyanophthalimidine (73; R=Me, R^1=H) (0.2 g.) in ethanol (10 ml.) was refluxed with N aqueous sodium carbonate (4 ml.) for 2.5 hrs. After the ethanol had been removed under reduced pressure, water and chloroform were added, and insoluble 3-carbamoyl-2-methyl-3-phenylphthalimidine (73; R=Me, R^1=H, $CONH_2$ for CN) (0.15 g.), filtered off. It was crystallised as colourless needles, m.p. 295-297° (from glacial acetic acid), $\nu_{max.}$ 3275, 3100 and 1680 $cm.^{-1}$ (Found: C, 72.0; H, 5.4; N, 10.4. $C_{16}H_{14}N_2O_2$ requires C, 72.2; H, 5.3; N, 10.5%). Evaporation of the dried chloroform extract followed by benzene washing of the solid thus obtained, yielded a further

crop (0.04 g.) of the amide (73; R=Me, R^1=H, $CONH_2$ for CN), m.p. 285-287°.

2,3-disubstituted-phthalimidines

3-Phenylphthalide (77), prepared (yield 91%) by the method of Pernot and Willemart,[152] was obtained as colourless needles, m.p. 111-114° (lit.,[152] 115°).

General Procedure

3-Phenylphthalide (0.005 mole, 1.05 g.), the amine (0.022 mole) and the amine hydrochloride (0.011 mole) were heated in a stream of dry nitrogen at approximately 190° for 7 hrs., then cooled, and poured into 2N HCl (25 ml.) The crude product which separated was collected and purified to give the phthalimidines, (73; R=Ph or $PhCH_2$, R^1=H, H for CN).

2,3-Diphenylphthalimidine (73; R=Ph, R^1=H, H for CN).

The crude product was washed with benzene and crystallised to give colourless needles (0.4 g., yield 30%), m.p. 192-195° (lit.,[153] 195°) (from ethanol), $\nu_{max.}$ 1680 $cm.^{-1}$, n.m.r: τ=1.98-2.87 (multiplet, aromatic, 14H); 3.93 (singlet CH, 1H).

2-benzyl-3-phenylphthalimidine (73; R=$PhCH_2$, R^1=H, H for CN).

The crude product was shaken with water and chloroform, and the layers separated. Concentration of the dried chloroform extract afforded the phthalimidine (73; R=$PhCH_2$, R^1=H, H for CN), (1.31 g., Yield 89%), which crystallised as colourless needles, m.p. 119-123° (lit.,[150] 123-124°), $\nu_{max.}$ 1690 $cm.^{-1}$, n.m.r: τ=2.0-3.0 (multiplet, aromatic, 14H); 4.64 (doublet, J=15 Hz, CH, 1H); 4.79 (singlet, CH, 1H); 6.28 (doublet, J=15 Hz, CH, 1H).

Reaction of the Cyanophthalimidines (73; R=Ph, $PhCH_2$, or Me, R^1=H) with Lithium Aluminium Hydride.

The cyanophthalimidine (0.3 g.), in dry ether (70 ml.) was added in one portion to a stirred suspension of lithium aluminium hydride (0.15 g.) in dry ether (15 ml.). After 5 minutes, excess of reagent was destroyed by adding water (8 ml.), followed by 20% potassium hydroxide (10 ml.). The organic layer, dried and evaporated, afforded the crude product as an oil, which was purified as described below.

2,3-Diphenylphthalimidine (73; R=Ph, R^1=H, H for CN) solidified when triturated with ethanol, m.p. 126-135°. Chromatography on silica gel, followed by crystallisation from ethanol gave the pure product as colourless needles (0.14 g.) m.p. 196-198°, i.r. spectrum identical with that of a synthetic sample prepared above.

2-Benzyl-3-phenylphthalimidine (73; R=$PhCH_2$, R^1=H, H for CN) solidified when triturated with ether, forming colourless needles (0.16 g.) m.p. 122-124° (from benzene/light petroleum) i.r. spectrum identical with that of a sample prepared above.

2-Methyl-3-phenylphthalimidine (73; R=Me, R^1=H, H for CN) was purified by chromatography on alumina using ether to elute the column. It formed colourless needles (0.1 g.) m.p. 106-107° (from ethanol/light petroleum), i.r. spectrum identical with that of a sample prepared as described above.

2,3-Disubstituted-3-phenylphthalimidines, by Hydrolysis of the Corresponding 3-Cyano or 3-Carbamoyl Compounds.

2-Methyl-3-phenylphthalimidine (73; R=Me, R^1=H, H for CN).

(a) A mixture of the cyanophthalimidine (73; R=Me, R^1=H) (0.2 g.) and

potassium hydroxide (0.7 g.) in trigol (7.0 ml.) was refluxed gently for 7 minutes. The cooled solution was then diluted with water, to give 2-methyl-3-phenylphthalimidine (73; R=Me, R^1=H, H for CN), as colourless needles (0.1 g.), m.p. 106-107° (lit.,[154] 105°) (from ethanol/light petroleum), $\nu_{max.}$ 1680 $cm.^{-1}$ (Found:C, 81.2; H, 6.0; N, 5.9. Calculated for $C_{15}H_{13}NO$: C, 80.8; H, 5.8; N, 6.3%).

The mother-liquors were acidified with 2N aqueous sulphuric acid, and extracted with chloroform. Evaporation of the dried extract gave an oil (0.1 g.), which solidified in contact with light petroleum, to yield a further crop of 2-methyl-3-phenylphthalimidine (0.05 g.)

(b) The amide (73; R=Me, R^1=H, $CONH_2$ for CN) (0.01 g.) was refluxed for 2.5 hrs. with 20% potassium hydroxide (3 ml.) then cooled, diluted with water, and extracted into chloroform. Evaporation of the dried chloroform extract gave a gum (0.007 g.), which slowly crystallised in contact with ether/light petroleum, to yield 2-methyl-3-phenylphthalimidine (73; R=Me, R^1=H, H for CN) (0.004 g.), m.p. 106-107°, i.r. spectrum identical with that of a sample prepared above.

2-Benzyl-3-phenylphthalimidine (73; R=$PhCH_2$, R^1=H, H for CN).

(a) The cyanophthalimidine (73; R=$PhCH_2$, R^1=H) (0.2 g.) was refluxed gently with potassium hydroxide (0.18 g.) in trigol (4 ml.), for 7 minutes. Dilution of the cooled solution with water gave impure 2-benzyl-3-phenylphthalimidine (73; R=$PhCH_2$, R^1=H, H for CN) which was purified by chromatography on alumina, eluting with benzene 50% ether. The phthalimidine crystallised as colourless needles (0.08 g.), m.p. 118-120° (from benzene /light petroleum). It was identified (mixed m.p. 118-120° and i.r. spect-

rum) with the sample prepared above.

(b) The amide (73; R=$PhCH_2$, R^1=H, $CONH_2$ for CN) (0.01 g.) was refluxed in 20% aqueous potassium hydroxide (3 ml.) for 2.5 hrs. The cooled solution was diluted with water, and extracted with chloroform. Evaporation of the dried chloroform extract left an oil, which slowly solidified on standing in contact with ethanol/light petroleum, to give 2-benzyl-3-phenylphthalimidine (73; R=$PhCH_2$, R^1=H, H for CN) (0.005 g.), m.p. 119-121°, i.r. spectrum identical with that of a sample synthesised as described above.

2,3-Diphenylphthalimidine (73; R=Ph, R^1=H, H for CN).

(a) The amide (73; R=Ph, R^1=H, $CONH_2$ for CN) (0.1 g.) was refluxed with 20% potassium hydroxide (8 ml.) for 2.5 hrs., cooled, and the precipitated solid collected. The product (0.07 g.) formed colourless needles, m.p. 190° (from aqueous ethanol), identical (mixed m.p. and i.r. spectrum) with an authentic sample prepared above.

(b) The cyanophthalimidine (73; R=Ph, R^1=H) (1.5 g.) and potassium hydroxide (0.6 g.) were heated in trigol (10 ml.) to just below reflux temperature, for 15 minutes, then cooled and diluted with water giving 2,3-diphenylphthalimidine (73; R=Ph, R^1=H, H for CN) as fine colourless needles (1.1 g.), m.p. 197-199° (from ethanol), identical (mixed m.p. and i.r. spectrum) with a synthetic sample, prepared above. Acidification of the aqueous layer yielded 3-N-phenylamino-3-phenylphthalide (74), as colourless needles (0.4 g.), m.p. 215-216° (from methanol) (lit.,[155] 221°), $\nu_{max.}$ 3350 and 1730 $cm.^{-1}$, identical (mixed m.p. 214-218° and i.r. spectrum) with a synthetic sample.

3-Phenylphthalide (77).

3-N-Phenylamino-3-phenylphthalide (74) (0.1 g.) and potassium hydroxide (0.06 g.) were refluxed in trigol (1 ml.) for one hour. Dilution of the

reaction mixture with water gave an oil, which solidified upon standing. Crystallisation from aqueous ethanol gave 3-phenyl-thalide (77), as a colourless solid (0.05 g.), m.p. 111-114° (lit.,[152] 115°), i.r. spectrum identical with that of an authentic sample.

(a) o-Benzoylbenzoic acid (1.5 g.) was refluxed gently for 1.25 hrs. in trigol(10 ml.) with potassium hydroxide (1.0 g.). The cooled solution was then diluted with water, acidified (2N H_2SO_4), and extracted with chloroform. Evaporation of the washed (saturated sodium hydrogen carbonate) organic extract gave 3-phenylphthalide as colourless needles (0.5 g.), m.p. 112-114° (from ethanol) (lit.,[152] 115°), i.r. spectrum identical with that of an authentic sample. The aqueous bicarbonate wash was then acidified (2N H_2SO_4) and extracted with chloroform. Evaporation of the dried extract yielded starting material (0.8 g.) as colourless platelets, m.p. 88-89° (from aqueous ethanol), identical i.r. spectrum.

In a similar experiment, o-benzoylbenzoic acid (1.5 g.) was refluxed gently for 5 minutes with potassium hydroxide (10 g.) in trigol (10 ml.), and worked up as before, giving 3-phenylphthalide as colourless needles (1.1 g.) m.p. 111-113° (from ethanol), i.r. spectrum identical with that of an authentic sample. The acidified bicarbonate washings afforded benzoic acid (0.35 g.) as colourless platelets, m.p. 118-120° (from water), i.r. spectrum identical with an authentic sample.

Azobenzene-2-carboxylic acid (76).

o-Nitrobenzylideneaniline (134) was prepared by the method of Knoevenagel,[156] as colourless needles (yield 73%) m.p. 62-66° (from aqueous ethanol) (lit.,[156] 69°).

o-Nitrosobenzanilide (68; Ph for $PhCH_2$).

o-Nitrobenzylideneaniline (9.9 g.), dissolved in dry benzene (200 ml.) was irradiated under nitrogen for 18 hrs, using a quartz jacketed Hanovia medium pressure ultraviolet lamp. The insoluble solid was collected, combined with material recovered by concentrating the benzene filtrate, washed with benzene and dried, to give the nitroso-compound (68; Ph for $PhCH_2$) (5.4 g.), m.p. 160° (lit.,[14] 171°), $\nu_{max.}$ 3225 and 1660 $cm.^{-1}$, which was used without further purification. Working up the benzene mother liquors afforded starting material (3.6 g.), m.p. 58-64°.

Reaction of o-Nitrosobenzanilide with Aqueous Ethanolic Sodium Carbonate.

o-Nitrosobenzanilide (0.12 g.), in ethanol (10 ml.) was refluxed for 1 hr., or stirred for 12 hrs. with N aqueous sodium carbonate (2 ml.). The clear solution was then acidified with 2N sulphuric acid and extracted with chloroform. The dried chloroform extract was then evaporated, yielding azobenzene-2-carboxylic acid (76) (0.09 g.) as orange needles, m.p. 87-91° (from aqueous ethanol), i.r. spectrum identical with that of an authentic sample, prepared below.

o-Nitrosobenzoic acid was prepared in 62% yield by the method of Heller.[157] It darkened at 180°, decomposing with frothing at 202°.

Azobenzene-2-carboxylic acid (76). A solution of aniline (1.9 g.) in glacial acetic acid (8 ml.) was cooled and treated with o-nitrosobenzoic acid (1.5 g.), and the mixture stirred at room temperature for 2 days. The reaction mixture was then poured into water (170 ml.) and extracted with ether (200 ml.). The ethereal layer was then washed with dilute sulphuric acid (200 ml.), water (50 ml.) and finally with saturated aqueous

sodium bicarbonate (100 ml.). The bicarbonate extract was acidified, extracted with ether, and the dried ether extract evaporated, to yield a dark gum which solidified on cooling. Leached with hot light petroleum, this gum afforded the azo-acid (76) which crystallised from the petrol extract on cooling (1.2 g.), m.p. 87-91° (from ethanol) (lit.,[158] 92°), $\nu_{max.}$ 2100, 3100 and 1730 $cm.^{-1}$

Reaction of α-(n-m-nitrobenzoyl-N-phenyl)aminophenylacetonitrile (59c; R=Ph, X=H) with Aqueous Ethanolic Sodium Carbonate.

The amide (59c; R=Ph, X=H) (0.01 mole, 3.6 g.), dissolved in ethanol (300 ml.) was stirred while N aqueous sodium carbonate (39 ml.) was added dropwise at room pemperature After 1 hr. the reaction mixture was adjusted to Ph 6 by the addition of a few drops of glacial acetic acid, and the yellow precipitate (1.1 g.) filtered off. Thin-layer chromatography on silica showed this solid to be a mixture of at least three compounds. Column chromatography failed to effect a separation of the mixture. The mother-liquors were concentrated under reduced pressure giving an orange solid which was treated with water and collected (2.55 g.). Thin-layer chromatography on silica showed the solid to be a mixture of at least three components. The mixture was chromatographed on alumina. Elution with benzene/10% ether gave 3-cyano-2,3-diphenyl-6-nitrophthalimidine (73; R=Ph, $R^1=NO_2$) (1.1 g.), which crystallised as colourless needles m.p. 224-225° (from glacial acetic acid), i.r. spectrum identical with that of a sample prepared below. Further elution with benzene/20% ether yielded 3-cyano-2,3-diphenyl-4-nitrophthalimidine (136) (0.07 g.), as colourless needles, m.p. 212-214° (from ethanol), $\nu_{max.}$ 1710, 1545 and 1350 $cm.^{-1}$ (Found: C, 71.3; H, 3.8; N, 11.7. $C_{21}H_{13}N_3O_3$ requires C, 71.0; H, 3.7; N, 11.8%).

Further elution with benzene/ether and then chloroform afforded solid fractions (total 1.15 g.), thin-layer chromatography of which indicated the presence of at least three compounds. Column chromatography failed to separate the mixture into its components.

Reaction of ∝-(N-2-chloro-5-nitrobenzoyl-N-phenyl)aminophenylacetonitrile (57c; R=Ph, X=Cl, Y=NO_2) with Aqueous Ethanolic Sodium Carbonate.

The amide (57c; R=Ph, X=Cl, Y=NO_2) (0.001 mole, 0.39 g.) in hot methanol (60 ml.) was treated with N aqueous sodium carbonate (4 ml.). An immediate deep red colour was produced which was rapidly discharged. After refluxing the solution for 30 minutes, the ethanol was removed under reduced pressure and the residue treated with water to give the solid product which was dried and crystallised. 3-Cyano-2,3-diphenyl-6-nitrophthalimidine (73; R=Ph, R^1=NO_2) formed colourless needles, m.p. 224-225° (from glacial acetic acid), $\nu_{max.}$ 1710, 1540 and 1360 $cm.^{-1}$ (Found: C, 70.8; H, 3.7; N, 11.9. $C_{21}H_{13}N_3O_3$ requires C, 71.0; H, 3.7; N, 11.8%).

Reaction of ∝-(N-3,5-Dinitrobenzoyl-N-phenyl)aminophenylacetonitrile (59c; R=Ph, X=NO_2) with Aqueous Ethanolic Sodium Carbonate.

The amide (0.001 mole, 0.4 g.) dissolved in methanol (60 ml.), was treated dropwise, with stirring, with N aqueous sodium carbonate (4 ml.). The reaction was stopped after 1.5 hrs. by neutralising (Ph 6) the reaction mixture with a few drops of glacial acetic acid, and the solvent removed under reduced pressure. The residue was then shaken with water and chloroform and the layers separated. Evaporation of the dried chloroform layer afforded a reddish-brown gum (0.4 g.) which was leached with benzene leaving an insoluble residue, (0.1 g.). The benzene extract was chromatographed on

alumina yielding on elution with benzene/50% ether, 3-cyano-4,6-dinitro-2,3-diphenylphthalimidine (137) (0.08 g.), which crystallised as colourless prisms, m.p. 226-228° (from ethanol), $\nu_{max.}$ 1720 $cm.^{-1}$ (Found: C, 63.2; H, 3.2; N, 14.0. $C_{21}H_{12}N_4O_5$ requires C, 63.0; H, 3.0; N, 14.0%). The aqueous layer upon acidification, gave an oil (0.08 g.) which yielded an unidentified yellow solid (0.03 g.) when triturated with ether.

Reaction of α-(N-5-Methyl-2-nitrobenzoyl-N-phenyl)aminophenylacetonitrile 56c; R=Ph, R^1=Me) with Ethanolic Sodium Ethoxide.

The amide (56c; R=Ph, R^1=Me) (0.001 mole, 0.37 g.) in absolute ethanol (50 ml.) was refluxed for 1 hr. with a solution of sodium (0.09 g.) dissolved in absolute ethanol (10 ml.) and the reaction mixture worked up as described in the general procedure above.

Chloroform extract (A) gave an oil (0.29 g.) which was purified by chromatography on alumina. Elution with benzene yielded 3-cyano-2,3-diphenyl-6-methylphthalimidine (73; R=Ph, R^1=Me) (0.09 g.) as colourless needles, m.p. 149-151° (from ethanol), $\nu_{max.}$ 1710 $cm.^{-1}$ (Found: C, 81.8; H, 4.9; N, 8.7. $C_{22}H_{16}N_2O$ requires C, 81.5; H, 4.9; N, 8.6%).

Extract (B) yielded a gum (0.05 g.) which could not be obtained crystalline and was not identified.

Chloroform extract (C) gave benzoic acid (0.02 g.), m.p. 115-118°, i.r. spectrum identical with an authentic sample.

Treatment of α-(N-5-methyl-2-nitrobenzoyl-N-phenyl)aminophenylacetonitrile (56c; R=Ph, R^1=Me), α-(N-2-chlorobenzoyl-N-phenyl)aminophenylacetonitrile (57c; R=Ph, X=Cl, Y=H), α-(N-2-methoxybenzoyl-N-phenyl)aminophenylacetonitrile (57c; R=Ph, X=OMe, Y=H), α-(N-2-chloro-5-nitrobenzoyl-N-phenyl)aminoacetonitrile (58a; R=Ph) and α-(N-2-chloro-5-nitrobenzoyl-N-

phenyl)aminopropionitrile (58b; R=Ph) with Aqueous Ethanolic Sodium Carbonate.

The amides (56c; R=Ph, R=Me), (57c; R=Ph, X=Cl, Y=H), (57c; R=Ph, X=OMe, Y=H), (58a; R=Ph) and (58b; R=Ph) were refluxed in ethanol with N aqueous sodium carbonate, as described, and worked up by the general procedure. They were recovered unchanged in yields of 97, 87, 98, 86 and 52% respectively.

Reactions of Substituted o-Nitrophenylethylene Oxides With Halogen Acids.

Preparation of the Epoxides.

Trans-1-Benzoyl-2-(o-nitrophenyl)ethylene oxide, (94; R^1=Bz, R^2=H) prepared by the method of Cromwell and Setterquist,[104] was obtained in 83% yield, as colourless needles, m.p. 115-118° (from ethanol), (lit.,[104] 111-113°) n.m.r: τ=2.58 (multiplet, aromatic, 9H); 5.35 (doublet, J=3 Hz, CH, 1H); 5.77 (doublet, J=3 Hz, CH, 1H).

Cis 1-Benzoyl-2-(o-nitrophenyl)ethylene oxide (94; R^1=H, R^2=Bz) was prepared from the trans epoxide (94; R^1=Bz, R^2=H), by the method of Cromwell and Setterquist. It was obtained as colourless needles (yield 70%) m.p. 174-176° (from ethanol) (lit.,[104] 174-176°).

1-Acetyl-2-(o-nitrophenyl)ethylene oxide (94; R^1=Ac, R^2=H). A mixture of o-nitrobenzaldehyde (15.1 g., 0.1 mole), chloroacetone (9.25 g., 0.1 mole), and anhydrous potassium carbonate (7.2 g.) in dry methanol (150 ml.) was stirred for 1.5 hrs. at room temperature. In the course of stirring, the colour changed from pale yellow to deep brown. The methanol was removed under reduced pressure and the residue treated with water to give a red oil, which was extracted into ether. The ether extract was washed with water and then with saturated aqueous sodium bisulphite solution (75 ml.). The precipitated bisulphite compound was collected and combined with material obtained by washing the ether layer with a further portion (30 ml.) of sodium bisulphite solution. The aqueous layer, shaken with chloroform and excess sodium bicarbonate solution, and the chloroform layer dried and evaporated, yielded a brown oil (1.5 g.) which was not obtained crystalline. The solid bisulphite addition compound, shaken with chloroform and excess saturated aqueous sodium bicarbonate solution, and the chloroform layer

dried and evaporated, gave an oil which afforded the solid product on crystallisation. The epoxide (11.9 g., 57%) formed colourless needles, m.p. 59-61° (from light petroleum), $\nu_{max.}$ 1700, 1540 and 1350 $cm.^{-1}$, n.m.r: τ=1.80-2.7 (multiplet, aromatic 4H); 5.4 (doublet, J=2 Hz, CH, 1H); 6.58 (doublet, J=2 Hz, CH 1H); 7.74 (singlet, CH_3, 3H). (Found: C, 57.4; H, 4.5; N, 7.1. $C_{10}H_9NO_4$ requires C, 57.0; H, 4.4; N, 6.8%).

2-Nitrobenzylideneacetylacetone (88; R^1=R^2=Ac) prepared by the method of Loudon and Wellings,[99] was obtained as colourless needles (yield 54%), m.p. 70-75° (from ethanol) (lit.,[99] 75°).

1,1-Diacetyl-2-(o-nitrophenyl)ethylene oxide (94; R^1=R^2=Ac). 2-nitrobenzylideneacetylacetone (0.004 mole, 0.93 g.) dissolved in methanol (20 ml.) was treated with potassium bicarbonate (0.51 g.) and 30% H_2O_2 (0.6 ml.) and the mixture stirred at room temperature for 12 hrs. The solution was then cooled, diluted with water (30 ml.) and shaken with two portions (30 ml.) of chloroform. The combined chloroform extracts were dried and evaporated giving an oil (0.8 g.) which crystallised with difficulty from ethanol/light petroleum, after being cooled in liquid nitrogen. The epoxide crystallised as colourless needles (0.16 g., yield 16%) m.p. 103-105° (from ethanol) $\nu_{max.}$ 1705, 1535, and 1350 $cm.^{-1}$ (Found: C, 57.9; H, 4.5; N, 5.8. $C_{12}H_{11}NO_5$ requires C, 57.8; H, 4.4; N, 5.6%).

o-Nitrobenzylidenebenzoylacetone (88; R^1=Bz, R^2=Ac). A solution of o-nitrobenzaldehyde (0.02 mole, 3.02 g.) and benzoylacetone (0.02 mole, 3.24 g.) in dry ether (100 ml.) was saturated with hydrogen chloride and the mixture left stoppered at room temperature for 24 hrs. Removal of the ether under reduced pressure afforded an oil, which was dissolved in chloroform and

washed with saturated aqueous sodium carbonate. Evaporation of the dried chloroform layer yielded an oil, which afforded the crude product (2.3 g.) in treatment with ethanol followed by ice cooling. A second crop (0.4 g.) was obtained by concentrating the ethanol mother liquors, followed by dilution with light petroleum and ice cooling. The benzylidene derivative was crystallised from ethanol (yield 2.3 g., 43%), m.p. 68-71° (lit.,[159] 77°). Acidification of the sodium carbonate wash yielded the N-oxide (87; R=Ph) (0.15 g.) m.p. 252-254° (from aqueous ethanol) (lit.,[159] 254°).

1-Acetyl-1-benzoyl-2-(o-nitrophenyl)ethylene oxide (94; R^1=Bz, R^2=Ac). o-Nitrobenzylidenebenzoylacetone (0.9 g.) in methanol, was treated with potassium bicarbonate (0.4 g.) and 30% hydrogen peroxide (0.5 ml.), and the suspension stirred for 6 hrs. at room temperature. The reaction mixture was then diluted with water (40 ml.) and the crude product (0.61 g.) collected and crystallised. The epoxide (94; R^1=Bz, R^2=Ac) formed colourless needles (0.45 g., 47%) m.p. 134-135° (from ethanol), $\nu_{max.}$ 1705, 1680, 1535 and 1355 $cm.^{-1}$, n.m.r: τ=1.73-2.70 (multiplet, aromatic, 9H); 4.88 (singlet, CH, 1H); 7.58(singlet, CH_3, 3H). (Found: C, 65.7; H, 4.4; N, 5.1. $C_{17}H_{13}NO_5$ requires C, 65.6; H, 4.2; N, 4.5%). In another preparation, using the same proportions of reagents, but with stirring at room temperature for 18 hrs., the yield of the epoxide (94; R^1=Bz, R^2=Ac) was found to drop to 32%.

o-Nitrobenzylidenedesoxybenzoin (88; R^1=Bz, R^2=Ph). A solution of o-nitrobenzaldehyde (3.02 g.) and desoxybenzoin (3.92 g.) in ether (100 ml.) was saturated with hydrogen chloride then left stoppered at room temperature for 24 hrs. The solvent was then removed, under reduced pressure, yielding an oil which solidified when triturated with light petroleum. The solid (2.7 g.) was collected and combined with a second crop (0.3 g.), obtained

from the concentrated mother liquors. The crude product crystallised as yellowish needles, m.p. 110-115° (from ethanol) (lit.,[159] 116-118°). The oil obtained by evaporating the petrol mother liquors was taken up in ether and shaken with saturated aqueous sodium bisulphite. The bisulphite addition compound was filtered off, combined with the aqueous layer, and shaken with sodium bicarbonate/sodium hydroxide and chloroform. Evaporation of the dried chloroform extract afforded o-nitrobenzaldehyde (1.48 g.), m.p. 40°, i.r. spectrum identical with an authentic sample. The ethereal layer was dried and evaporated, yielding a brown oil (1.7 g.), i.r. spectrum identical with an authentic sample of desoxybenzoin.

Attempted Epoxidation of o-Nitrobenzylidenedesoxybenzoin (88; R^1=Bz, R^2=H). o-Nitrobenzylidenedesoxybenzoin (0.98 g.), in methanol (25 ml.) was treated with potassium bicarbonate (0.35 g). and 30% hydrogen peroxide (0.41 ml.) at room temperature, and stirred for 8 hrs. A second portion of hydrogen peroxide (0.41 ml.) was then added, and the stirring continued for a further hour. The contents of the flask were then diluted with water (35 ml.) and the solid (0.97 g.) collected. It was identified as starting material, by its i.r. spectrum and m.p. 102-105°. A similar attempt at the epoxidation using 10% sodium hydroxide, and 30% hydrogen peroxide, heated at 60° also failed, starting material being recovered in good yield.

Reaction of trans 1-Benzoyl-2-(o-nitrophenyl)ethylene Oxide (94; R^1=Bz, R^2=H) with Ethereal Hydrogen Chloride.

(a) A solution of the epoxide (10.76 g.) in dry ether (1500 ml.) was saturated with dry hydrogen chloride, then left stoppered at room temperature for 24 hrs. The precipitated hydrochloride was filtered off, washed with a little dry ether and combined with two further crops obtained

by resaturating the ether mother liquors with hydrogen chloride, total (5.1 g.). Crystallised from ethanol it afforded 6-chloro-3,4-dihydroxy-2-phenylquinoline-1-oxide (98; R=Ph, X=Cl) as pale yellow needles (4.9 g., 43%), m.p. 190° (change in crystalline form, finally decomposing at 270°), $\nu_{max.}$ 3400 and 2400 (broad) $cm.^{-1}$ (Found: C, 62.4; H, 3.9; N, 5.1; Cl, 12.5. $C_{15}H_{10}NO_3Cl$ requires C, 62.3; H, 3.5; N, 4.9; Cl, 12.4%). It gave an intense blue colour with ferric chloride in ethanol. The ether, removed from the filtrate, gave an oil which was taken up in chloroform, and the solution washed with saturated aqueous sodium bicarbonate, dried, and evaporated, leaving a semi-solid residue. Trituration with ether, followed by filtration removed a small amount of unidentified solid (0.15 g.). The ether filtrate concentrated and diluted with light petroleum, afforded 1-benzoyl-2-chloro-1-hydroxy-2-o-nitrophenylethane (117) as colourless needles, (6.68 g.), m.p. 95-97° (from benzene/light petroleum) $\nu_{max.}$ 3400, 1670, 1530 and 1370 $cm.^{-1}$, n.m.r: τ =2.0-2.7 (multiplet, aromatic, 9H), 4.05 (doublet, J=7 Hz, CH, 1H); 4.48 (doublet, J=7 Hz, CH, 1H); 6.07 (broad singlet, OH, 1H). (Found: C, 52.9; H, 4.1; N, 4.5. $C_{15}H_{12}ClNO_4$ requires C, 59.0; H, 3.9; N, 4.6%).

α-Haloketone Test.

The chlorohydrin (117) (0.1 g.) in glacial acetic acid (3 ml.) was treated with potassium iodide (0.1 g.) and the mixture boiled for 10 seconds. The solution was then cooled, and treated with freshly prepared starch solution. No deep blue colour was observed. Identical experiments carried out on chloroacetone and phenacyl bromide gave positive results, while those carried out on o-nitrobenzyl chloride and p-nitrobenzyl bromide proved negative.

(b) The chalcone epoxide (94; R^1=Bz, R^2=H) (0.27 g.) in ethanol(20 ml.) was heated at 80° overnight with concentrated hydrochloric acid (2 ml.). Removal of the solvent under reduced pressure gave an oily residue which was shaken with water and chloroform. The dried organic layer freed of solvent yielded an oil (0.23 g.), which afforded 6-chloro-3,4-dihydroxy-2-phenyl-quinoline-1-oxide (98; R=Ph, X=Cl) as yellow needles (0.02 g.) m.p. 180-190° (decomp.), i.r. spectrum identical with that of a sample prepared above. Concentration of the filtrate gave an oil which was not identified.

Reaction of cis-1-Benzoyl-2-o-(nitrophenyl)ethylene Oxide (94; R^1=H, R^2=Bz) with Ethereal Hydrogen Chloride.

The epoxide (94; R^1=H, R^2=Bz) (0.5 g.), in dry ether (200 ml.) was saturated with dry hydrogen chloride and the solution left stoppered at room temperature for 24 hrs. The precipitated hydrochloride (0.54 g.) was filtered off, washed with a little ether, and recrystallised from aqueous ethanol. The product (0.48 g., 90%), m.p. 190° (change in form, finally decomposing at 270°), was identical (i.r. spectrum and mixed m.p.) with a sample of the N-hydroxy compound (98; R=Ph, X=Cl) prepared as in (a) above.

1-Benzoyl-2-o-nitrophenylethylene Oxide.

The chlorohydrin (117) (0.153 g.) in methanol (5 ml.) was treated dropwise with ice cooling with a solution of sodium (0.012 g.) in methanol (0.5 ml.) and the mixture stirred for 3 hrs. A drop of glacial acetic acid was then added, and the chalcone epoxide (94; R^1=Bz, R^2=H) (0.09 g.) filtered off. Crystallised from ethanol it formed colourless needles, m.p. 112-115° (lit.;[104] 111-113°), i.r. spectrum identical with that of authentic material.

2-Phenylquinoline Picrate.

The chlorohydrin (117) (0.001 mole) was hydrogenated in ethanol (10 ml.), over 10% palladium on charcoal (0.06 g.). The filtered reaction mixture was evaporated under reduced pressure giving an oil, which was shaken with chloroform and saturated aqueous sodium bicarbonate. Evaporation of the dried chloroform layer gave an oil (0.19 g.), which was leached with hot light petroleum, leaving a residue. Evaporation of the petroleum extract afforded a low melting solid (0.15 g.), which was shaken with hot ethanolic picric acid, to give the picrate of 2-phenylquinoline as yellow cubes (0.07 g.) m.p. 192-194° (decomp.) (from ethanol) (lit.,[160] 190-192°). (Found: C, 58.1; H, 3.2; N, 12.9. Calculated for $C_{21}H_{14}N_4O_7$: C, 58.1; H, 3.2; N, 12.9%).

Oxidation of 1-Benzoyl-2-chloro-1-hydroxy-2-o-nitrophenylethane (117).

The chlorohydrin (117) (0.15 g.) was heated at 85° with concentrated nitric acid (2 ml.), for 12 hrs., then poured into cold water (15 ml.) and extracted with chloroform. Evaporation of the dried chloroform extract yielded a mixture of benzoic acid and o-nitrobenzoic acid. Sublimation on to a "cold finger" removed benzoic acid (0.08 g.) m.p. 110-118°, the residue being o-nitrobenzoic acid (0.08 g.), m.p. 132-134°. These products were further characterised by comparison of their i.r. spectra with those of authentic samples.

Reaction of 1-Acetyl-2-o-nitrophenylethylene Oxide (94; R^1=Ac, R^2=H) with Ethereal Hydrogen Chloride.

The epoxide (94; R^1=Ac, R^2=H) (0.02 mole, 4.14 g.) dissolved in dry ether (100 ml.) was treated with dry hydrogen chloride until saturated, then stoppered and left at room temperature for 15 hrs. The solid was then filtered off and combined with a second crop obtained by resaturating the

ether mother liquors to give the unstable hydrochloride (1.0 g.). Crystallised from ethanol it afforded 6-chloro-1,4-dihydro-1,3-dihydroxy-2-methyl-4-oxoquinoline (98; R=Me, X=Cl) which formed pale yellow needles (0.86 g., 19%) m.p. 230-235° (decomp.) (from ethanol), $\nu_{max.}$ 3200, 2650 (br.) and 2250 (br.) $cm.^{-1}$. (Found: C, 52.9; H, 3.8; N, 6.4; Cl, 15.7. $C_{10}H_8ClNO_3$ requires C, 53.3; H, 3.6; N, 6.2; Cl, 15.8%).

The ether mother liquors, washed with saturated aqueous sodium bicarbonate, dried and evaporated, afforded an oil (3.1 g.) which ran as two spots on thin-layer chromatography. The oil was redissolved in ether, shaken with saturated aqueous sodium bisulphite solution (10 ml.) and the solid addition compound filtered off. The filtrate was then shaken with a second portion of sodium bisulphite solution, and the layers separated. Evaporation of the dried ether layer, afforded 1-chloro-1-o-nitrophenylbut-1-ene-3-one (120) as an oil (1.5 g.), $\nu_{max.}$ (film) 1690, 1600,1535 and 1355 $cm.^{-1}$, n.m.r: τ=1.80-2.61 (multiplet, aromatic + CH), 7.50 (singlet, CH_3, 3H). The chloroketone treated with Brady's solution afforded a 2,4-dinitrophenylhydrazone which crystallised as red prisms, m.p. 182-185° (decomp.) (from glacial acetic acid), $\nu_{max.}$ 3350 (w), 1620, 1600, 1825 and 1240 $cm.^{-1}$ (Found: C, 47.8; H, 3.1; N, 17.2. $C_{16}H_{12}ClN_5O_6$ requires C, 47.3; H, 3.0, N, 17.3%), and gave a positive sodium fusion test for chlorine.

The sodium bisulphite compound and the bisulphite washings were combined, shaken with excess of saturated aqueous sodium bicarbonate solution and chloroform, and the chloroform layer separated, dried and evaporated to give 2-o-nitrophenylbutane-1,3-dione as an oil (0.7 g.), $\nu_{max.}$ 3400, 1720, 1680, 1535 and 1350, n.m.r: τ=1.6-2.71 (multiplet, aromatic, 4H); 3.01

(singlet, CH, 1H); 5.85 (singlet, CH, 1H); 7.46 (singlet, CH_3, 3H). Treated in the cold with Brady's solution, the aldehydo-ketone (119) afforded a mono-dinitrophenylhydrazone which formed yellow needles, m.p. 222-223° (decomp.) (from glacial acetic acid), $\upsilon_{max.}$ 3300, 1685, 1620, 1520 and 1340 $cm.^{-1}$ (Found: C, 49.6; H, 3.3; N, 18.1. $C_{16}H_{13}N_5O_7$ requires C, 49.6; H, 3.4; N, 18.1%).

Reaction of 1-Benzoyl-2-o-nitrophenylethylene Oxide (94; R^1=Bz, R^2=H) with Ethereal Hydrogen Bromide.

A solution of the epoxide (94; R^1=Bz, R^2=H) (10.37 g.) dissolved in dry ether (1500 ml.) was treated until saturated with dry hydrogen bromide, then stoppered and left at room temperature for 2 days. The insoluble hydrochloride was collected, washed with ether, and combined with a further crop obtained by resaturating the ether mother liquor and leaving the solution stoppered at room temperature for 5 days (total, 2.31 g., 18%). Crystallised, it afforded 3,4-dihydroxy-2-phenylquinoline-1-oxide (98; R=Ph, X=H) as yellow needles, m.p. 150-160° (decomp.) (from ethanol), $\upsilon_{max.}$ 3200 (w) and 2650 (very broad) $cm.^{-1}$ (Found: C, 70.5; H, 4.3; N, 5.6. $C_{15}H_{11}NO_3$ requires C, 71.1; H, 4.4; N, 5.5%). The quinoline (98; R=Ph, X=H) gave an intense blue colour with ferric chloride in ethanol.

The ethereal mother liquors, concentrated under reduced pressure, gave a red oil which was dissolved in chloroform and the solution washed with saturated aqueous sodium bicarbonate. Evaporation of the dried chloroform extract left an oily solid (12.5 g.) which was collected and crystallised to give 2,3-dibromo-3-o-nitrophenyl-1-phenylpropan-1-one (121) which formed colourless needles (8.1 g., 51%), m.p. 162-164° (from ethanol) identical (mixed m.p. 162-164° and i.r. spectrum) with an authentic sample.[161]

1-o-Nitrophenyl-3-phenylpropen-3-one (88; R^1=Bz, R^2=H) was prepared by the method of Sorge,[161] and formed colourless needles (yield 26%), m.p. 120-123° (lit.,[161] 124°), $\nu_{max.}$ 1660 and 1605 $cm.^{-1}$

2,3-Dibromo-3-o-nitrophenyl-1-phenylpropan-1-one (121) was prepared by the method of Sorge[161] (yield 92%), m.p. 162-165° (from ethanol) (lit.,[161] 167-168°), $\nu_{max.}$ 1685, 1525 and 1350 $cm.^{-1}$, n.m.r: τ=1.85-2.50 (multiplet, aromatic, 9H); 1.53 (doublet, J=10 Hz, CH, 1H); 4.10 (doublet, J=10 Hz, CH, 1H).

Reaction of 1-Benzoyl-2-o-nitrophenylethylene Oxide (94; R^1=Bz, R^2=H) with Ethereal Hydrogen Chloride, in the Presence of Hydroquinone.

A mixture of the epoxide (94; R^1=Bz, R^2=H) (0.0135 mole, 3.6 g.) and hydroquinone (0.0135 mole, 1.48 g.) dissolved in dry tetrahydrofuran (75 ml.) was saturated with dry hydrogen chloride and left stoppered at room temperature overnight. Excess tetrahydrofuran was then removed under reduced pressure and the residual oil treated with dry ether, to give the hydrochloride of 3,4-dihydroxy-2-phenylquinoline-1-oxide, which afforded the free base (98; R=Ph, X=H) on crystallisation, as pale yellow needles (0.92 g., 27%), m.p. 150-160° (decomp.) (from aqueous ethanol), i.r. spectrum identical with that of the sample prepared above.

The ethereal mother liquors were evaporated under reduced pressure and the residual gum applied in benzene to an alumina column. Elution with benzene/50% light petroleum yielded 1-chloro-1-o-nitrophenyl-3-phenylprop-1-ene-3-one (120; Bz for Ac), as colourless needles (0.55 g.), m.p. 66-68° (from aqueous ethanol), $\nu_{max.}$ 1655, 1600 and 1350 $cm.^{-1}$, (Found: C, 63.0; H, 3.7; N, 4.9. $C_{15}H_{10}ClNO_3$ requires C, 62.6; H, 3.5; N, 4.9%), n.m.r. (only aromatic peaks). Further elution with benzene afforded starting material (0.5 g.), m.p. 115° (from ethanol), i.r. spectrum identical with that of an

authentic sample.

o-Nitroacetophenone was prepared by the method of Reynolds and Hauser.[162] It was obtained as a pale yellow liquid (yield 92%) which distilled in the range 147-150°/12 mm., (lit.,[162] 158-159°/16 mm.)

The chalcone (135) was obtained in 81% yield by the method of Barnes et al.[22] It formed colourless needles m.p. 125-127° (lit.,[22] 128°) (from ethanol).

1-o-Nitrobenzoyl-2-phenylethylene Oxide (122) prepared by the method of Barnes et al.,[22] crystallised as colourless needles (yield 60%) m.p. 75-78° (lit.,[22] 78°) (from ethyl acetate/light petroleum).

1-Chloro-2-hydroxy-1-o-nitrobenzoyl-2-phenylethane (123).

A solution of the epoxide (122) (0.6 g.) in dry ether (60 ml.) was saturated with dry hydrogen chloride, and left stoppered at room temperature for 24 hrs. The solvent was then removed under reduced pressure giving a solid which was treated with ether/light petroleum and collected. 1-Chloro-2-hydroxy-1-o-nitrobenzoyl-2-phenylethane (123) crystallised as colourless prisms (0.5 g.), m.p. 135-137° (from ethanol), $\nu_{max.}$ 3450, 1700, 1535 and 1360 $cm.^{-1}$ (Found: C, 59.5; H, 4.0; N, 4.7. $C_{15}H_{12}ClNO_4$ requires C, 59.0; H, 3.9; N, 4.6%).

Reaction of the Chlorohydrin (123) with Aqueous Sodium Hydroxide.

The chlorohydrin (123) (0.2 g.) was refluxed for 5 mins. with 10% sodium hydroxide (4 ml.), until the suspended solid dissolved. The aqueous solution was cooled, shaken with chloroform, and the chloroform layer dried and evaporated to yield benzaldehyde (0.04 g.), i.r. spectrum identical with that of an authentic sample. It was further characterised by conversion

into the 2,4-dinitrophenylhydrazone which formed orange needles, m.p. 235-237° (from glacial acetic acid) (lit.,[160] 237°). The basic aqueous layer was acidified (2N aqueous sulphuric acid) yielding anthroxanic acid (124) as fluffy colourless needles which were collected and dried (0.09 g.), m.p. 190-192° (lit.,[160] 190°), identical i.r. spectrum with that of an authentic sample.

Reaction of 1-Acetyl-2-o-nitrophenylethylene Oxide, (94; R^1=Ac, R^2=H) with Ethereal Hydrogen Bromide.

The epoxide (94; R^1=Ac, R^2=H) (2.07 g.) dissolved in dry ether (150 ml.) was saturated with dry hydrogen bromide at room temperature, stoppered and left overnight. No solid came down. The solution was concentrated under reduced pressure giving a dark oil (2.45 g.) which did not solidify, even after standing in contact with ether for several days. The solution was washed with saturated aqueous sodium bicarbonate solution, dried and concentrated, yielding a dark oil (1.7 g.). Column chromatography on alumina gave only unidentifiable gums. The sodium bisulphite wash was decomposed with sodium carbonate, extracted with chloroform, and the organic layer dried and evaporated to dryness, yielding a gum (0.2 g.) which was not identified.

Reaction of 1-Acetyl-2-o-nitrophenylethylene Oxide (94; R^1=Ac, R^2=H) with Hydrogen Chloride, in the Presence of Hydroquinone.

A solution of the epoxide (94; R^1=Ac, R^2=H) (0.04 mole, 8.28 g.) and hydroquinone (0.04 mole, 4.4 g.) in dry tetrahydrofuran (20 ml.) was saturated with dry hydrogen chloride, stoppered and left overnight at room temperature. Excess solvent was then pumped off under reduced pressure, and the residual oil treated with ether (100 ml.), to give the unstable hydrochloride of

1,4-dihydro-1,3-dihydroxy-2-methyl-4-oxoquinoline (98; R=Me, X=H) (2.1 g., 23%), which on crystallisation yielded the 1-hydroxy compound (98; R=Me, X=H) as yellow needles, m.p. 204-210° (decomp.) (from dimethylformamide), $\nu_{max.}$ 3150 (w), 2650 and 2250 $cm.^{-1}$ (all broad). (Found: C, 63.2; H, 5.0; N, 8.0. $C_{10}H_9NO_3$ requires C, 62.8; H, 4.7; N, 7.3%). Evaporation of the ether mother liquors left a dark tarry mass which did not crystallise and which could not separated on alumina. This was not further investigated.

Reaction of 1,1-Diacetyl-2-o-nitrophenylethylene Oxide (94; R^1=R^2=Ac) with Ethereal Hydrogen Chloride.

The epoxide (94; R^1=R^2=Ac) (0.16 g.) dissolved in dry ether (40 ml.) was saturated with dry hydrogen chloride, then left stoppered at room temperature for 48 hrs. The precipitated solid was filtered off to give 6-chloro-1,4-dihydro-1,3-dihydroxy-2-methyl-4-oxoquinoline hydrochloride (0.1 g.). Recrystallised from aqueous ethanol it afforded the parent N-hydroxyquinoline (98; R=Me, X=Cl) (yield 0.09 g.), m.p. 225-230° (decomp.), i.r. spectrum identical with a sample prepared above. On standing, a white solid displaying an i.r. peak at 1780 $cm.^{-1}$, was deposited from the ethereal mother liquor. Crystallisation from aqueous ethanol however, afforded the N-hydroxyquinoline (98; R=Me, X=Cl) (0.015 g.), m.p. 225°, i.r. spectrum identical to the first crop. The total yield of N-hydroxyquinoline was 0.1 g. (70%).

Reaction of 1-Acetyl-1-benzoyl-2-o-nitrophenylethylene Oxide (94; R^1=Bz, R^2=Ac) with Hydrogen Chloride in Tetrahydrofuran.

A solution of the epoxide (94; R^1=Bz, R^2=Ac) (0.25 g.) dissolved in dry tetrahydrofuran (30 ml.) was saturated at room temperature with dry hydrogen chloride, then left stoppered for 2 days. The solvent was then removed under reduced pressure, and the residue triturated with ether, giving

6-chloro-1,4-dihydro-1,3-dihydroxy-2-methyl-4-oxoquinoline (98; R=Me, X=Cl) which crystallised as yellow needles (0.15 g., 83%), m.p. 225-230° (decomp.) (from aqueous ethanol), identical (mixed m.p. and i.r. spectrum) with a sample prepared above. The ethereal mother liquors were shaken with aqueous sodium bicarbonate and separated. The aqueous layer was then acidified and extracted with chloroform. Evaporation of the dried chloroform layer afforded an oil (0.01 g.) which solidified on cooling and was identified by i.r. spectrum and m.p. 118-120° as benzoic acid.

In a similar experiment using dry ether as solvent, the starting material was recovered after standing at room temperature for 24 hrs. with hydrogen chloride.

Acetylation of 6-Chloro-1,4-dihydro-1,3-dihydroxy-4-oxoquinolines.

The N-hydroxyquinoline (0.2 g.) was heated at 100° (water bath), with acetic anhydride (0.5 ml.) till the solid dissolved. The reaction mixture was then cooled and diluted with water, to give the crude product as an oily solid, which was collected and crystallised. In this way 6-chloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline (98; R=Ph, X=Cl) gave the monoacetyl derivative (101; R=Ph, X=Cl) of 6-chloro-1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinoline (99; R=Ph, X=Cl) which formed colourless needles (0.12 g.), m.p. 266-272° (from ethanol), i.r. spectrum identical with that of a sample prepared below. 6-Chloro-1,4-dihydro-1,3-dihydroxy-2-methyl-4-oxoquinoline (98; R=Me, X=Cl) likewise gave the monoacetyl derivative (101; R=Me, X=Cl) of 6-chloro-1,4-dihydro-3-hydroxy-2-methyl-4-oxoquinoline (99; R=Me, X=Cl), which formed colourless needles (0.05 g.), m.p. 296-298° (decomp.) (from aqueous ethanol), i.r. spectrum identical with that of a sample prepared below.

1,4-Dihydro-3-hydroxy-4-oxoquinolines. Solutions of the N-hydroxyquinolines (98; R=Ph or Me, X=Cl or H) (0.1 g.) in 70% V/V aqueous ethanol (10 ml.), was refluxed with dithionite (0.1 g.) for 30 minutes. A further portion (0.1 g.) of dithionite was then added and refluxing continued for a further 30 minutes. The reaction mixture was then filtered hot, concentrated under reduced pressure and diluted with water, to give the products which were collected and crystallised.

6-Chloro-1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinoline (99; R=Ph, X=Cl) formed pale yellow needles (yield quantitative), m.p. 286-290° (decomp.) (from ethanol), $\nu_{max.}$ 3100 and 1630 $cm.^{-1}$ (Found: C, 65.7; H, 4.7; N, 5.4. $C_{15}H_{10}ClNO_2$ requires C, 66.5; H, 3.7; N, 5.2%). The hydroxyquinoline (99; R=Ph, X=Cl) (0.1 g.), heated in acetic anhydride (1.0 ml.), till the suspended solid dissolved (30 secs.), followed by removal of the solvent under reduced pressure, and trituration of the resultant gum with water afforded the monoacetoxy-derivative (101; R=Ph, X=Cl) as colourless platelets (0.085 g., 74%), m.p. 275-277° (from ethanol), $\nu_{max.}$ 3050 and 1745 $cm.^{-1}$, n.m.r.: (trifluoroacetic acid), τ=1.44, 1.9, 2.25 (aromatic, 8H); 7.72 (singlet, CH_3, 3H). (Found: C, 65.1; H, 4.3; N, 4.9. $C_{17}H_{12}ClNO_3$ requires C, 65.1; H, 3.8; N, 4.5%). Refluxed for 1.5 hrs. in acetic anhydride (3 ml.), the hydroxyquinoline (99; R=Ph, X=Cl) yielded the diacetoxy-derivative (102; R=Ph, X=Cl), as colourless needles (0.06 g., 46%), m.p. 153-155° (from ethanol/light petroleum), $\nu_{max.}$ 1775 and 1210 $cm.^{-1}$, n.m.r: τ=1.85-2.64 (multiplet, aromatic, 8H), 7.57 (singlet, Me, 3H), 7.89, (singlet, Me, 3H). (Found: C, 64.7; H, 3.8; N, 3.8. $C_{19}H_{14}ClNO_4$ requires C, 64.3; H, 3.9; N, 3.9%).

The diacetoxy-compound (102; R=Ph, X=Cl) (0.05 g.) was refluxed for 30 minutes with 10% sodium hydroxide solution (2 ml.). The suspended solid gradually dissolved on heating. The cooled solution acidified with glacial

acetic acid, yielded 6-chloro-1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinoline (99; R=Ph, X=Cl) as yellow needles (0.035 g.), m.p. 285° (from ethanol), i.r. spectrum identical with that of a sample prepared above.

Hydrogenation of the N-hydroxy compound (98; R=Ph, X=Cl), in ethanol, over 10% palladium on charcoal, afforded 1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinoline (99; R=Ph, X=H), as yellow needles, m.p. 265-270° (from aqueous ethanol), i.r. spectrum identical with a sample prepared as described below.

1,4-Dihydro-3-hydroxy-4-oxo-2-phenylquinoline (99; R=Ph, X=H), formed pale yellow needles (yield quantitative) m.p. 268-273° (decomp.) (from aqueous ethanol), $\nu_{max.}$ 3200 and 1630 $cm.^{-1}$ (Found: C, 80.0; H, 4.7; N, 6.2. $C_{15}H_{11}NO_2$ requires C, 80.0; H, 4.7; N, 5.9%).

Warmed in acetic anhydride for 30 seconds, it gave the monoacetoxy-derivative (101; R=Ph, X=H), which crystallised as colourless needles (yield quantitative), m.p. 203-206° (from ethanol), $\nu_{max.}$ 1775 (sh) and 1750 $cm.^{-1}$, n.m.r: τ=2.35-2.78 (multiplet, aromatic, 3H); 7.95 (singlet, CH_3). (Found: C, 73.1; H, 4.6; N, 5.2. $C_{17}H_{13}NO_3$ requires C, 73.1; H, 4.7; N, 5.0%).

When a sample of the dihydroxyquinoline (99; R=Ph, X=H) (0.1 g.) was refluxed in acetic anhydride (3 ml.) for 2 hrs., the crude product (0.12 g.) was shown by thin-layer chromatography to be a mixture. Crystallisation from aqueous ethanol afforded the diacetoxy-derivative (102; R=Ph, X=H), as colourless needles, (0.05 g., 37%), m.p. 94-96° (from aqueous ethanol), $\nu_{max.}$ 1760 $cm.^{-1}$, n.m.r: τ=1.72-2.78 (multiplet, aromatic, 9H); 7.51 (singlet, Me, 3H); 7.8 (singlet, Me, 3H). (Found: C, 71.5; H, 4.6; N, 4.5. $C_{19}H_{15}NO_4$ requires C, 71.0; H, 4.7; N, 4.4%).

The mother liquors, on standing, yielded the monoacetoxy-derivative

(101; R=Ph, X=H) (0.02 g.), identified by m.p. 200-203° and i.r. spectrum with a sample prepared above.

6-Chloro-1,4-dihydro-3-hydroxy-2-methyl-4-oxoquinoline (99; R=Me, X=Cl) formed pale yellow needles (yield quantitative), m.p. 315-320° (decomp.) (from ethanol), $\nu_{max.}$ 3275 and 1640 $cm.^{-1}$ (Found: C, 57.6; H, 4.0; N, 6.7. $C_{10}H_8ClNO_2$ requires C, 57.3; H, 3.8; N, 6.9%).

Refluxed in acetic anhydride for 20 seconds, it gave a quantitative yield of the monoacetoxy-derivative (101; R=Me, X=Cl), as colourless needles, m.p. 296-298° (from aqueous ethanol), $\nu_{max.}$ 3200, 1740 and 1640 $cm.^{-1}$, n.m.r: (TFA), τ=1.5-2.09 (multiplet, aromatic, 3H); 7.17 (singlet, Me, 3H); 7.37 (singlet, Me, 3H). (Found: C, 57.2; H, 4.0; N, 5.7. $C_{12}H_{10}ClNO_3$ requires C, 57.3; H, 4.0; N, 5.6%).

When refluxed in acetic anhydride for 2 hrs., the hydroxyquinoline (99; R=Me, X=Cl) gave the diacetoxy-derivative (102; R=Me, X=Cl), as colourless prisms (yield quantitative), m.p. 147-149° (from aqueous ethanol), $\nu_{max.}$ 1760 $cm.^{-1}$, n.m.r: τ=1.97-2.73 (multiplet, aromatic, 3H); 7.40 (singlet, Me, 3H); 7.56 (singlet, Me, 3H); 7.63 (singlet, Me, 3H). (Found: C, 57.0; H, 4.1; N, 4.5. $C_{14}H_{12}ClNO_4$ requires C, 57.2; H, 4.1; N, 4.8%).

1,4-Dihydro-3-hydroxy-2-methyl-4-oxoquinoline (99; R=Me, X=H) formed pale yellow needles (yield quantitative), m.p. 293-297° (decomp.) (from ethanol), $\nu_{max.}$ 3200 and 1640 $cm.^{-1}$ (Found: C, 68.8; H, 5.0; N, 8.2. $C_{10}H_9NO_2$ requires C, 68.6; H, 5.1; N, 8.0%).

Warmed in acetic anhydride for 20 seconds, it gave the monoacetoxy-derivative (101; R=Me, X=H) as colourless prisms (yield quantitative), m.p. 295-297° (from ethanol), $\nu_{max.}$ 1750 and 1640 $cm.^{-1}$, n.m.r: (TFA) τ=1.38-2.03 (multiplet, aromatic); 7.15 (singlet, Me); 7.36 (singlet, Me). (Found: C, 67.4; H, 5.4; N, 8.1. $C_{12}H_{11}NO_3$ requires C, 66.3; H, 5.1; N, 6.5%).

The monoacetoxy-derivative was also obtained by refluxing the hydroxy-quinoline (99; R=Me, X=H) in acetic anhydride for 2 hrs.

Oxidation of 2-Substituted 1,4-dihydro-3-hydroxy-4-oxoquinolines with Manganese Dioxide.

6-Chloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline-1-oxide (105; R=Ph, X=Cl). The N-hydroxyquinoline (98; R=Ph, X=Cl) (0.2 g.) dissolved in dry acetone (40 ml.) was stirred over a period of 12 hrs. with mildly active manganese dioxode (1.2 g.). The reaction was monitored at regular intervals by means of thin-layer chromatography on silica, eluted with benzene/25% ether. As the reaction proceded the brightly coloured red or brown spot corresponding to the quinone increased in size, while the pale yellow spot at the origin, corresponding to starting material, gradually faded. After the reaction had proceded to completion (12 hrs.) the contents of the flask were filtered through a pad of sodium sulphate, and the filtrate was concentrated under reduced pressure to yield the crude quinone as an oil, which solidified when triturated with ether/light petroleum.

The quinone (105; R=Ph, X=Cl) formed deep red needles (yield 85%) m.p. 172-177° (decomp.) (from benzene/light petroleum), $\nu_{max.}$ 1700 and 1640 $cm.^{-1}$ (Found: C, 63.5; H, 2.8; N, 4.9. $C_{15}H_8C_2NO_3$ requires C, 63.0; H, 2.8; N, 4.9%).

A solution of the quinone (105; R=Ph, X=Cl) (0.05 g.), in 70% V/V aqueous ethanol (5 ml.) was shaken with dithionite (0.05 g.) for 30 minutes. The solution was then diluted with water (15 ml.) and the product, 6-chloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline (98; R=Ph, X=Cl) collected (0.035 g.), m.p. 190° (decomp.), i.r. spectrum identical with that of a sample prepared above.

(b) A solution of the quinone (105; R=Ph, X=Cl) (0.06 g.) in 70% V/V aqueous ethanol (10 ml.) was refluxed with sodium dithionite (0.06 g.) for 30 minutes. A fresh portion of dithionite (0.06 g.) was then added and refluxing continued for a further 30 minutes. The filtered reaction mixture was evaporated, the residue treated with water, and the solid collected. Crystallisation yielded 6-chloro-1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinoline (99; R=Ph, X=Cl) as yellow needles (0.03 g.), m.p. 285-288° (from ethanol), identical (mixed m.p. and i.r. spectrum) with a sample prepared above.

3,4-Dihydro-3,4-dioxo-2-phenylquinoline-1-oxide (105; R=Ph, X=H).
1,4-Dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline (98; R=Ph, X=H) (0.2 g.) in dry acetone (40 ml.) was stirred for 1.25 hrs. at room temperature with manganese dioxide (1.2 g.). The progress of the reaction was monitored by thin-layer chromatography, as previously described. When conversion appeared complete, the filtrate was worked up as described above. The quinone (105; R=Ph, X=H) formed red needles (quantitative yield), m.p. 167-170° (from ethanol), $\nu_{max.}$ 1700, 1640 and 1625 (sh) $cm.^{-1}$ (Found: C, 71.2; H, 3.6; N, 5.5. $C_{15}H_9NO_3$ requires C, 71.6; H, 3.6; N, 5.6%).

6-Chloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline (106; R=Ph, X=Cl).
6-Chloro-1,4-dihydro-3-hydroxy-2-phenylquinoline (99; R=Ph, X=Cl) (0.2 g.) dissolved in dry acetone (25 ml.), was stirred with manganese dioxide (1.2 g.) at room temperature for 4 hrs., the reaction being followed to completion by thin-layer chromatography. The reaction mixture was worked up as described above and the resulting dark solid collected and crystallised. The quinone (106; R=Ph, X=Cl) formed dark purple needles (yield 50%), m.p. 149-152° (from benzene/light petroleum), $\nu_{max.}$ 1680 $cm.^{-1}$ (Found: C, 63.5; H, 3.2; N, 4.8. $C_{15}H_8ClNO_2$ requires C, 66.7; H, 3.0; N, 5.2%).

3,4-Dihydro-3,4-dioxo-2-phenylquinoline (106; R=Ph, X=H).

The hydroxyquinoline (99; R=Ph, X=H) (0.2 g.), in dry acetone (60 ml.), was treated with manganese dioxide (1.2 g.) and the mixture stirred at room temperature for 25 minutes, the reaction being followed by thin-layer chromatography. The reaction mixture, worked up as described above, afforded a dark red gum which solidified when triturated with ether. The quinone (106; R=Ph, X=H) formed brown needles (yield 60%), m.p. 90-93° (from benzene/light petroleum, $\nu_{max.}$ 1680 $cm.^{-1}$ (Found: C, 75.7; H, 3.8; N, 5.8. $C_{15}H_9NO_2$ requires C, 76.6; H, 3.8; N, 6.0%).

3,4-Dihydro-3,4-dioxo-2-methylquinoline-1-oxide (105; R=Me, X=H).

The N-hydroxyquinoline (98; R=Me, X=H) (0.06 g.), in dry acetone (20 ml.), was stirred at room temperature with manganese dioxide (0.36 g.) for 2.2 hrs., the reaction being followed by thin-layer chromatography, as usual. Working up the reaction mixture as described above, gave a sticky red solid which was treated with light petroleum and collected. The product formed fine red needles (yield 90%) m.p. 149-151° (from ethanol), $\nu_{max.}$ 1700, 1640 $cm.^{-1}$ (Found:C, 63.0; H, 3.8; N, 7.5. $C_{10}H_7NO_3$ requires C, 63.4; H, 3.7; N, 7.4%).

6-Chloro-3,4-dihydro-3,4-dioxo-2-methylquinoline-1-oxide (105; R=Me, X=Cl).

6-Chloro-1,4-dihydro-1,3-dihydroxy-2-methyl-4-oxoquinoline (98; R=Me, X=Cl) (0.14 g.), in dry acetone (50 ml.), was stirred with manganese dioxide (0.84 g.) for 1.25 hrs. at room temperature, the reaction being followed by thin-layer chromatography, as previously described. Worked up in the usual fashion, the reaction mixture afforded a red solid which was collected and crystallised. The product (105; R=Me, X=Cl) formed fine red needles, (yield 72%), m.p. 187-189° (from ethanol), $\nu_{max.}$ 1700, 1635 $cm.^{-1}$ (Found: C, 53.8; H, 2.6; N, 6.3. $C_{10}H_6C_2NO_3$ requires C, 53.8; H, 2.7; N, 6.3%).

Oxidation of the hydroxyquinoline (99; R=Me, X=H) was attempted using (a) manganese dioxide in acetone as described above, (b) manganese dioxide in dimethylformamide, and (c) silver oxide as described by Boyer.[107] In each case, the products were either gums or solids which left an inorganic residue on burning. These were not further investigated.

Quinolino [3,4-b] quinoxalines(107, 108).

Solutions of the quinones (105; R=Ph, X=Cl or H) and (106; R=Ph, X=Cl or H) in ethanol, were refluxed with the equivalent amount of o-phenylenediamine for 5-10 minutes. After cooling, the yellow precipitates were cooled, collected and crystallised.

6-Chloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline-1-oxide (105; R=Ph, X=Cl) (0.1 g.) and o-phenylenediamine (0.04 g.) gave the N-oxide (107; R=Ph, X=Cl) as fine yellow needles (0.1 g.), m.p. 245° (from glacial acetic acid). (Found: C, 70.3; H, 3.4; N, 11.8. $C_{21}H_{12}ClN_3O$ requires C, 70.5; H, 3.4; N, 11.8%).

3,4-Dihydro-3,4-dioxo-2-phenylquinoline-1-oxide (105; R=Ph, X=H) (0.1 g.) and o-phenylenediamine (0.04 g.) gave the N-oxide (107; R=Ph, X=H) as fine yellow needles (0.1 g.), m.p. 270-272° (from glacial acetic acid) (lit.,[22] 239-240°) (Found: C, 77.6; H, 4.0; N, 12.8. Calculated for $C_{21}H_{13}N_3O$, C, 78.0; H, 4.0; N, 13.0%).

6-Chloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline (106; R=Ph, X=Cl) (0.04 g.) and o-phenylenediamine (0.02 g.) gave the quinolinoquinoxaline derivative (108; R=Ph, X=Cl) as fine yellow needles (0.04 g.), m.p. 253-255° (from glacial acetic acid). (Found: C, 74.4; H, 3.5; N, 12.0. $C_{21}H_{12}ClN_3$ requires C, 73.9; H, 3.5; N, 12.3%).

3,4-Dihydro-3,4-dioxo-2-phenylquinoline (106; R=Ph, X=H) (0.04 g.)

and o-phenylenediamine (0.02 g.) gave the quinolinoquinoxaline derivative (108; R=Ph, X=H) as a yellow solid (0.035 g.), m.p. 221-224° (from glacial acetic acid). (Found: C, 82.1; H, 4.3; N, 13.6. $C_{21}H_{13}N_3$ requires C, 82.1; H, 4.2; N, 13.7%).

Refluxing the quinones (105; R=Me, X=Cl or H) in ethanol with o-phenylenediamine, for five minutes, failed to yield the expected quinoxaline derivatives. The solutions became very dark during heating, and no precipitate appeared on standing in the cold. Removal of the solvent gave only unidentifiable gums.

2-Chloro-7,12-dihydro-6-phenylquinolino[3,4-b]quinoxaline (109)

The N-oxide (107; R=Ph, X=Cl) (0.05 g.), in 70% v/v aqueous ethanol (15 ml.), was refluxed with sodium dithionite (0.05 g.) for 30 minutes. A further portion of dithionite (0.05 g.) was then added, and the refluxing continued for a further 30 minutes. The reaction mixture was then filtered hot, concentrated, and diluted with water, to give an unstable purple compound, which was collected and dried (0.045 g.), m.p. 265-270° crude, $\nu_{max.}$ 3500 $cm.^{-1}$ Molecular weight 343 (Mass Spectrum).

The dihydro-compound (109) (0.01 g.), dissolved in acetone (20 ml.), was stirred with manganese dioxide (0.06 g.) at room temperature for 3 hours. The manganese dioxide was then filtered off and washed with hot chloroform. Evaporation of the combined filtrate and washings afforded the quinolinoquinoxaline (108; R=Ph, X=Cl), as yellow needles (0.01 g.), m.p. 248-252°, identical (mixed m.p. 251° and i.r. spectrum) with a sample prepared above.

Oxidation of 1,4-Dihydro-3-hydroxy-4-oxo-2-phenylquinoline (99; R=Ph, X=Cl or H) with Chromium Trioxide.

(a) The hydroxyquinoline (99; R=Ph, X=Cl) (0.1 g.), in glacial acetic acid

(10 ml.), was treated slowly, with stirring, with a suspension of chromium trioxide (0.5 g.) in glacial acetic acid (10 ml.). The mixture was warmed to 40° and then stirred for 24 hrs. at room temperature. The solid acid (103; X=Cl) was isolated by diluting the reaction mixture with water (20 ml.). It crystallised as colourless needles (0.075 g.), m.p. 260–263° (from ethanol), $\nu_{max.}$ 3100, 1700, 1685 (sh), 1665 and 1610 $cm.^{-1}$ (Found: C, 60.8; H, 3.7; N, 5.1. $C_{14}H_{10}ClNO_3$ requires C, 60.9; H, 3.6; N, 5.1%).

The acid (103; X=Cl) (0.1 g.), refluxed in acetic anhydride (2 ml.) for 5 minutes, and the solution cooled and diluted with water (5 ml.), afforded 6-chloro-4-oxo-2-phenyl-3,1-benzoxazine (104; X=Cl) as colourless needles (0.09 g.), m.p. 195–197° (from ethanol), $\nu_{max.}$ 1745, and 1620 $cm.^{-1}$ (Found: C, 66.2; H, 2.9; N, 5.5. $C_{14}H_8ClNO_2$ requires C, 65.2; H, 3.1; N, 5.4%).

(b) The hydroxyquinoline (99; R=Ph, X=H) (0.14 g.), in glacial acetic acid (7.0 ml.), treated and stirred with a suspension of chromium trioxide (0.54 g.) in glacial acetic acid (7.0 ml.) at room temperature for 5 hrs. and the reaction mixture diluted with water (100 ml.) and extracted with chloroform, afforded the acid (103; X=H) as fine colourless needles (0.08 g.), m.p. 199–201° (from aqueous ethanol), $\nu_{max.}$ 3100, 1700, 1685 (sh), 1655 and 1610 $cm.^{-1}$ (Found: C, 67.6; H, 5.1; N, 6.2. Calculated for $C_{14}H_{11}NO_3$: C, 69.7; H, 4.6; N, 5.8%).

The acid (103; X=H) (0.02 g.), refluxed in acetic anhydride (0.4 ml.) for 20 seconds, and the solution diluted with water (4 ml.), afforded 4-oxo-2-phenyl-3,1-benzoxazine (104; X=H) (0.01 g.), m.p. 118–121° (lit.,[163] 122°) (from ethanol), i.r. spectrum identical with that of an authentic sample.

4,4'-Dichloroazoxybenzene-2,2'-dicarboxylic acid (100).

The N-hydroxyquinoline (98; R=Ph, X=Cl) (0.1 g.) was stirred overnight in

glacial acetic acid (6 ml.), with a solution of 6% w/v aqueous potassium dichromate (4 ml.). The contents of the flask were then diluted with water (12 ml.), and an unidentified solid filtered off (0.02 g.). The mother liquors were extracted with chloroform, and the dried organic layer concentrated under reduced pressure, giving a semi-solid (0.08 g.). Trituration with ether/light petroleum yielded 4,4'-dichloroazoxybenzene-2,2'-dicarboxylic acid (0.05 g.), m.p. 258-260° (lit.,[99] 264°), i.r. spectrum identical with that of an authentic sample. Evaporation of the mother liquors gave benzoic acid (0.02 g.), identified by melting point and i.r. spectrum.

6-Chloro-1,4-dihydro-2-methyl-3-nitro-4-oxoquinoline (115)

The quinoline (114) (3.3 g.) and concentrated nitric acid (33 ml.) were heated at 100° for one hour. The deep brown solution was cooled and poured with stirring onto ice (200 g.). After the ice had melted, the yellow solid (115) (1.72 g.) was collected and washed with two 50 ml. portions of boiling water, dried and crystallised. The product formed colourless plates (1.6 g.), m.p. 344-348° (from aqueous dimethylformamide), $\nu_{max.}$ 3200-2600, 1640, 1520, 1380 and 1360 $cm.^{-1}$ (Found: C, 51.0; H, 2.9; N, 11.6. $C_{10}H_7ClN_2O_3$ requires C, 50.3; H, 2.9; N, 11.7%).

3-Amino-6-chloro-1,4-dihydro-2-methyl-4-oxoquinoline (115; NH_2 for NO_2)

The nitro-compound (115) (1.42 g.) and granulated tin (10 g.) were heated in concentrated hydrochloric acid (30 ml.) at 100° for 2.5 hours, by which time most of the tin had dissolved. The amine hydrochloride was collected from the cooled solution, shaken with dilute ammonia, and the free amine (115; NH_2 for NO_2) collected and crystallised. It formed colourless needles (0.67 g.), m.p. 325-330° (from dimethylformamide), $\nu_{max.}$ 3380, 3280, 3100-2700 and 1640 $cm.^{-1}$ (Found: C, 57.6; H, 4.3; N, 13.7. $C_{10}H_9ClN_2O$

requires C, 57.7; H, 4.3; N, 13.4%).

The acidic filtrate was neutralised with solid sodium bicarbonate, yielding unreacted nitro-compound (115) (0.27 g.), m.p. 330-335°, i.r. spectrum identical with that of an authentic sample.

6-Chloro-3-diazo-3,4-dihydro-2-methyl-4-oxoquinoline (116)

The amine (115; NH_2 for NO_2) (0.48 g.), in concentrated hydrochloric acid (8.0 ml.), was warmed slightly and treated with sodium nitrite (0.15 g.). The suspended solid dissolved, and after 10 minutes at room temperature, the solution was refluxed for 10 minutes, then left on a water bath at 100° for a further 1.5 hours. The cooled solution, neutralised with ammonia, gave the quinone diazide (116), which crystallised as yellow needles, m.p. 128-130° (decomp.) (from water), $\nu_{max.}$ 2120, 2100 and 1640 $cm.^{-1}$ (Found: C, 54.6; H, 2.7; N, 18.5. $C_{10}H_6ClN_3O$ requires C, 54.5; H, 2.7; N, 19.1%).

The diazoquinoline (116) was unchanged after being refluxed for 7.5 hours with 46% sulphuric acid, however refluxing with 20% aqueous potassium hydroxide gave only unidentifiable material, in low yield. When the quinone diazide (116) was refluxed with chromium trioxide, in aqueous acetic acid, an unidentifiable brown solid was obtained, which left a residue on burning.

Reactions of Substituted o-Nitrophenylethylene Oxides with Lewis Acids.

N-(α-hydroxyphenacyl)-2,1-benzisoxazolone (125; R=Bz).

A solution of the chalcone epoxide (94; R^1=Bz, R^2=H) (1.0 g.) dissolved in dry benzene (50 ml.) was stirred and treated in one portion with stannic chloride (1.2 g.). After 15 minutes, the contents of the flask were poured onto crushed ice (100 g.), and stirred to break up the dark sticky mass which formed. When the ice had melted, the benzene layer was separated, dried and evaporated under reduced pressure, to yield N-(α-hydroxyphenacyl)-2,1-benzisoxazolone (125; R=Bz), which crystallised as pale yellow prisms (0.93 g.), m.p. 125-128° (from benzene), $\nu_{max.}$ 3350, 1740 and 1695 $cm.^{-1}$, n.m.r: τ=1.65-2.75 (multiplet, aromatic, 9H); 3.56(singlet, CH, 1H); 5.18 (broad singlet, OH, 1H); Mol. Wt., 269 (mass spectrum). (Found: C, 67.0; H, 4.1; N, 5.2. $C_{15}H_{11}NO_4$ requires C, 66.9; H, 4.1; N, 5.2%), i.r. spectrum identical with that of material synthesised below.

N-Desyl-2,1-benzisoxazolone (125; R=Bz, Ph for OH).

(a) A solution of the chalcone epoxide (94; R^1=Bz, R^2=H) (0.002 mole, 0.54 g.) dissolved in dry benzene (40 ml.) was stirred and treated with acetic anhydride (0.004 mole, 0.38 ml.), then dropwise with stannic chloride (0.008 mole, 0.94 ml.). After 15 minutes, the solution was poured onto crushed ice (100 g.). Benzene (100 ml.) was then added, and the layers separated. The dried benzene extract, evaporated under reduced pressure, gave a light gum (0.63 g.), which solidified in contact with light petroleum, affording N-desyl-2,1-benzisoxazolone (125; R=Bz, Ph for OH) as colourless needles (0.3 g.), m.p. 115-118° (from ethanol), $\nu_{max.}$ 1730 and 1685 $cm.^{-1}$ n.m.r: τ=2.1-2.9 (multiplet, aromatic, 14H); 3.6 (singlet, CH, 1H). (Found: C, 75.9; H, 4.5;

N, 4.4. $C_{21}H_{15}NO_3$ requires C, 76.6; H, 4.6; N, 4.3%).

Evaporation of the petrol mother liquors gave an oil (0.2 g.) which crystallised from benzene/light petroleum, yielding N-phenylglyoxyloyl-anthranilic acid (126; R=Bz) (0.05 g.), m.p. 189-192°, i.r. spectrum identical with that of a sample synthesised below.

(b) N-(∝-hydroxyphenacyl)-2,1-benzisoxazolone (125; R=Bz) (0.001 mole, 0.27 g.) in dry benzene (30 ml.) was treated with acetic anhydride (0.002 mole, 0.21 g.), then dropwise with stirring with stannic chloride (0.004 mole, 0.47 ml.). After 15 minutes, the solution was poured onto ice (50 g.). The organic layer was separated, dried and evaporated under reduced pressure, leaving a light gum, which crystallised from ethanol, to give the benzisoxazolone derivative (125; R=Bz, Ph for OH) (yield 0.14 g.), m.p. 116°, i.r. spectrum identical with a sample prepared in (a) above.

Evaporation of the ethanol mother liquors gave a semi-solid, which was triturated with ether/light petroleum and crystallised, yielding N-acetyl-2,1-benzisoxazolone (130; Ac for H) as colourless needles (0.03 g.), m.p. 115-117° (from ethanol), i.r. spectrum identical with that of an authentic sample.[164]

When the benzisoxazolone derivative (125; R=Bz, Ph for OH) (0.1 g.) was refluxed for 2 minutes in 10% v/v aqueous sodium hydroxide or stirred in water (3 ml.) with potassium carbonate (0.1 g.) for 45 minutes, benzil was obtained as an insoluble solid (0.03 g.), m.p. 90-92° (lit.,[149] 95°), i.r. spectrum identical with that of an authentic sample. The alkaline mother liquors, just acidified with glacial acetic acid, extracted with chloroform, and the dried extract evaporated, gave anthranilic acid (0.02 g.), m.p. 135-137° (lit.,[149] 144°), i.r. spectrum identical with that of an authentic sample.

Reaction of 1-Benzoyl-2-(o-nitrophenyl)ethylene Oxide (94; R^1=Bz, R^2=H) with Hydrogen Chloride in the Presence of Stannic Chloride.

The chalcone epoxide (94; R^1=Bz, R^2=H) (0.002 mole, 0,54 g.), dissolved in dry ether (100 ml.) was treated with hydrogen chloride for 5 minutes, and then with stannic chloride (0.47 ml.). There was an immediate reaction, the solution turning a blue colour, and a brown oil formed. Treatment with hydrogen chloride was continued for 1 hr. and the flask was then stoppered and left at room temperature overnight. The ethereal solution was decanted from the residual solid which was treated with water, collected and dried. It crystallised as pale yellow needles (0.1 g.), m.p. 248-250° (from glacial acetic acid), $\nu_{max.}$ 1755 and 1740 (sh) $cm.^{-1}$ (Found: C, 68.2; H, 2.9). Evaporation of the ethereal filtrate gave an oil, which solidified upon trituration with water, yielding N-phenylglyoxyloylanthranilic acid (126; R=Bz) (0.44 g.), m.p. 189-191° i.r. spectrum identical with that of a sample synthesised as described below.

N-Phenylglyoxyloylanthranilic Acid (126; R=Bz).

(a) The chalcone epoxide (94; R^1=Bz, R^2=H) (0.6 g.), in dry ether (125 ml.), was treated with borontrifluoride etherate (5 ml.). The resulting slightly orange solution was refluxed on the water bath for 15 minutes, then poured into water (200 ml.). The ether layer was separated, washed with water, and dried. Evaporation under reduced pressure gave a brown oil (0.58 g.), which solidified upon cooling. The solid was broken up in petrol and collected. Crystallisation of the crude product from benzene gave, as first crop, N-phenylglyoxyloylanthranilic acid (126; R=Bz) as yellow prisms (0.14 g.), m.p. 190-192° (from benzene), $\nu_{max.}$ 1695 and 1665 $cm.^{-1}$ (Found: C, 67.2; H, 4.2; N, 5.1. $C_{15}H_{11}NO_4$ requires C, 67.0; H, 4.1; N, 5.2%). Mol. Wt. 269

(mass spectrum).

The concentrated mother liquors upon standing gave a second crop of crystals, identified as N-(∝-hydroxyphenacyl)-2,1-benzisoxazolone (125; R=Bz) (0.19 g.), m.p. 125°, identical (mixed m.p. and i.r. spectrum) with an authentic sample. The mother liquors concentrated to dryness, gave a red-brown oil (0.18 g.), which was not identified.

(b) The benzisoxazolone (125; R=Bz) (0.25 g.) was refluxed for 1 hr. with p-toluenesulphonic acid (0.03 g.) in benzene (30 ml.). The solution was then cooled and the N-phenylglyoxyloylanthranilic acid collected (0.13 g.), m.p.190-192°, i.r. spectrum identical with that of a synthetic sample (see below). The mother liquors after concentration to half volume, yielded a further crop (0.095 g.) of the product, m.p. 188-190°.

(c) The benzisoxazolone (125; R=Bz) (0.2 g.) was stirred for 12 hrs. in concentrated sulphuric acid (3 ml.), and the solution then poured, with stirring, into water (12 ml.). The resulting solid was collected and crystallised from benzene, to give N-phenylglyoxyloylanthranilic acid (126; R=Bz), (0.18 g.), m.p. 192-194°, i.r. spectrum identical with that of a sample synthesised below.

(d) The benzisoxazolone (125; R=Bz) (0.2 g.), dissolved in dry acetone (40 ml.), was stirred with activated manganese dioxide (1.2 g.) at room temperature for 10 hrs. The reaction mixture was then filtered, and the filtrate concentrated under reduced pressure, affording an oil (0.2 g.). Trituration with ether gave a solid mixture (0.05 g.), separated by crystallisation from benzene into N-phenylglyoxyloylanthranilic acid (126; R=Bz) (0.015 g.), m.p. 190-194°, i.r. spectrum identical with that of authentic material, and starting material (125; R=Bz) (0.025 g.), m.p. 125-130°, i.r.

spectrum identical with authentic material. Evaporation of the ethereal mother liquors, and crystallisation of the solid obtained from benzene/light petroleum, afforded a further crop of the acid (126; R=Bz) (0.09 g.), m.p. 191-194°.

(e) The chalcone epoxide (94; R^1=Bz, R^2=H) (0.002 mole, 0.54 g.), in dry ether (100 ml.), was stirred and treated with acetic anhydride (0.004 mole, 0.38 ml.), followed by stannic chloride (0.008 mole, 0.94 ml.). After 25 minutes the reaction mixture was poured on to crushed ice (40 g.) and allowed to come to room temperature. After separation, the organic layer was dried and concentrated under reduced pressure, giving an oil (0.48 g.), which solidified when triturated with ether/light petroleum, yielding N-phenylglyoxyloylanthranilic acid (126; R=Bz) (0.4 g.) as yellow prisms, m.p. 189-191° (from benzene), i.r. spectrum identical with that of an authentic sample prepared below.

Unambiguous Synthesis of N-Phenylglyoxyloylanthranilic Acid (126; R=Bz).

Benzoylformic acid prepared by the method of Corson and Dodge[165] was obtained crude, as faintly yellow needles, m.p. 59-63° (lit.,[166] 63-64°), $\nu_{max.}$ 3200-2400, 1730 and 1660 $cm.^{-1}$ and was used without further purification.

Benzoylformyl Chloride.

Benzoylformic acid (10 g.) was warmed with thionyl chloride (10 ml.) on a water bath at 70-80° for 1.5 hrs. Distillation of the excess thionyl chloride under reduced pressure, left the crude acid chloride, $\nu_{max.}$ 1770, 1730 and 1690 $cm.^{-1}$ which was used without further purification.

N-Phenylglyoxyloylanthranilic Acid (125; R=Bz).

Anthranilic acid (0.01 mole, 1.37 g.), dissolved in 10% sodium hydroxide (10 ml.) was treated with benzoylformyl chloride (0.01 mole, 1.69 g.), and the mixture shaken for 10 minutes. Acidification with 2N aqueous sulphuric

acid yielded the crude product as a yellow solid (1.9 g.) which was collected and dried. It was then leached with hot benzene (20 ml.) and filtered to give N-phenylglyoxyloylanthranilic acid (126; R=Bz) which formed yellow prisms (1.1 g.), m.p. 190-192° (from benzene), $\upsilon_{max.}$ 1695 and 1665 $cm.^{-1}$ Evaporation of the benzene extract yielded N-benzoylanthranilic acid (0.5 g.) which crystallised as yellow needles, m.p. 180° (from benzene) (lit.,[167] 180-181°), i.r. spectrum identical with that of an authentic sample.

2-Benzoyl-4-oxo-3,1-benzoxazine (127).

(a) N-Phenylglyoxyloylanthranilic acid (126; R=Bz) (0.25 g.) was refluxed gently with sodium acetate (0.1 g.) and acetic anhydride (5 ml.), for 5 minutes. The acetic anhydride was then removed under reduced pressure, giving the product as a solid which was collected, washed with water, and dried. Crystallised, it formed colourless needles (0.15 g.), m.p. 147-149° (from ethanol), $\upsilon_{max.}$ 1755 and 1670 $cm.^{-1}$ (Found: C, 72.1; H, 3.7; N, 5.6. $C_{15}H_9NO_3$ requires C, 71.7; H, 3.6; N, 5.6%).

(b) The benzisoxazolone (125; R=Bz) (0.25 g.) was heated gently with sodium acetate (0.3 g.) and acetic anhydride (1.0 ml.), until the suspended solid dissolved. The cold solution, diluted with water, gave 2-benzoyl-4-oxo-3,1-benzoxazine (127) (0.2 g.), as colourless needles, m.p. 147-149° (from ethanol), identical (i.r. spectrum and mixed m.p.) with the sample prepared above.

(c) The benzisoxazolone (125; R=Bz) (0.25 g.), dissolved in acetic anhydride (2 ml.) was treated with concentrated sulphuric acid (0.05 ml.), and left at room temperature for 13 hrs. It was then poured on to ice (5 g.), yielding a brown oil, which was extracted into chloroform. Evaporation of the dried chloroform extract, left a brown oil (0.2 g.), which on crystallisation,

yielded 2-benzoyl-4-oxo-3,1-benzoxazine (127) (0.08 g.), m.p. 145-147° (from ethanol), i.r. spectrum identical with that of the sample prepared in (a) above.

Reaction of 1-o-Nitrobenzoyl-2-phenylethylene Oxide (122) with Stannic Chloride, in Benzene.

The chalcone epoxide (122) (0.001 mole, 0.27 g.) in dry benzene (25 ml.), was stirred and treated dropwise at room temperature with fresh stannic chloride (0.002 mole, 0.23 ml.). After 15 minutes, the solution was poured on to ice (50 g.), and the mixture allowed to melt. The dried organic layer was concentrated under reduced pressure, yielding a light gum (0.32 g.), which solidified on cooling, giving 1-chloro-2-hydroxy-1-o-nitrobenzoyl-2-phenylethane (123) as colourless prisms, m.p. 135-137° (from ethanol), i.r. spectrum identical with the sample prepared as described on page 116.

ω-Hydroxy-o-nitrosoacetophenone (128; H for Ac) was prepared from o-nitrophenylethylene oxide, by the method of Arndt and Partale.[103] It formed colourless needles (yield 36%), m.p. 99-102° (lit.,[103] 103-104°), $\nu_{max.}$ 3360 and 1680 $cm.^{-1}$ and was used without further purification.

Methylene-bis-2,1-benzisoxazolone (129) was obtained as a by-product in the preparation of ω-hydroxy-o-nitrosoacetophenone. It was isolated by concentrating the mother liquors under reduced pressure, at room temperature, and treatment of the residue obtained with water. Crystallised, it formed colourless needles, m.p. 157-160° (from ethanol) (lit.,[103] 162°), $\nu_{max.}$ 1750 $cm.^{-1}$ n.m.r: τ=2.1-2.85 (multiplet, aromatic, 8H); 4.50 (singlet, CH_2, 2H).

Reaction of ω-Hydroxy-o-nitrosoacetophenone (128; H for Ac) with Boron-trifluoride Etherate.

ω-Hydroxy-o-nitrosoacetophenone (128; H for Ac) (0.002 mole, 0.33 g.), in dry benzene (50 ml.), was treated with borontrifluoride etherate (0.004 mole, 0.52 ml.), dropwise, with stirring. After 15 minutes, the reaction mixture was poured on to crushed ice (50 g.), and allowed to come to room temperature. After removal of a solid residue, the layers were separated. Evaporation of the dried organic layer afforded an oil (0.17 g.) which solidified when triturated with ether, yielding the methylene-bis-benzisoxazolone (129) (0.1 g.), as a colourless solid, m.p. 155-157° (from ethanol), identical (i.r. spectrum and mixed m.p. 155-157°) with an authentic sample.

Reactions of o-Nitrophenylethylene Oxide (94; R^1=R^2=H) with Lewis Acids.

(a) Stannic Chloride.

The epoxide (94; R^1=R^2=H) (0.005 mole, 0.83 g.), dissolved in dry benzene (30 ml.) was treated dropwise with stirring at room temperature, with stannic chloride (2.35 ml.), and stirring continued for 15 minutes. Tarry material quickly formed. Crushed ice (50 g.) was then added, and after thawing, the benzene layer was separated, dried and evaporated to give a light gum. Trituration with ethanol yielded a solid (0.15 g.) which was collected and crystallised to give methylene-bis-benzisoxazolone (129) as colourless needles, m.p. 158-162° (from ethanol) (lit.,[103] 162°), i.r. spectrum identical with that of an authentic sample.

The tarry material left behind in the reaction flask was broken up, extracted into chloroform and the extract filtered to remove insoluble material. Removal of the chloroform left a green gum (0.4 g.), which, triturated with ethanol, gave an impure solid. This material could not be

made to crystallise, and left a large white residue on burning. It was not further investigated.

(b) Borontrifluoride Diethyletherate.

The epoxide (94; R^1=R^2=H) (0.0025 mole, 0.42 g.), in dry benzene (30 ml.), was treated dropwise, with stirring, with borontrifluoride etherate (0.005 mole, 0.64 ml.), and the solution left for 15 minutes at room temperature. Ice (50 g.) was then added, and the tarry material broken up and removed by filtration. The benzene layer was separated from the filtrate, dried and evaporated, yielding an oil (0.19 g.), which crystallised from ethanol to give the compound (129) as colourless needles (0.15 g.), m.p. 157-160° (lit.,[103] 162°), i.r. spectrum identical with that of an authentic sample.

(c) Borontrifluoride Diethyletherate in the Presence of Acetic Anhydride.

o-Nitrophenylethylene oxide (94; R^1=R^2=H) (0.0025 mole, 0.42 g.) and acetic anhydride (0.005 mole, 0.47 ml.), in benzene (30 ml.) were treated with borontrifluoride etherate, as in (b) above. After removal of the tarry material, the dried benzene layer was evaporated to yield an oil (0.22 g.), which gave the bis-benzisoxazolone (129) (0.1 g.) on crystallisation, m.p. 159-163° (from ethanol), i.r. spectrum identical with that of authentic material.

Reaction of 1-Acetyl-2-(o-nitrophenyl)ethylene Oxide (94; R^1=Ac, R^2=H) with Lewis Acids.

(a) Stannic Chloride.

The epoxide (94; R^1=Ac, R^2=H) (1.0 g.), in dry benzene (50 ml.), was treated with stannic chloride (1.2 g.), with stirring in an ice-bath. After 15 minutes, the reaction mixture was poured on to ice (100 g.), and allowed to come to room temperature. The layers were then separated. Evaporation of

the dried organic extract gave a red oil (0.55 g.) which did not crystallise from the usual solvents. Thin-layer chromatography indicated a mixture of several compounds. These were not separated on a column of silica gel, and were not further investigated.

(b) Stannic Chloride in the Presence of Acetic Anhydride.

The epoxide (94; R^1=Ac, R^2=H) (0.41 g.) in dry benzene (30 ml.) was treated with acetic anhydride (0.38 ml.), followed by stannic chloride (0.94 ml.). The solution rapidly became dark. After being stirred for 15 minutes, the reaction mixture was poured onto crushed ice. The dried organic extract, concentrated under reduced pressure, yielded a sticky solid (0.44 g.), which was triturated with ether and collected. this material left a large white residue when ignited and was not investigated further.

(c) Borontrifluoride Etherate

The epoxide (94; R^1=Ac, R^2=H) (0.002 mole, 0.42 g.) in dry benzene (60 ml.) was treated with borontrifluoride etherate (0.004 mole, 0.52 ml.) and the mixture stirred at room temperature for 15 minutes, then poured onto ice (50 g.). The dried benzene layer, evaporated under reduced pressure, afforded a red oil (0.25 g.) which solidified when triturated with benzene/light petroleum. The solid (0.12 g.), formulated as ω-acetyl-ω-hydroxy-o-nitrosoacetophenone (128) formed colourless platelets, m.p. 134-136° (from benzene), $\upsilon_{max.}$ 3200, 1700 and 1650 $cm.^{-1}$, n.m.r: τ=1.92-2.84 (multiplet, aromatic, 4H); 4.5 (broad singlet, CH+OH, 2H); 7.75 (singlet, methyl, 3H). Mol. Wt. 207 (mass spectrum). (Found: C, 58.2; H, 4.3; N, 6.5. $C_{10}H_9NO_4$ requires C, 58.0; H, 4.4; N, 6.8%).

A portion of the hydroxy-compound (128) (0.1 g.) was refluxed in acetic anhydride (0.5 ml.) for 5 minutes, then diluted with water and

scratched. The solid which separated was collected and dried. It crystallised as colourless prisms (0.05 g.), m.p. 119-121° (from ethanol/water), i.r. spectrum identical with a sample of the nitroso-compound (128; OAc for OH) prepared below.

(d) Borontrifluoride Etherate in the Presence of Acetic Anhydride.

A mixture of the epoxide (94; R^1=Ac, R^2=H) (0.002 mole, 0.41 g.) and acetic anhydride (0.004 mole, 0.38 ml.), in dry benzene (30 ml.), was stirred and treated with borontrifluoride diethyletherate (0.004 mole, 0.52 ml.). Stirring was continued for a further 15 minutes and the solution was then poured on to ice (50 g.). Evaporation of the dried benzene layer gave a red oil (0.31 g.) which, triturated with ether, yielded a solid (0.15 g.), formulated as ω-acetoxy-ω-acetyl-o-nitrosoacetophenone (128; OAc for OH), m.p. 119-121° (from ethanol/light petroleum), $\upsilon_{max.}$ 1760 and 1680 $cm.^{-1}$, n.m.r: τ=1.78-2.81 (multiplet, aromatic, 4H); 3.55 (singlet, CH, 1H); 7.70 (singlet, methyl, 3H); 7.78 (singlet, methyl, 3H), mol. wt. 249 (mass spectrum). (Found: C, 57.8; H, 4.4; N, 5.7. $C_{12}H_{11}NO_5$ requires C, 57.8; H, 4.4; N, 5.6%). Concentration of the ethereal mother liquors gave an unidentified red gum.

Synthesis of N-Substituted 2,1-Benzisoxazolones.

(a) o-Hydroxylaminobenzoic acid was prepared (yield 89%) by the method of Bamberger and Pyman,[164] and used in the next stage, without further purification.

2,1-Benzisoxazolone[164] (130) prepared by refluxing o- hydroxylaminobenzoic acid in dilute sulphuric acid for 40 seconds, was obtained as colourless needles (yield 69%) m.p. 108-110° (from benzene) (lit.,[164] 112°), $\upsilon_{max.}$ 3050 and 1710 (broad) $cm.^{-1}$

Warmed in acetyl chloride, it afforded the N-acetyl derivative[164]

as colourless needles, m.p. 116-117° (lit.,[164] 118°) (from ethanol), $\nu_{max.}$ 1780, 1760 and 1700 $cm.^{-1}$, n.m.r: τ=1.9-2.8 (multiplet, aromatic, 4H), 7.52 (singlet, CH_3, 3H).

N-Substituted-2,1-benzisoxazolones (125; R=Bz or Ac).

A mixture of 2,1-benzisoxazolone (130) (0.002 mole) and phenylglyoxal (0.002 mole), in water (3 ml.), was stirred and heated at 60° for 10 minutes. The solid which quickly formed was filtered off, dried and crystallised.

N-(α-Hydroxyphenacyl)-2,1-benzisoxazolone (125; R=Bz) formed pale yellow prisms (yield 80%), m.p. 125-128° (from benzene), identical (mixed m.p. and i.r. spectrum) with a sample obtained as described above.

N-(α-hydroxyacetonyl)-2,1-benzisoxazolone (125; R=Ac), formed colourless needles (yield 56%), m.p. 130-132° (from benzene), $\nu_{max.}$ 3470, 1755, 1620 and 1610 $cm.^{-1}$, n.m.r: τ =2.06-2.79 (multiplet, aromatic, 4H); 4.40 (singlet, CH, 1H); 5.99 (broad singlet, OH, 1H); 7.44 (singlet, Me, 3H). (Found: C, 57.7; H, 4.8; N, 6.8. $C_{10}H_9NO_4$ requires C, 58.0; H, 4.4; N, 6.8%).

The benzisoxazolone (125; R=Ac) dissolved in cold 10% v/v aqueous sodium hydroxide and reacidified with 2N aqueous sulphuric acid, gave 2,1-benzisoxazolone (130) identified by its m.p. 109-111° (lit.,[164] 112°) and i.r. spectrum with an authentic sample.

(b) A solution of 2,1-benzisoxazolone (130) (0.17 g.) and phenylglyoxal (0.1 g.) in dry benzene (20 ml.) was cooled and treated dropwise, with stirring, with stannic chloride (0.21 ml.). Tar formed, and after 15 minutes the mixture was poured onto ice (10 g.). The separated organic layer, dried and evaporated under reduced pressure, yielded a brown gum (0.1 g.), which gave a solid (0.05 g.) in contact with benzene. The i.r. spectrum

showed this to be a mixture of N-(α-hydroxyphenacyl)-2,1-benzisoxazolone (125; R=Bz) and N-phenylglyoxyloylanthranilic acid (126; R=Bz). Separation was achieved by shaking with chloroform and aqueous sodium bicarbonate. The chloroform layer was dried and evaporated, affording the benzisoxazolone (125; R=Bz) (0.03 g.), m.p. 125°, i.r. spectrum identical with that of a sample prepared above. The aqueous layer was acidified and extracted with chloroform. Evaporation of the dried extract gave the N-acylanthranilic acid (126; R=Bz) (0.015 g.), m.p. 195°, i.r. spectrum identical with that of a sample prepared above.

Reactions of Substituted o-Nitrophenylethylene Oxides with Acetic Acid and Formic Acid.

1-Benzoyl-2-o-nitrophenylethylene oxide and glacial acetic acid.

The epoxide (94; R^1=Bz, R^2=H) (2.5 g.) was refluxed in glacial acetic acid (50 ml.) for 2 hours. The solution was concentrated under reduced pressure, and the residue treated with water and chloroform. Evaporation of the washed (sodium bicarbonate) and dried chloroform extract gave a semi-solid (1.3 g.) which was dissolved in benzene and diluted with petrol, yielding 1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinoline (99; R=Ph, X=H), as colourless needles (0.15 g.), m.p. 265-270° (from methanol), i.r. spectrum identical with that of an authentic sample, prepared as above. The benzene/petrol mother liquors, on evaporation, yielded a dark gum (0.8 g.), which was not identified.

Acidification of the bicarbonate extract with 2N aqueous sulphuric acid gave an oil, which was extracted into chloroform. The dried chloroform extract, concentrated under reduced pressure, afforded a red gum (1.2 g.), which gave a red solid (0.24 g.) when triturated with methanol. Crystallised, the solid formed red platelets, m.p. 214-218° (decomp.) (from aqueous ethanol), $\nu_{max.}$ 1725, 1690 and 1680 $cm.^{-1}$ (Found: C, 63.8; H, 4.0; N, 11.2%). This material was not identified. Evaporation of the methanol mother liquors afforded a red gum from which hot light petroleum extracted benzoic acid (0.25 g.) m.p. 116°, i.r. spectrum identical with that of an authentic sample.

1-Benzoyl-2-o-nitrophenylethylene oxide and formic acid.

The epoxide (94; R^1=Bz, R^2=H) (2.69 g.) was refluxed in 98% formic acid (30 ml.) for 45 minutes. Excess formic acid was then removed under reduced pressure, leaving a black residue, which was dissolved in chloroform, shaken first with water, and then with saturated aqueous sodium bicarbonate. Evaporation of

the dried chloroform layer afforded a dark tar (1.1 g.). Thin layer chromatography on silica, on elution with benzene or ether indicated the presence of at least three products. Attempted separation by chromatography on alumina was unsuccessful. The sodium bicarbonate layer was acidified with 2N aqueous sulphuric acid, and extracted with chloroform. Evaporation of the dried extract yielded a black oil (1.1 g.) which solidified when triturated with petrol. The solid was collected and crystallised twice from aqueous ethanol, to yield N-phenylglyoxyloylanthranilic acid (126; R=Bz) as off white needles (0.4 g.), m.p. 190-192°, i.r. spectrum identical with that of a sample prepared previously. Evaporation of the petrol mother liquors afforded benzoic acid (0.11 g.), m.p. 114-116°, i.r. spectrum identical with that of an authentic sample.

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Base-catalysed Transformations of *NN*-Disubstituted *o*-Nitrobenzamides

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Base-catalysed Transformations of *NN*-Disubstituted *o*-Nitrobenzamides

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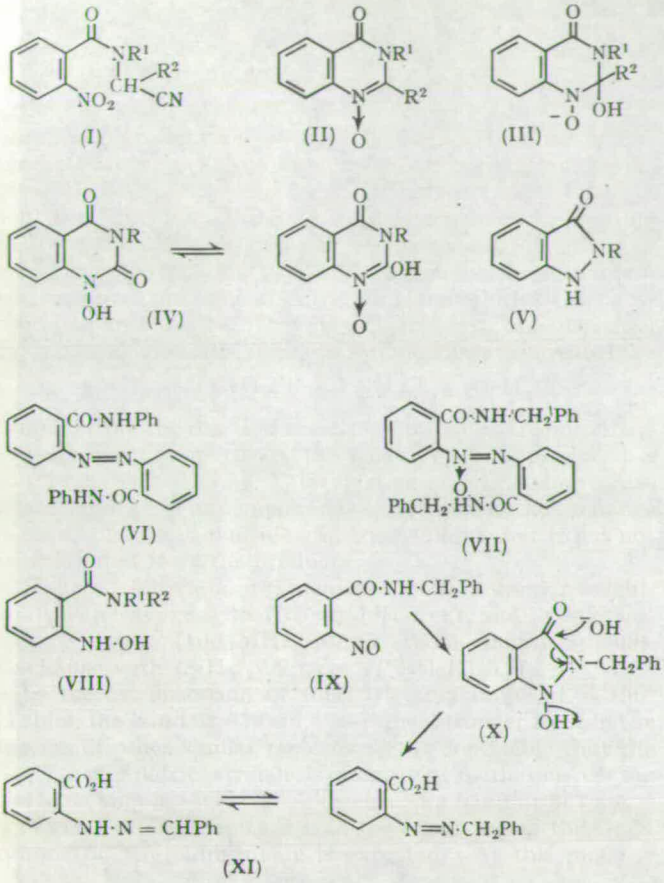
IN the formation[1] of 2-alkoxy-1-hydroxyquinazolones by base-catalysed cyclisation of *N*-cyanomethyl-*o*-nitrobenzamide (I; $R^1 = R^2 = H$), interaction of the nitro-group with the side-chain cannot be preceded by isomerisation to an aci-nitro-tautomer.[2] Cyclisation reactions of this type[2,3] provide strong evidence for the ability of the intact nitro-group to function as the electrophile in aldol-type condensations. Further support for this contention has now been obtained from a study of the base-catalysed reactions of a series of *NN*-disubstituted-*o*-nitrobenzamides (I).

Treatment of the amides (I; R^1 = Me, CH_2Ph, or Ph, $R^2 = H$) with a variety of basic catalysts (ethanolic sodium ethoxide; aqueous sodium hydroxide; piperidine) afforded consistently high yields of products subsequently identified as the 1-hydroxyquinazolinediones (IV; R = Me, CH_2Ph, or Ph). These potentially tautomeric heterocycles are presumably derived from an initially formed cyanoquinazoline 1-oxide (II; R^1 = Me, CH_2Ph, or Ph, R^2 = CN) by conversion into, and loss of hydrogen cyanide from, an adduct (III; R^2 = CN).[1] The higher yields of cyclised products obtained from the amides (I; R^1 = Me, CH_2Ph, or Ph, $R^2 = H$) compared[1] with the parent compound (I; $R^1 = R^2 = H$) may be attributed to the enhanced acidity of the methylene group in the former, and to the absence of side reactions stemming from the presence in the side-chain of a competing nucleophilic centre (*i.e.* ·*N*-*H*).

In contrast, the methyl-substituted amides (I; R^1 = CH_2Ph or Ph, R^2 = Me) warmed with sodium ethoxide in ethanol afforded the indazolone derivatives (V; R = CH_2Ph



or Ph). Since under similar conditions the amide (I; R^1 = H, R^2 = Me) is converted into the oxide (II; R^1 = H, R^2 = Me), indazolone formation in these reactions is compatible with a course involving the initial formation of the quinazoline 1-oxides (II; R^1 = CH_2Ph or Ph, R^2 = Me), followed by ring opening of the derived hydrates (III; R^1 = CH_2Ph or Ph, R^2 = Me), and cyclisation of the resulting *N*-acetylhydroxylamines (VIII; R^1 = CH_2Ph or Ph, R^2 = Ac) or the corresponding hydroxylamino-amides (VIII; R^1 = CH_2Ph or Ph, R^2 = H). The presence of hydroxylamino-intermediates in these reactions may be inferred from the formation of a mixture of the indazolone (V; R = Ph) and the azo-compound (VI) when the amide (I; R^1 = Ph, R^2 = Me) was warmed with sodium carbonate in aqueous ethanol. On the other hand the conversion of the amide (I; R^1 = CH_2Ph, R^2 = Me) under similar conditions into a mixture of the azoxy-compound (VII) and the hydrazone (XI), requires the additional presence of the nitrosoamide (IX) readily produced by mild oxidation[4] of the hydroxylamine (VIII; R^1 = CH_2Ph, R^2 = H) in the alkaline medium. Moreover ring opening of a 1-hydroxyindazolone (X) derivable from the nitrosoamide (IX) by cyclisation, is a plausible course for the formation of the hydrazone (XI). Such a course finds analogy in the known[3,5] base-catalysed ring scission of 1-hydroxyindolinones and is further substantiated by the conversion of the readily accessible *o*-nitrosobenzanilide[6] in warm aqueous ethanolic sodium carbonate into azobenzene 2-carboxylic acid. Attempts to isolate the intermediate 1-hydroxyindazolones from reactions of this type have so far been unsuccessful.

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