Studies of Neighbouring Group Interaction in ortho-Nitrobenzene Derivatives

by

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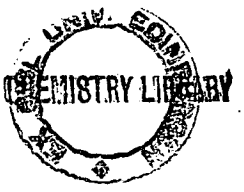

Post-Graduate Lecture Courses

Attended from 1973-1976.

" Carbonium Ions " by B. Capon (Univ. of Glasgow)

" The Use of Phosphorous in Organic Synthesis " by Prof. J.I.G. Cadogan (Univ. of Edinburgh)

" Biomimetic Organic Chemistry " by Dr. M. Paton (Univ. of Edinburgh)

" Molecular Rearrangements " by Dr. G. Tennant (Univ. of Edinburgh)

" Electrocyclic Processes " by Dr. A. Bellamy (Univ. of Edinburgh)

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I would like to express my gratitude to Dr. G. Tennant for his constant guidance throughout the course of this work and to Prof. J. I. G. Cadogan for the opportunity to work in this department. Thanks are also due to members of the technical staff for analytical and spectroscopic services. Finally thanks are due to Mrs. J. Gorrie for her care and patience in typing this thesis.

DECLARATION

I declare that this thesis is entirely my own composition and that the work described herein, has not been submitted for any other degree. Where work due to others has been included, this fact has been indicated.

ABSTRACT OF THESIS

A new synthesis of quinoline-2,3-dicarboxylic acid 1-N-oxides has been developed, involving the base-catalysed cyclisation of 2-nitrobenzylidene derivatives having an active methylene group in the side-chain. The hitherto inaccessible 2-nitrobenzylidene derivatives were prepared by the condensation of 2-nitrobenzaldehydes with the triphenylphosphoranes of electron-deficient olefines.

The novel base-catalysed cyclisation of 3-(2'-nitrobenzoyl)-pentane-2,4-dione as first described by Bayne (Ph.D. Thesis, Edinburgh 1975), has been extended to a variety of 2-nitrobenzoylalkanones, to give a convenient synthesis of 2-acyl-3-hydroxyquinolines. Suitable substrates were prepared by the reaction of 2-nitrobenzoyl chlorides with the magnesium enolate of active methylene compounds. However, only purely ketonic substrates cyclised, amide, ester and sulphonyl substrates failing to do so. Attempts to gain further evidence in support of the assigned structures as quinolines were largely unsuccessful. In support of a dianionic species as the reactive intermediate in these cyclisations, sodium amide in liquid ammonia has been shown to catalyse the formation of 2-acetyl-3-hydroxy-6-methylquinoline from 3-(5'-methyl-2'-nitrobenzoyl)pentane-2,4-dione.

The acid-catalysed reactions of 2-acyl-3-(2'-nitrophenyl)-oxiranes have been further investigated. The reaction of 2,2-dibenzoyl-3-(2'-nitrophenyl)oxirane with hydrogen chloride in dioxan has been improved upon by heating the oxirane with concentrated hydrochloric acid in acetic acid to give a near quantitative yield of the product, 6-chloro-1,3-dihydroxy-2-phenylquinolin-4(1H)-one. However, those oxiranes with a halogen substituent in the 5-position of the nitro-

phenyl ring faied to yield cyclised products. The reaction of 2-acyl-3-(2'-nitrophenyl)oxirane with acetyl chloride in acetic acid afforded 3-acetoxy-6-chloroquinolin-4(1H)-one derivatives by an unknown mechanism. Also, in the presence of polyphosphoric acid, various 2-acyl-3-(2'-nitrophenyl)oxiranes afforded N-glyoxyloylanthranilic acid derivatives. On the other hand, substituted 2,2-dibenzoyl-3-(2'-nitrophenyl)oxiranes afforded a new synthesis of 3-(phenylglyoxyloyl)-2,1-benzisoxazoles.

The photochemical cyclisation of β-amino-2-nitro-β-(4'-nitrophenyl)styrene to give 3-(4'-nitrophenyl)cinnoline 1-N-oxide was reinvestigated and extended to the simple 6-bromo and 6-chlorocinnolines. Attempts to rigorously prove the structure of these products were unsuccessful. An interesting solvent dependancy was discovered. No cinnoline products were isolated from solvents other than ethanol, but in dioxan, acetonitrile or acetone, the products were 2-(4'-nitrophenyl)indolin-3-one 1-N-oxides.

A new synthesis of 3-aminocinnoline 1-N-oxides has been developed, involving the photochemical cyclisation of 2-nitrophenylacetamidine derivatives.

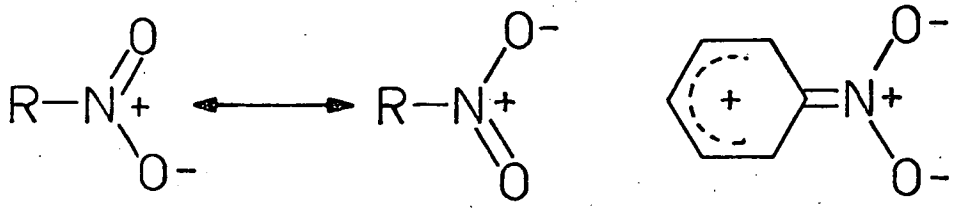
Contents

Chapter I

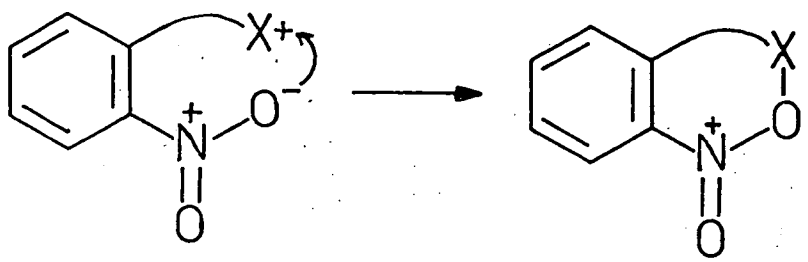
INTRODUCTION

Neighbouring Group Interactions in 2-Nitrobenzene Derivatives

In aliphatic nitro compounds the nitro group may be considered as a resonance hybrid of the canonical forms [(1) ↔ (2)] . However, when the nitro group is directly attached to a benzene ring, a third canonical form (3) must be considered[1] in which the ring bears a positive charge and the nitro group a net negative charge. The contribution of this third canonical form (3) implies that the nitro group has a tendency to be coplanar with the ring due to the partial double bond character imparted to the carbon-nitrogen bond. This effect will tend to place the oxygen atoms of the nitro group in close steric proximity to an ortho-substituent on the benzene ring thus promoting one possible mode of interaction namely, that in which the negatively charged oxygen atom undergoes electrophilic attack by the side-chain [(4) → (5)] .

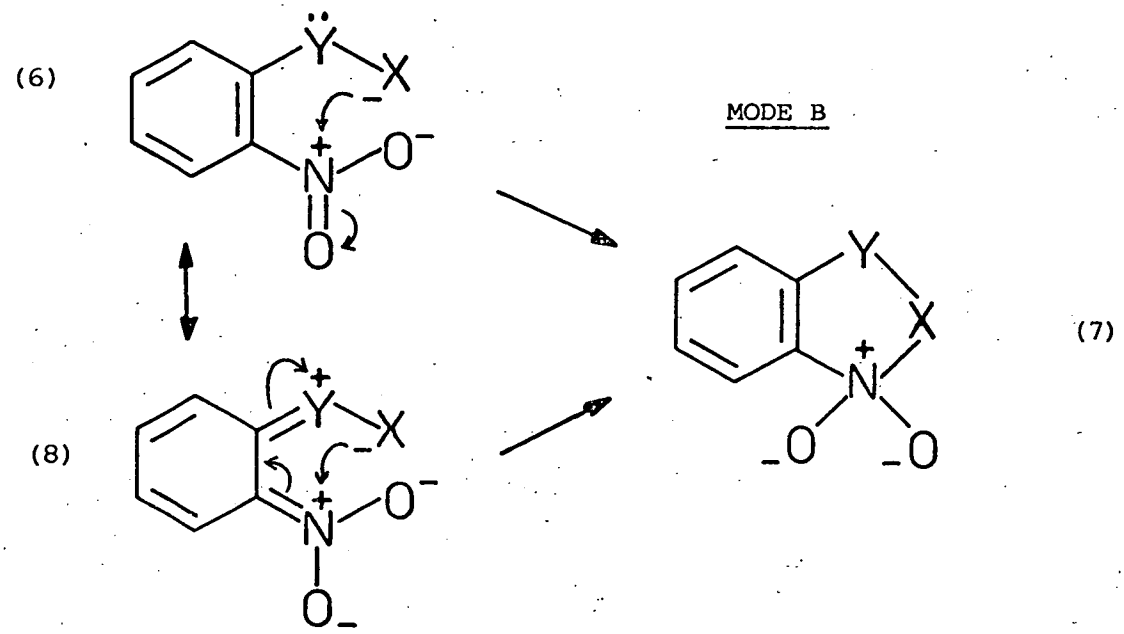


(1) (2) (3)



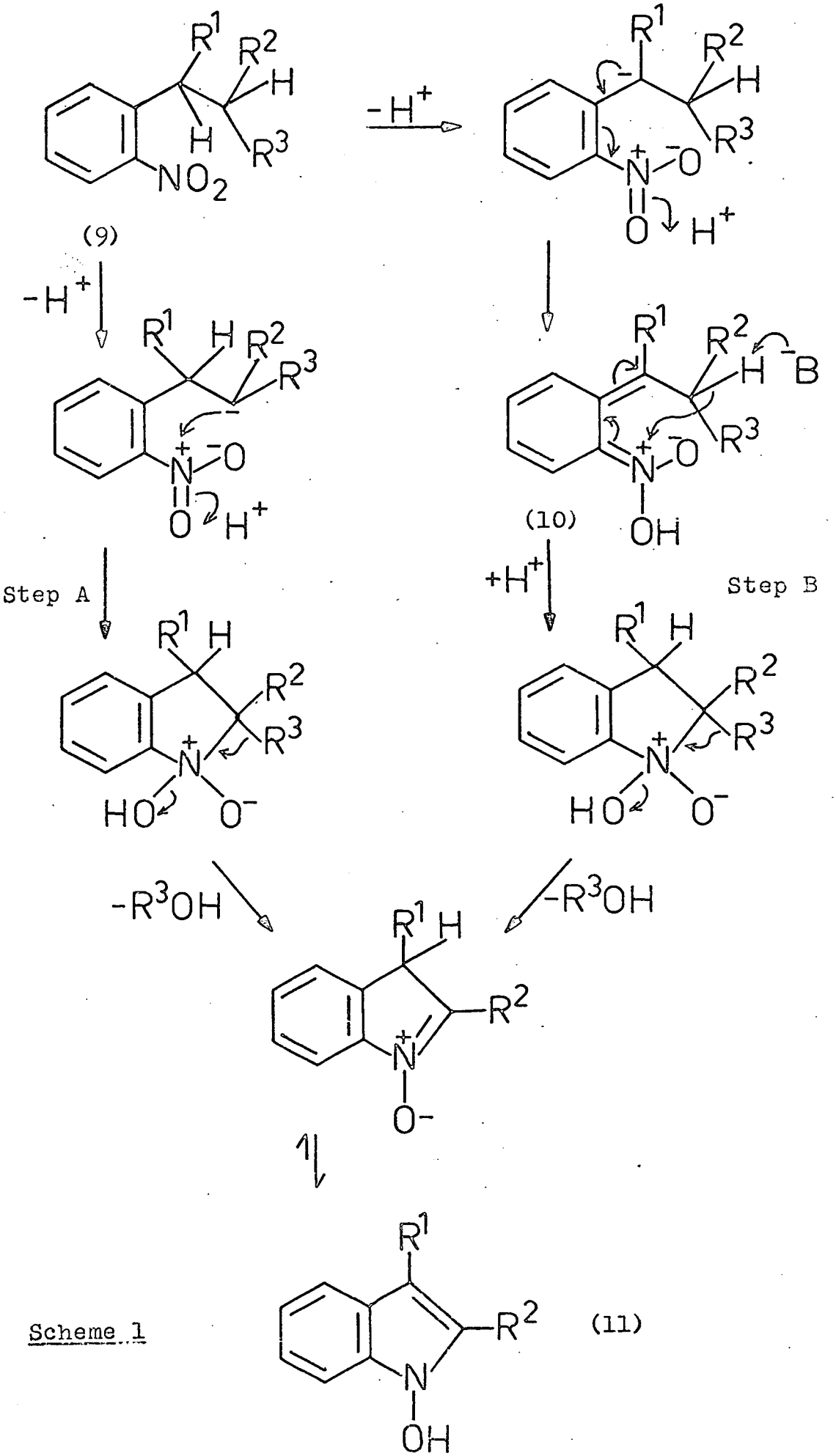
(4) Mode A (5)

Another possible mode of interaction would be that in which the nitro group undergoes nucleophilic attack by the side-chain at the positively charged nitrogen atom [(6) → (7)] or [(8) → (7)] .



In practice both modes of interaction are observed. The latter, mode B, is the most easily demonstrated as, in most cases the product is found to contain the N → X bond formed in the initial interaction. Mode A on the other hand is only observable indirectly since intermediates of the type (5) are not usually isolated but tend to undergo further complex transformations leading to the ultimate products. That neither mode of interaction is found to occur intermolecularly except in a few isolated cases,[2] demonstrates the steric requirement for nitro group-side-chain interaction.

The following thesis describes the results of investigations into new examples of the nitro group-side-chain interactions described above. The presentation and discussion of these results is preceded by a summary of related reactions already described in the literature.


(9)
(10)
Step A
Step B
Scheme 1
(11)

In addition, the thesis also includes an account of investigations into the photochemical reactions of some ortho-nitrobenzene derivatives and the discussion and presentation of these results is again preceded by a summary of related reactions already described in the literature.

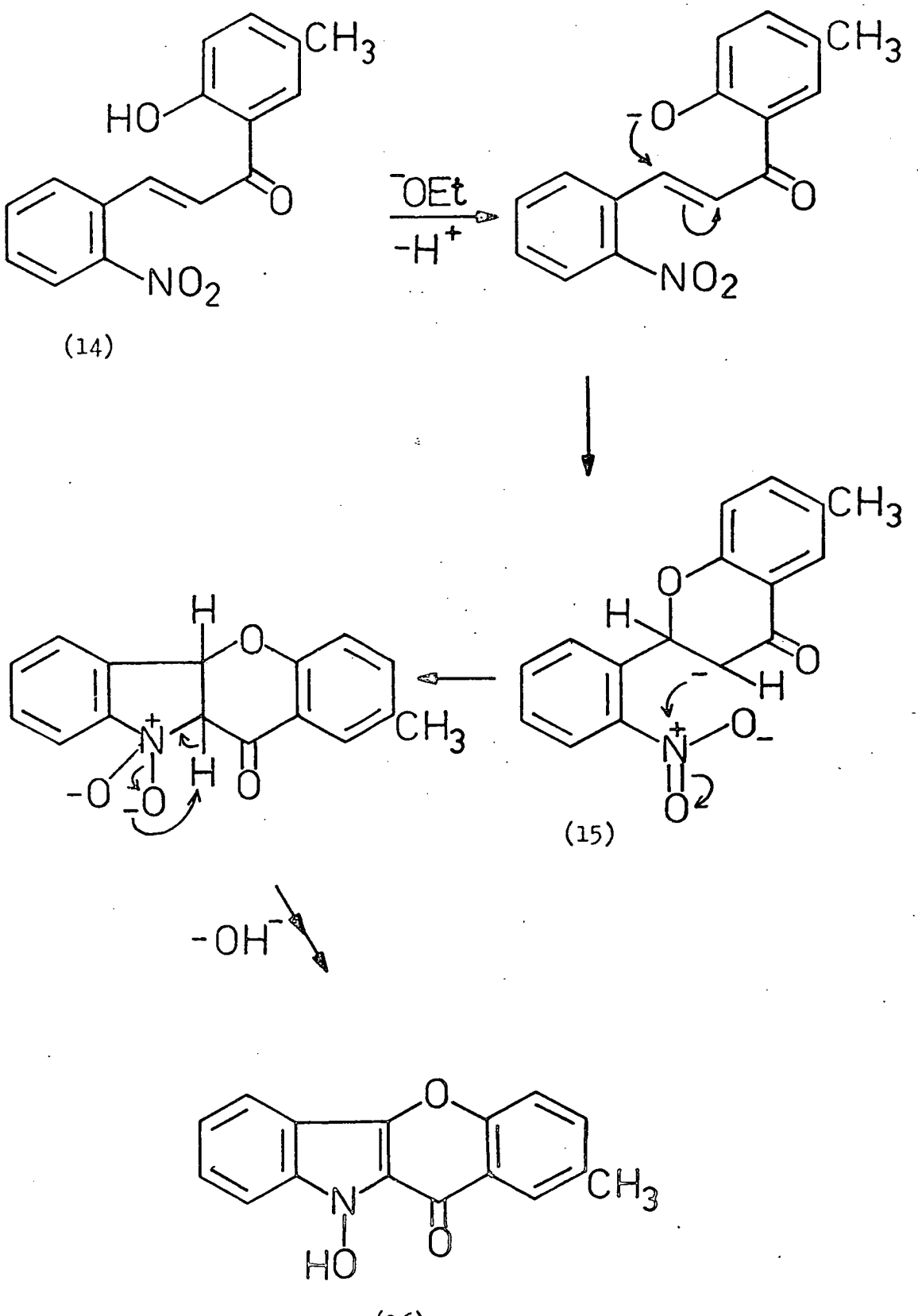
A Summary of Reactions Involving Nitro Group-Side-Chain Interactions in 2-Nitrobenzene Derivatives

A. Interaction between the Nitro Group and a Nucleophilic Carbanionic Centre in the Side-Chain

The positively charged nitrogen atom, of the nitro group, is susceptible to nucleophilic attack by carbanionic centres in ortho-side-chains of 2-nitrobenzene derivatives in reactions that are analogous to aldol condensations in which the nitro group plays an equivalent role to the carbonyl moiety. Reactions of this type often lead to cyclisation with formation of a carbon-nitrogen double bond, the nitrogen atom of which is oxygenated. Hence the products of such reactions will be heterocyclic N-oxides or their N-hydroxy tautomers which, in many cases, cannot be synthesised by more conventional methods.

(i) Cyclisations Leading to Five-Membered Heterocycles

1-Hydroxyindoles (11a-d)[3-6] are produced in largely good yields by the base-catalysed cyclisation of 2-nitrobenzyl derivatives (9a-d). The base-catalysed nature of these cyclisations and the requirement of at least one electron-withdrawing group in the β-position of the side-chain demonstrates their similarity to aldol-type condensations. Since the ortho- nitrobenzyl carbanions can tautomerise (scheme 1) to the aci-nitro structures (10), this cyclisation may involve either nucleophilic attack on the nitro group [step (A)] or on the modified nitro group [step (B)]. However it is not possible, in this case, to make a decision as to the actual mechanism operating.

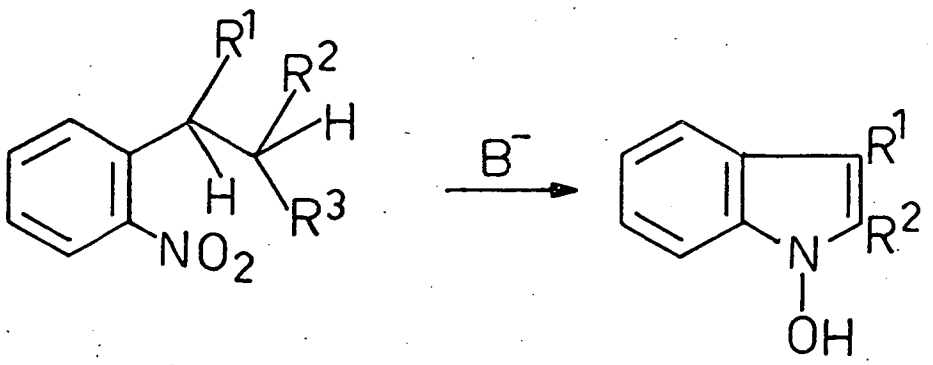


(14)

(15)

(16)

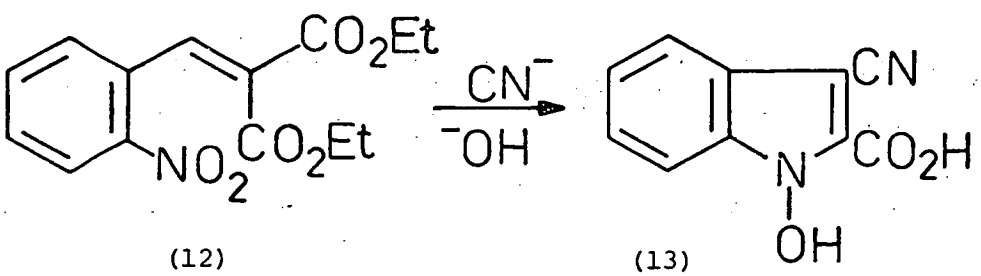
Scheme 2



(9)	R^1	R^2	R^3
a;	H	CO_2Me	CO_2Me
b;	H	COMe	CO_2Et
c;	CN	p-NO_2Ph	H
d;	CN	COPh	H

(11)	R^1	R^2
a;	CO_2H	CO_2H
b;	H	COMe
c;	CN	p-NO_2Ph
d;	CN	COPh

Cyclisations[4,5] of a closely related type are involved in the formation of 1-hydroxyindoles by the reaction of 2-nitrobenzylidene derivatives with cyanide ion [e.g. (12) → (13)].

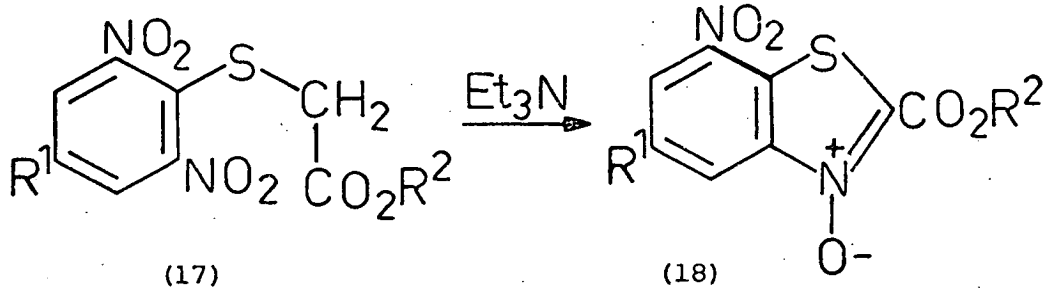


(12) (13)

An interesting example of this type of cyclisation (Scheme 2) has been reported by Dean et.al.[7] They have shown that 5'-methyl-2'-hydroxy-2-nitrochalcone (14) undergoes base-catalysed cyclisation via the flavone (15), in high yield, to afford 10-hydroxy-2-methyl-11H-[1]-benzopyrano[3,2-b]indol-11-one (16). This reaction which is analogous to the cyanide ion-catalysed formation of N-hydroxyindoles from

2-nitrobenzylidene derivatives, involves initially an intramolecular Michael addition of the phenolate anion to the unsaturated side-chain followed by an aldol-type condensation between the nitro group and the ortho acidic β-centre produced.

The base-catalysed cyclisation[8] of 2-nitrophenylthioacetic esters (17) to benzothiazole N-oxides (18) provides a straightforward example of an aldol-type ortho-nitro group side-chain condensation leading to a five-membered heterocyclic N-oxide. These cyclisations are catalysed by triethylamine and give high yields of the products (18) which are not available by more orthodox synthetic methods such as peracid oxidation of the corresponding benzothiazoles.

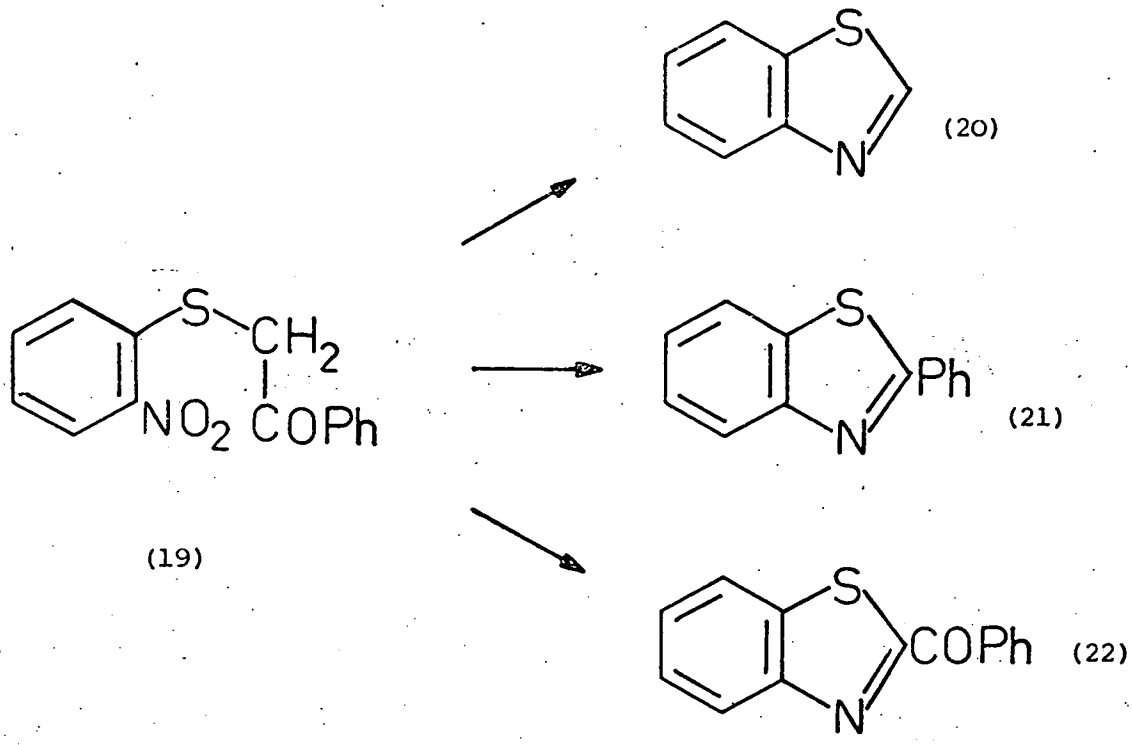


(17) (18)

R^1= CF_3, NO_2

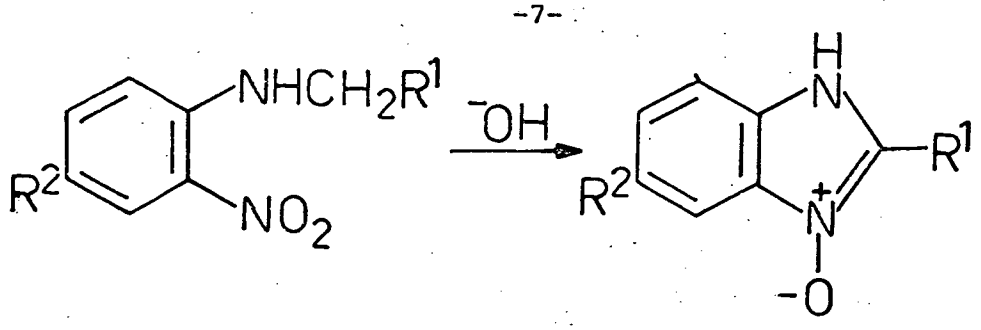
R^2= Me , Et

In contrast to the ready formation of benzothiazole N-oxides by the triethylamine-catalysed cyclisation of 2-nitrophenylthioacetic esters (17), the similar substrate (19)[9] under strongly basic conditions affords a complex mixture from which the benzothiazoles (20), (21) and (22) are isolated in low yields.



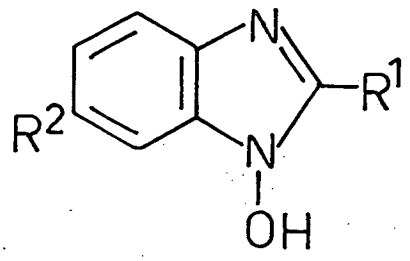
The author[9] has shown that the proportion of benzothiazole (20) increases as the strength of the base increases and that the ketone (22) is efficiently converted into benzothiazole (20) by potassium tert. butoxide in tert. butanol. However, the point at which the reduction involved in this reaction occurs, is still unclear.

An important route to benzimidazole N-oxides (24) involves the cyclisation by hydroxide ion of N-substituted 2-nitroanilines (23) containing an active methylene group.[10-13] The mechanism of these reactions would appear to be similar to that involved in the N-hydroxyindole synthesis described previously. In relation to the mechanistic aspect of benzimidazole N-oxide formation Smith et.al.[14] compared the base-catalysed cyclisation of substituted N-benzyl-2-nitroaniline derivatives (25 a-d). Whereas (25b) failed to cyclise, the para-nitrobenzyl derivative (25d) did produce the corresponding benzimidazole

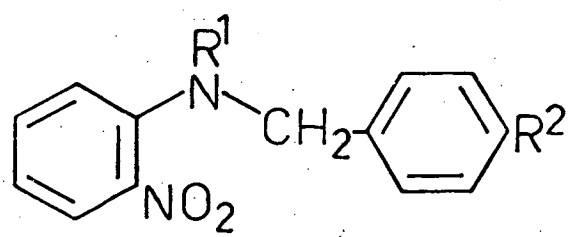


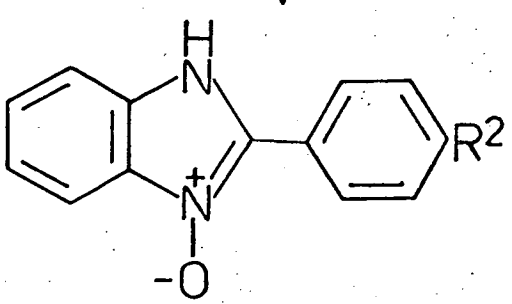
(23)

(24)



N-oxide (28b) showing the necessity of an acidic methylene group. However, both (25a) and (25c) did cyclise under identical conditions to give the corresponding benzimidazole-N-oxides (28a) and (28b), respectively. A kinetic study showed that the para-nitrobenzyl derivative (25c)

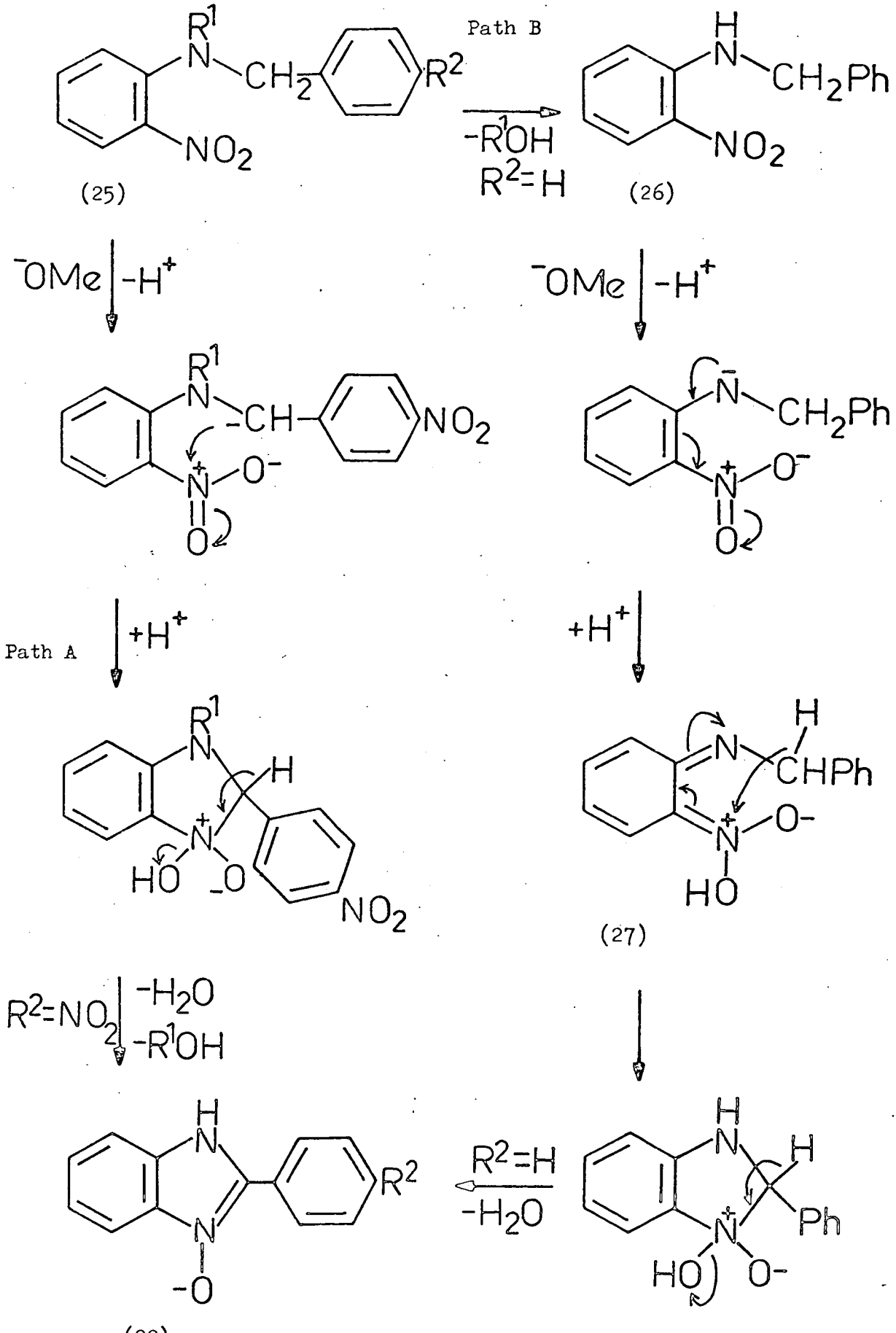




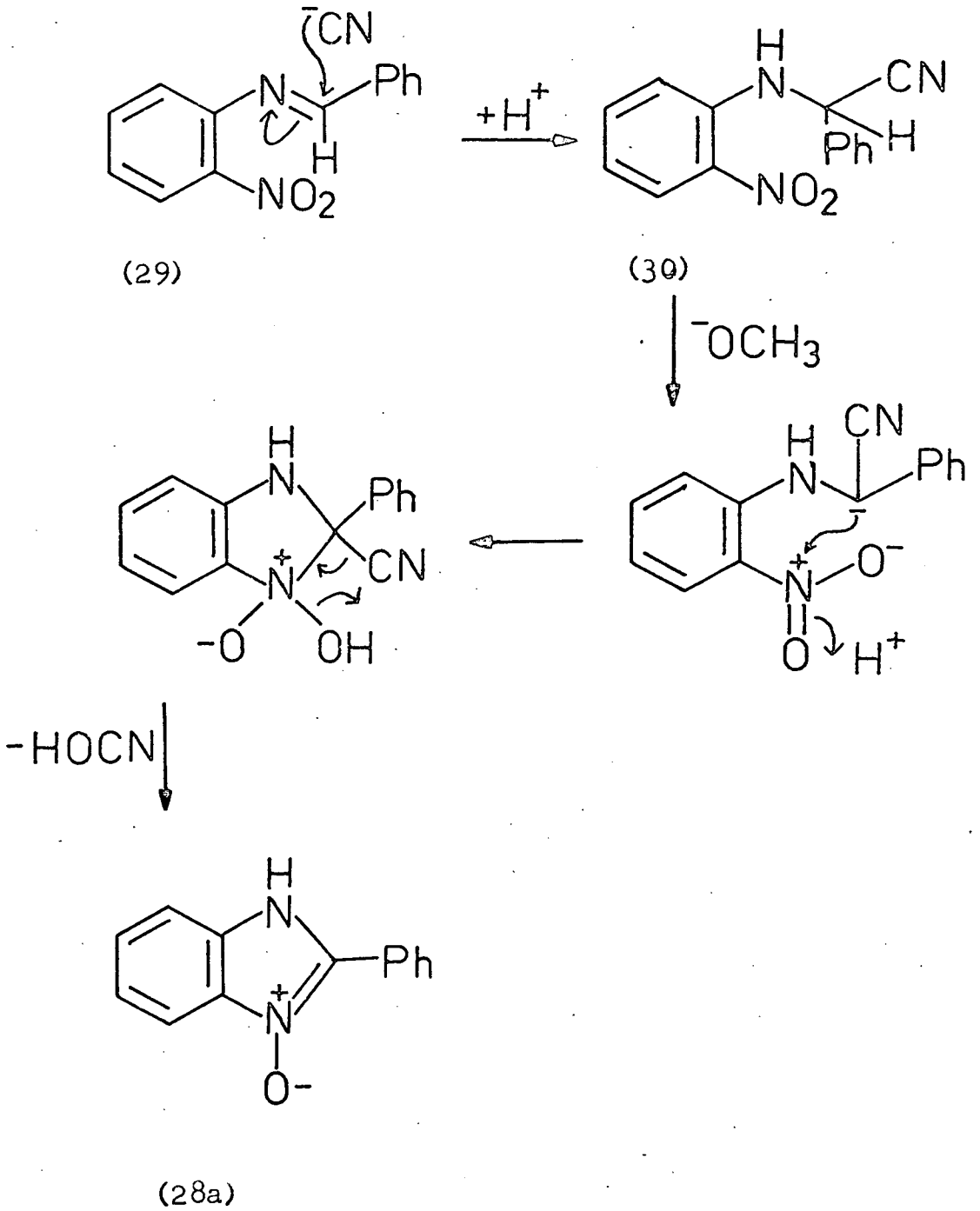
(25)	R^1	R^2
a;	PhCO	H
b;	TSO_2	H
c;	PhCO	NO_2
d;	TSO_2	NO_2

(T = para-tolyl)

(28)	R^2
a,	H
b,	NO_2


Path B
-R¹OH
R²=H
(25)
(26)
⁻OMe
-H⁺
⁻OMe
-H⁺
Path A
+H⁺
+H⁺
(27)
R²=NO₂
-H₂O
-R¹OH
R²=H
-H₂O
(28)

Scheme 3


CN
Ph
N
H
NO2
+H+
H
N
CN
Ph
H
NO2
(29)
(30)
-OCH3
H
N
CN
Ph
O-
O
H+
H
N
Ph
CN
N
-O
OH
-HOCN
H
N
Ph
N
O-
(28a)

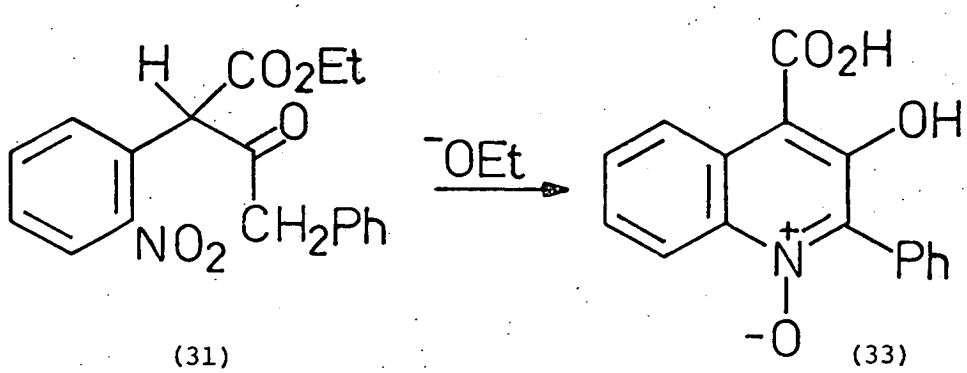
Scheme 4

cyclised prior to deacylation (i.e. Path A of Scheme 3). However, the benzyl derivative (25a) would not be expected to cyclise since the methylene group is too weakly acidic as indicated by the failure of (25b) to undergo cyclisation. Deacylation of the substrate (25a) would however produce N-benzyl-2-nitroaniline (26) which has been shown to cyclise to the benzimidazole-N-oxide (28a) (Path B of Scheme 3). This fact demonstrates the importance of there being a mobile benzylic hydrogen in such compounds which presumably allows formation of the aci-nitro tautomer(27) containing a more acidic methylene group than that of the nitro tautomer.

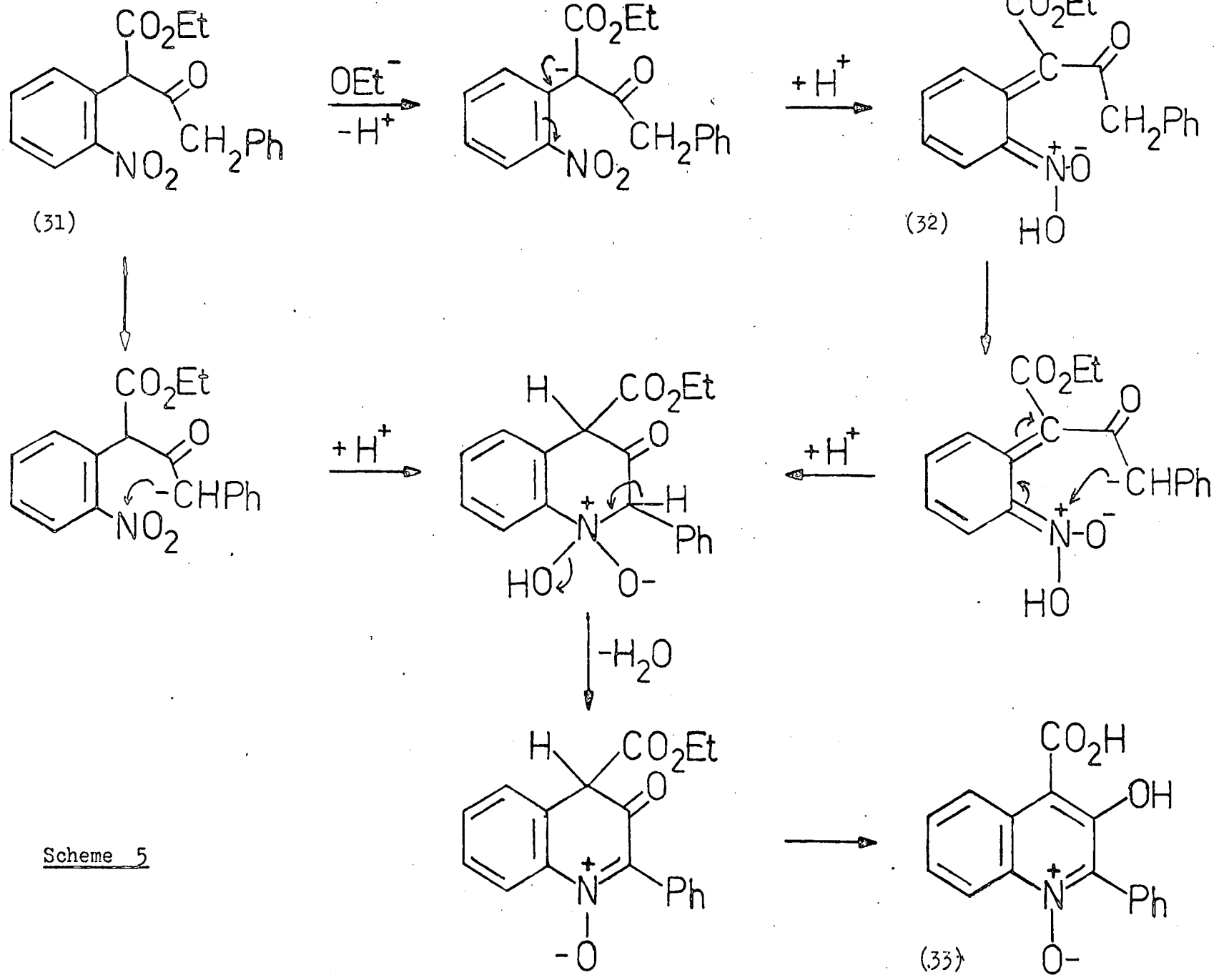
The benzimidazole N-oxide (28a) may also be prepared under milder conditions[15] by the cyclisation of the anil (29) with methanolic potassium cyanide (Scheme 4). This transformation can be explained by the initial formation of a hydrogen cyanide adduct (30) and its aldol-type cyclisation to give the product (28a).

(ii) Cyclisations Leading to Six-Membered Heterocycles.

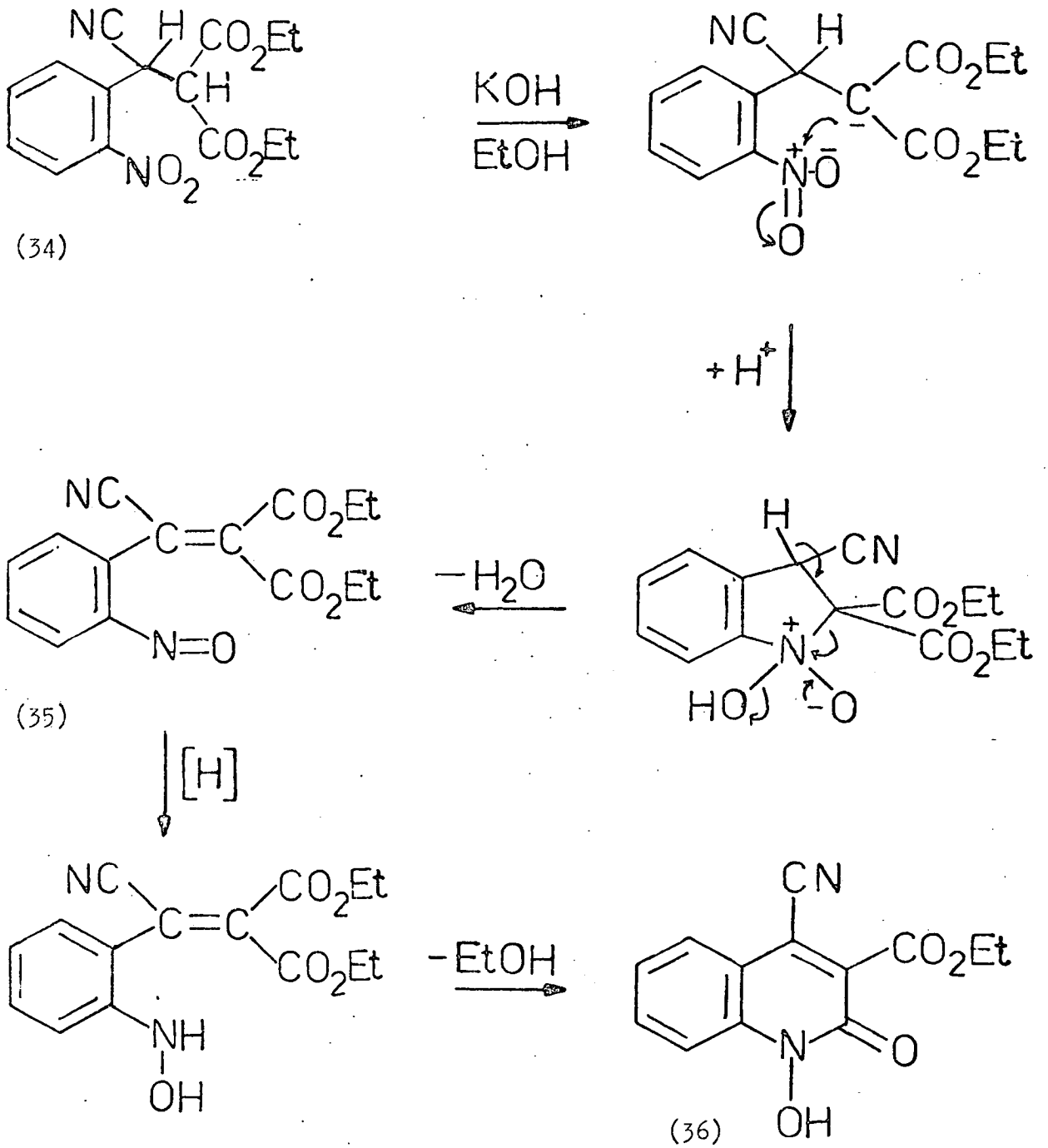
Aldol-type condensation involving carbanionic attack on the nitro group to ultimately give six-membered heterocycles is illustrated by the conversion[16,17] of the keto-ester (31) in ethanolic sodium ethoxide into the quinoline N-oxide (33). The acidic nature of the benzylic methine



(31) (33)



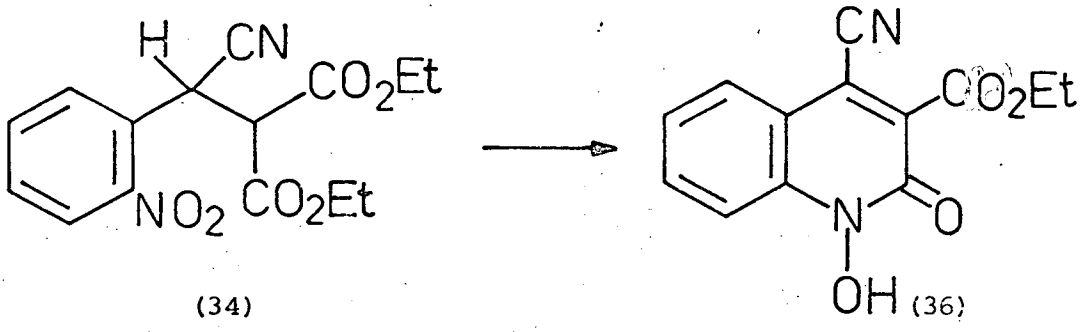
Scheme 5


NC H CO2Et
CH
CO2Et
NO2
(34)
KOH
EtOH
NC H
CO2Et
C
CO2Et
N O
O
+H+
NC
C=C
CO2Et
CO2Et
N=O
(35)
−H2O
H
CN
CO2Et
CO2Et
N
HO
O
[H]
NC
C=C
CO2Et
CO2Et
NH
OH
−EtOH
CN
CO2Et
N
O
OH
(36)

Scheme 6

hydrogen allows the possible implication of an aci-nitro tautomeric form of the substrate (32) in the reaction mechanism. (Scheme 5).

In contrast to their cyclisation in weakly basic media to 1-hydroxy-indoles (cf. page 3) ortho-nitrobenzyl derivatives of the type (34) are converted by treatment with ethanolic potassium hydroxide into hydroxamic acids of the type (36)[4]. Reactions of this type can be explained in

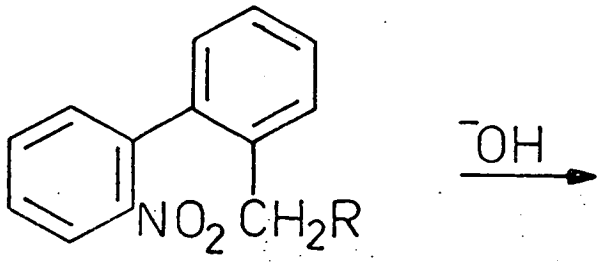


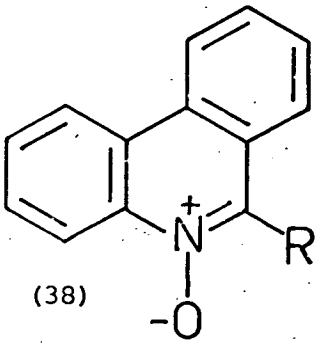
(34) (36)

terms of a course (Scheme 6) initiated by nucleophilic attack on the ortho-nitro group by a carbanionic centre generated in the side-chain followed by dehydration to give the nitroso intermediate (35). The nitroso intermediate then requires to undergo reduction in the ethanolic alkaline medium to account for formation of the formal quinoline 1-N-oxide which exists as the hydroxamic acid (36).

The cyclisation[18,19] of 2-nitrobiphenyl derivatives (37) having an active methylene group in the 2'-position is catalysed by methanolic sodium hydroxide and affords phenanthridine N-oxides (38).

The cyclisation of the amide [(37a) → (38a)][15] proceeds less readily than that of the nitrile [(37b) → (38b)] while the benzyl derivative (37c) fails to cyclise at all. These substituent effects on the ease of cyclisation together with the general base-catalysis observed, again demonstrates the aldol-type nature of these reactions.





(38)

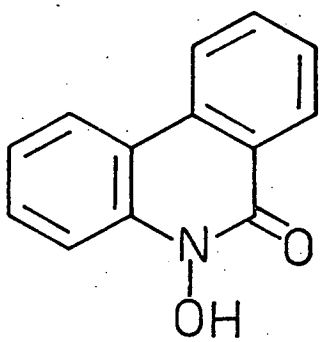
(37) R

a; $CONH_2$

b; CN

c; Ph

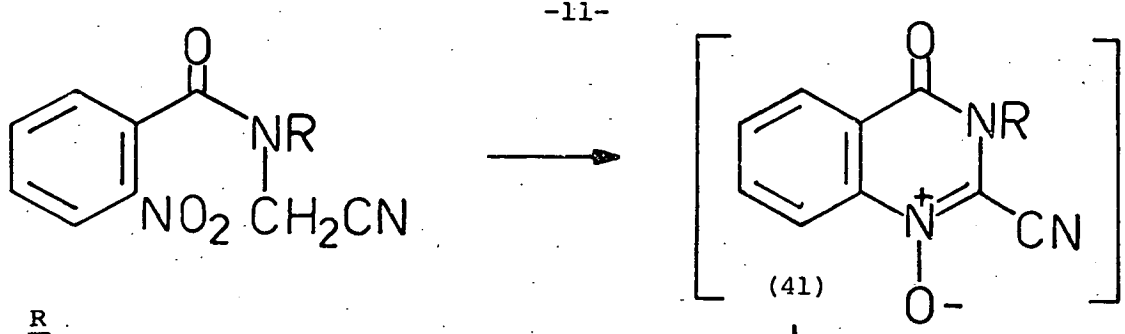
d; SO_2Ph



(39)

The sulphonyl compound (37d) cyclises readily in the presence of methanolic sodium hydroxide to give, not the expected sulphone (38d) but the hydroxamic acid (39) which presumably arises by nucleophilic displacement of the sulphonyl group in the sulphone (38d) by hydroxide ion.

In many of the base-catalysed cyclisations already discussed, both a nitro and an aci-nitro mechanism have been possible. However, the base-catalysed cyclisation reactions of 2-nitrobenzamidoacetonitrile derivatives to give N-oxygenated quinazolines can only proceed by interaction of the carbanionic centre in the side-chain with the intact ortho-nitro group and cannot involve an aci-nitro tautomer. Thus, in ethanolic sodium ethoxide the 2-nitrobenzamido-acetonitrile derivatives (40) give,[20] by direct aldol-type condensation, the N-hydroxyquinazolinediones (42) presumably via the intermediacy of the quinazoline N-oxides (41). The N-hydroxyquinazolines (42a-d) are formed in high yield. On the other hand, (42a) is only formed in low yield when the amide (40a) is heated under reflux with potassium tert-butoxide in tert.butanol. When the same substrate is heated under reflux with ethanolic sodium ethoxide the ether (43) is isolated, again



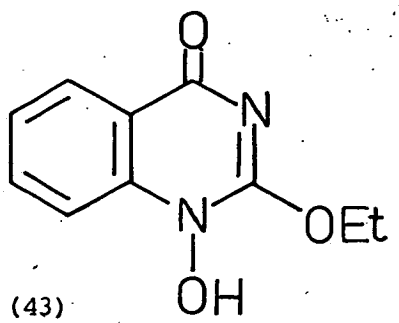
(40) R

a; H

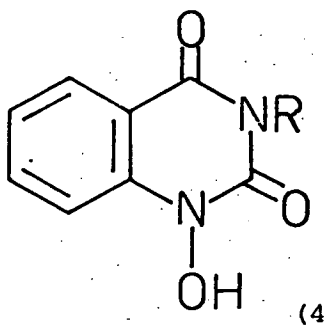
b; CH_2

c; CH_2Ph

d; Ph



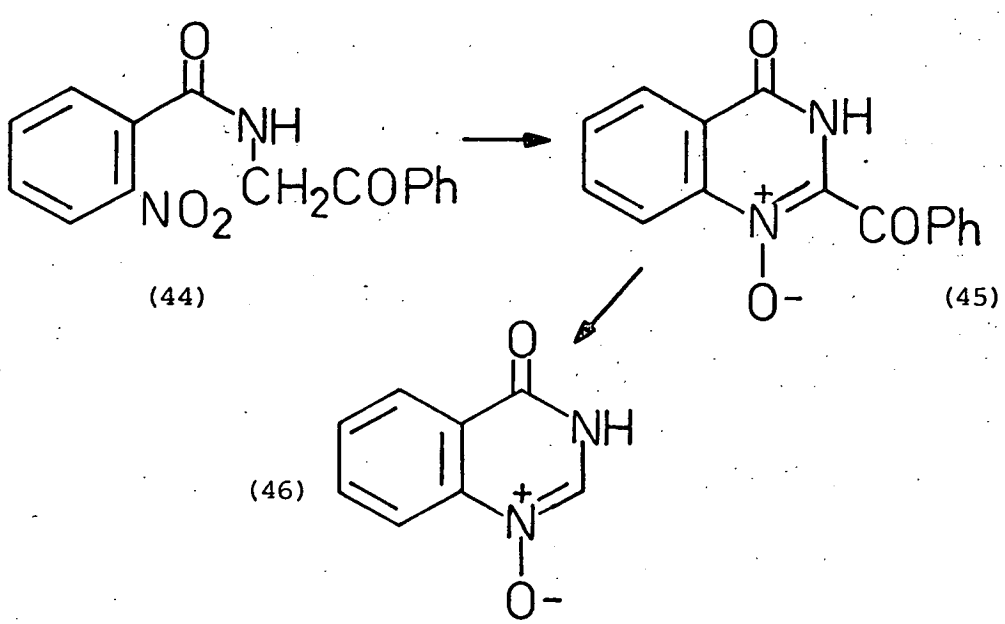
(43)



(42)

only in low yield. This decreased efficiency of cyclisation is attributed to the weakly acidic amide nitrogen forming a competitive nucleophilic centre with the methylene group under the strongly alkaline conditions of the reaction.

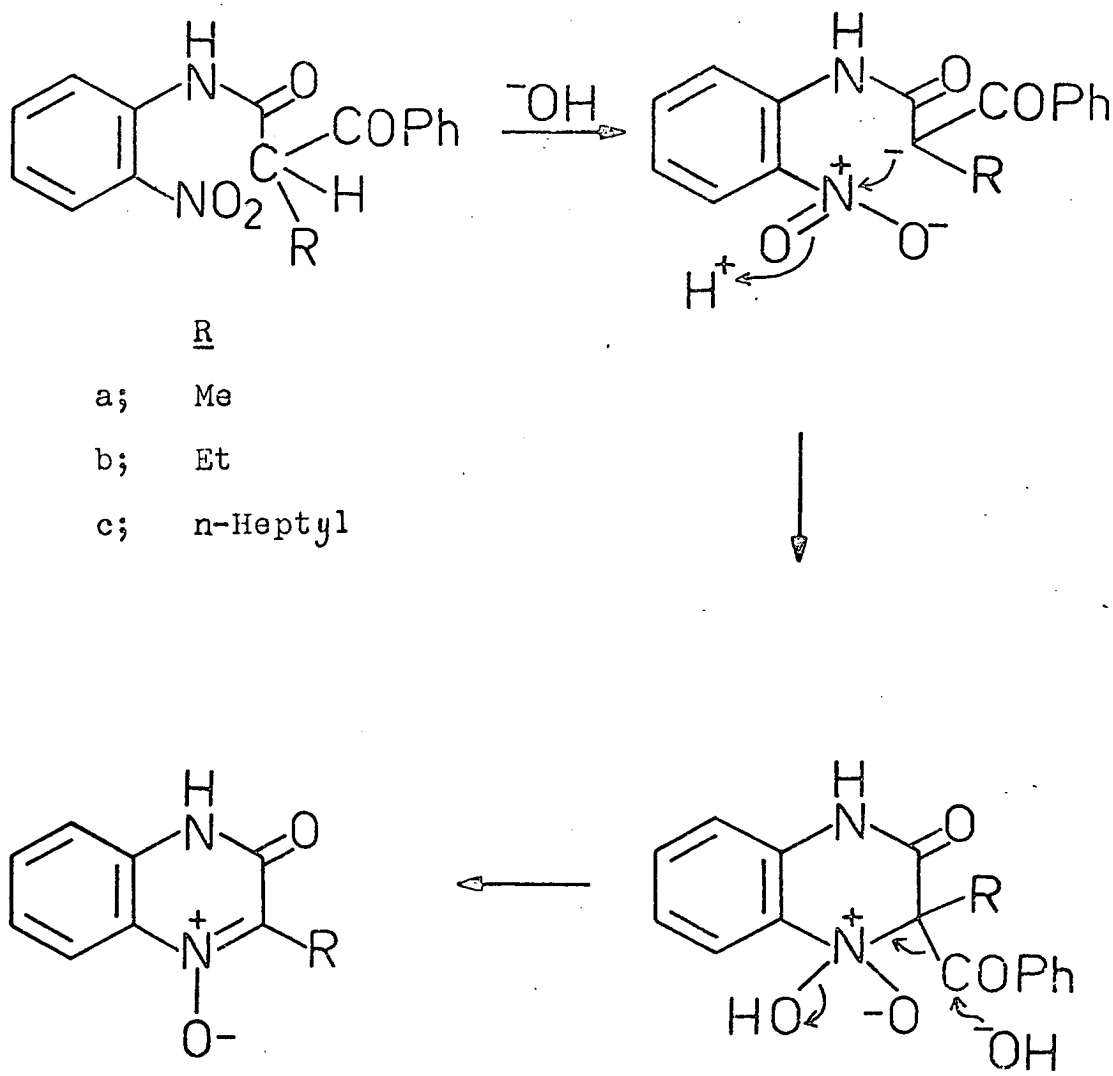
The intermediacy of quinazoline N-oxides in the cyclisations [(40) → (42)] is supported by the isolation of the quinazoline N-oxide (46)[21] in the cyclisation of the 2-nitrobenzamide derivative (44) to the quinazoline N-oxide (45) which undergoes debenzoylation at the 2-position to give the final product (46).



(44)

(45)

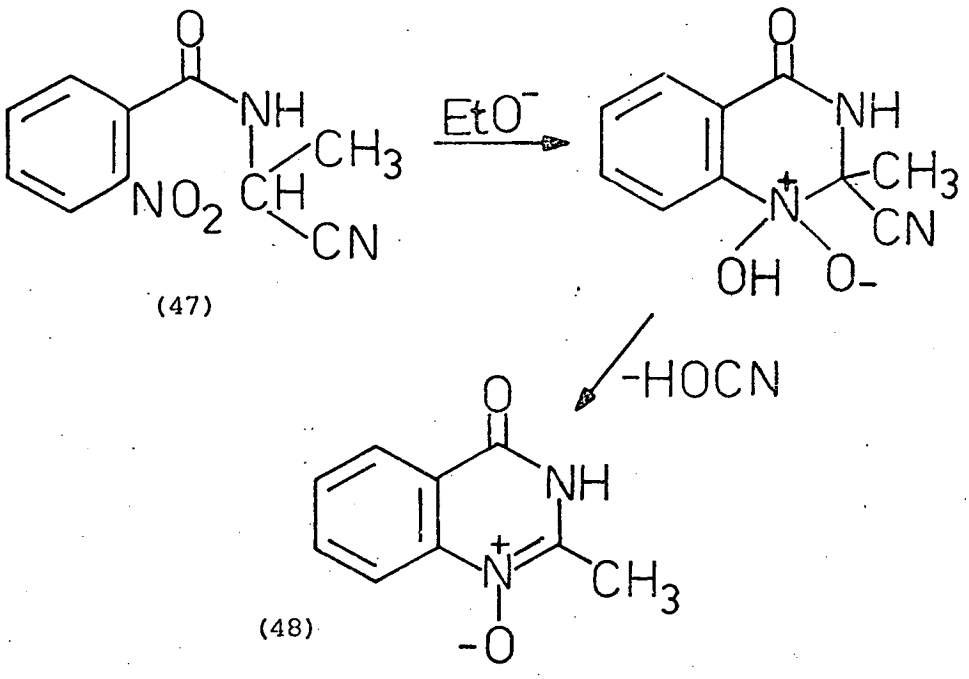
(46)


H
N
O
COPh
C
H
NO2
R
-OH
H
N
O
COPh
R
N+
O
O-
H+
R
a; Me
b; Et
c; n-Heptyl
H
N
O
R
N+
COPh
HO
-O
-OH
H
N
O
R
N+
O-

(51)

Scheme 7

In the base-catalysed cyclisation of the amide derivative (47)[21], the isolated product is the quinazoline N-oxide (48) in contrast to the



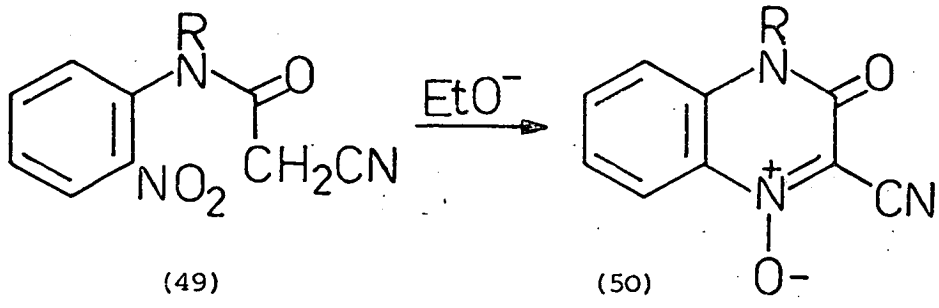
(47)

(48)

base-catalysed reaction of the acetonitrile derivatives (40a - d) presumably due to the preferential extrusion of the elements of isocyanic acid over those of methanol.

The base-catalysed cyclisation of ortho-nitroacetanilide derivatives provides a good general synthetic route to quinoxalin-2(1H)-one 4-N-oxides. Thus, 3-cyanoquinoxalin-2(1H)-one 4-N-oxides (50) are the products of the cyclisation of α-cyano-2-nitroacetanilides (49) under a variety of basic conditions.[22] The successful cyclisation of the amides (49b) and (49c) supports a mechanism involving the intact nitro group and not its aci-nitro tautomer, in a direct aldol-type condensation.

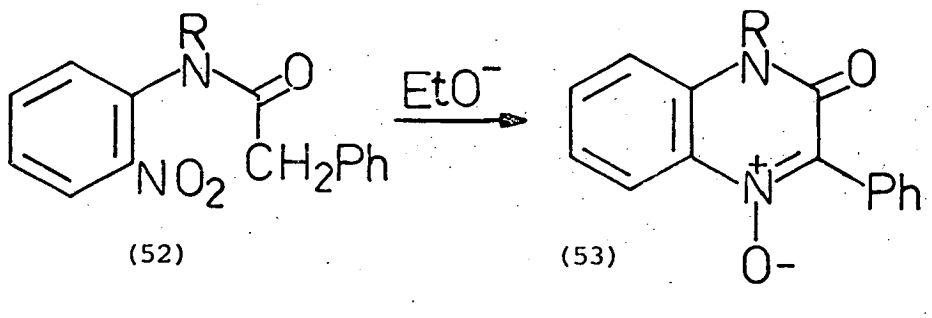
2-Alkylquinoxalin-3(4H)-one 1-N-oxides (51) may be formed by a process of deacylation[23] during the base-catalysed cyclisation of the ketones (a-c) which cannot undergo a strict aldol-type condensation but retain an active methine centre. (Scheme 7).



(49) (50)

	R
a;	H
b;	CH_3
c;	CH_2Ph

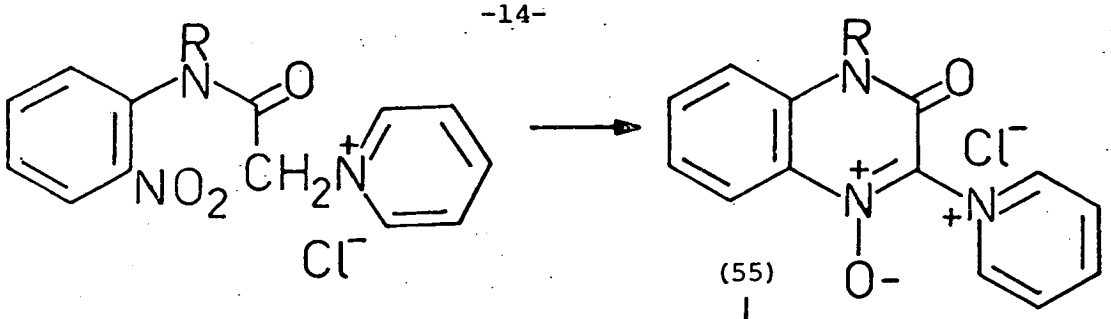
In the case of α-aryl-2-nitroacetanilides (52) the methylene group is less active than that of the cyano compounds (49) but nevertheless good yields of 2-arylquinoxaline N-oxides[24,25] (53) are obtained by warming the substrates (52) with aqueous alkali in pyridine.



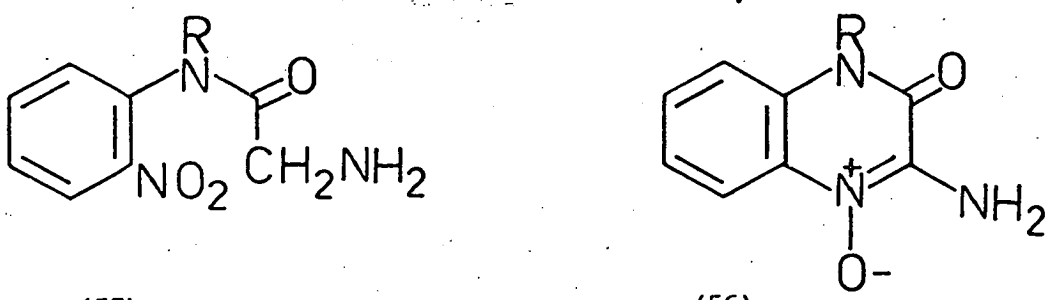
(52) (53)

R = H, CH_3

Pyridinium salts of the type (54)[22,26] undergo base-catalysed cyclisation in methanolic piperidine to afford 3-aminoquinoxalin-2(1H)-one 4-N-oxides (56) which are presumably formed by the base-catalysed degradation of the pyridine ring in the initial product of cyclisation (55).



(54) (55)

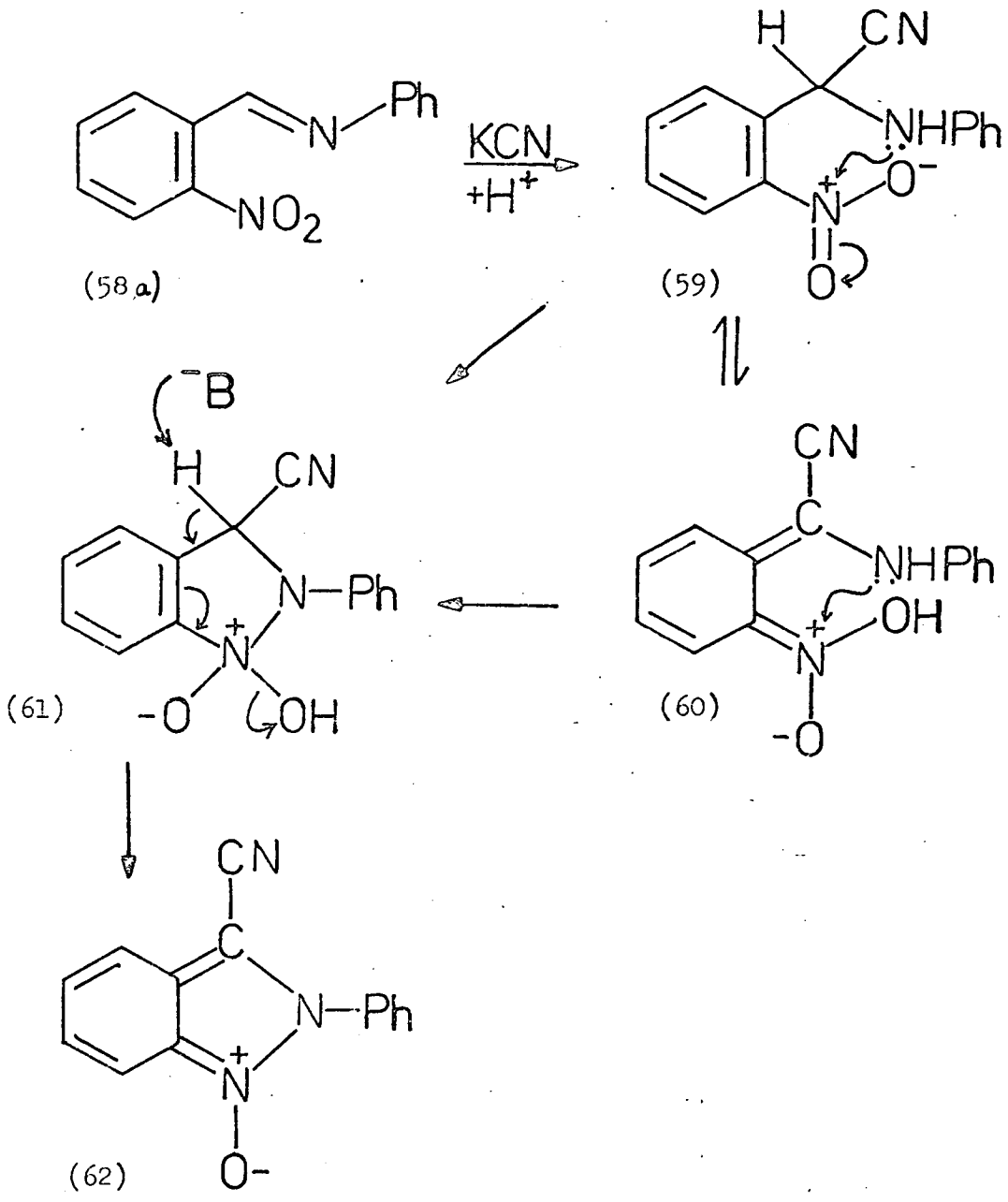


(57) (56)

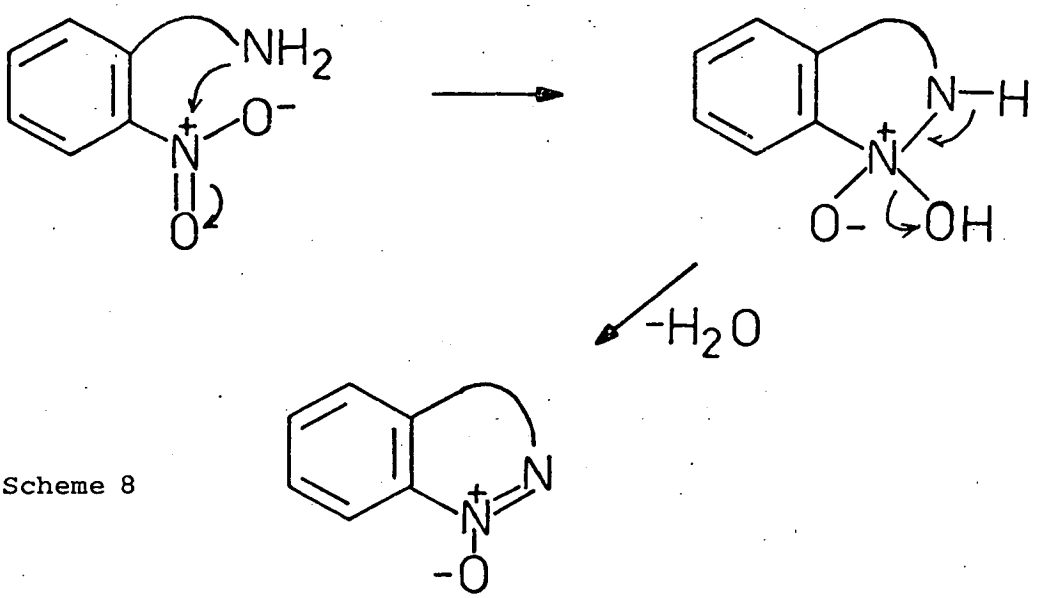
The importance of this reaction is that the product (56) cannot be obtained by direct cyclisation of amides of the type (57) due to the deactivation of the methylene group by the amino group.

B. Interaction between the Nitro Group and a Nucleophilic Nitrogen Centre in the Side-Chain.

Interaction between a suitably situated nucleophilic nitrogen centre in a side-chain and an ortho-nitro group will lead, by analogy with the carbanionic situation discussed before, to a heterocyclic compound containing a nitrogen-nitrogen double bond which is oxygenated on the nitrogen that is directly attached to the benzene ring. (Scheme 8). Often the heterocyclic N-oxides formed in these reactions cannot be synthesised by more orthodox methods.


Ph
N
NO2
KCN
+H+
H
CN
NHPh
O-
N+
O
(58,a)
(59)
B-
H
CN
N—Ph
N+
-O
OH
(61)
CN
C
NHPh
OH
N+
-O
(60)
CN
C
N—Ph
N+
O-
(62)

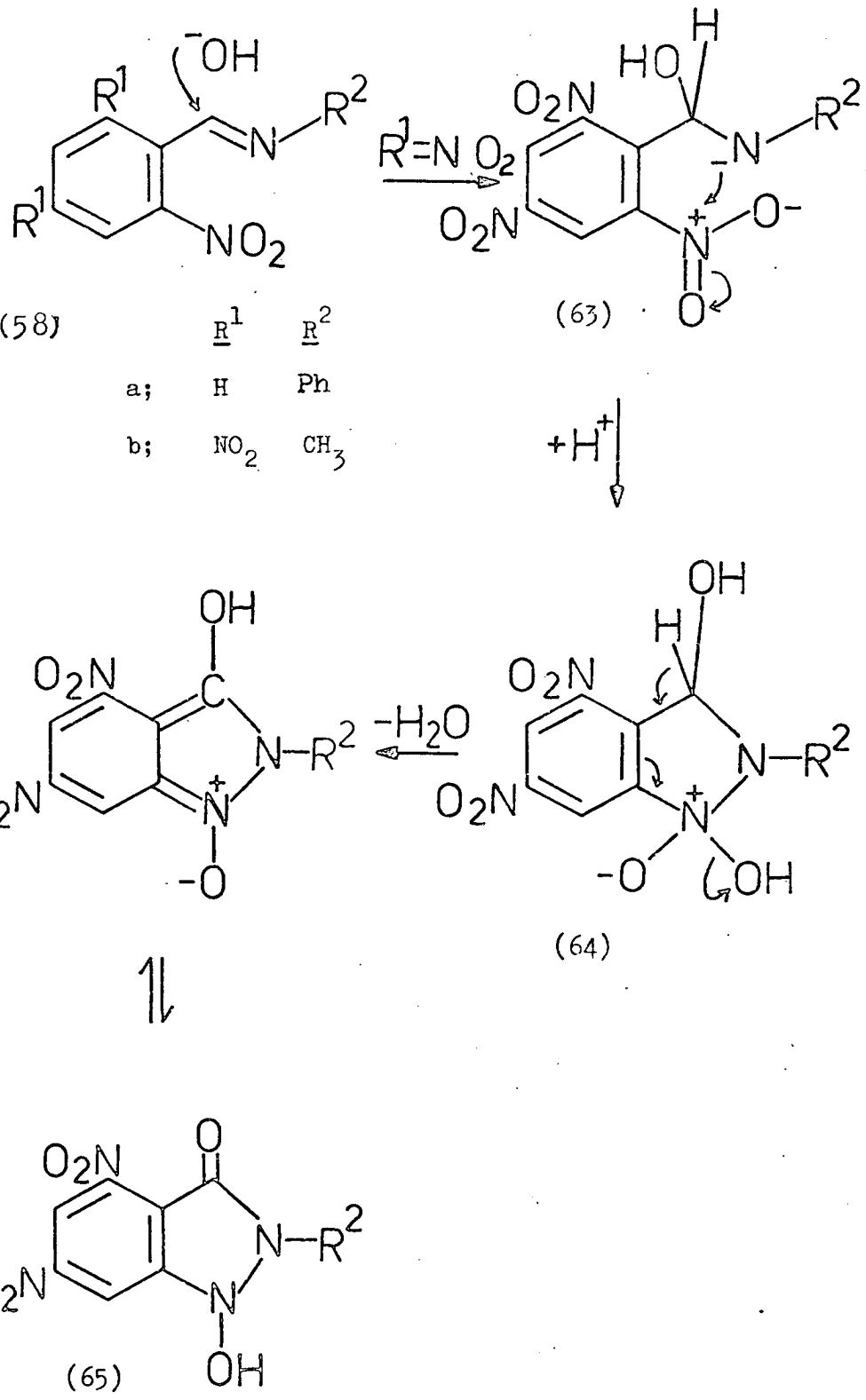
Scheme 9



Scheme 8

i) Cyclisations Leading to Five-Membered Heterocycles.

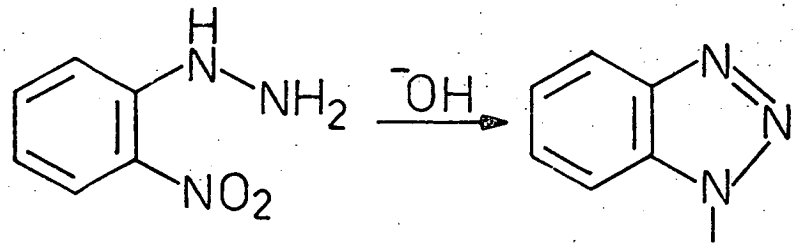
In cyclisations akin to the transformation of 2-nitrobenzylidene derivatives into 1-hydroxyindoles (see p. 3), 2-nitrobenzylidene anils are converted into indazole N-oxides under basic conditions. Thus, treatment of the anil (58a) with aqueous potassium cyanide followed by acetic acid affords, in good yield 3-cyano-2-phenylindazole 1-N-oxide (62)[27,28]. This transformation may be explained by the initial formation of a hydrogen cyanide adduct [(59); (Scheme 9)]. Again there is the possibility of both a nitro and an aci-nitro mechanism and it is not possible to say which in fact,operates. The necessity for base-catalysis may be attributable to the fact that an aci-nitro mechanism is operating and that the base is required to effect the tautomerism of the nitro group [Scheme 9; (59) → (60)]. Alternatively,the base may only be required to effect the stabilisation of the cyclic intermediate (61) which is produced by a thermal cyclisation of the hydrogen cyanide adduct (59). The intermediacy of such a hydrogen cyanide adduct is evidenced by the conversion[29] of the cyano compound (59) in hot sodium carbonate solution into the indazole N-oxide (62).


OH
R1
R2
N
R1
NO2
(58)
R1 R2
a; H Ph
b; NO2 CH3
R1=N O2
H
HO
O2N
R2
N
O2N
O-
N+
O
(63)
+H+
OH
O2N
C
N-R2
O2N
N+
-O
-H2O
OH
H
O2N
N-R2
O2N
N+
-O
OH
(64)
O
O2N
N-R2
O2N
N
OH
(65)

Scheme 10

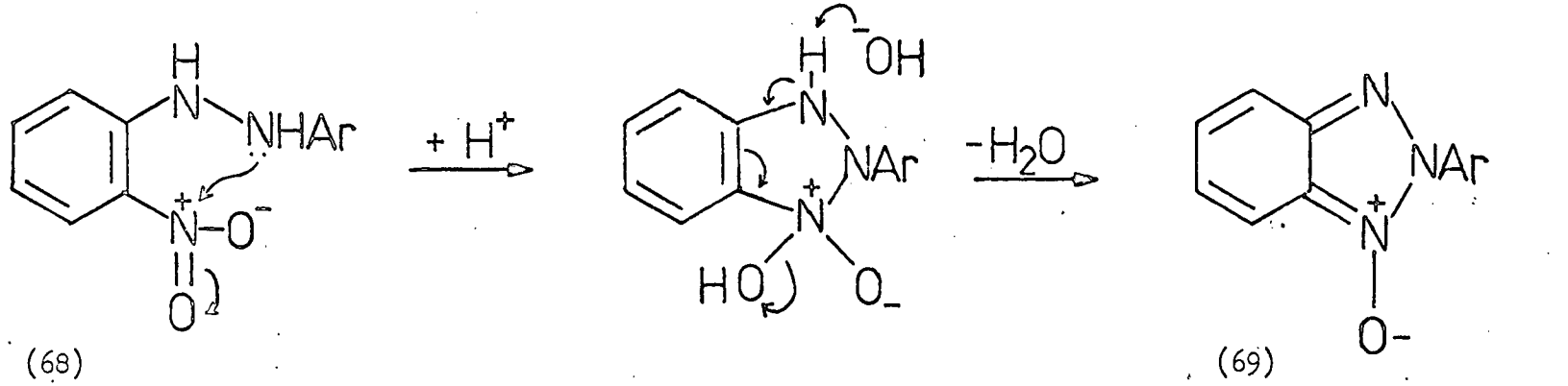
In contrast to its ready cyclisation in the presence of cyanide ion, the anil (58a) fails to cyclise[31] under the influence of hydroxide ion by the possible route shown in Scheme 10. However, the trinitro-anil (58b) is readily converted by warming with ethanolic sodium carbonate into the indazole (65b).[30-32] This cyclisation can be explained by the formation of a hydrate (63) favoured by the enhanced electron-deficiency of the benzylidene double bond, due to the electron-withdrawing power of the trinitrobenzene ring, an effect less important in the compound (58a). The hydrate (63), so formed can cyclise (Scheme 10) in a similar fashion to the hydrogen cyanide adduct (59) described previously. Again, there is the possibility that cyclisation of the hydrate (63) occurs directly or after isomerism to an aci-nitro tautomer.

The base-catalysed cyclisation of substituted 2-nitrophenylhydrazines provides a general route[33] to N-oxygenated benzotriazoles. Thus 2-nitrophenylhydrazine (66a)[34] itself, under the influence of hydroxide ion, affords 1-hydroxylbenzotriazole (67a). Similarly, 2-nitrohydrazobenzene (68; Ar = phenyl)[35,36] affords the 2-phenylbenzotriazole

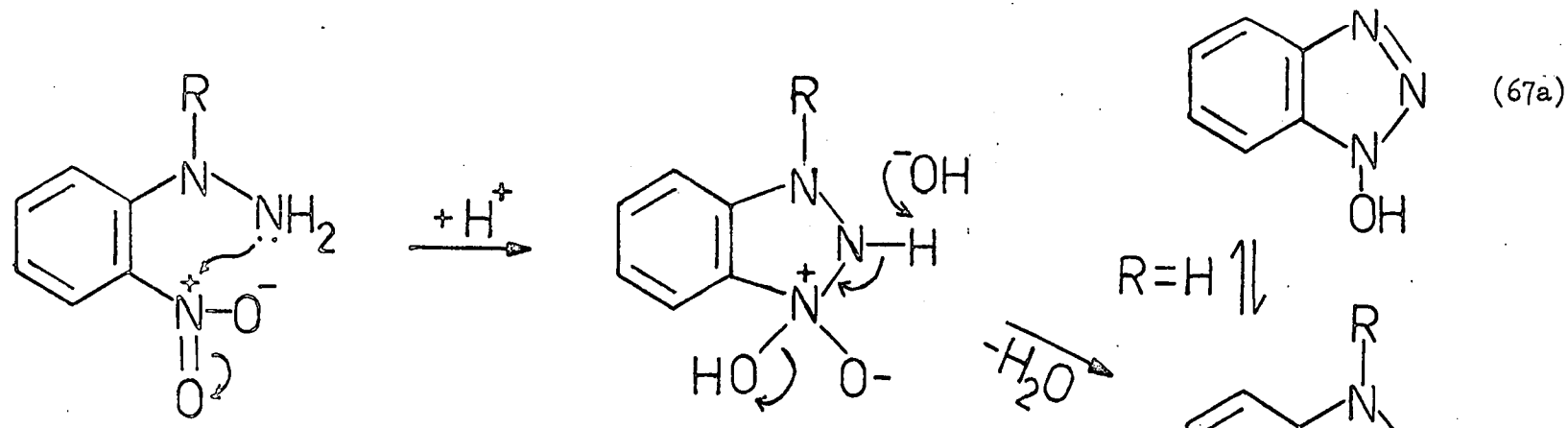


(66a) (67a)

1-N-oxide (69; Ar = phenyl). The successful base-catalysed cyclisation[37] of the N,N-disubstituted hydrazine (66b) to give the benzotriazole (67b, Scheme 11) does not allow the possibility of an aci-nitro mechanism



(68) (69)



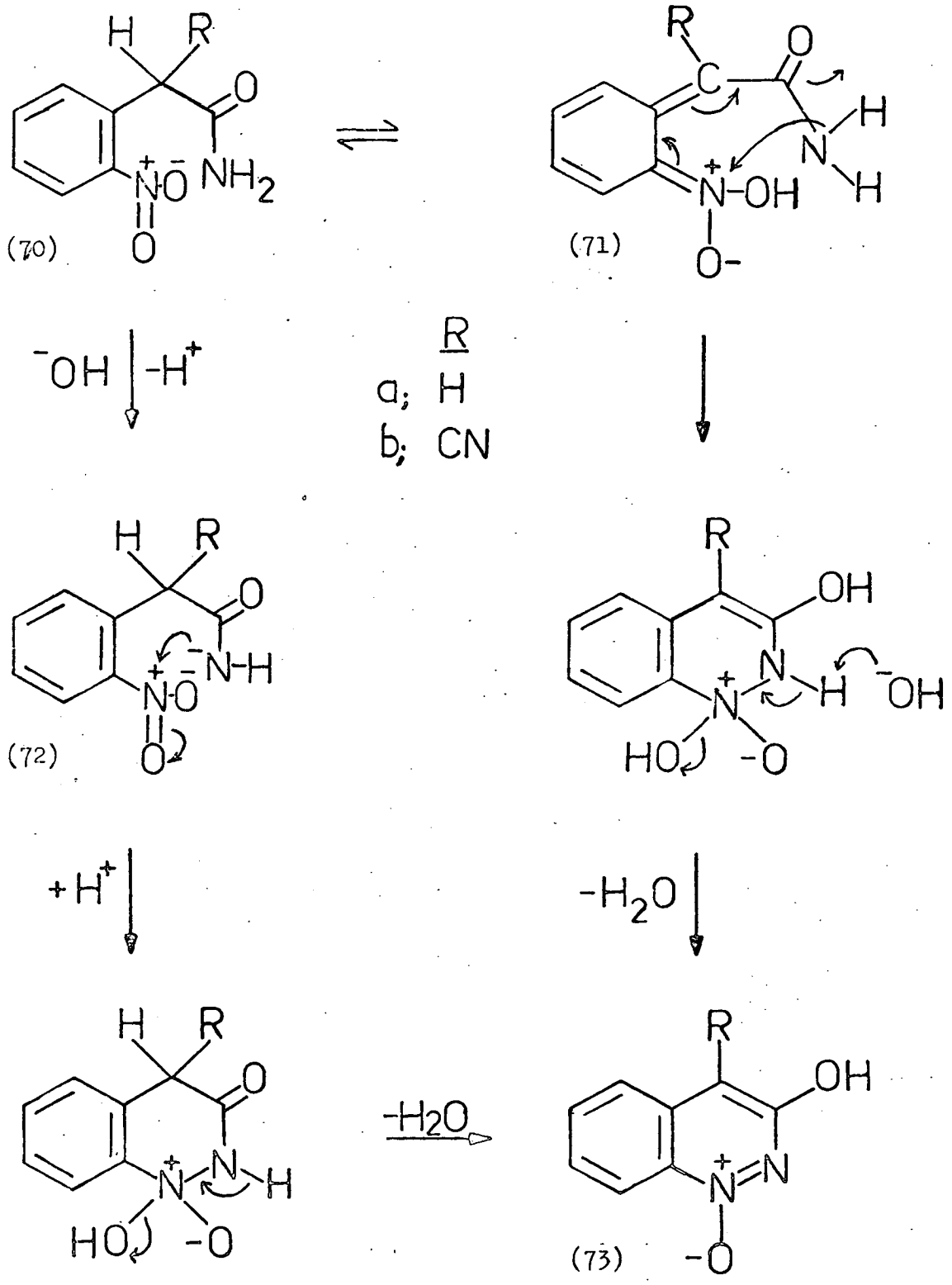
(66) (67a) (67)

R

a; H

b; Me

Scheme 11



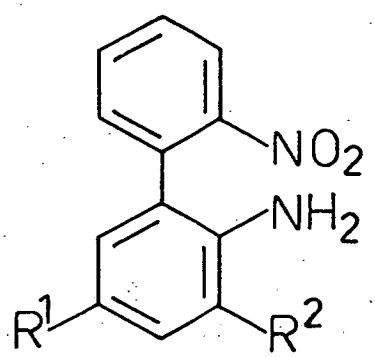
Scheme 12

as there is no capacity for such tautomerism in this substrate (66b). Consequently, it might be inferred that a direct aldol-type condensation is the mechanism of formation of the benzotriazoles (Scheme 11). The possibility of an aci-nitro mechanism cannot however, be dismissed in the formation of the triazoles (69) and (67a).

ii) Cyclisations Leading to Six-Membered Heterocycles.

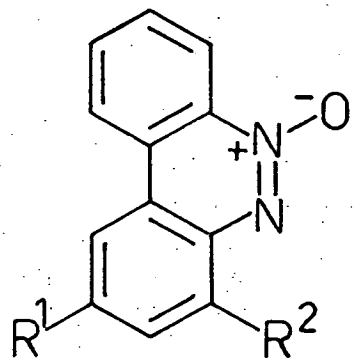
The base-catalysed interaction of a weakly basic nitrogen centre such as that in 2-nitrophenylcyanoacetamide (70b) with the ortho-nitro group provides a synthesis of 4-cyano-3-hydroxycinnoline 1-N-oxide (73b)[38]. The amides (70) however, require to have a mobile benzylic hydrogen in order for cyclisation to be successful. Thus, 2-nitrophenylacetamide (70a) fails[39] to undergo base-catalysed cyclisation to give the cinnoline (73a). The necessity for a mobile benzylic hydrogen may indicate that an aci-nitro tautomer (71) is involved in the mechanism (Scheme 12) and the presence of hydroxide ion, therefore, is required to catalyse the formation of this aci-nitro tautomer. The subsequent cyclisation [(71)→ (73)] may be assumed to be non-catalysed, the nucleophilicity of the amide being sufficiently great for successful intramolecular attack on the aci-nitro group. Alternatively, the function of the base may be to generate the resonance-stabilised anion (72) of the amide, which then undergoes an intramolecular aldol-type condensation to give the product (73). However, on this basis, it is difficult to explain satisfactorily the non-reaction of the amide (70a).

Fused cinnolines of the type (75) are also formed in high yields by the cyclisation[39-41] of 2-amino-2'-nitrobiphenyl derivatives (74 a→c) under strongly alkaline conditions (e.g. in methanolic sodium methoxide). Whereas the aminobiphenyl (74c) is successfully cyclised to the corresponding benzocinnoline (75c) under the influence of benzyltrimethylammonium



(74)

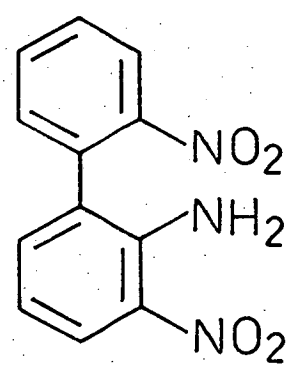
$^{-}OCH_3$



(75)

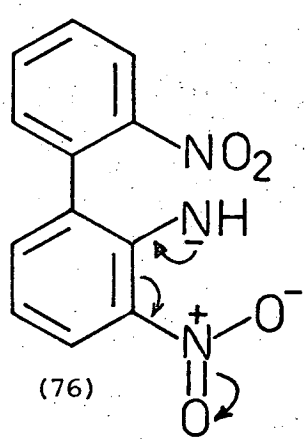
	R^1	R^2
a;	H	H
b;	Br	Br
c;	NO_2	H_2
d;	H	NO_2

hydroxide[42] as the basic catalyst, the closely related isomer (74d) is resistant to cyclisation. This might be explained by the greater combined -M and -I effects that the 3-nitro group in (74d), compared with the same effects of the 5-nitro group in (74c), have upon the nucleophilicity of the respective amide ions. Thus, the amide ion (76)

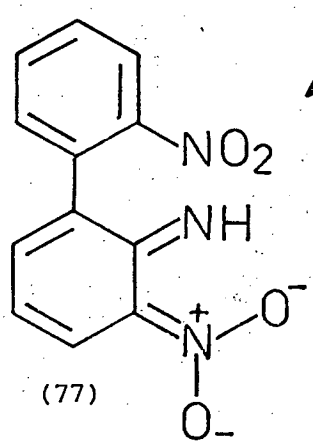


(75d)

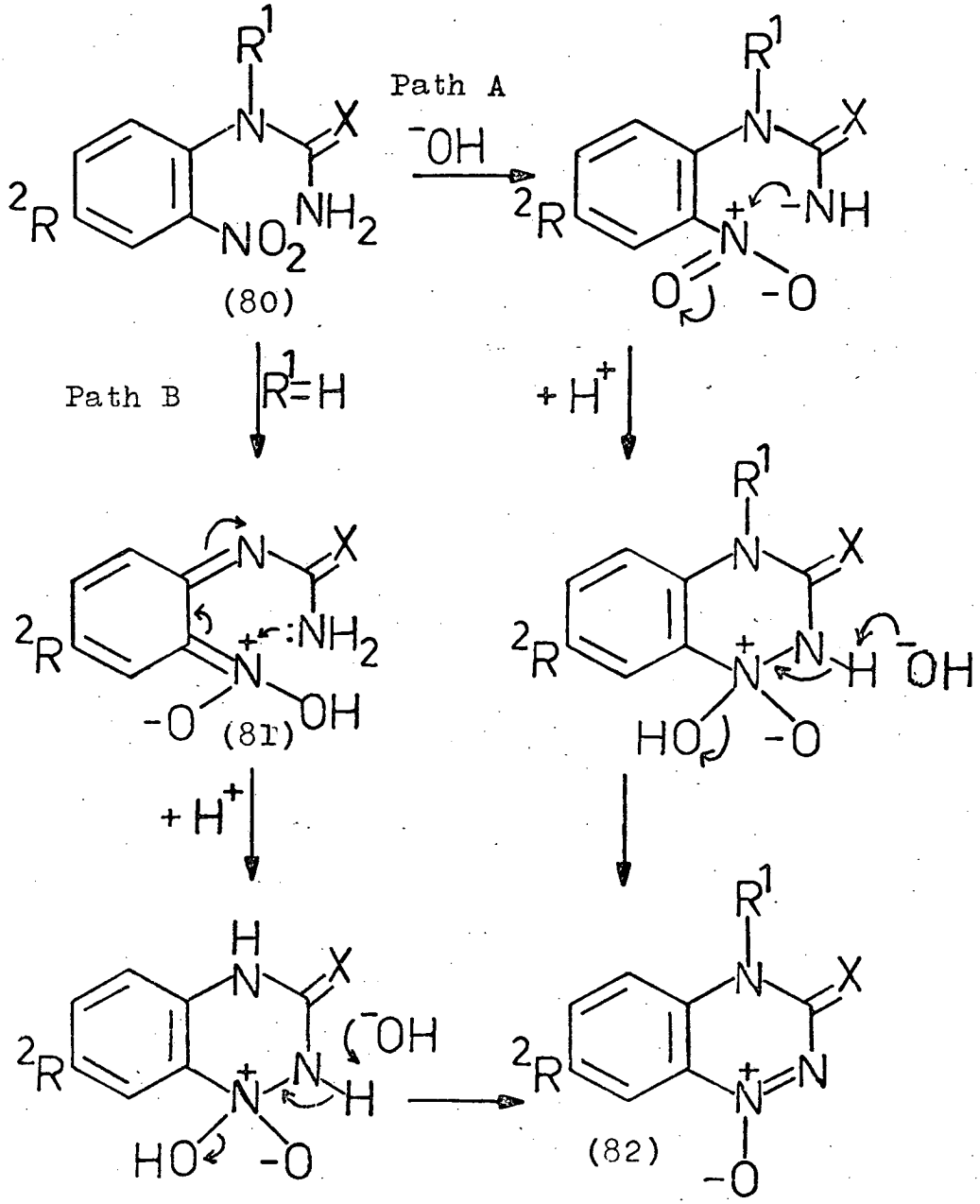
$-H^+$



(76)



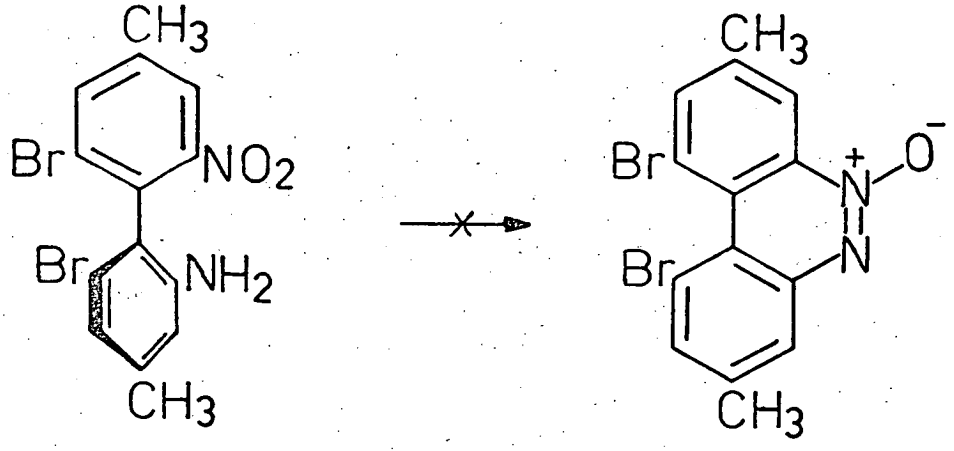
(77)



	R^1	R^2	X
a;	H	H	O
b;	H	Cl	O
c;	H	H	S
d;	CH_3	H	O

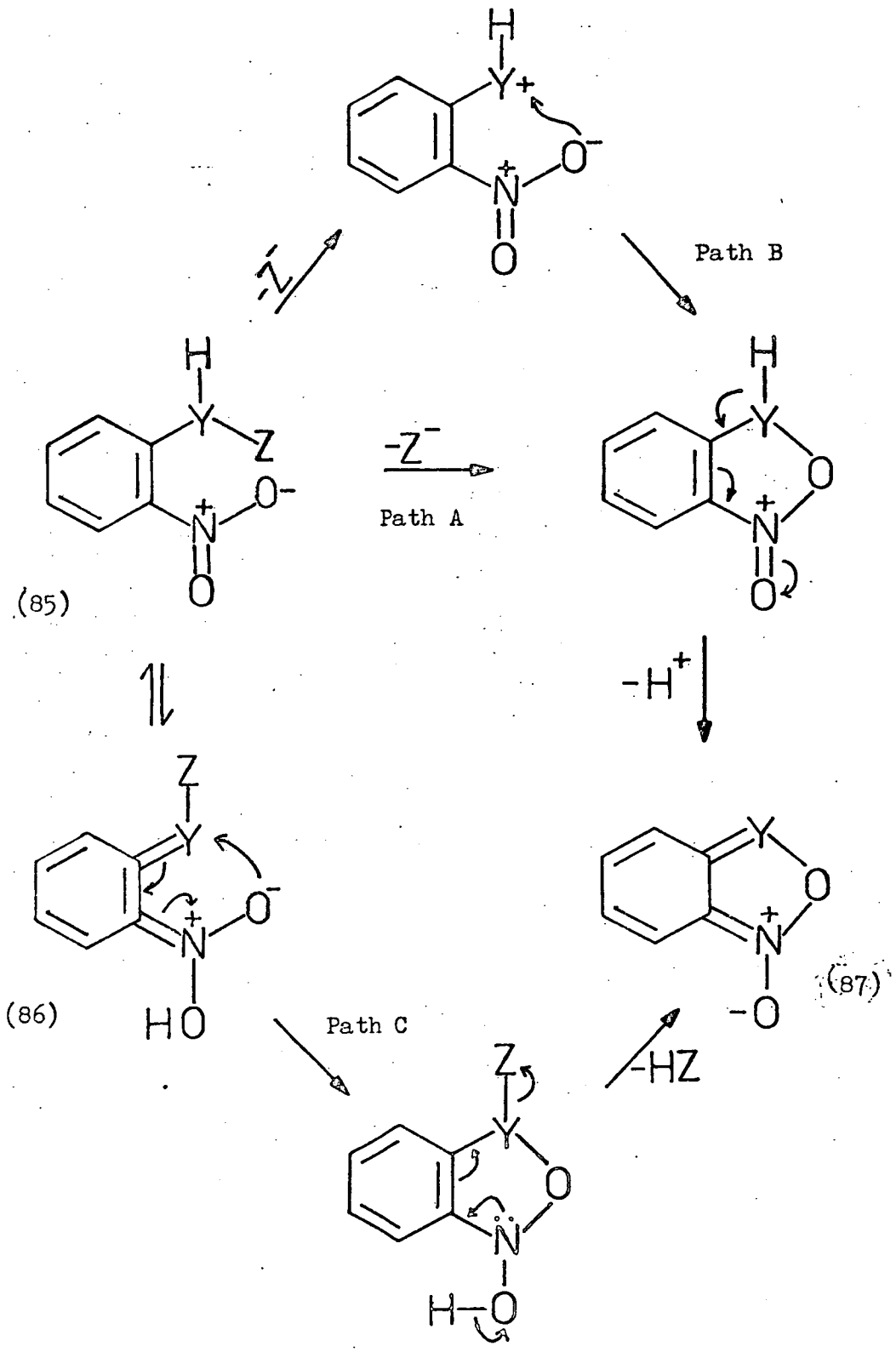
Scheme I3

will be the least nucleophilic due to the stabilisation effect of the resonance shown (76) ⟷ (77) . The dibromobiphenyl derivative (78) is also resistant to cyclisation[40] under a variety of basic conditions. This can be explained in terms of a steric restriction imposed by the bulky bromo-substituents whereby the nitro group and the nucleophilic amide ion centre cannot approach close enough to each other for a successful aldol-type condensation to occur with formation of a planar product (79).



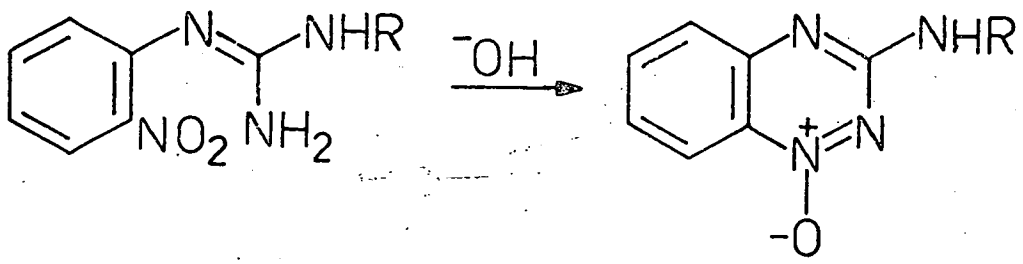
(78) (79)

Benzo-1,2,4-triazine N-oxides are formed in high yield by the base-catalysed cyclisation of ortho-nitrophenylureas and related compounds despite the relatively low nucleophilicity of the nitrogen centre in the ortho-side-chain of such substrates. Thus, 2-nitrophenylureas (80 a and b) and 2-nitrophenylthiourea (80c) are converted in warm aqueous alkali into the corresponding benzotriazinone 1-N-oxides (82a and b) and the benzotriazinethione 1-N-oxide (82c), respectively (Scheme 13). Substitution of the aniline hydrogen in the urea (80a) by a methyl group makes the resulting compound (80d), resistant to cyclisation.[43] This result may implicate an aci-nitro mechanism in the successful cyclisations of the compounds (80 a-c). (Path B; Scheme 13). Similarily 2-nitrophenyl-guanidines (83a and b) readily cyclise[44] in the presence of hydroxide ion



Scheme 14

to afford the 3-aminobenzo-1,2,4-triazine 1-N-oxides (84a and b) in moderate to good yields.



(83) R (84)

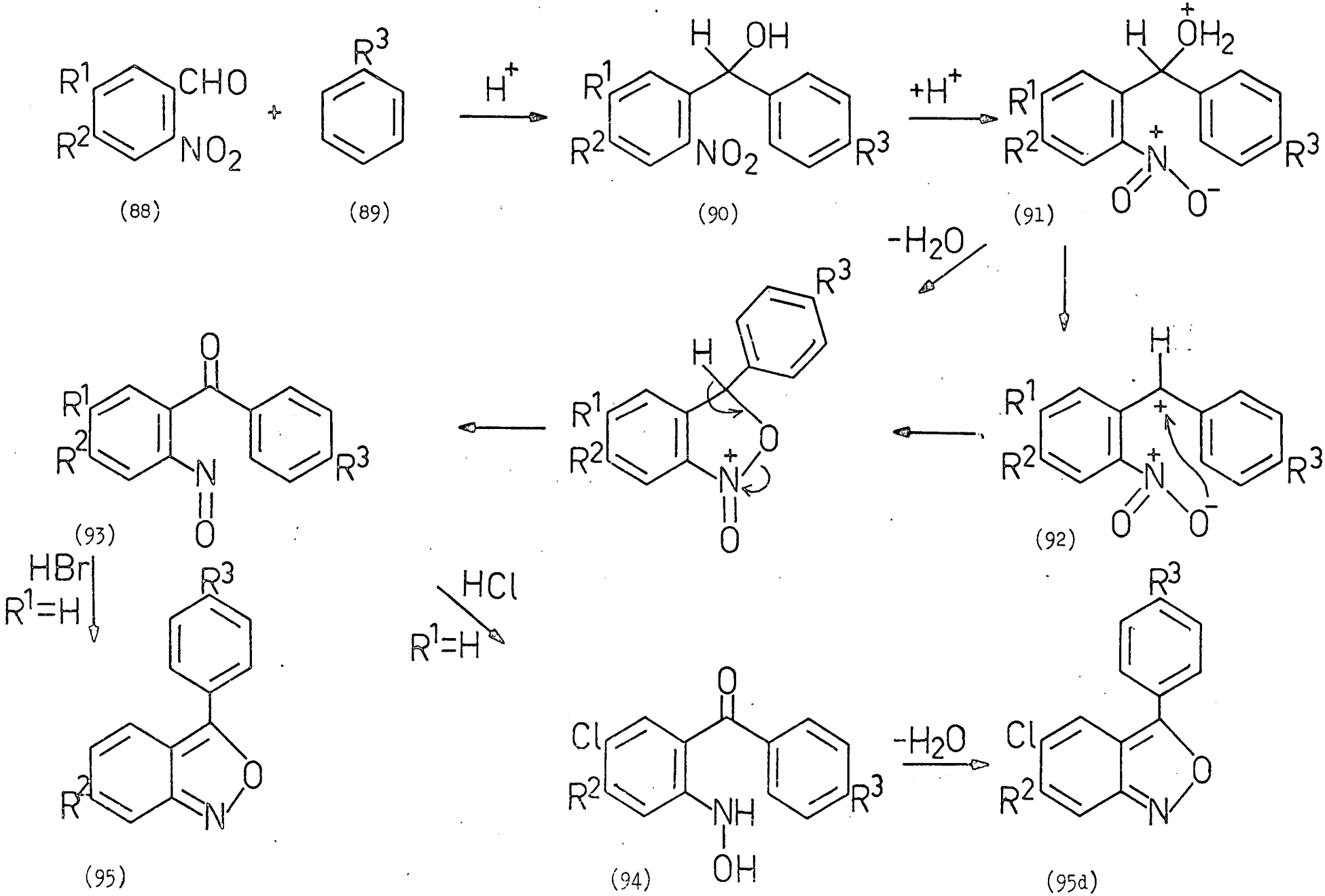
a; H

b; Ph

C. Interactions Involving Electrophilic Attack on the Nitro Group by the Side-Chain

The electron rich oxygen atoms of the nitro group in an ortho-substituted nitrobenzene derivative are electronically and hence sterically suited for interaction with an electrophilic centre in the side-chain (cf. page 1). An interaction of this type corresponds to an intramolecular nucleophilic substitution in the side-chain by an oxygen atom of the nitro group. Consequently the interaction may be considered as either a concerted process (Path A of Scheme 14) or as a stepwise process (Path B of Scheme 14). Alternatively, where structurally possible, electrophilic interaction may be preceded by rearrangement to an aci-nitro tautomer [(85) ⟷ (86)] which by path C (Scheme 14) effects displacement of the leaving group. All three possible pathways (A,B and C) can lead theoretically, to the heterocyclic structure (87).

However, with one possible exception (cf. page 27), direct evidence for electrophilic attack by the side-chain on an ortho-nitro group as depicted in Scheme 14, is lacking. Indirect evidence for such interaction is based

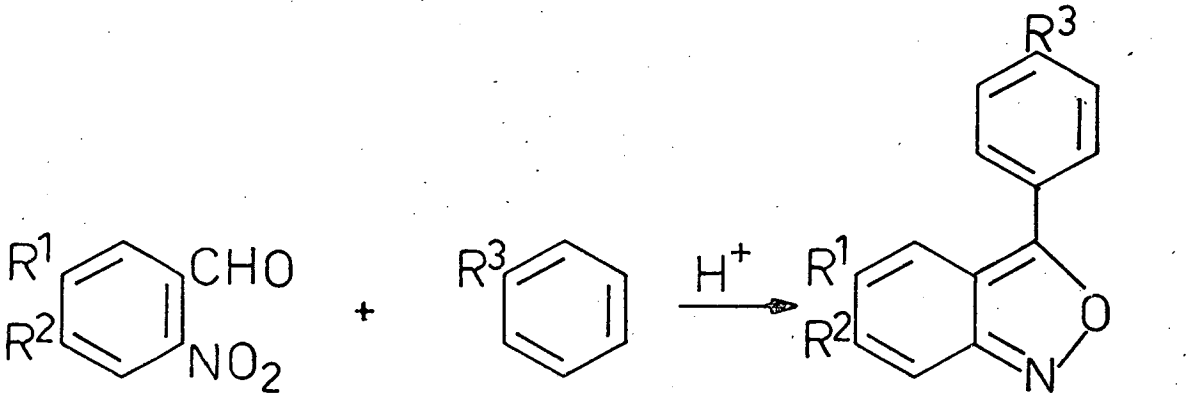


Scheme 15

on mechanistic interpretations of various acid-catalysed reactions of ortho-nitrobenzene derivatives. These reactions show net oxidation of the side-chain and net reduction of the nitro group leading to heterocyclic or non-cyclic products.

i) Interactions between the Nitro Group and an Electrophilic Carbon Centre in the Side-Chain

Nucleophilic participation by an ortho-nitro group is probably the key step in the acid-catalysed reactions of benzhydrol intermediates (90) formed by the addition of 2-nitrobenzaldehydes (88) to substituted benzenes (89) under a variety of acidic conditions to afford various

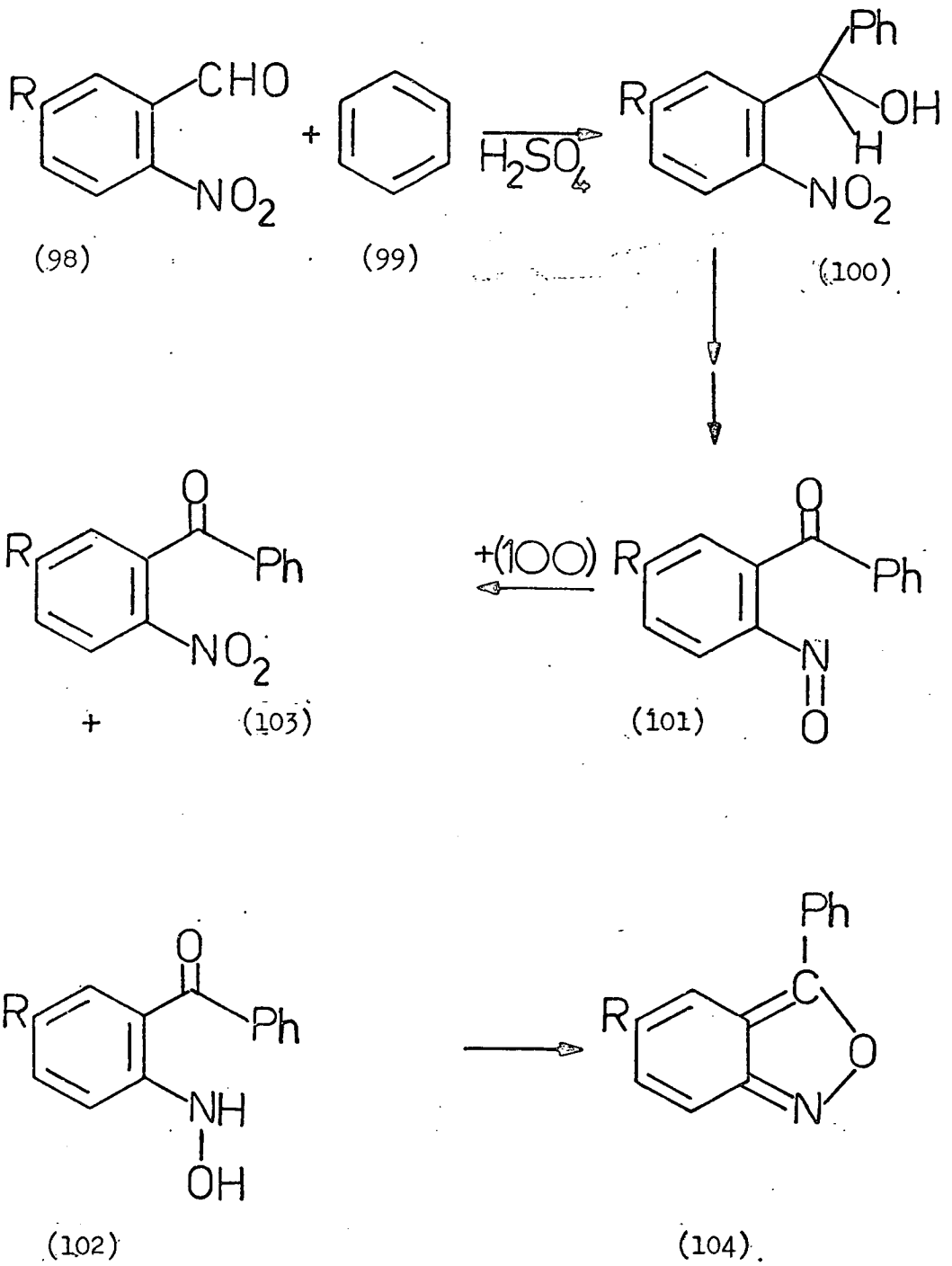


(88)	R^1	R^2
a;	H	H
b;	H	H
c;	H	NO_2

(89)	R
a;	H
b;	OH
c;	Br

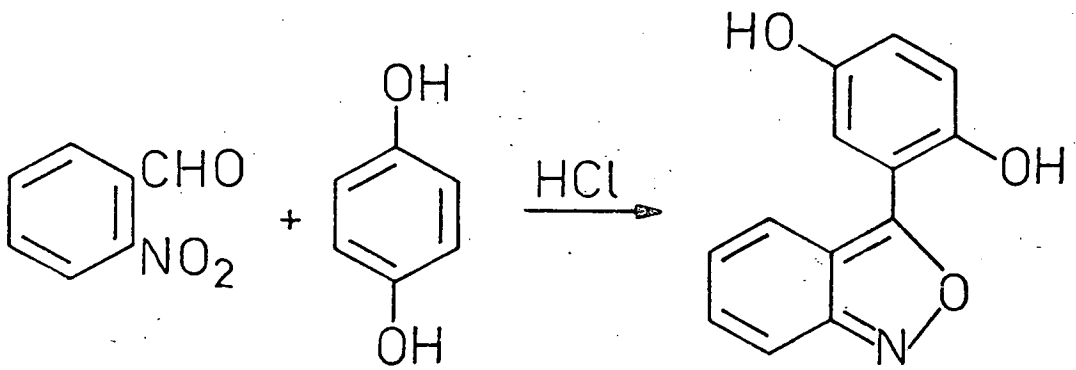
(95)	R^1	R^2	R^3
a;	H	H	H
b;	H	H	OH
c;	H	NO_2	Br

3-aryl-2,1-benzisoxazoles (anthranils) as ultimate products. The course (Scheme 15) of such reactions may involve a stepwise mechanism in which the conjugate acid (91) of the benzhydrol intermediate (90) loses water to form a discrete carbonium ion (92) which then undergoes nucleophilic attack by the nitro group followed by rearrangement to give the nitroso-ketone (93). Alternatively, a concerted mechanism in which the conjugate acid (91) loses water with concomitant nucleophilic attack at the reaction centre by the nitro group to give the same nitrosoketone (93), may operate.


R
CHO
NO2
(98)
+
(99)
H2SO4
Ph
OH
H
R
NO2
(100)
O
Ph
R
NO2
+
(103)
+(100)
O
Ph
R
N
O
(101)
O
Ph
R
NH
OH
(102)
Ph
C
R
O
N
(104)

Scheme 16

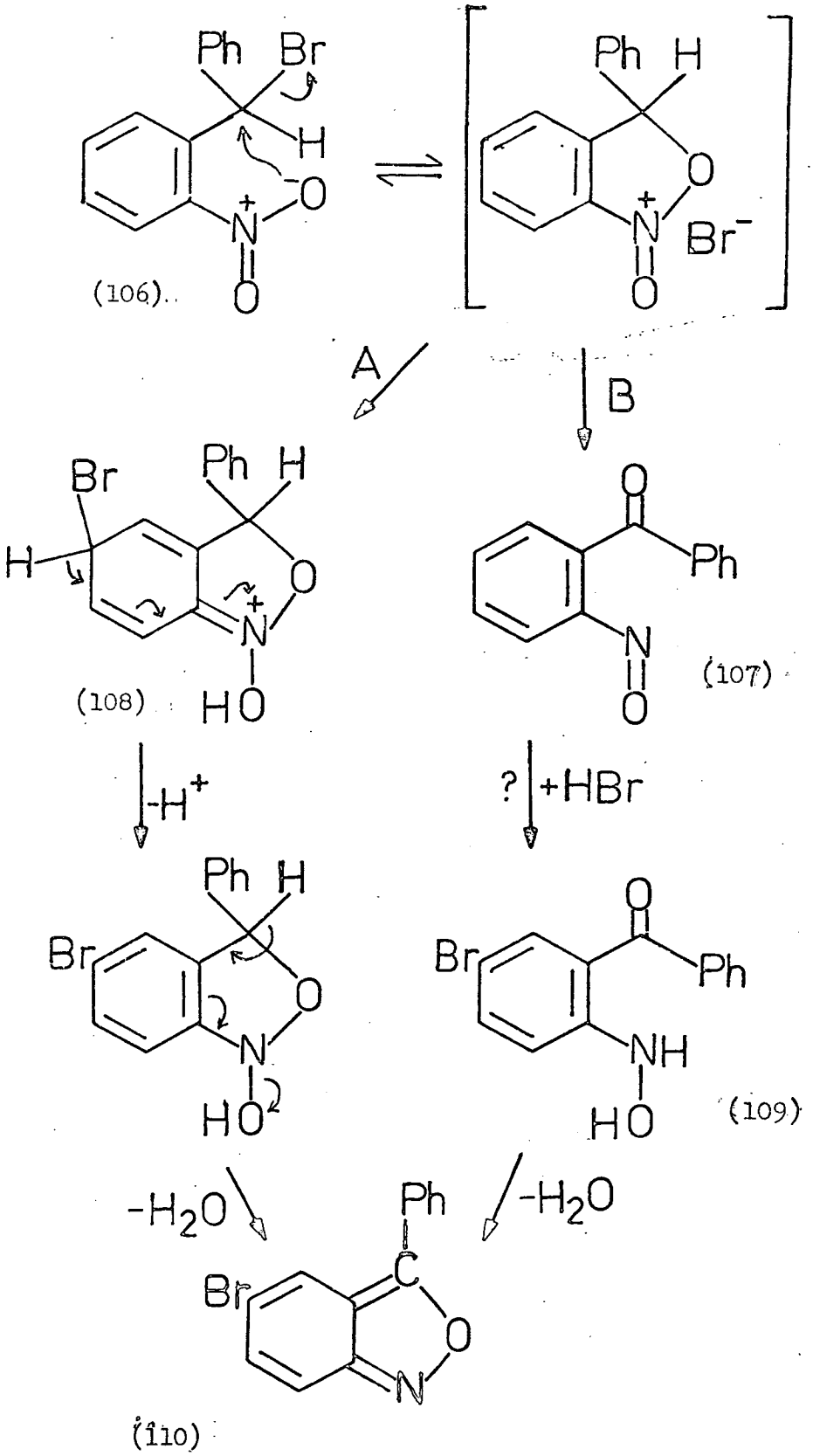
When the acid catalyst present is hydrogen chloride[45,46] the nitrosoketone (93) is then reduced to the hydroxylaminoketone (94) with introduction of a chlorine atom [(93) → (94)] followed by cyclisation to give the halogenated anthranil (95d). However, in the presence of hydrogen bromide[45] the same reduction step is effected without introduction of a bromine atom to give an anthranil of the type (95a-c). When a 2-nitrobenzaldehyde derivative is reacted under the influence of hydrogen chloride with quinol (96)[45], again no halogen is introduced into the product (97) since the reduction of the resulting nitrosoketone intermediate is effected by quinol itself.



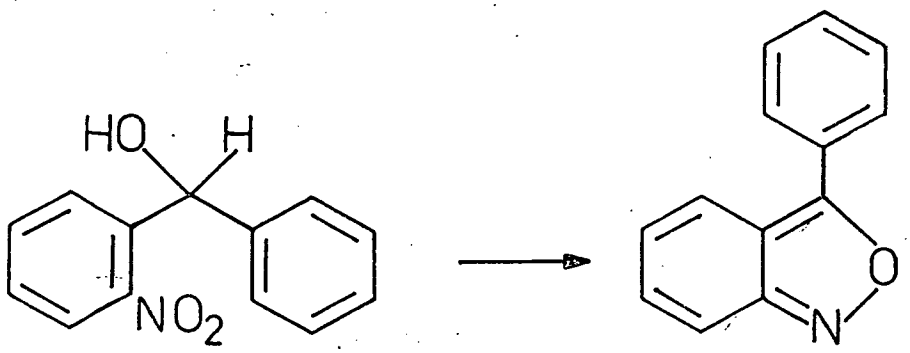
(88a) (96) (97)

Anthranil formation from 2-nitrobenzaldehydes and simple benzene derivatives under the influence of concentrated sulphuric acid[47-49] is again rationalised on the basis of initial benzhydrol formation. (Scheme 16). The reduction step in this instance is readily explained by reaction of the nitrosoketone (101) with unreacted benzhydrol (100) to give the hydroxylaminoketone (102) which cyclises to the product (104). The isolation of 2-nitrobenzophenone (103) as a by-product lends weight to this mechanism.

In further support of a benzhydrol intermediate in such reactions is the conversion of the benzhydrol (105) under the influence of para-toluenesulphonyl chloride[50] or concentrated sulphuric acid[51] into 3-phenylanthranil (95a).

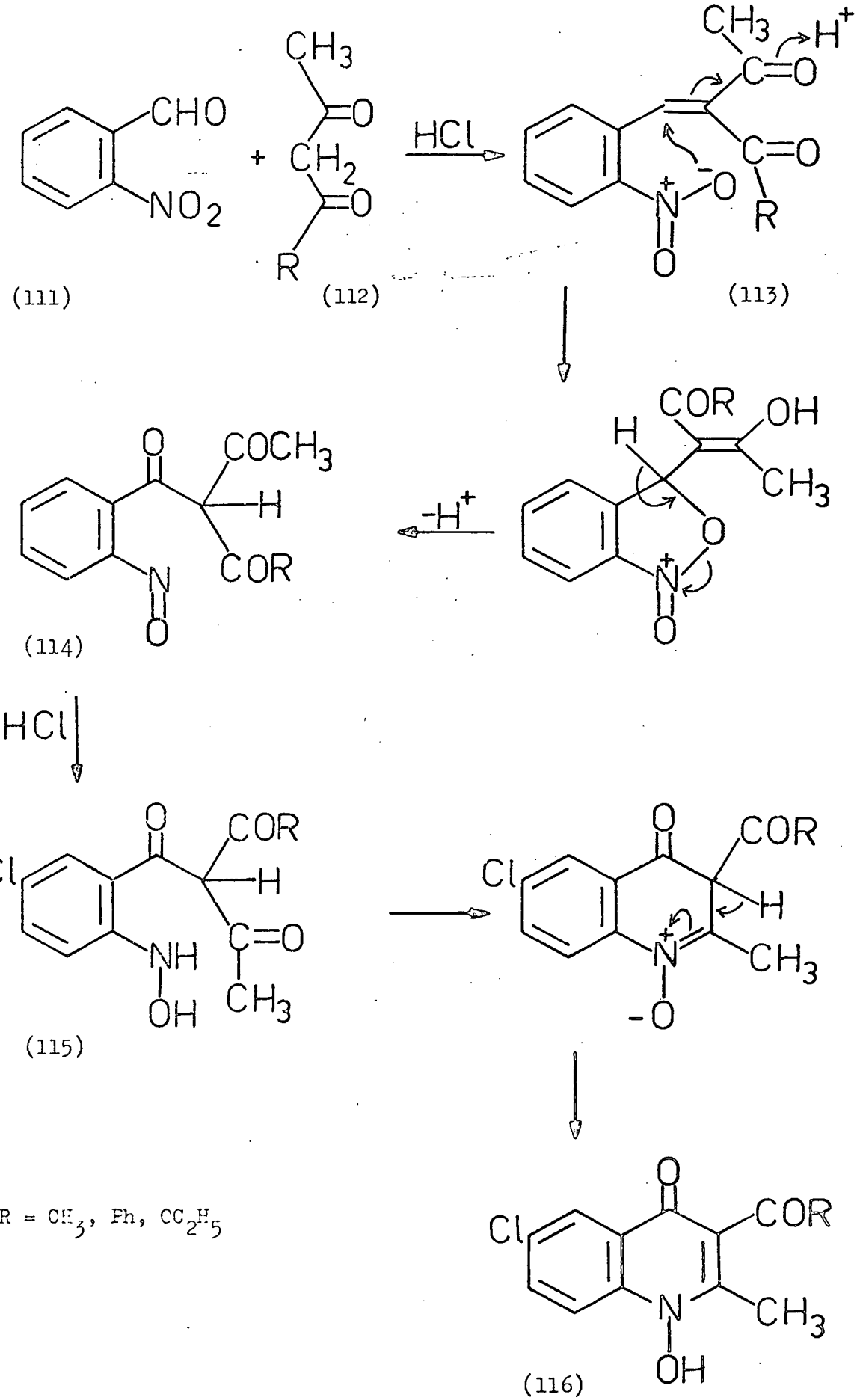

Ph Br
H
O
N
O
(106)
Ph H
O
N
Br⁻
A
B
Br
Ph H
H
O
N
HO
(108)
O
Ph
N
O
(107)
-H⁺
? +HBr
Ph H
Br
O
N
HO
O
Ph
Br
NH
HO
(109)
-H₂O
-H₂O
Ph
C
Br
O
N
(110)

Scheme 17



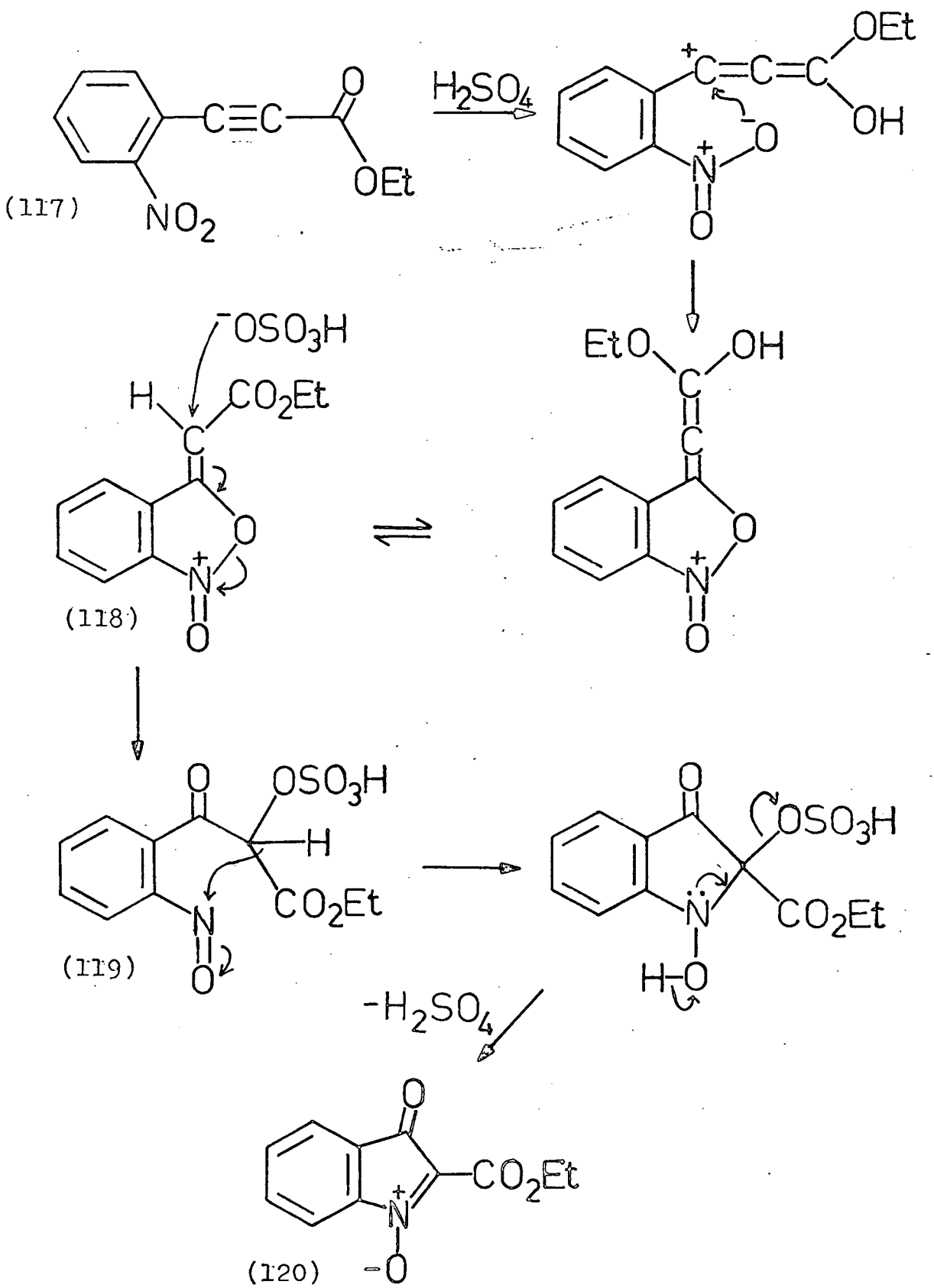
(105) (95a)

The solvolysis of 2-nitrobenzhydryl bromide (106)[52,53] in 90% aqueous acetone at 45° affords 2-nitrosobenzophenone at a rate 83 times faster than the corresponding solvolysis of 4-nitrobenzhydryl bromide which affords 4-nitrobenzyl alcohol. This result is readily explained by nucleophilic participation by an oxygen atom of the ortho-nitro group in the expulsion of the bromide ion, a process which is not possible in the case of 4-nitrobenzydryl bromide. (Scheme 17). When the solvolysis is carried out in acetic acid in the presence of hydrogen bromide, the rate of solvolysis[53] of ortho-nitrobenzhydryl bromide is 1450 times faster than the corresponding solvolysis of the 4-nitrobenzhydryl bromide which may demonstrate a significant anchimeric assistance by the nucleophilic oxygen atom of the ortho-nitro group. Also, in contrast to the reactions of 2-nitrobenzhydrol intermediates in the presence of hydrogen bromide[45] discussed previously, the isolated product in the latter reaction of 2-nitrobenzhydryl bromide (106) is the brominated anthranil (110). The incorporation of a bromine atom in the product (110) is explained[52] by a solvent-cage effect in which ionisation is immediately followed by ion-pair return to give product [Scheme 17; (106) → (108) → (110)]. A mechanism involving the intermediacy of the nitroso-compound (107) followed by its reduction to a hydroxylamino intermediate (109) with inclusion of a bromine atom would not be expected from other related work[45] and this would suggest that in



R = CH_3, Ph, CC_2H_5

Scheme 18

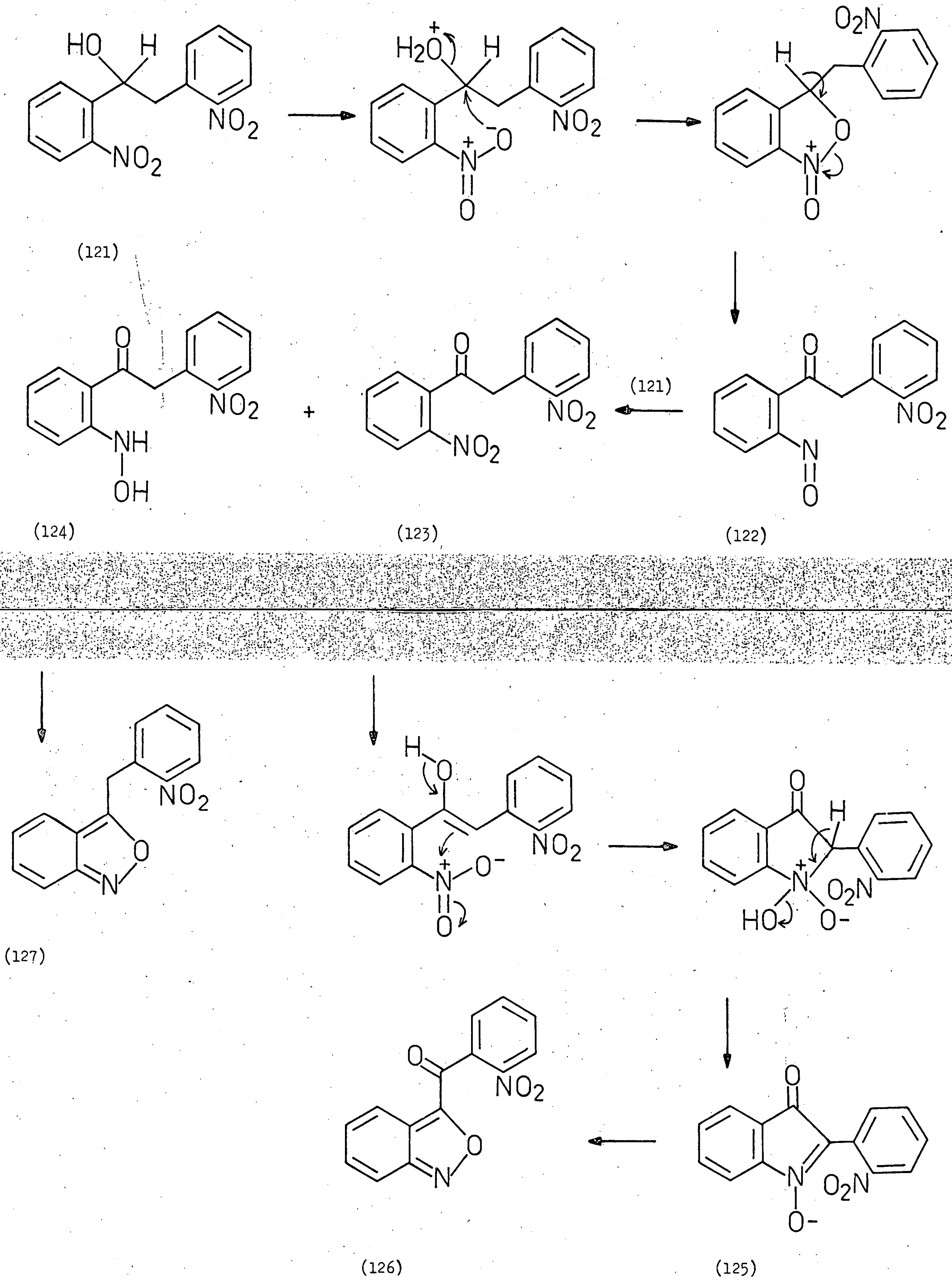


Scheme 19

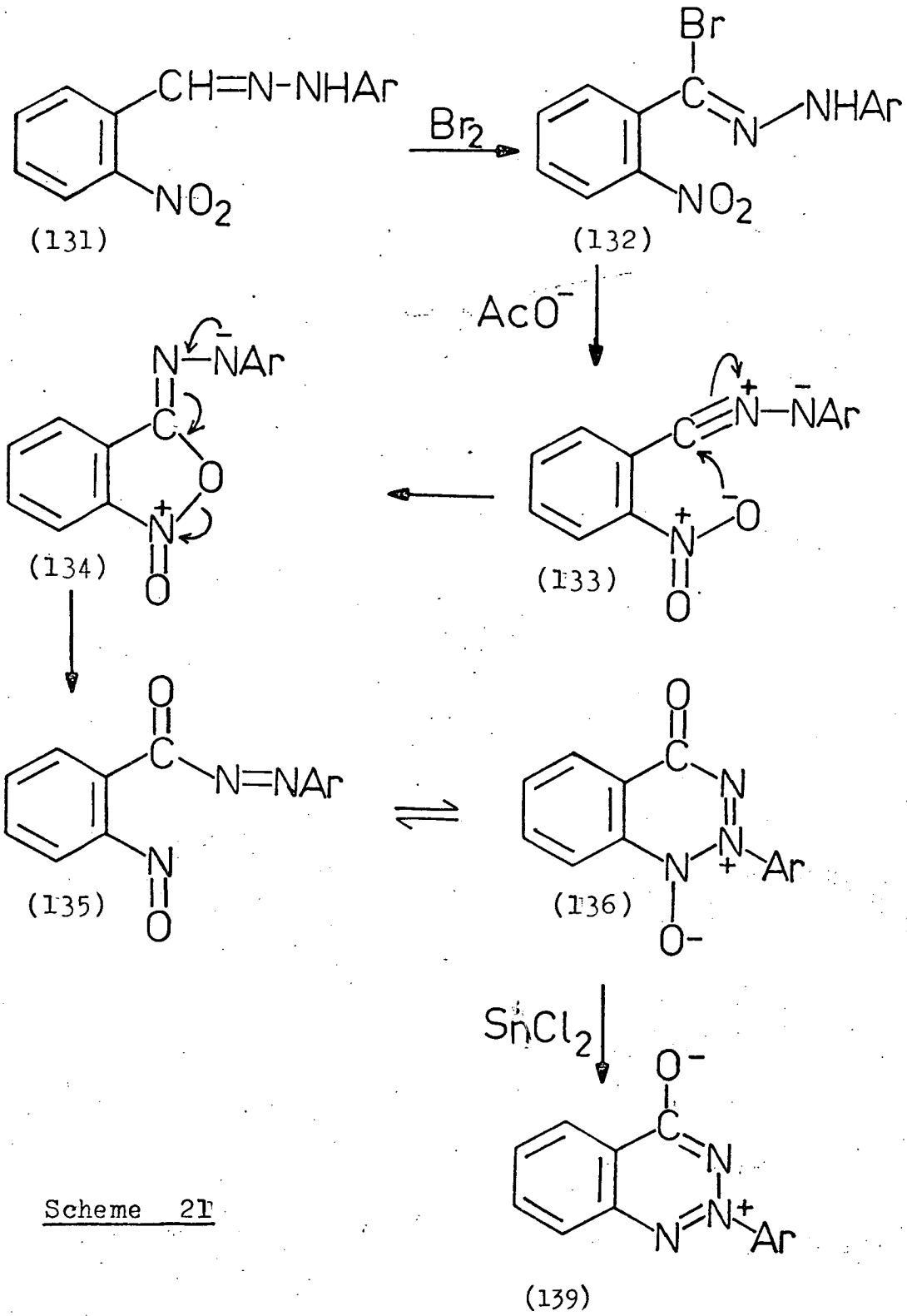
this case, the ion-pair return mechanism (Path A; Scheme 17) is operating.

Ortho-nitrobenzaldehyde (111) condenses with active methylene compounds (112) containing at least one acetyl group to give, in the case of hydrogen chloride as catalyst, high yields of chlorinated N-hydroxyquinolinones (116)[45,54]. (Scheme 18). The benzylidene derivatives (113) formed in the initial step of the reaction have been isolated and shown[45,54] to be intermediates in the quinoline formation. Consequently, the mechanism of the reaction can be explained (Scheme 18) by electrophilic attack by the protonated side-chain of the benzylidene intermediate (113) on the ortho-nitro group to give the nitrosoketone intermediate (114) reduction of which by hydrogen chloride affords the chlorinated hydroxylamino intermediate (115). Subsequent cyclisation of the hydroxylamino intermediate (115) then affords the hydroxyquinolinone (116). This plausible mechanism however, fails to explain why apparently suitable 2-nitrobenzylidene derivatives (e.g. diethyl 2-nitrobenzylidenemalonate; ethyl 2-nitrobenzylidenecyanoacetate) do not afford the corresponding N-hydroxyquinolinones in the presence of hydrogen chloride.

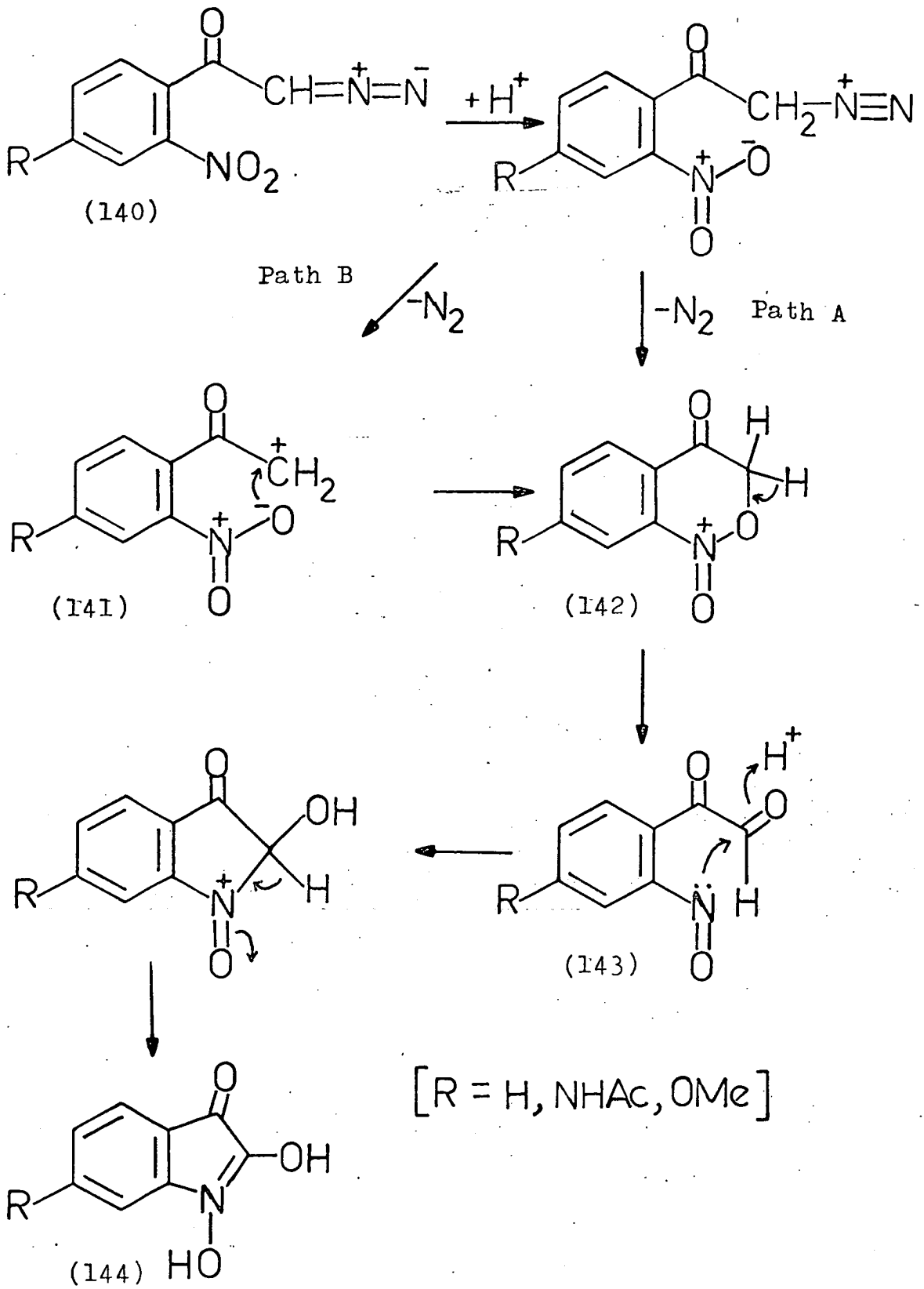
The interaction of an ortho-nitro group with an acetylenic bond under acid-conditions is exemplified by the conversion of ethyl 2-nitrophenylpropiolate (117) into 2-ethoxycarbonylisatogen (120)[55] in the presence of concentrated sulphuric acid (Scheme 19). A possible mechanism for this reaction (Scheme 19) is initiated by direct interaction of the nitro group with the protonated side-chain, in a similar fashion to that described for the initial step of quinoline formation from benzylidene precussors (see above). The cyclic intermediate (118) then undergoes ring-opening to give the nitrosoketone intermediate (119). Subsequent cyclisation of this intermediate (Scheme 19) affords the isatogen (120).



Scheme 20

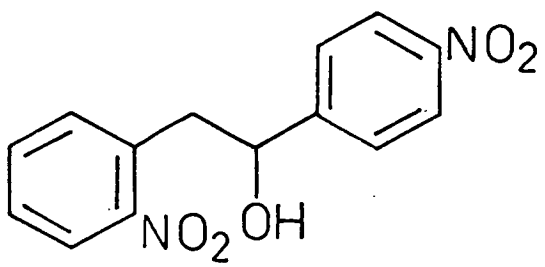

CH=N-NHAr
NO2
Br2
Br
C
N
NHAr
NO2
AcO-
N-NAr
O
N
O
(131)
(132)
(133)
(134)
(135)
(136)
(139)
(137)
(138)
SnCl2
Ar

Scheme 21

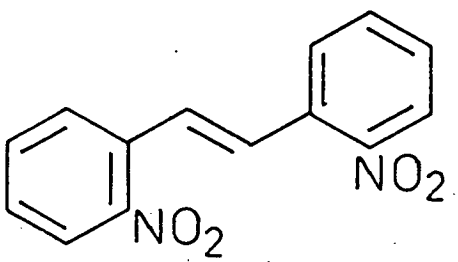


Scheme 22

An isatogen (125) is also the product[56] in cyclisation of 1,2-bis-(2'-nitrophenyl)ethanol (121) with concentrated sulphuric acid in ethanol. The mechanism of this reaction can be postulated to involve only the nitro group in the 1-phenyl ring, as the isomer (128) does not afford cyclised products under the reaction conditions. Further, dehydration

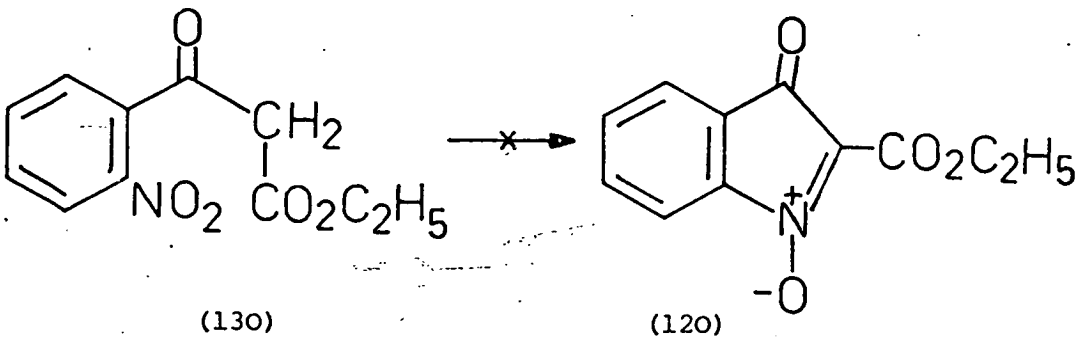


(128)



(129)

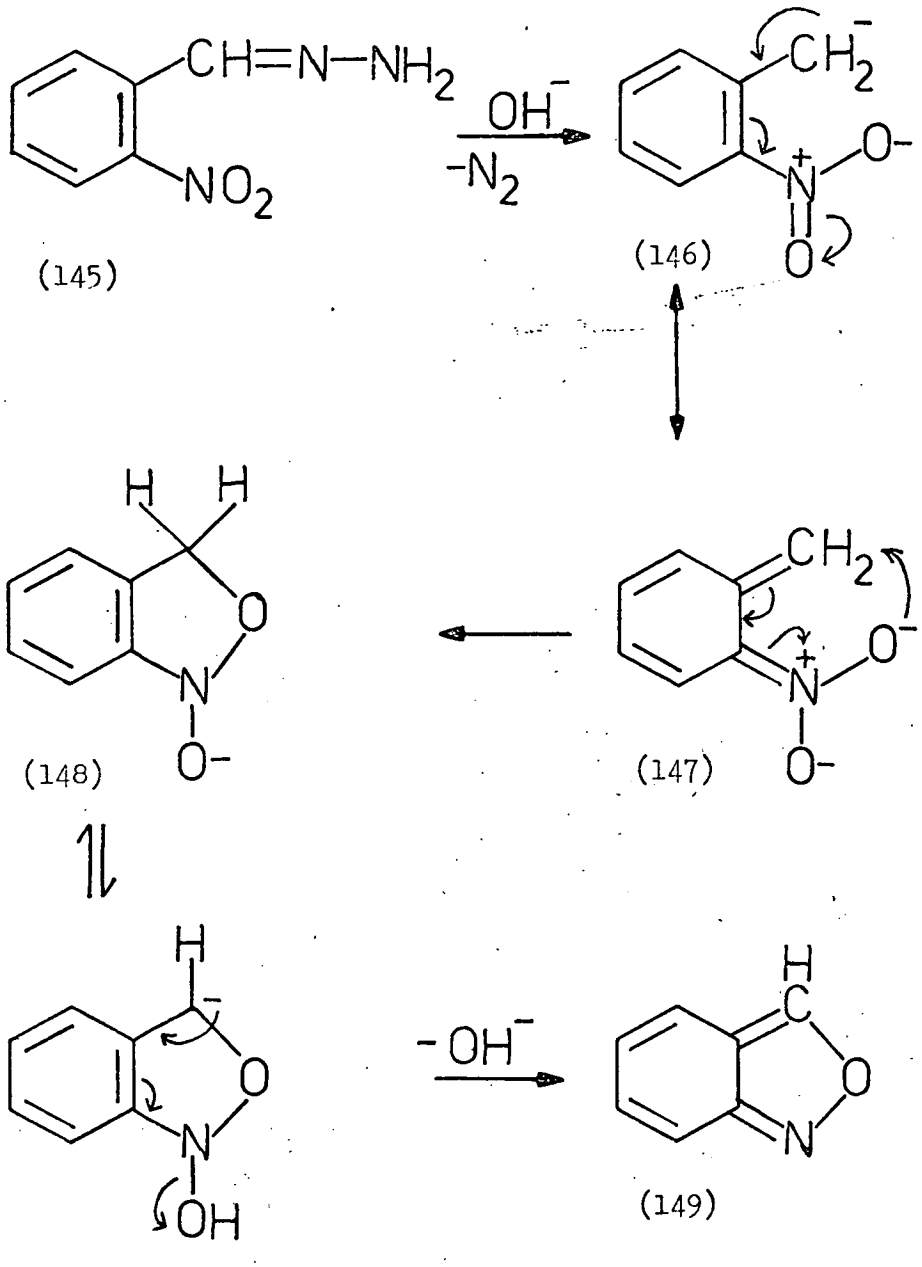
of the alcohol (121) to give the stilbene (129) cannot be a step in the mechanism as the compound (129) has been shown to be inert under the reaction conditions. Thus, a plausible mechanism for the reaction (Scheme 20) involves initial intramolecular nucleophilic attack by the nitro group at the benzylic carbon in the protonated alcohol, as shown, to give the nitrosoketone intermediate (122) which could then serve to oxidise the unreacted alcohol (121) to the nitroketone (123) with concomitant reduction to the hydroxylaminoketone (124). The nitroketone (123) could then undergo an aldol-type condensation to afford the isatogen (125). The documented[57,58] acid-catalysed conversion of isatogens into anthranils then accounts for the isolation of the 3-aroylanthranil (126). However, this proposed mechanism suffers from the criticism that the acid-catalysed conversion of ethyl 2-nitrobenzoylacetate (130) into an isatogen (120), namely 2-ethoxycarbonylisatogen does not occur. Further, no 3-(2'-nitrobenzyl)anthranil (127) derived by the expected cyclisation of the proposed hydroxylaminoketone intermediate (124) was isolated from the reaction mixture.



(130) (120)

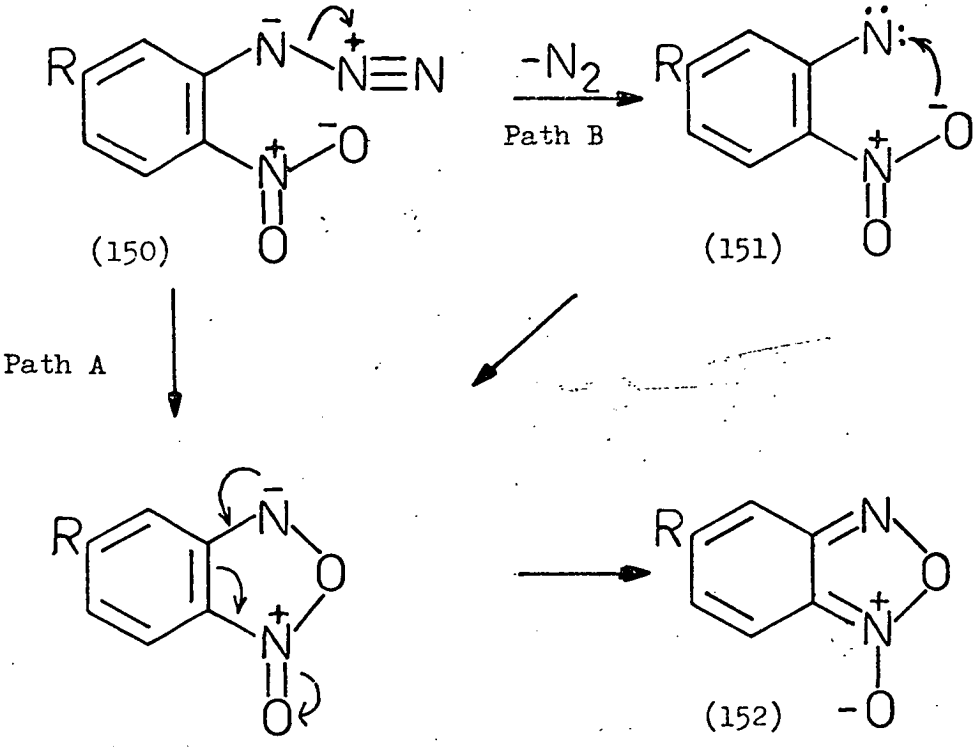
Mild oxidation of 2-nitrobenzaldehyde arylhydrazones (131) provides a synthesis[59] of the structurally unusual benzo-1,2,3-triazinium betaines (136). Thus, using bromine in the presence of sodium acetate as the reagent, the mechanism of these cyclisations may be formulated as in Scheme 21. The initial bromination of the benzylic carbon is followed by base-catalysed elimination of hydrogen bromide to afford the azomethine ylide (133) which undergoes cyclisation by intramolecular nucleophilic attack on the ylide side-chain by the ortho-nitro group. The cyclic intermediate (134) then ring-opens to afford the nitrosodiazoketone (135) cyclisation of which (Scheme 21) affords the betaine (136). The initially proposed structure[59] (137) for this product and a second, revised structure[60] (138) were based only on spectral data and elemental analysis. Kerber[61] however, proposed the dipolar structure (136) which has since been proved by an unambiguous synthesis[62] of the product of its reduction (139) whose X-ray analysis[63] has been obtained.

The generation of a carbenium ion centre in a side-chain adjacent to a nitro group in ortho-nitro benzene derivatives affords a potential electrophilic interaction of the type being discussed. Thus, 1-hydroxy-isatins (144)[64,65] are the products of the decomposition of 2-nitrobenzoyl-diazomethanes (140). The mechanism[66] involved in these reactions may be either a concerted process (Path A, Scheme 22) in which the expulsion

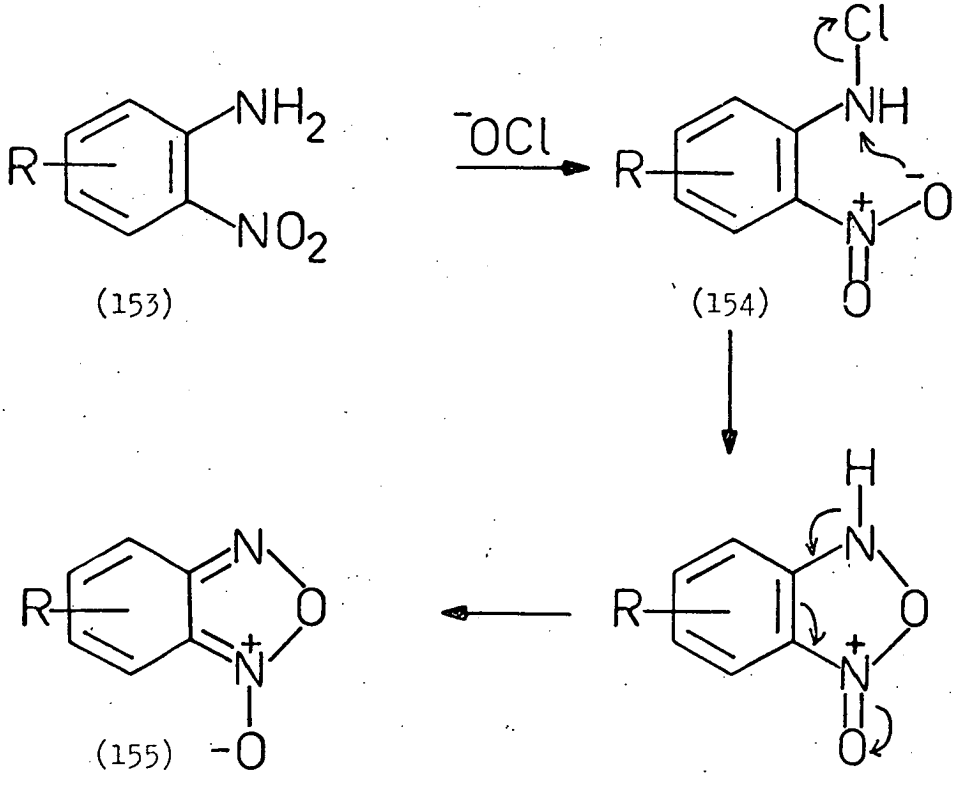

CH=N–NH2
NO2
OH⁻
–N2
CH2⁻
O-
N+
O
(145)
(146)
H H
O
N
O-
CH2
O-
N+
O-
(148)
(147)
H
O
N
OH
–OH⁻
H
C
O
N
(149)

Scheme 23

Scheme 24



Scheme 25

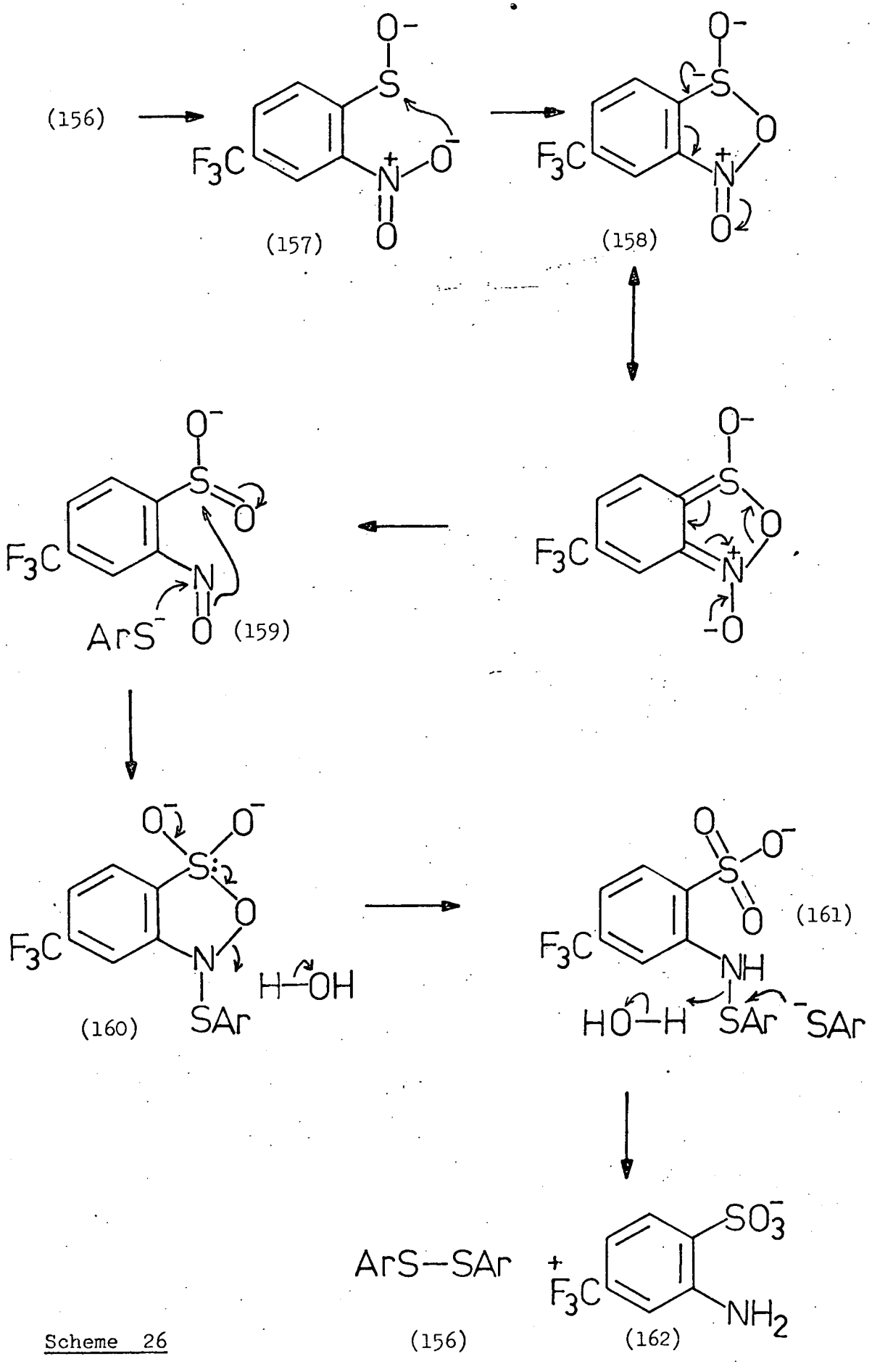


of molecular nitrogen is synchronous with nucleophilic attack by an oxygen atom of the nitro group, or it may be a stepwise process whereby a discrete carbenium ion intermediate (141) is formed (Path B, Scheme 22). Both mechanisms result in the cyclic intermediate (142) which rearranges to give the nitroso-α-dicarbonyl intermediate (143). Subsequent cyclisation affords the N-hydroxyisatin (144).

As would be imagined most cases of electrophilic attack on an ortho-nitro group are perpetrated by electron deficient centres. However, a few examples are known in which interaction is base-catalysed and the nitro group or more correctly, the aci-nitro group bears a negative charge. Thus the base-catalysed cyclisation of 2-nitrobenzaldehyde hydrazone (145) to afford anthranil (149) may be rationalised (Scheme 23) by initial solvolysis of the hydrazone (145) to produce the mesomeric 2-nitrobenzyl anion [(146) ⟷ (147)]. Reacting in the form (147), the aci-nitro anion may then undergo intramolecular Michael-type addition of an oxygen of the aci-nitro group to the ortho-side-chain to give the cyclic intermediate (148) which aromatises as shown, to afford the anthranil (149).

ii) Interactions between the Nitro Group and an Electrophilic Nitrogen Centre in the Side-Chain.

The thermal conversion of 2-nitrophenylazides (150)[68] into benzofuroxans (152) exemplifies electrophilic attack on the nitro group by a nitrogen atom under essentially neutral conditions and is noteworthy in being one of the few cases where the original nitro group to side-chain N-O bond is retained in the product (Scheme 24). The interaction between the nitro-group and side-chain may occur as the initial step of this reaction, i.e. the expulsion of nitrogen may be synchronous with formation of the N-O bond (Path A, Scheme 24). Alternatively, a discreet nitrene intermediate (151) may be formed (Path B, Scheme 24) as the initial step followed by



Scheme 26

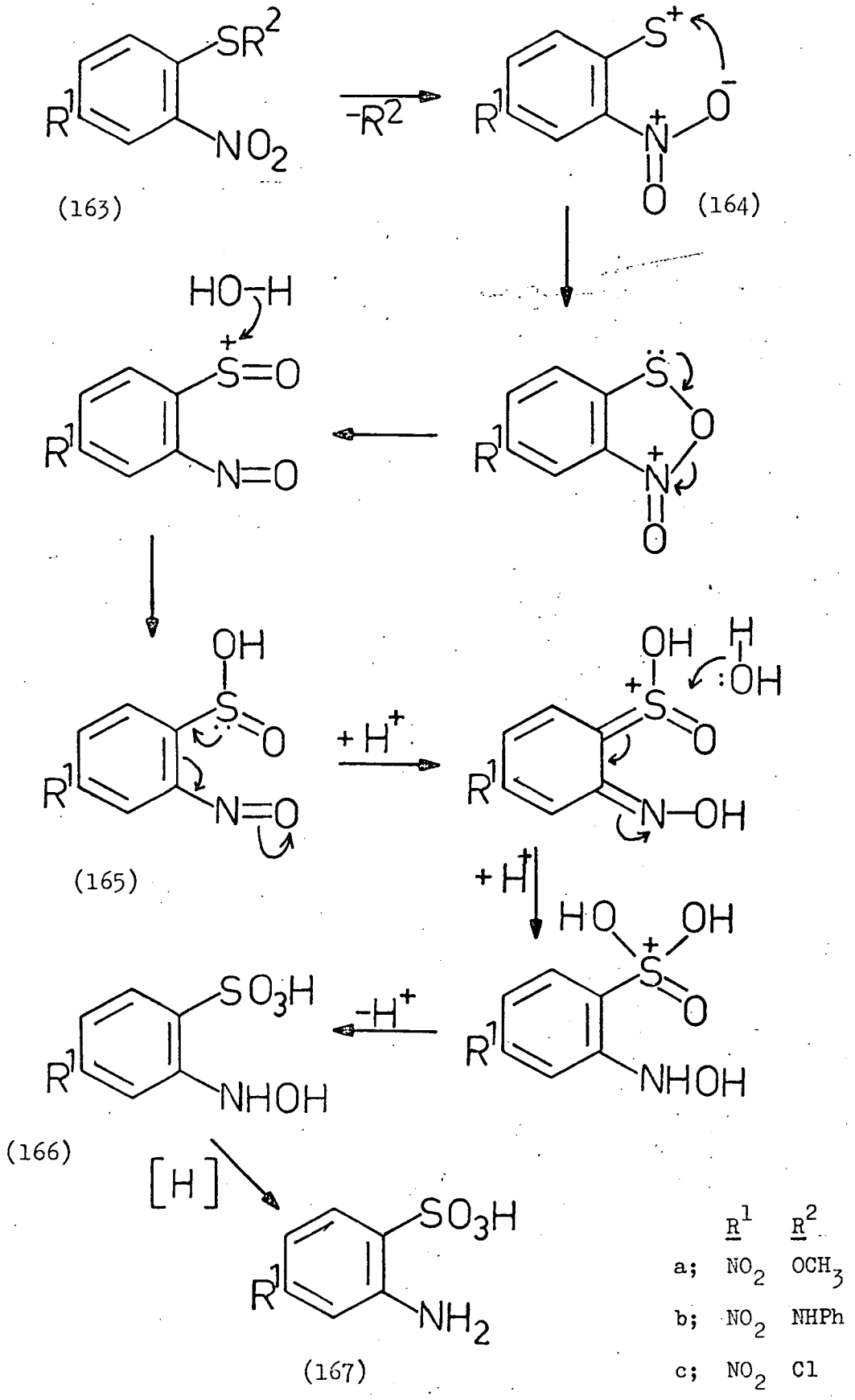
electrophilic attack of the nitrene centre on the ortho-nitro group. The common intermediate of both paths is simply a mesomeric form of the benzofuroxan (152).

An alternative route to benzfuroxans involves the hypochlorite oxidation[70,71] of ortho-nitroanilines (152) (Scheme 25). This method can be rationalised[72,73] by postulating the initial formation of an N-chloroamine (154) which undergoes intramolecular nucleophilic attack, with expulsion of chloride ion, by an oxygen of the ortho-nitro group. (Scheme 25) to give the product (155).

iii) Interactions between the Nitro Group and an Electrophilic Sulphur Centre in the Side-Chain.

Electrophilic attack by sulphur in an ortho-side-chain at an oxygen atom of a nitro group invariably leads to non-cyclicised products in which the sulphur atom is oxidised to the level of a sulphinic or sulphonic acid.

A base-catalysed electrophilic interaction between a sulphur side-chain and an ortho-nitro group was observed by Hogg[74] in studies concerned with the kinetics of the base-catalysed solvolysis of bis-(2-nitro-4-trifluoromethylphenyl)disulphide (156). Among the isolated products of this reaction was 2-amino-3-trifluoromethylbenzenesulphonic acid (162). This product was explained by the production of 2-nitrobenzenesulphenate ion (157) from solvolysis of the disulphide followed by a series of bimolecular reactions involving only the sulphur side-chain. The sulphenate ion (157) is suggested to undergo intramolecular electrophilic attack by the electron-deficient sulphur atom at an oxygen atom of the nitro group (Scheme 26) to give a cyclic intermediate (158) in which the sulphur atom has been formally reduced. An electron rearrangement and ring-opening then gives the 2-nitroso-3-trifluoromethylbenzenesulphinate ion (159) which can further



	R^1	R^2
a;	NO_2	OCH_3
b;	NO_2	NHPh
c;	NO_2	Cl
d;	H	Cl

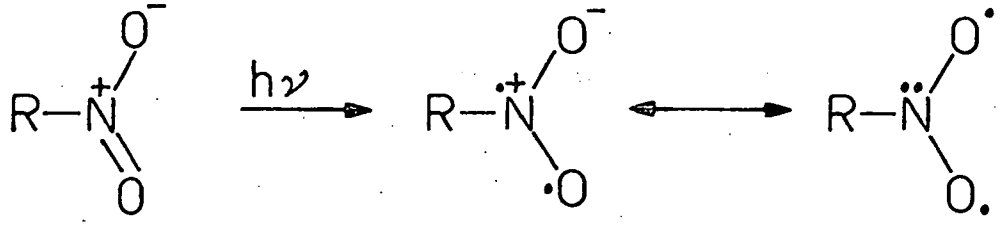
Scheme 27

suffer addition of a thiolate ion present in the reaction mixture, to afford a cyclic intermediate (160). Ring-opening with concomitant oxidation of sulphur followed by solvolysis of the sulphur-amino bond by another molecule of the thiolate ion affords the aminosulphonic acid (162) and a molecule of the disulphide (156).

Several equally complex, acid-catalysed electrophilic interactions are known. Thus, the 2-nitrobenzenesulphenyl derivatives[75] (163a and b) yield, in strongly acidic media (e.g. concentrated sulphuric acid), the orthanilic acid (167a) in low to moderate yields. The reaction may be postulated to proceed by initial formation of a nitrophenylsulphenium ion intermediate [Scheme 27; (164)] evidenced[76] by the red colour produced in these reactions. The electrophilic sulphenium ion (164) then attacks the nitro group with formation of the nitrososulphinic acid intermediate (165) which undergoes a further oxidation-reduction by the formal donation of two electrons from the sulphur to the nitrogen to afford the 2-hydroxylaminosulphonic acid (166). As the isolated product is the aminosulphonic acid (167), obviously an intermolecular reduction must occur at some point in the reaction mechanism. This may in fact occur as shown [Scheme 27, (166) → (167)] since in the similar reaction of the sulphenyl chloride (163c) in acetic acid[77] the O-acetyl derivative of the hydroxylaminosulphonic acid (166c) can be isolated. Orthanilic acid is also the product of methanolysis of 2-nitrophenylsulphenyl chloride (163d)[78].

D. Photochemically Induced Neighbouring Group Interactions in 2-Nitrobenzene Derivatives

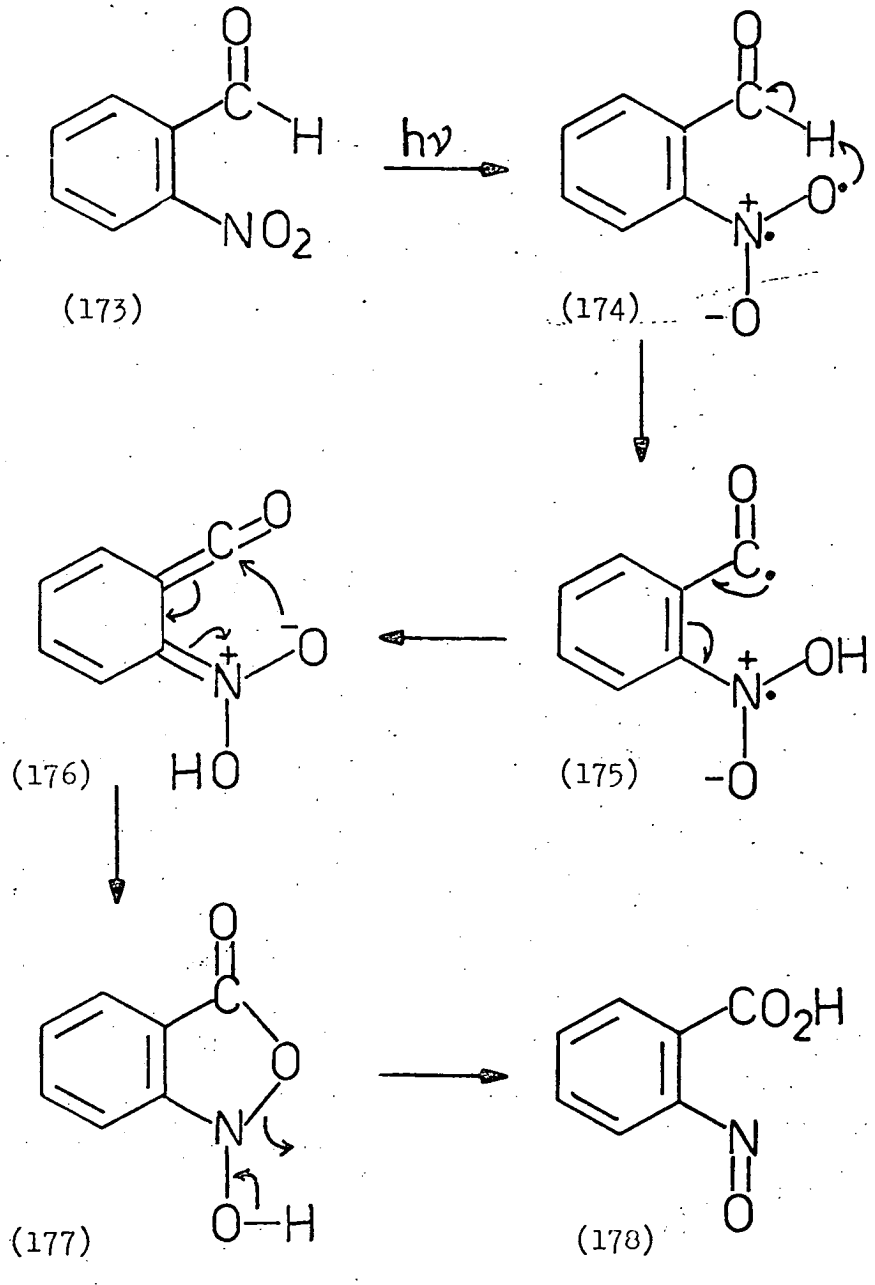
For the purpose of rationalising the photochemical processes involving a nitro group, it is convenient to postulate a triplet ($n \rightarrow \pi^*$) photo-excited state of the nitro group as the lowest-lying excited state and consequently that which reacts.[79] This $^3(n,\pi^*)$ photo-excited state corresponds, in valence bond terms, to a resonance hybrid of the structures (169) and (170).



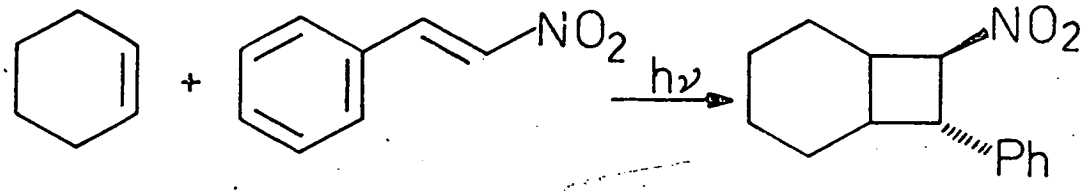
(168) (169) (170)

Structure (169) is analogous to Zimmerman's representation of the $^3(n,\pi^*)$ state of a carbonyl group. Both structures (169) and (170) imply considerable diradical character in this excited state. A singlet ($n \rightarrow \pi^*$) excited state is considered to be too short-lived to be important in the photochemical processes undergone by nitro compounds.

Several photochemical processes are known for organic nitro compounds which directly involve an excited state of the nitro group. In other photochemical processes the nitro group simply confers reactivity on other functional groups in the molecule, itself remaining unchanged in the overall reaction. Such a reaction is exemplified by the photo-cyclo-addition[80] of trans-β-nitrostyrene (171) to cyclohexene to give the cyclobutene derivative (172).

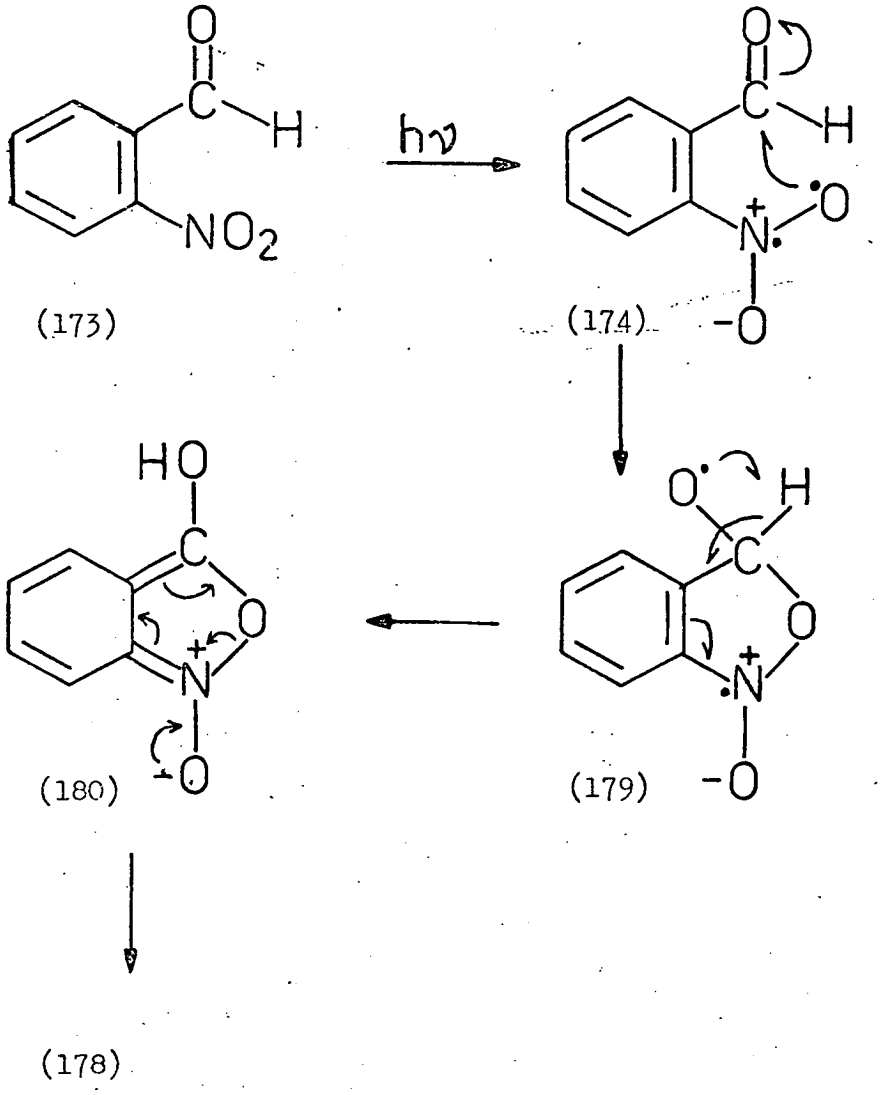


Scheme 28

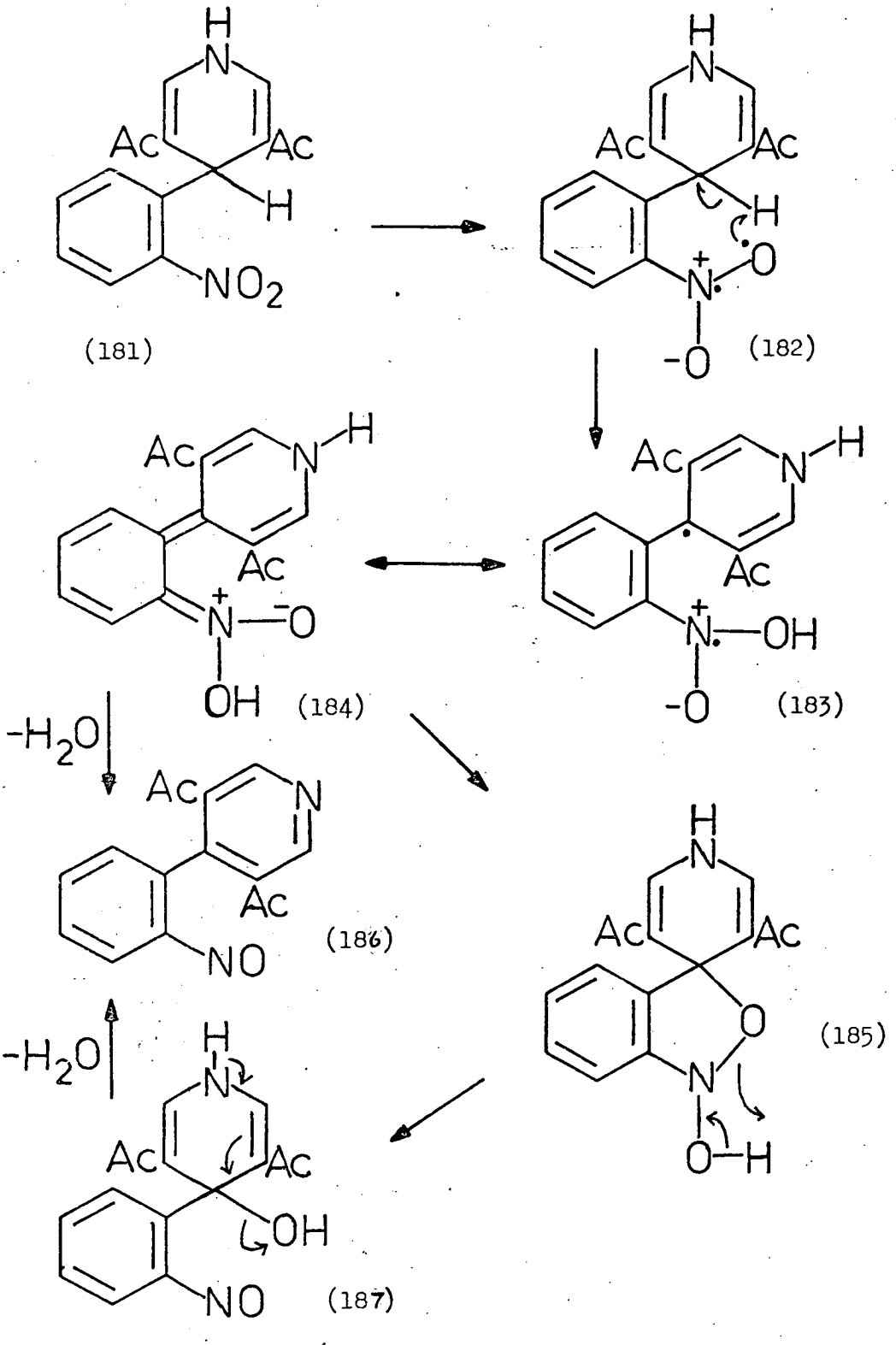


(171) (172)

However, processes of interest in photochemically induced nitro-group side-chain interactions in aromatic ortho-nitro compounds are generally of the former type in which the nitro group is modified in the course of the photochemical reaction. Such processes may be categorised[79] by the primary photochemical process involved-namely, hydrogen abstraction or oxygen transfer. In some cases however, either hydrogen abstraction or oxygen transfer may be involved and it can then become difficult to identify the particular primary photochemical process by which a chemical transformation is initiated. Thus, one of earliest examples of a photochemical reaction involving an aromatic nitro compound-namely the conversion of 2-nitrobenzaldehyde (173) into 2-nitrosobenzoic acid[81] (178) may be rationalised[82] (Scheme 28) in terms of a primary photochemical process involving hydrogen abstraction from the aldehyde group by the $^3(n,\pi^*)$ state of the nitro group [(174) → (175)]. The acyl radical in (175) then pairs with the nitrogen radical to afford the aci-nitro ketene intermediate (176) cyclisation of which gives the unstable N-hydroxybenzisoxalone (177). Rearrangement of the heterocycle (177) then affords the 2-nitrosobenzoic acid (178).



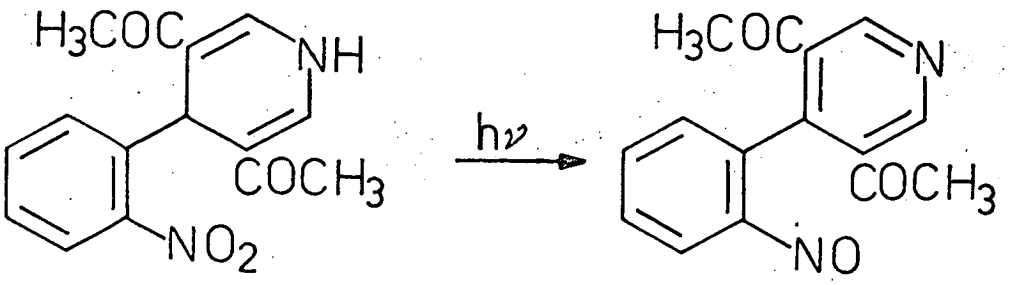
Scheme 29



Scheme 30

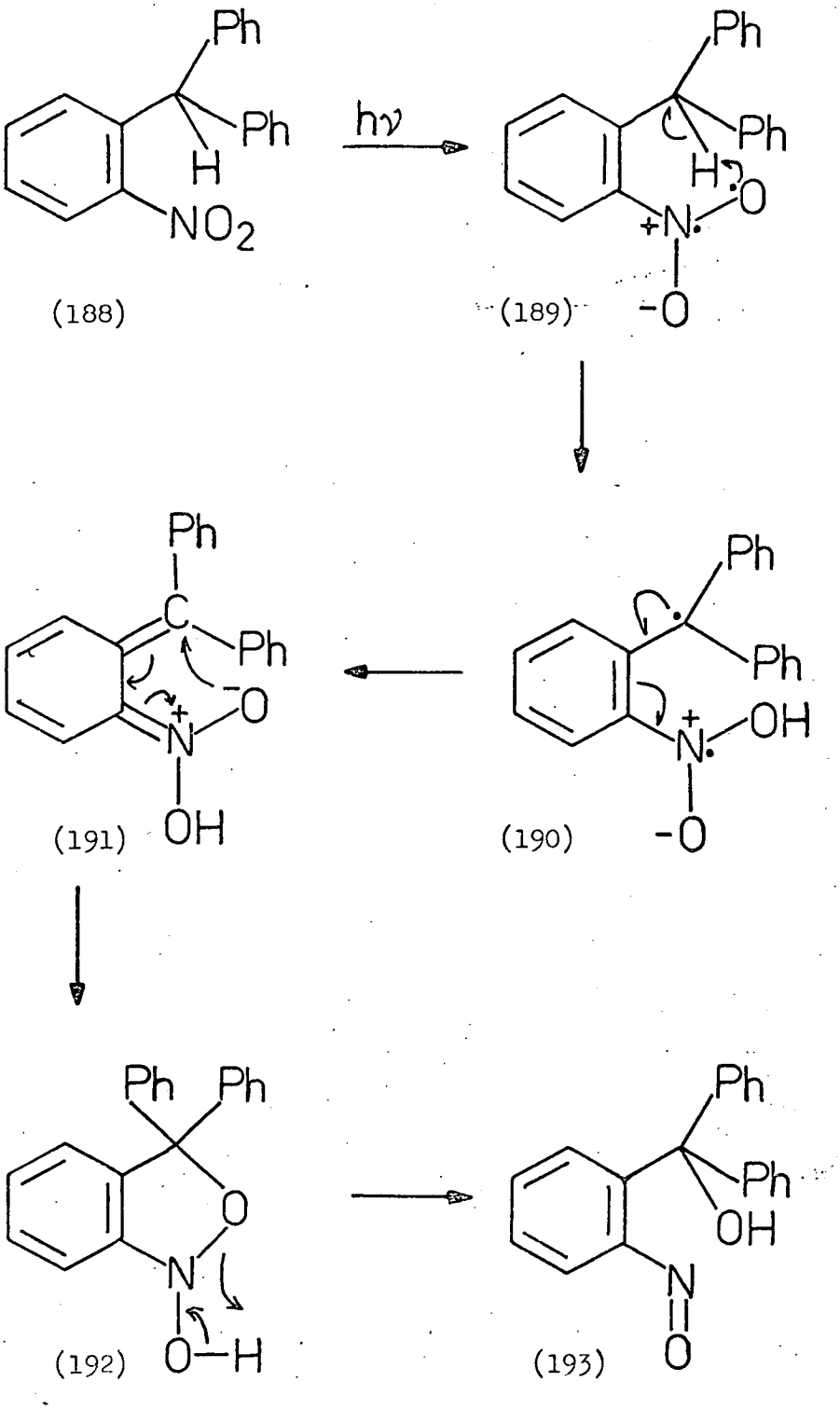
Alternatively, the transformation [(173) → (178)] may be postulated to involve oxygen transfer as the primary photochemical process of the photo-excited nitro compound (Scheme 29) whereby a new C-O bond is formed [(174) → (179)]. Hydrogen transfer [(179) → (180)] followed by ring-opening of the hydroxybenzisoxazole N-oxide (180) then accounts for formation of 2-nitrosobenzoic acid (178).

Many other 2-nitrobenzene derivatives which have a benzylic hydrogen, but lack a carbonyl group, give products derived by intramolecular oxidation-reduction akin to that described for 2-nitrobenzaldehyde. These reactions lend some weight to hydrogen abstraction being the primary photochemical process in the 2-nitrobenzaldehyde photoisomerisation. Berson and Brown[83] proposed such a mechanism (Scheme 30) to account for the photochemical transformation of the 1,4-dihydropyridine derivative (181) into the 4-nitrosophenylpyridine derivative (186). Obviously,



(181) (186)

the alternative mechanism (Scheme 29) involving primary formation of a carbon-oxygen bond is not feasible for structural reasons in the substrate (181). Consequently, the only mechanism open involves primary hydrogen abstraction [(182) → (183)]. Electron-pairing then gives an aci-nitro intermediate (184) which may undergo cyclisation [(184) → (185)] followed by ring-opening and dehydration of the



Scheme 31

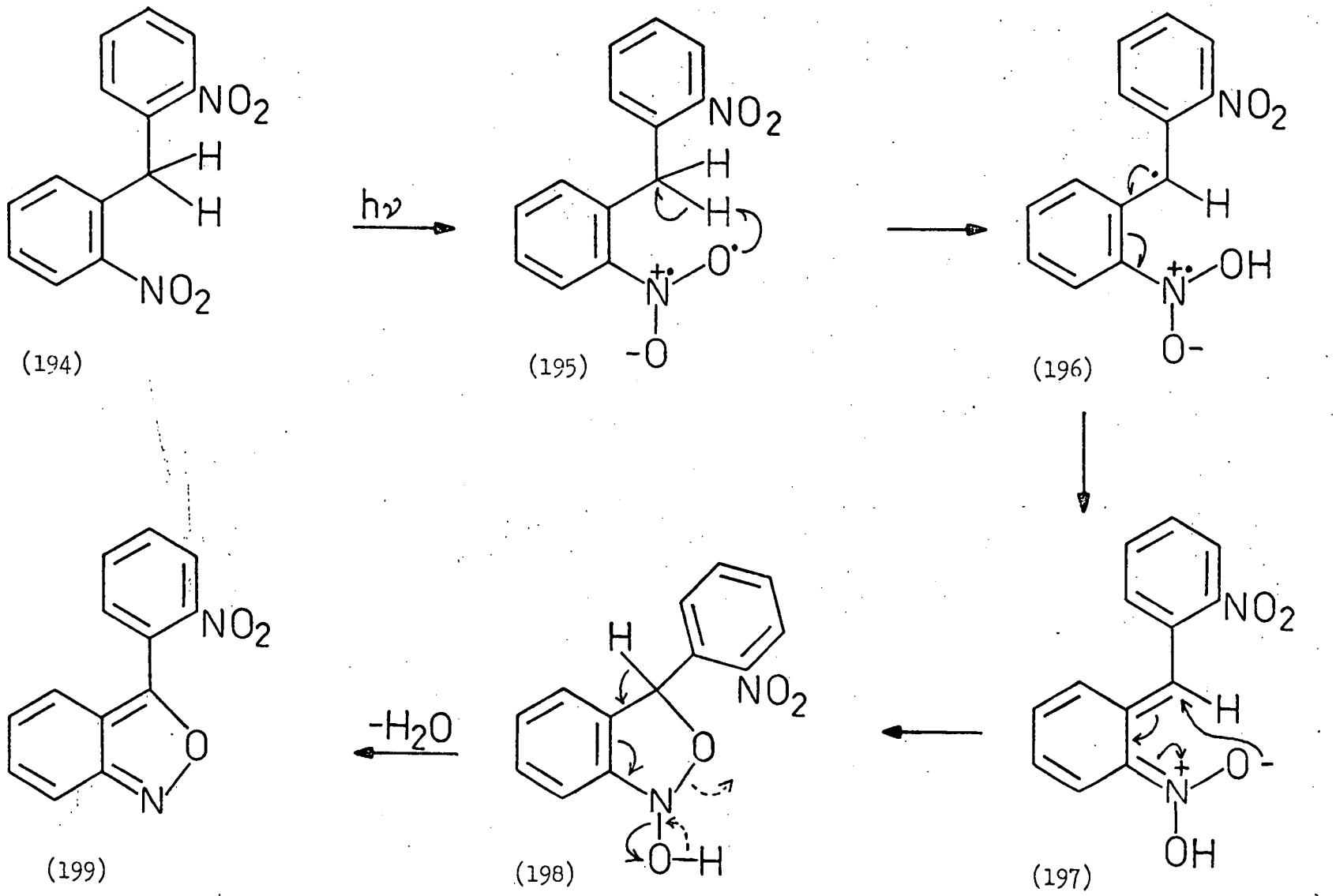
resulting nitroso-alcohol (187) to give the product (186). A more direct route to the product however would be a dehydration as shown [(184) → (186)][84] without oxygen transfer occurring.

Tanasescu has shown that intramolecular photochemical oxidation of a tertiary benzylic carbon by an ortho-nitro group can also occur as in the photochemical formation of the 2-nitrosocarbinol (193) from the nitro precursor [(188); (Scheme 31)]. The abstraction of the methine hydrogen by the $^3(n,\pi)$ state of the nitro group [(189) → (190)] is favoured by the formation of a stable triphenylmethyl radical (190). Electron-pairing then gives the aci-nitro intermediate (191) which can then cyclise by a two-electron process to give the cyclic intermediate. Ring-opening of the latter then explains the formation of the 2-nitroso-carbinol (193).

From the examples of photochemical reactions of 2-nitrobenzene derivatives described above, it can be seen that in all cases where hydrogen abstraction is postulated as the primary photochemical process, the role of the photo-excitation is to catalyse the formation of an aci-nitro tautomer of the substrate. The question thus arises as to the nature of the subsequent reactions of this aci-nitro tautomer. A photochemical reaction of this aci-nitro tautomer however, need not be considered as, by analogy with certain chemically-catalysed reactions (cf. page 15) of 2-nitrobenzene derivatives which are postulated to react via their aci-nitro tautomers, a dark reaction of the said tautomer is sufficient to explain the formation of 2-nitrosobenzene derivatives.

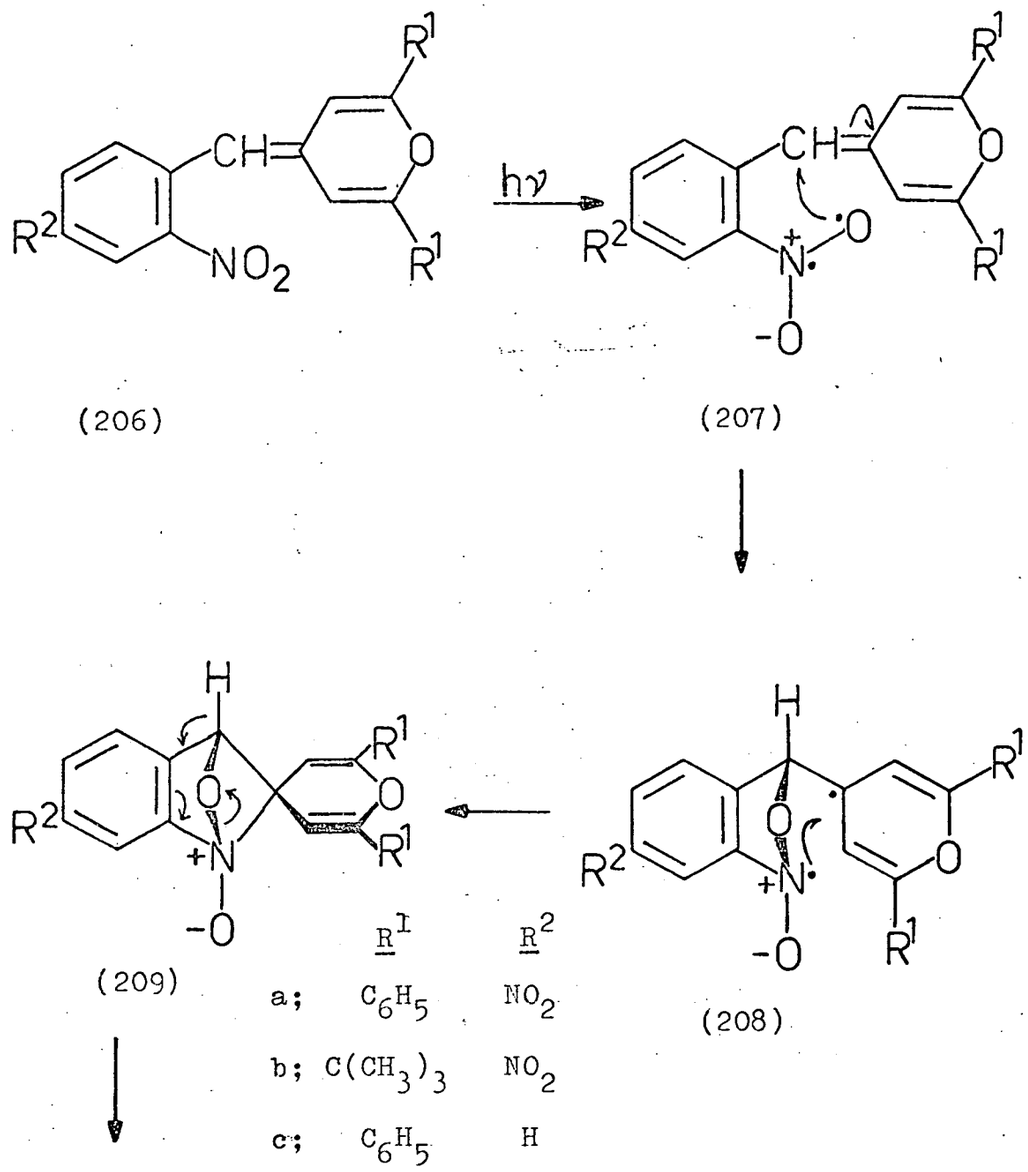
The formation of 2-nitrosobenzene derivatives in these intramolecular photochemical oxidation-reduction processes can, by further reaction, (either dark or photochemical) lead to the formation of heterocyclic compounds. Thus, Joshua and Ramdas[85] have shown that the products of photolysis of 2,2'-dinitrodiphenylmethane (194) in ethanol are the diazepine (204) and to a lesser extent the acridone (205) (Scheme 32).

Scheme 32

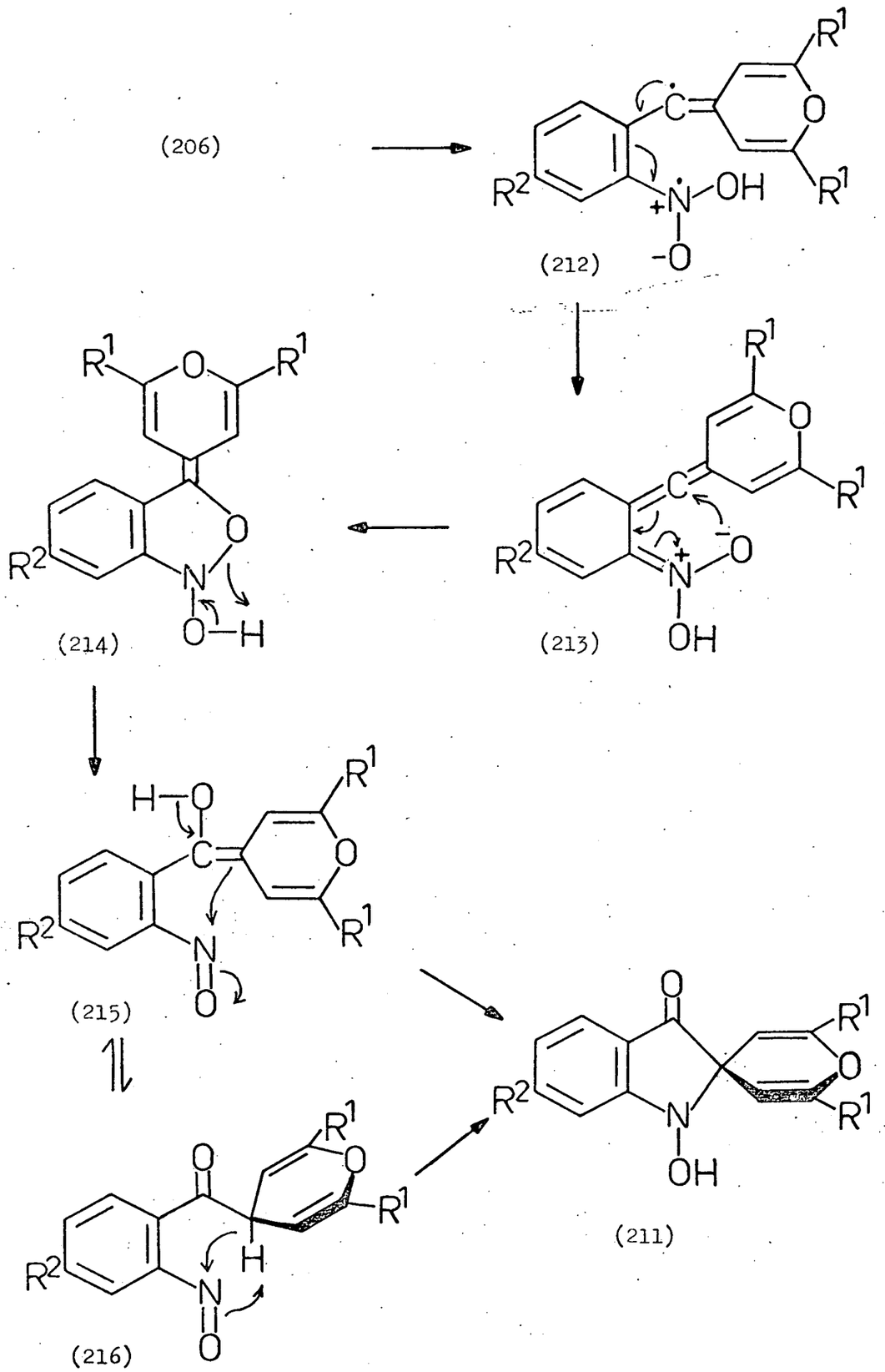

NO2
H
H
NO2
hν
(194)
(195)
(196)
OH
O-
(197)
(198)
(199)
-H2O
O
N
OH
(200)
(201)
N=O
hν
(202)
(203)
(204)
-H2O
(205)
-[NO3]
[H]
NH
+

However, in the presence of a catalytic amount of concentrated sulphuric acid the major product is the 3-(2'-nitrophenyl)anthranil (199). The formation of all these products can be explained (Scheme 32) by an initial hydrogen abstraction from the benzylic carbon by the $^3(n,\pi^*)$ excited state of the nitro group followed by radical-coupling to give the aci-nitro tautomer [(194) → (197)] which then cyclises to give the cyclic intermediate (198). Protonation of the N-hydroxy group of this intermediate followed by loss of water and deprotonation (full arrows) readily explains the formation of the anthranil (199) in the presence of an acid-catalyst. Alternatively, in essentially neutral media, the same intermediate (198) can ring-open to give the nitroso-alcohol [broken arrows, (198) → (200)]. A repetition of the the photochemical process involving the reduction of the remaining nitro group in (200) with concomitant oxidation of the alcohol group to a ketone affords the dinitrosoketone (201). Disproportionation between (201) and unreacted nitrosoalcohol (200) provides the necessary reduction required to produce the intermediate (202) which can condense with loss of water, to afford the diazepine N-oxide (204). The formation of the nitroso-ketone (203) is suggested to explain, by a cyclisation involving a photo-reduction, the production of the acridone (205).

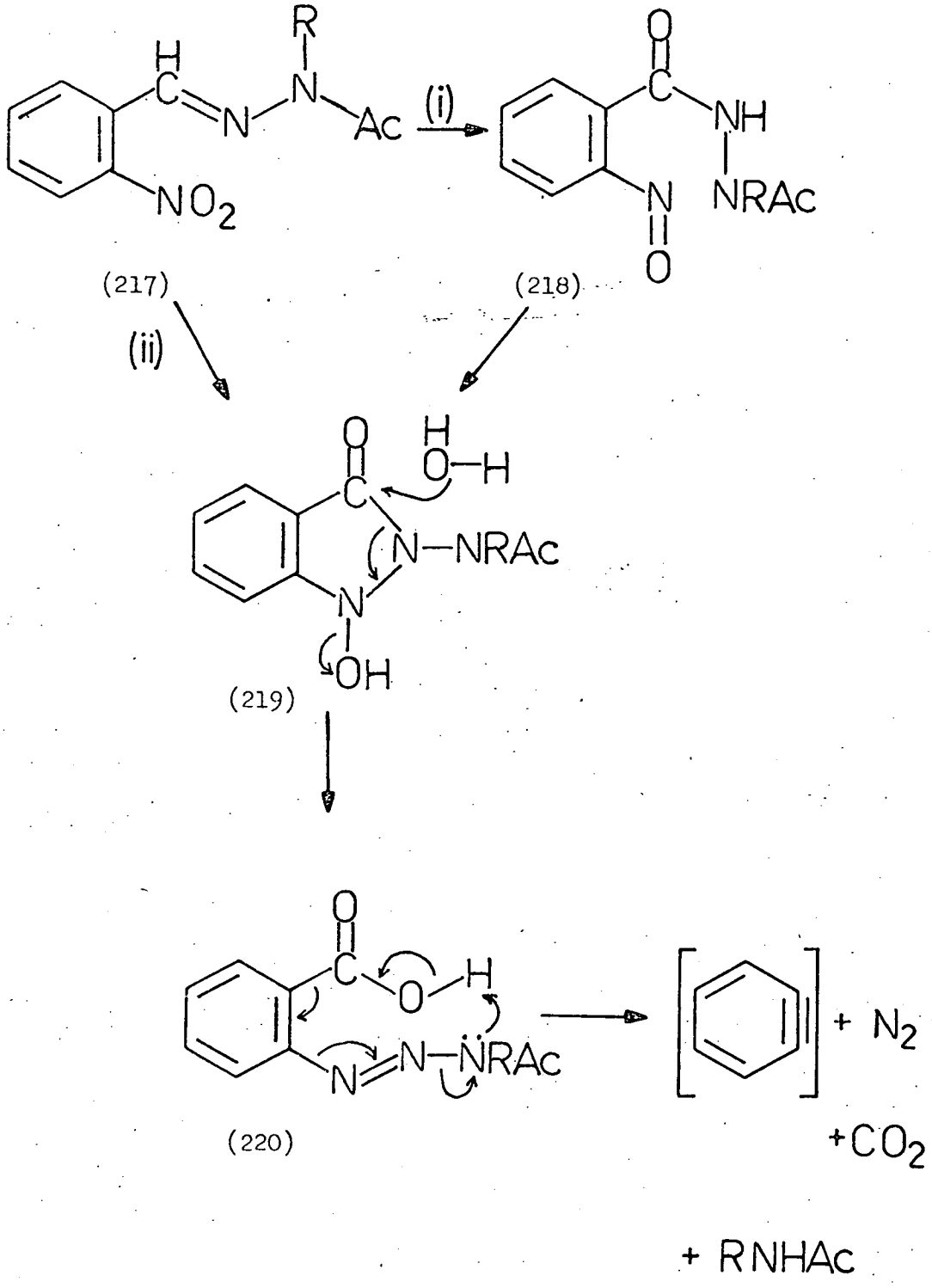
Analogous to the photochemical oxidation-reduction processes described for 2-nitrobenzaldehyde are the photochemical transformations undergone by 2-nitrobenzylidene derivatives. Van Allan[86] observed the formation of the spiro-pyranoindolinones(211) (Scheme 33 and 34) by the photolysis in methylene chloride of the 4-(2'-nitrobenzylidene)pyrans (206a and b) at room temperature and by the photolysis of the 4-(2'-nitrobenzylidene)pyran (206c) at -60° in toluene. A mechanism



Scheme 33



Scheme 34



i = Hydrogen abstraction

ii = Oxygen transfer

R = Alkyl, (not H)

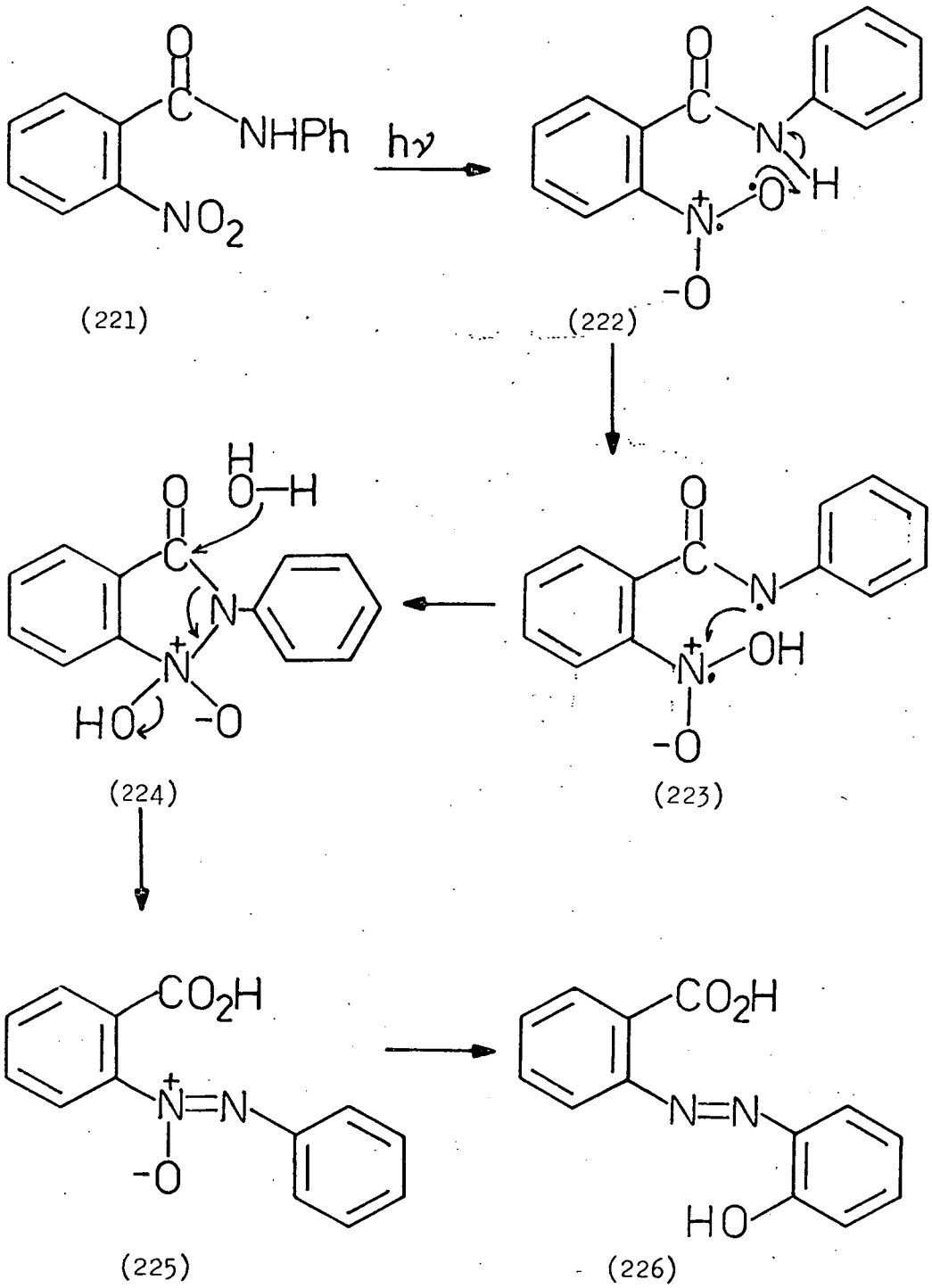
Scheme 35

(Scheme 33) based on addition of the oxygen atom in the $^3(n,\pi^*)$ excited state of the nitro group to the benzylidene side-chain [(207) → (208)] followed by radical-coupling to give the bridged bicyclic intermediate (209) and subsequent ring-opening [(209) → (210)] explains the formation of the spiro-product (211).

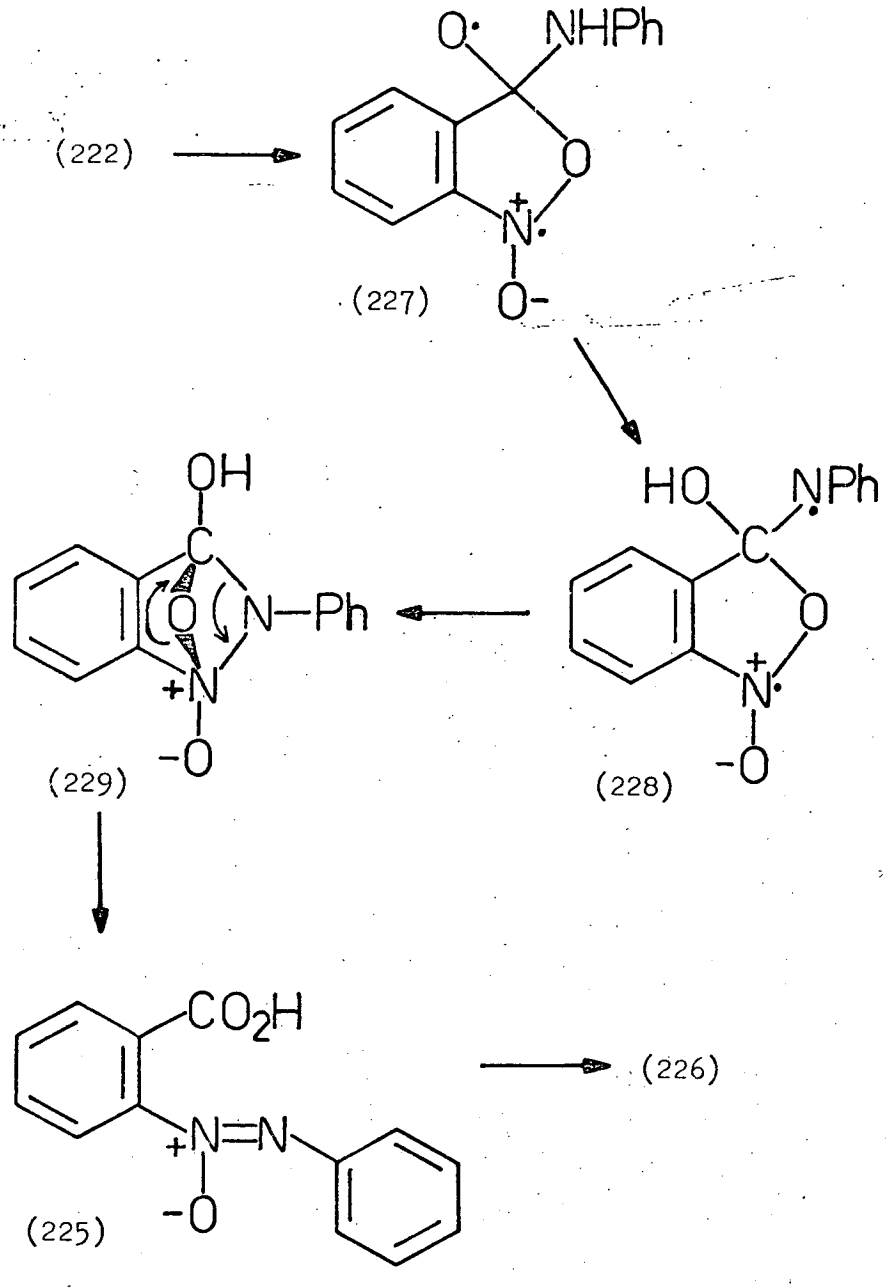
Alternatively, a primary process involving a hydrogen abstraction (Scheme 34) leading to the aci-nitro allene [(206) → (213)] which is analogous to the ketene intermediate in the mechanism postulated for the photoisomerisation of 2-nitrobenzaldehyde (Scheme 28, page 31), may be invoked. Cyclisation of the aci-nitro tautomer (213) followed by ring-opening affords the nitroso-enol (215) which may tautomerise to the ketone (216) or cyclise by nucleophilic attack on the nitro group to give the spiro-N-hydroxyspiro-pyranoindolinone (211).

An interesting photochemical generation of benzyne from the photolysis of 2-nitrobenzylidene hydrazones (217) (Scheme 35) has been reported by Maki et al[87]. This reaction can be rationalised by postulating the intermediate formation of 2-nitrosobenzhydrazide derivatives (218) by a photochemical intramolecular oxidation-reduction process between the nitro group and the side-chain which again may occur by a primary process involving hydrogen abstraction. Alternatively, a mechanism involving oxygen-transfer could account for the formation of the N-hydroxyindazolones (219) directly. (Scheme 35). These mechanisms are directly analogous to those postulated for the formation of the pyranoindolinones discussed above (cf. page 34). Ring-opening [(219) → (220)] and subsequent fragmentation explain the formation of benzyne.

In those reactions discussed already, hydrogen abstraction has always occurred from the benzylic position but examples are known where hydrogen abstraction may occur from other positions on the ortho side-chain. Thus Gunn and Stevens[88] postulate hydrogen abstraction from the benzamide nitrogen as the primary step in the photochemical con-



Scheme 36



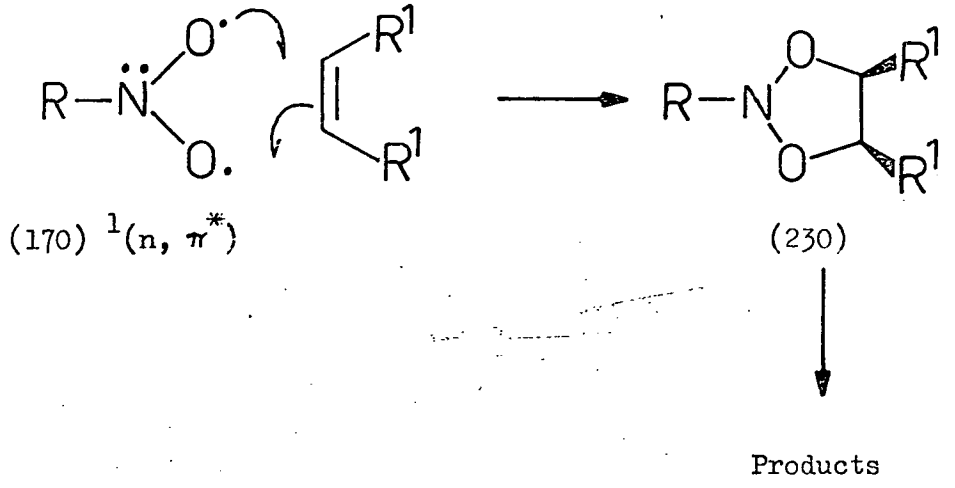
Scheme 37

version (Scheme 36) of 2-nitrobenzanilide (221) into the hydroxyazobenzene carboxylic acid (226). The resulting biradical (223) can then undergo radical coupling to give the cyclic intermediate (224) followed by nucleophilic attack of hydroxide at the carbonyl group with concomittant ring-opening to afford the azoxy-carboxylic acid (225). A photochemical rearrangement of this azoxy-acid (225) then accounts for formation of the product (226).

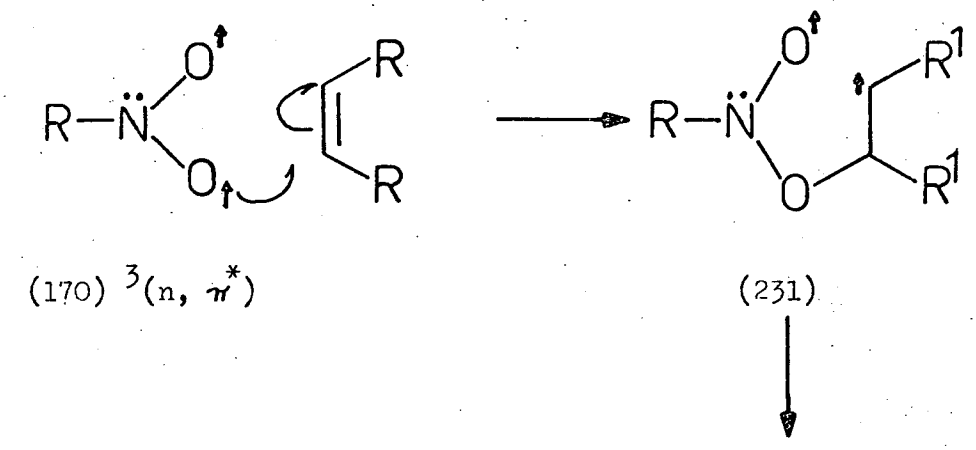
However, a mechanism involving oxygen transfer, akin to that postulated for the 2-nitrobenzaldehyde rearrangement (Scheme 29), may be proposed (Scheme 37). Again, formation of a bridged bicyclic intermediate [(222) ↠ (229)] by radical coupling as postulated for the similar reactions of the benzylidenepyrans [(206); Scheme 33] or of the hydrazones [(217, Scheme 35] can explain the formation of the azoxy-carboxylic acid (225) and thus of the hydroxy-azocarboxylic acid (226).

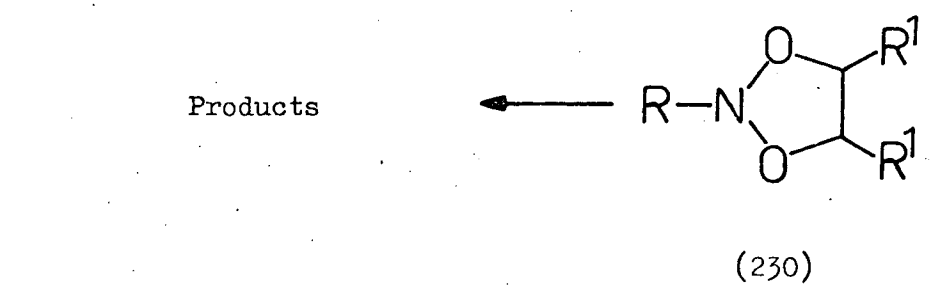
The primary photochemical process of oxygen transfer from an aromatic nitro group to an ortho-side-chain may occur not only with the formation of one carbon-oxygen single bond as described in Scheme 29, but also by a 1,2-photocycloaddition process[89] to give an intermediate having two new carbon-oxygen single bonds (230). This process may only be concerted if a singlet excited state of the nitro group $^{1}(n,\pi^*)$ is involved (Scheme 38). However, it is likely that a $^{3}(n,\pi^*)$ species is involved[79,90] and consequently the cycloaddition must be a stepwise process involving a spin-inversion (Scheme 39) in the biradical intermediate (231).

An intermolecular photocycloaddition of this type has been proposed (Scheme 40) to explain the oxidative cleavage products isolated from the reaction of nitrobenzene with alkenes such as 2-methylbut-2-ene or cyclohexene (232). In the latter case the formation of adipaldehyde (235) and azobenzene (237) can be rationalised[79] by the formation of the

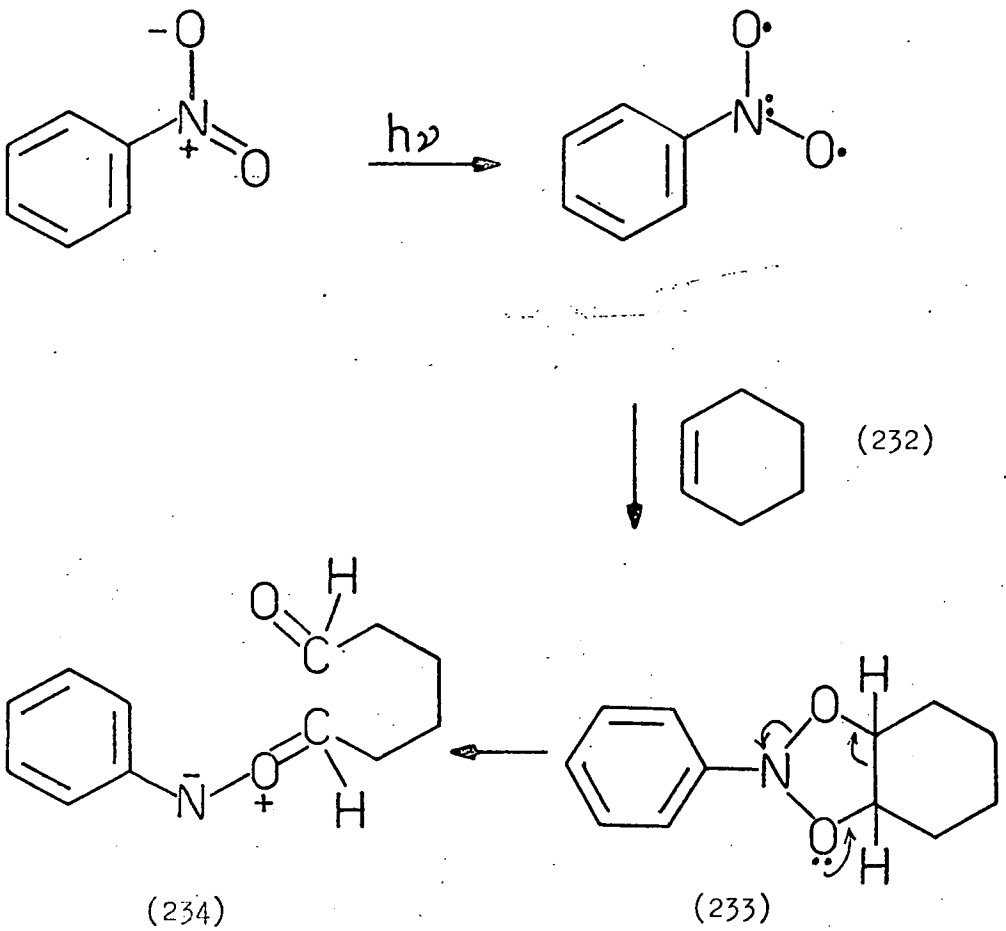


Scheme 38





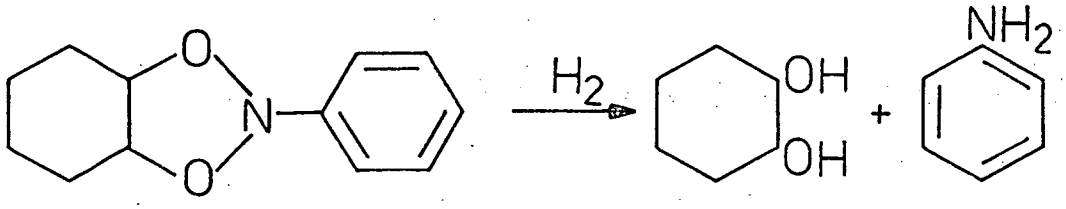
Scheme 39



Scheme 40

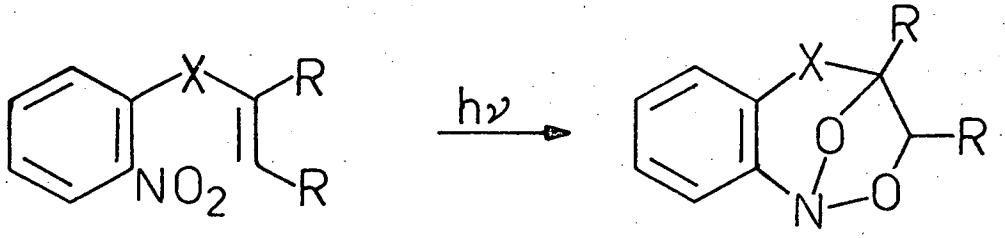
cycloadduct (233) which breaks down as shown (Scheme 40) with the formation of the aldehyde (235) and phenyl nitrene (236). The azobenzene (237) is suggested to be formed by reaction of the phenyl nitrene with a molecule of (234).

A number of the 1,3,2-dioxazolidine adducts formed in such photochemical reactions have been isolated.[90] Thus, the adduct (233) produced by irradiating a mixture of cyclohexene and nitrobenzene at -70°, can be isolated as a crystalline solid at -80° and was characterised by catalytic reduction to aniline and the cis-cyclohexane diol (238)



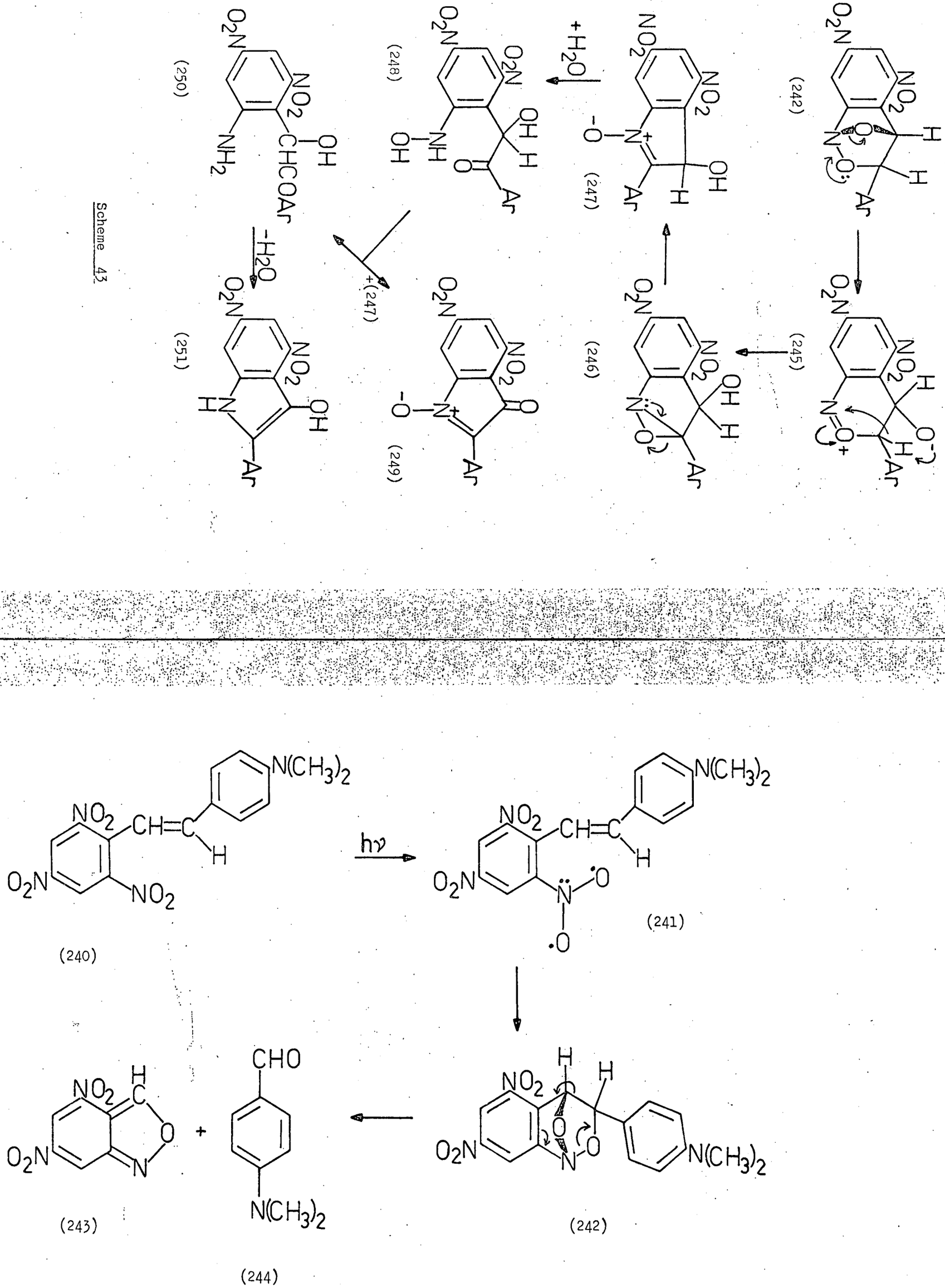
(233) (238)

The possibility of an intramolecular cycloadduct (239) thus arises, as depicted in a general way in Scheme 41. Thus a bicyclic 1,3,2-dioxazolidine intermediate has been invoked by Splitter and Calvin[91]



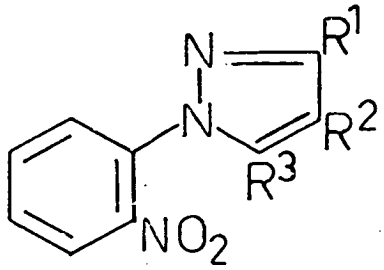
Scheme 41

to rationalise the photochemical conversion of the 2-nitrostilbene (240) into the 2-phenylisatogen (249). Smaller amounts of the indoxyl (251), para-N,N-dimethylaminobenzaldehyde (244) and the anthranil (243) were also isolated. The formation of the aldehyde (244) and the anthranil (243) is readily explained[79] (Scheme 42) by direct decomposition of the

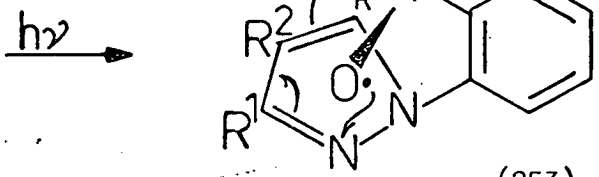


Scheme 42

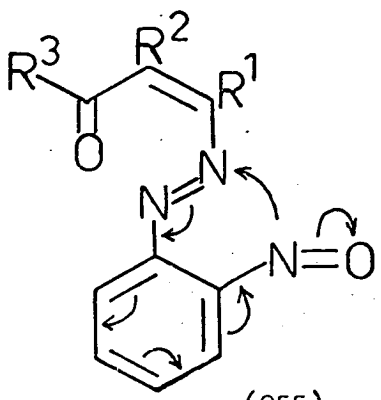
Scheme 43



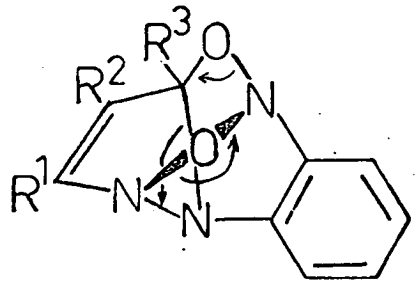
(252)



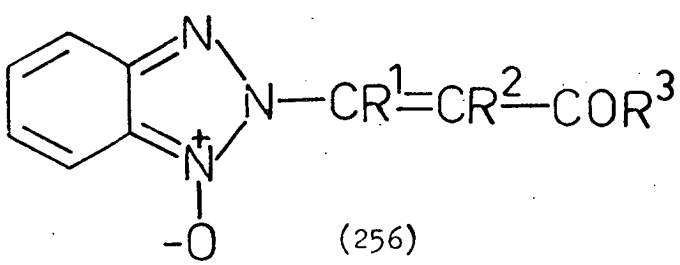
(253)



(255)



(254)



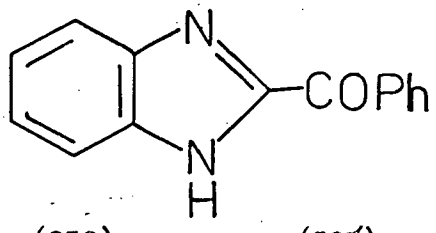
(256)

	$\underline{R}^1$	$\underline{R}^2$	$\underline{R}^3$
a;	CH_3	H	CH_3
b;	CH_3	Br	CH_3
c;	Bu^t	H	Bu^t
d;	CH_3	H	H

Scheme 44

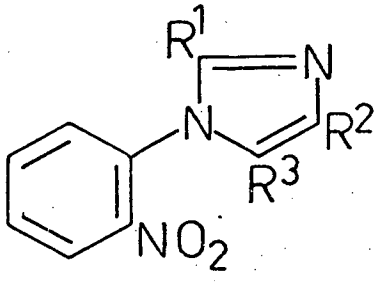
Scheme 45

	R^1	R^2	R^3
a;	H	Ph	H
b;	Ph	H	H
c;	H	Ph	Ph

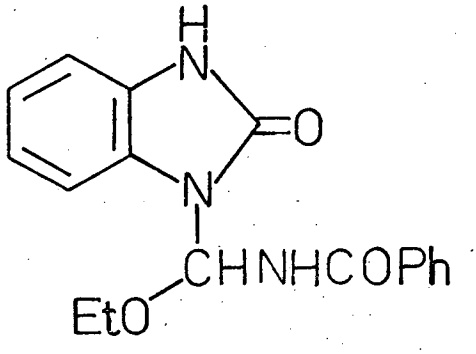


(258) (50%)

$h\nu$ ↑ (257a)

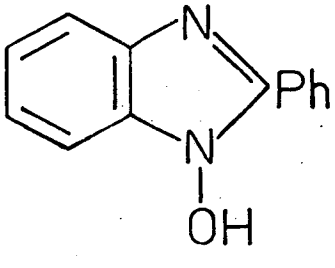


$h\nu$ → (257b)



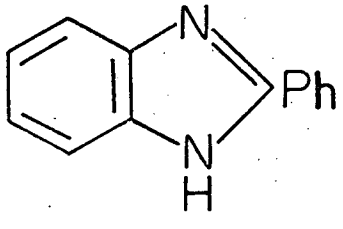
(259) (80%)

$h\nu$ ↓ (257c)



(260) (30%)

+

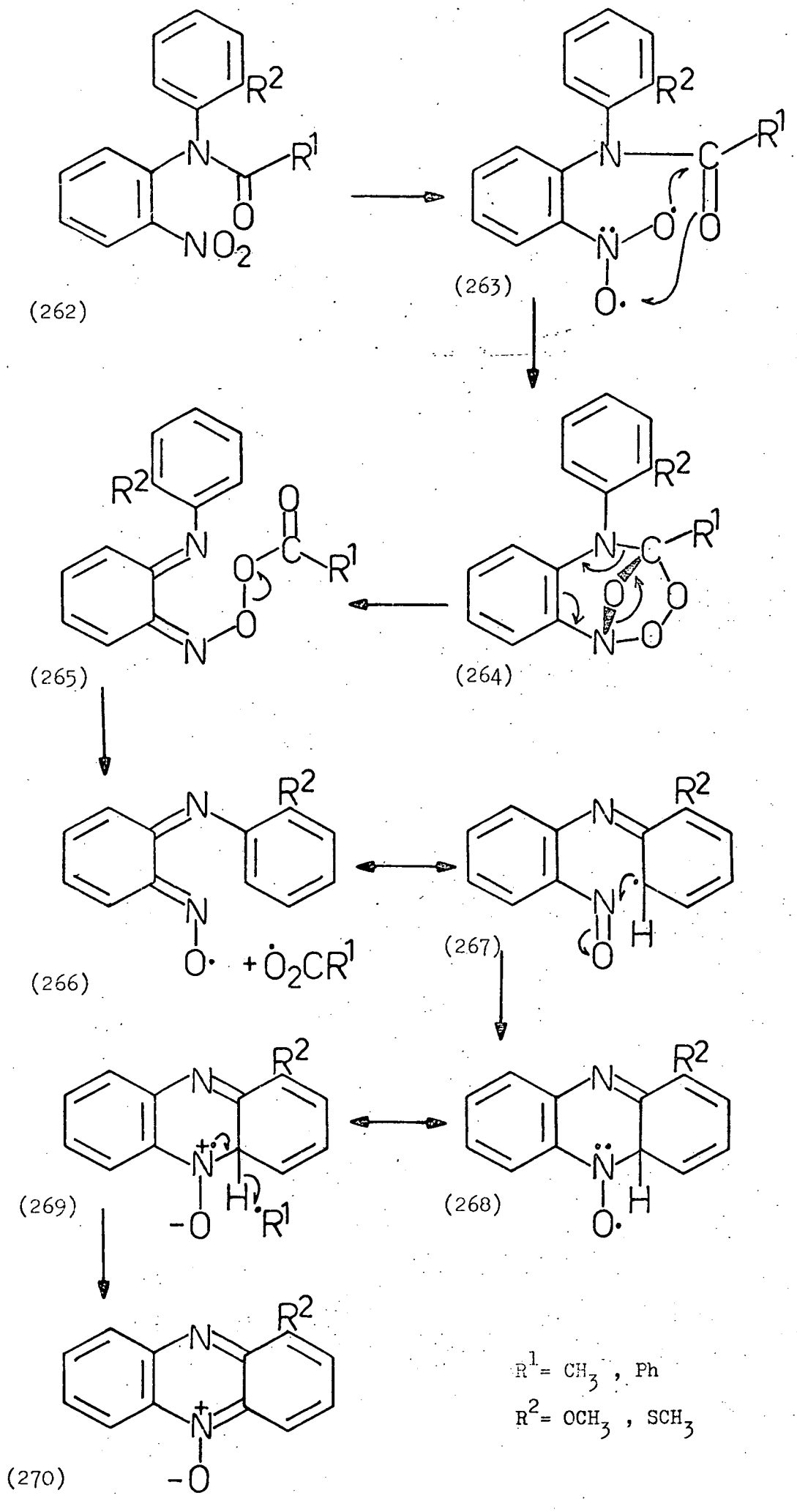


(261) (20%)

cycloadduct (242). The formation of the intermediate (247) derived from the cycloadduct (242) as shown in Scheme 43, gives rise by hydration to the hydroxylamino-keto-alcohol (248). Intermolecular oxidation-reduction between (247) and (248) then produces the isatogen (249) and the aminoketone (250), respectively. Cyclisation of the aminoketone (250) then accounts for the formation of the indoxyl (251).

More recently, Jacquier[92] has invoked intramolecular 1,4-photocycloaddition of a nitro group across a diene framework to explain the photoformation of benzotriazole N-oxides (256) from 1-(2'-nitrophenyl)-pyrazoles (252) (Scheme 44). The addition of the $^3(n,\pi^*)$ excited state of the nitro group to the azadiene system (cf. 253) produces the bridged polycyclic intermediate (254) which can break down by a two-electron process to afford the nitrosophenylazo derivative (255). An electrocyclisation of this azo derivative (255) then accounts for the formation of the product (256). An analogous mechanism is also invoked[93] to account for the formation of a variety of benzimidazole products [(258)-(261)] by irradiation of 1-(2,4-dinitrophenyl)imidazoles [(257 a-c), (Scheme 45)].

Photocycloaddition of a nitro group to a carbonyl group has been proposed by Maki[94] to explain the formation of phenazine N-oxides (270) on irradiation of N-acyl-2-nitrodiphenylamines (262) (Scheme 46). The necessity for the N-acyl substituent in (262) is shown by the fact that when it is replaced by hydrogen or an alkyl group, no reaction occurs. The absence of a substituent at R^2 in (262) leads to over-reaction and reduced yields of the phenazine-N-oxides. In these transformations it is suggested that the $^3(n,\pi^*)$, 1,3-diradical form of the nitro group adds across the carbonyl group giving a 1,2,4,3-trioxazolidine intermediate (264). This would be expected to be less stable than the

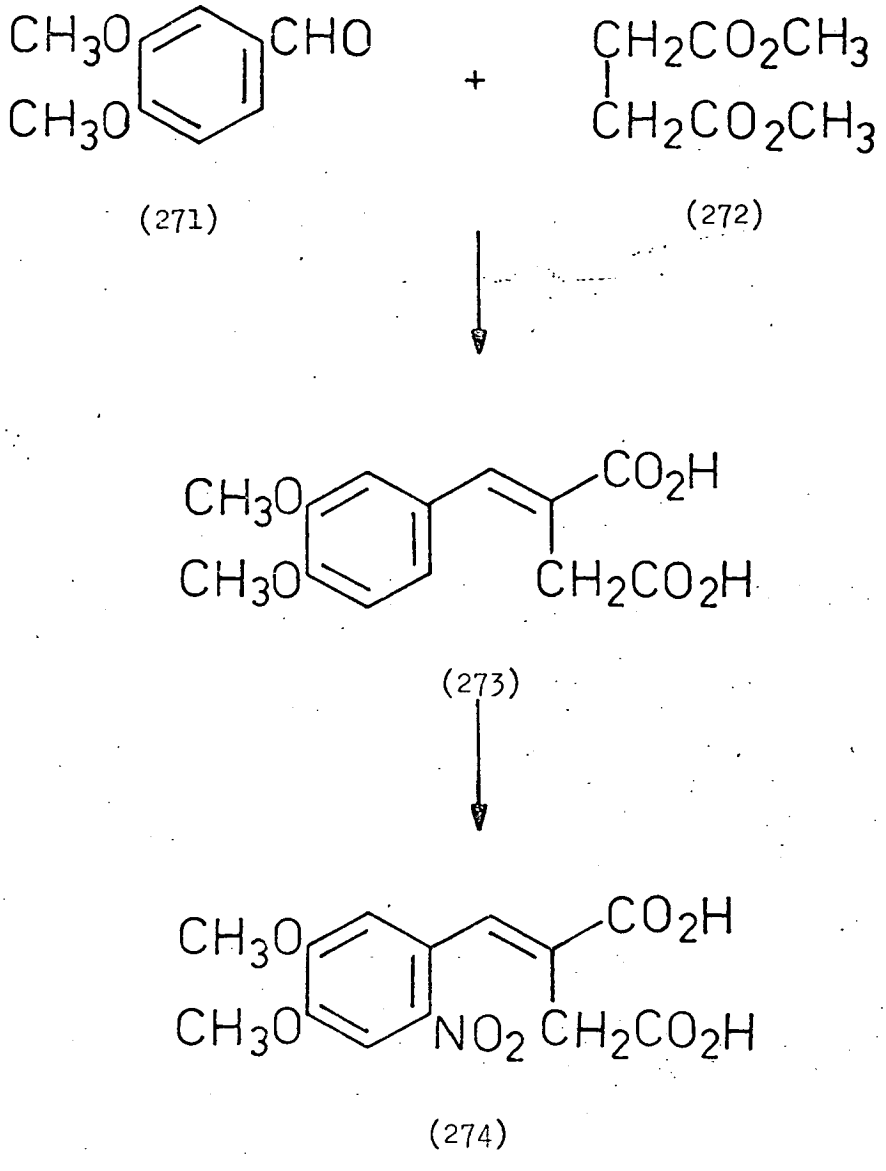


Scheme 46

aforementioned dioxazolidine analogues and so decomposes readily to give a mesomeric nitroxide radical (266) and a carboxylate radical by way of initial ring-opening to give the peroxide (265). The mesomeric nitroxide radical may then undergo intramolecular radical addition to give the hydroxylamino radical [(267) → (268)]. A process of electron-demotion to give the charge-separated radical (269) followed by hydrogen abstraction, possibly by the $\underline{R}^1$ radical, then affords the phenazine N-oxide (270).

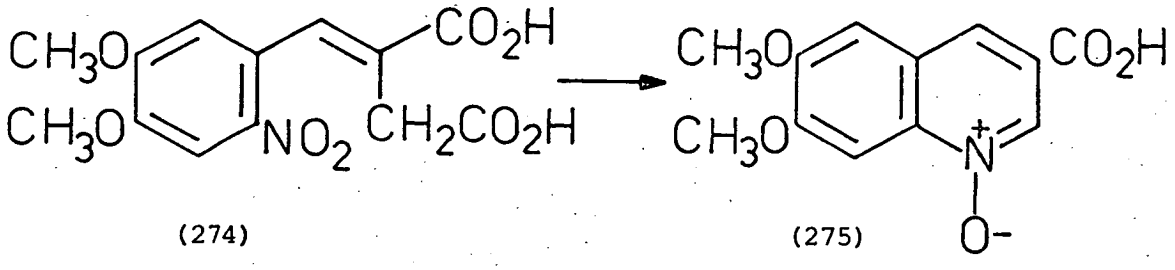
CHAPTER TWO

The Base-Catalysed Cyclisation Reactions of Some 2-Nitrobenzylidene Derivatives: A New Synthesis of Quinoline 1-Oxides


CH3O
CHO
CH3O
+
CH2CO2CH3
CH2CO2CH3
(271)
(272)
CH3O
CO2H
CH3O
CH2CO2H
(273)
CH3O
CO2H
CH3O
NO2
CH2CO2H
(274)

Scheme 47

Certain 2-nitrobenzene derivatives (cf. Introduction) can undergo base-catalysed cyclisation involving an aldol-type condensation between an active methylene group in the side chain and the ortho-nitro group to give six-membered heterocyclic N-oxides (cf. p. 11). One such reaction is the base-catalysed cyclisation of 2-nitroveratrylidene-succinic acid (274)[95] to the quinoline 1-oxide (275) in aqueous ethanolic sodium hydroxide. This reaction however is not a general one. The

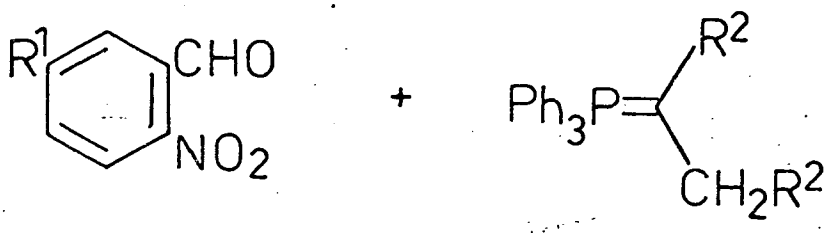


(274) (275)

potential of this reaction as a general route to quinoline 1-oxides (and the quinolines derived by subsequent reduction) which are not readily available by other means, suffers from the lack of a good general method for the synthesis of the benzylidene precursors. Thus the synthesis of the benzylidene derivative (274) involves the difficult, low yield Stobbe condensation[96,97] of 3,4-dimethoxybenzaldehyde (271) with dimethyl succinate (272) followed by nitration of the diacid (273) obtained. (Scheme 47).

It was therefore decided in the present work to devise an alternative synthetic route to 2-nitrobenzylidene derivatives of the type (274) and hence to investigate the scope and synthetic utility of cyclisations of the type [(274) → (275)].

The formation of carbon-carbon double bonds by the condensations of various aldehydes and ketones with triphenylphosphoranes (the Wittig reaction[98]) is well documented and among the many examples is the

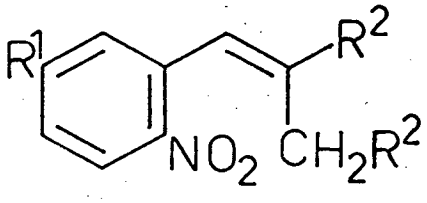


(279) $\underline{R}^1$

a; H
b; Br
c; Cl

(280) $\underline{R}^2$

a; COPh
b; $CO_2C_2H_5$

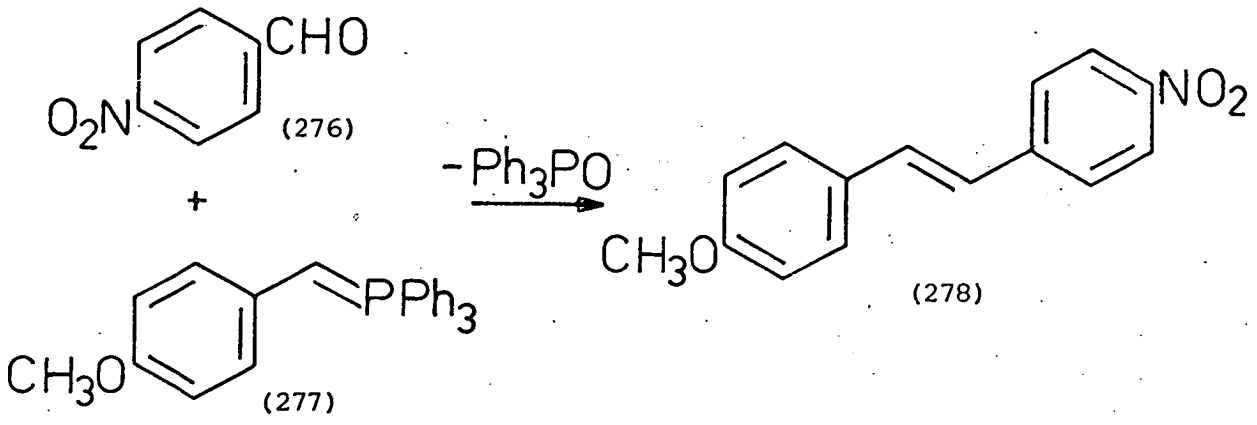


(281)

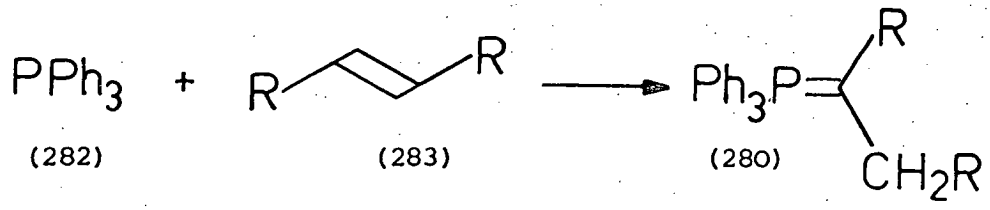
	$\underline{R}^1$	$\underline{R}^2$
a;	H	COPh
b;	H	$CO_2C_2H_5$
c;	Br	$CO_2C_2H_5$
d;	Cl	$CO_2C_2H_5$

Scheme 48

condensation[99] of para-nitrobenzaldehyde (276) with para-methoxybenzylidenetriphenylphosphorane (277) to give 4-methoxy-4'-nitrostilbene (278).



Thus the condensation of 2-nitrobenzaldehydes (279) (Scheme 48) with phosphoranes of the type (280) where R^2 is electron-withdrawing, offers an alternative route to the 2-nitrobenzylidene derivatives (281) having an active methylene group suitably placed for cyclisations of the type [(274) → (275)]. The particular phosphoranes (280) required for such Wittig condensations are readily available by the reaction of triphenylphosphine (282) with electron deficient olefines (283).



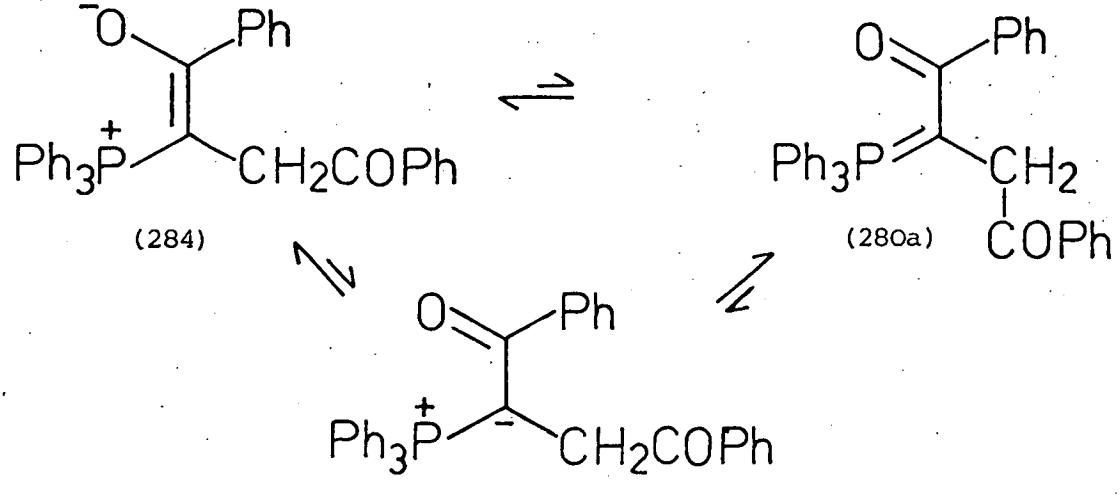
R

a; COPh

b; CO_2Et

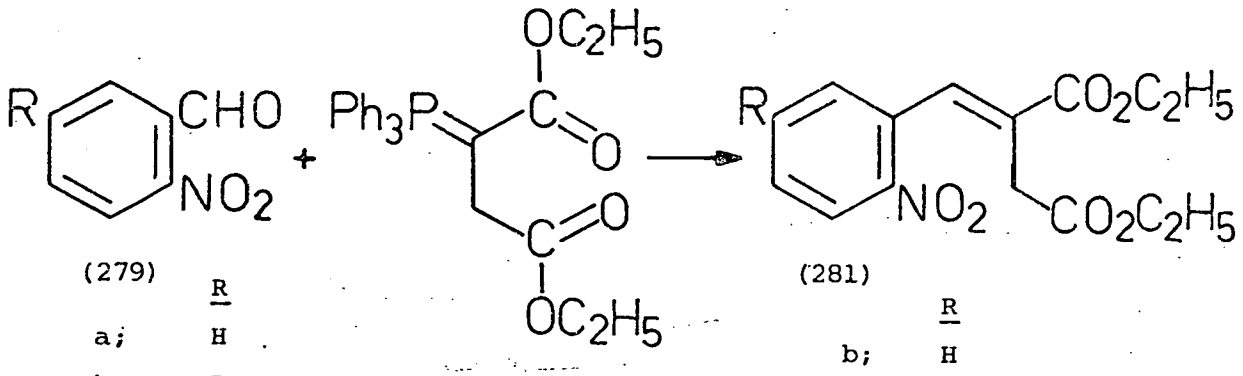
As an initial approach to this study it was decided to attempt the Wittig condensation of 2-nitrobenzaldehyde (279a) with 1,2-dibenzoylethylidenetriphenylphosphorane (280a).[100] The phosphorane (280a) was prepared by the method of Ramirez et.al.[100] by stirring triphenylphosphine (282) and trans-dibenzoylethylene (283a) in dimethoxyethane over a period

of 12 h. However, it was also found that if a mixture of triphenylphosphonium bromide and 1,2-dibenzoylethylene (283a) were heated under reflux in acetonitrile for only 15 minutes a comparable yield of the phosphorane (280a) could be obtained. This latter method is based on the reaction conditions used by Eyjolfsson[101] in the acid-catalysed formation of other triphenylphosphoranes discussed later. Attempts to condense the phosphorane (280a) with 2-nitrobenzaldehyde proved unsuccessful. Thus, refluxing the phosphorane (280a) with 2-nitrobenzaldehyde (279a) in benzene for 22 h or stirring the two reactants at room temperature in benzene for 72 h yielded only dibenzoylethylene and mixtures of triphenylphosphine, dibenzoylethylene, unreacted phosphorane (280a) and 2-nitrobenzaldehyde. The failure of the phosphorane (280a) to condense may be attributed in part to its instability with respect to triphenylphosphine and dibenzoylethylene.[100] Ramirez[100] attributes this instability of the phosphorane (280a) to steric repulsion within the molecule and the weakly nucleophilic nature of triphenylphosphine. The reactivity of the phosphorane (280a) in the Wittig condensation is also dependant upon the charge at the α-carbon. Since the phosphorane (280a) is best represented[100] by the phosphobetaine structure (284) there is little net negative charge at the α-carbon, i.e., the ylide structure



(284) (280a) (285)

(285) contributes very little to the overall electronic condition of the phosphorane (280a) , thus providing a further reason for lack of reactivity in the Wittig condensation. Hence,by changing the olefin it should be possible to obtain a phosphorane with a sufficiently nucleophilic α-carbon to react with 2-nitrobenzaldehyde in a Wittig condensation. Such an olefin was found to be diethyl fumarate (283b) which is reported[101] to react with triphenylphosphine (282) to give 1,2,-bis(ethoxycarbonyl) ethylidenetriphenylphosphorane (280b). This phosphorane (280b) was successfully condensed with 2-nitrobenzaldehyde, using the conditions described by Eyjohlfsson,[101] to afford the 2,3-bis(ethoxycarbonyl)-1-(2'-nitrophenyl)propene (281b) in excellent yield. The problem often associated with Wittig condensations of this type, namely contamination of the product with triphenylphosphine, was readily overcome by recrystallising the crude product from 60% v/v aqueous ethanol. The structure of the hitherto unknown 2-nitrobenzylidene derivative (281b) is assigned on the basis of its elemental analysis and mass spectrum which showed a parent ion (M^+, 307) consistent with that expected of the product (281b). The i.r. spectrum of the product (281b) showed two carbonyl bands. The band at 1720 cm^{-1} is assigned to the carbonyl stretching frequency of the 3-ethoxycarbonyl group. The slightly lower frequency band, at 1710 cm^{-1}, is assigned to the 2-ethoxycarbonyl group which is conjugated with the olefinic bond. The ^1H n.m.r. spectrum is also in accord with the 2-nitrobenzylidene derivative (281b) structure. The signal at τ 1.86 is a doublet and is assigned to the H-(3) of the benzene ring. The singlet at τ 1.98 is assigned to the olefinic hydrogen (see p. 56). The very low field resonance of this olefinic proton is attributed to the electron-withdrawing effect of the 2-nitrophenyl and ethoxycarbonyl substituents. The complex multiplet in the range τ 2.30-2.59 is assigned to the remaining three aromatic protons. The two overlapping quartets



(279)

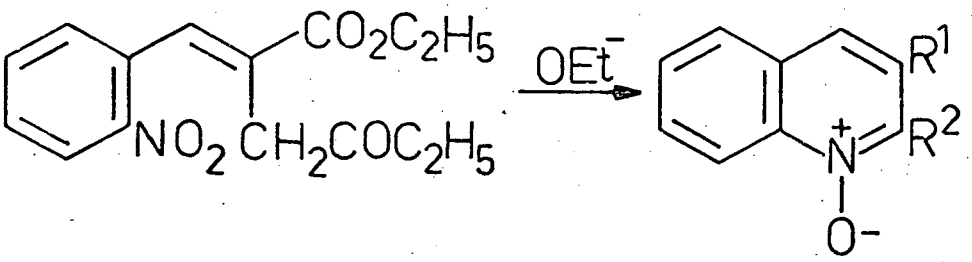
	R
a;	H
b;	Br
c;	Cl

(281)

	R
b;	H
c;	Br
d;	Cl

at τ 5.76 and 5.90 and the two overlapping triplets at τ 8.67 and 8.77 are assigned to the methylene and methyl groups, respectively, of the ester substituents. The synthesis of the 2-nitrobenzylidene derivative (281b) was readily extended to the synthesis of the bromo-derivative (281c) and the chloro-derivative (281d).

The benzylidene derivative (281b) was refluxed in ethanolic sodium ethoxide in an attempt to effect its base-catalysed cyclisation to the quinoline 1-oxide (286a). Sodium ethoxide was chosen as the basic catalyst in the attempted cyclisation, in the hope that further hydrolysis of any 2,3-bis(ethoxycarbonyl)quinoline 1-oxide (286a) produced, would be avoided. In practice however, no neutral product was obtained but



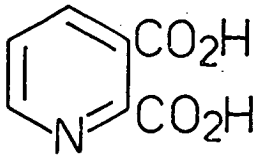
(281b)

(286)

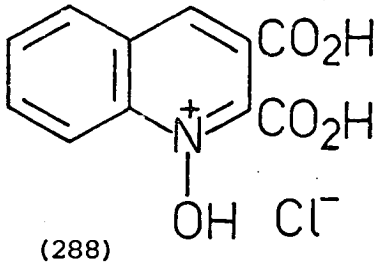
	R^1	R^2
a;	CO_2Et	CO_2Et
b;	CO_2H	CO_2Et
c;	CO_2Et	CO_2H
d;	CO_2H	CO_2H

acidification of the mixture afforded a compound, in low yield (10%), which gave analytical and spectral data consistent with an ethoxycarbonyl-quinoline-carboxylic acid 1-oxide. In particular its mass spectrum showed a parent ion (m/e, 261) and a major fragment ion at m/e 245 (i.e. M^+-16), typical of a heterocyclic N-oxide.[102] Also, the i.r. spectrum of the product showed the characteristic bands (2720 and 2620 cm^{-1}) of a carboxylic acid OH stretching mode. The presence of a high carbonyl band (1740 cm^{-1}) is attributed to an ester group and the carbonyl band of the acid carbonyl stretching frequency is seen at 1700 cm^{-1}. The formulation of the product as 2-ethoxycarbonylquinoline-3- carboxylic acid 1-oxide (286b) is based on its stability to thermal decarboxylation. The alternative structure, 3-ethoxycarbonylquinoline-2-carboxylic acid (286c) would be expected to undergo facile thermal decarboxylation by analogy with the known[103] quinoline-2,3-dicarboxylic acid which readily undergoes thermal decarboxylation at the 2-position.

On standing, the acidic aqueous phase deposited a solid whose i.r. spectrum and high melting point indicated it to be a salt. Treatment of this salt with concentrated hydrochloric acid afforded a solid whose i.r. spectrum showed a hydrogen-bonded hydroxyl band at 2450 cm^{-1} and bands at 1760 and 1735 cm^{-1} attributable to two distinct carbonyl groups. Bands attributable to a nitro group were absent. These features are consistent with the formulation of this product as quinoline-2,3-dicarboxylic acid N-oxide (286d). However, the actual values of the carbonyl bands in the proposed 2,3-dicarboxylic acid N-oxide are high for hydrogen-bonded carboxyl groups. Thus, in 2,3-pyridinic acid (287) the carbonyl stretching frequency is found at 1600 cm^{-1} due to hydrogen bonding. This would suggest that the isolated product (286d) could in fact be the hydrochloride derivative (288). The presence of a positive charge on the quinoline nucleus would

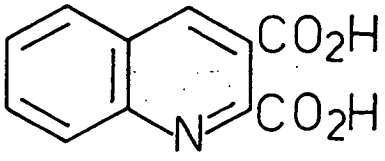


(287)



(288)

(289)

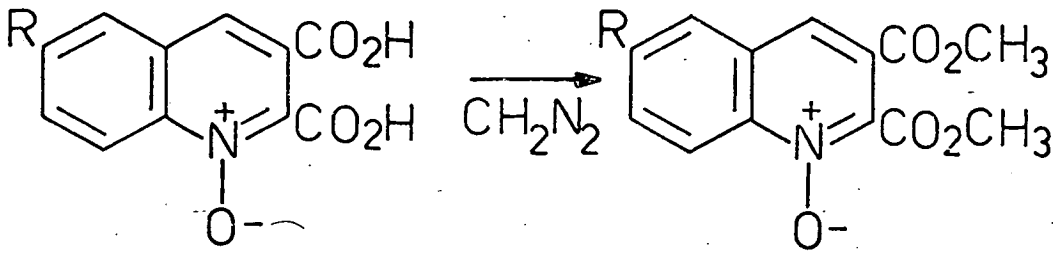


thus counter the effect of the hydrogen bonding which would tend to lower the carbonyl stretching frequency. The mass spectrum of the supposed dicarboxylic acid N-oxide (286d) did not show a parent ion of m/e 233, but showed a peak at m/e 189 (i.e. m^+-44), resulting from decarboxylation, presumably at the 2-position. The ^1H n.m.r. spectrum of the 2,3-dicarboxylic acid (286d) showed a doublet at τ 1.3 attributed to the H-(8) proton and a singlet at τ 1.53 due to the H-(4) proton. Three other aromatic protons were also present. The 2,3-dicarboxylic acid (286d) underwent thermal decarboxylation in the solid state at 130° without melting. This is analogous to the known behaviour of quinoline-2,3-dicarboxylic acid (289)[103] which undergoes thermal decarboxylation at 105°.

In an effort to rigorously establish the structure of the quinoline-1-oxide (286d), attempts were made to reduce it to the known compound,[103] quinoline-2,3-dicarboxylic acid (acridinic acid)(289). Thus the quinoline 1-oxide (286d) was subjected to catalytic hydrogenation. The i.r. spectrum of the resulting product differed from that of the starting material (286d) in that the hydroxyl band appeared at a higher frequency and only a single carbonyl band (1740 cm^{-1}) was present. The mass spectrum of the crude product indicated the presence of

quinoline-2,3-dicarboxylic acid (289) at m/e 217 and quinoline-3-carboxylic acid 1-oxide (290a), at m/e 189, the latter probably arising by decarboxylation of the starting material (see later). However, crystallisation afforded a product which was shown to be identical to that obtained in an attempt to prepare the quinoline-2,3-dicarboxylic acid 1-oxide (286d) for elemental analysis. This product was shown to be the hitherto unknown quinoline-3-carboxylic acid 1-oxide (290a) on the basis of its elemental analysis and its mass spectrum which showed a parent ion at m/e 189 and a peak at m/e 173 (i.e. $M^+ - 16$), consistent with the known mode of breakdown of N-oxides on electron impact.[102] Attempts were made to establish the structure of the quinoline-3-carboxylic acid 1-oxide (290a) by way of its reduction to the known compound[104] quinoline-3-carboxylic acid (291). An initial attempt using dithionite to bring about the reduction was unsuccessful. However, using triethyl phospite the required deoxygenation was readily achieved. The m.p. (275°) of the product (291) was identical to that reported[104] for quinoline-3-carboxylic acid (291) and concordant analytical and spectral data were also obtained. Reduction to the known acid (291) thus rigorously proves the structure of the decarboxylation product, as quinoline-3-carboxylic acid 1-oxide (227a) and provides further support for the formulation of the product of cyclisation of the benzylidene derivative (281b) as quinoline-2,3-dicarboxylic acid 1-oxide (286d).

Since quinoline-2,3-dicarboxylic acid 1-oxide (286d) could not be obtained in an analytically pure state due to its facile thermal decarboxylation, the presence of the 2,3-dicarboxyl function was established by esterification with diazomethane to afford the thermally stable 2,3-bis(methoxycarbonyl)quinoline 1-oxide (292a), which gave analytical and spectral data consistent with its formulation.



(286) R

d; H

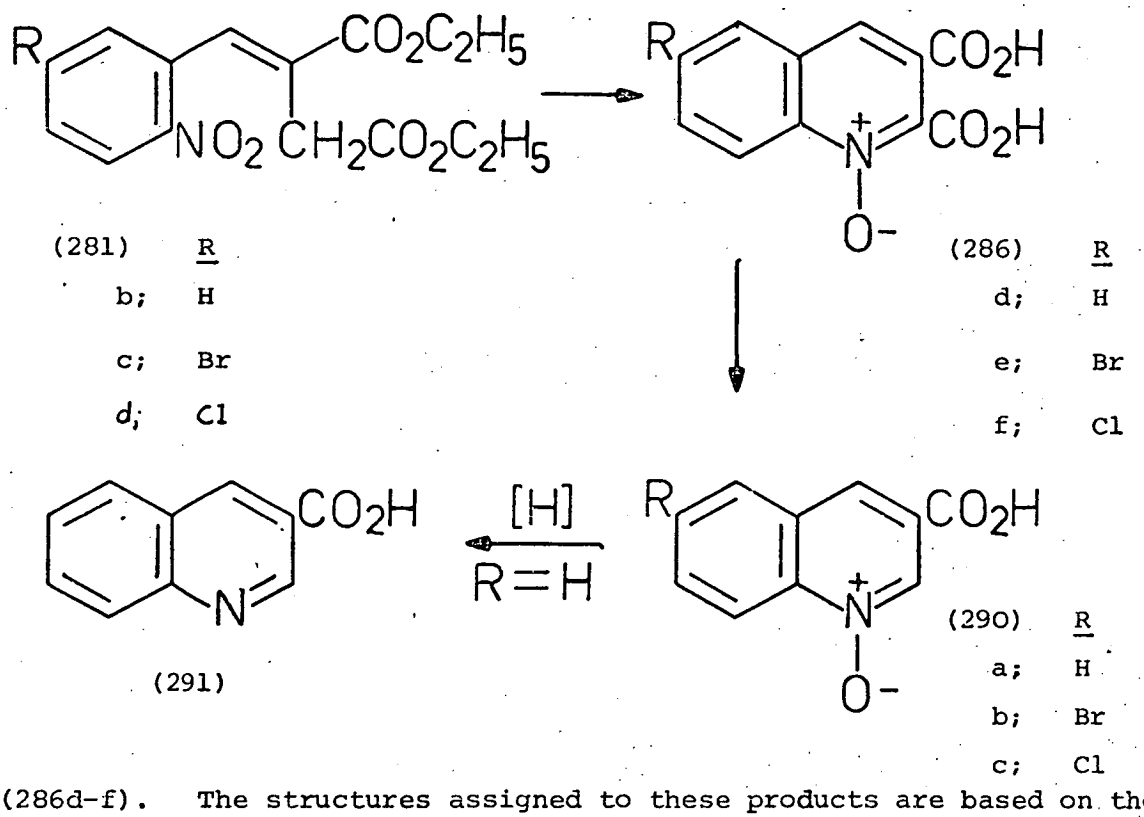
e; Br

(292) R

a; H

b; Br

The cyclisation of the 2,3-bis(ethoxycarbonyl)-1-(2'-nitrophenyl) propene derivatives (281 b-d) was also effected by heating them with dilute aqueous alkali but in this case the exclusive products, in high yields, were the corresponding quinoline-2,3-dicarboxylic acid 1-oxides



(281) R

b; H

c; Br

d; Cl

(286) R

d; H

e; Br

f; Cl

(291)

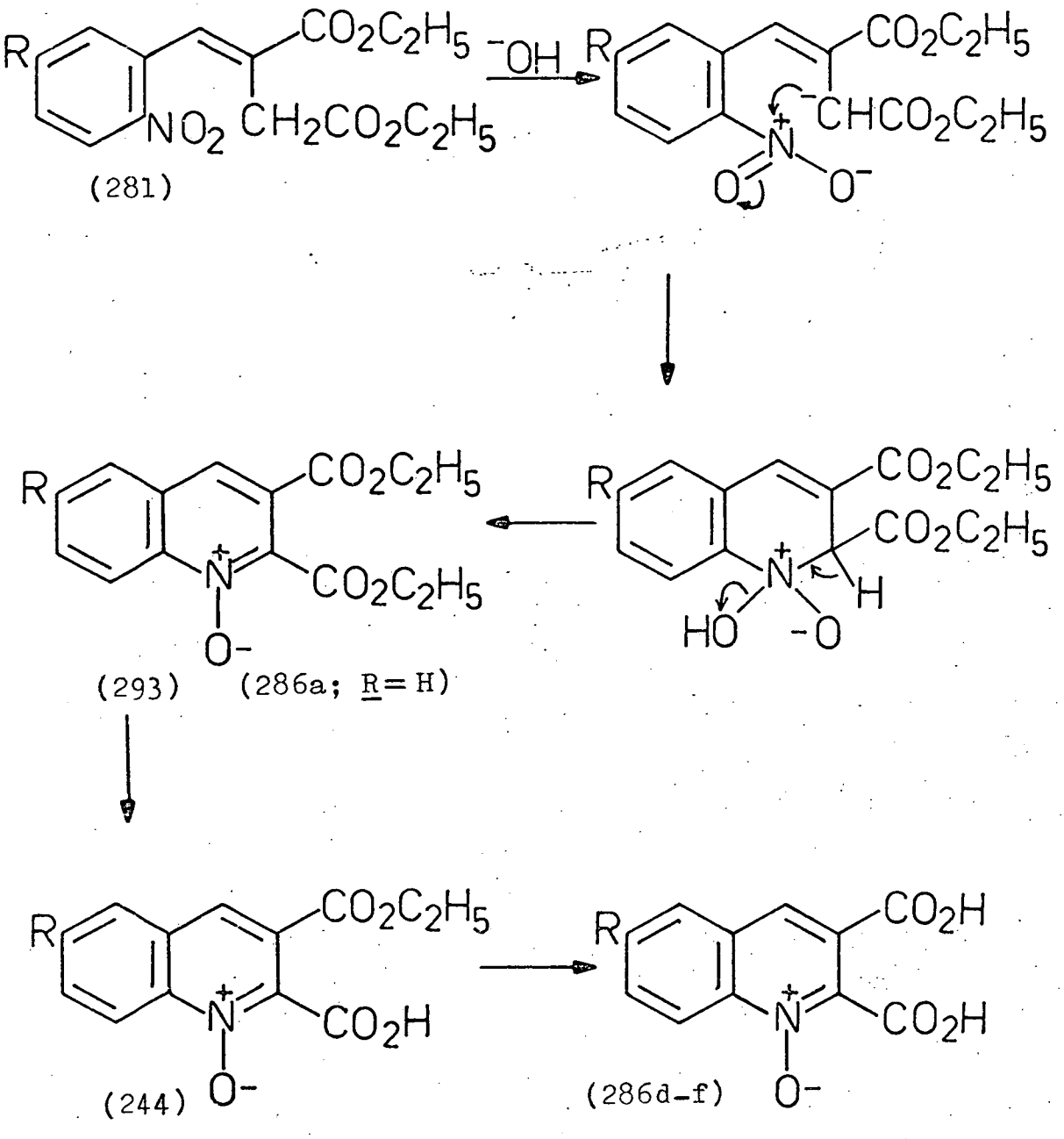
(290) R

a; H

b; Br

c; Cl

(286d-f). The structures assigned to these products are based on their i.r. spectra which lacked adsorption due to a nitro group but contained bands attributable to two carboxyl groups. As in the case of the parent



R = H, Br, Cl

Scheme 49

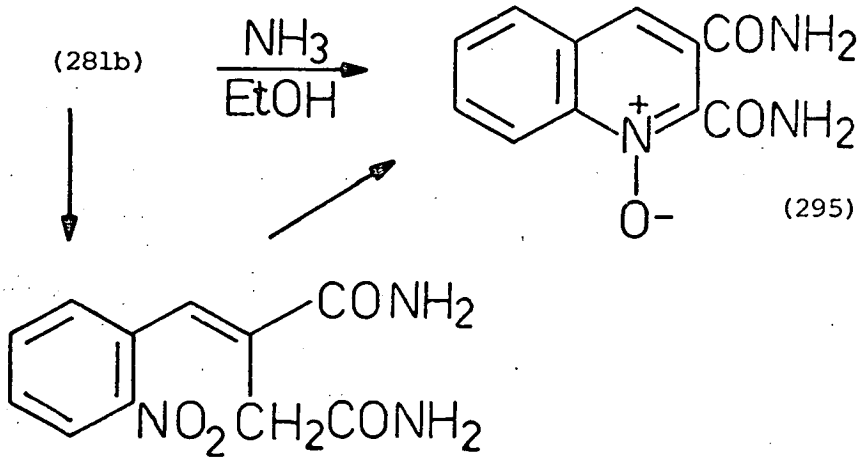
compound (286d), the chloro- and bromo- compound (286 e and f) underwent facile decarboxylation at the 2-position upon crystallisation, to afford the corresponding quinoline-3-carboxylic acid 1-oxides (290 b and c) which were characterised by their elemental analysis and their i.r. and mass spectra. The bromo-diacid (286e) was also characterised as its dimethyl ester (292b).

The foregoing results demonstrate that the 2-nitrobenzylidene derivatives, (281 b-d) readily undergo base-catalysed cyclisation on heating with aqueous alkali, to afford high yields of the corresponding quinoline-2,3-dicarboxylic acid 1-oxides (286 d-f) which are relatively stable as their alkali metal salts but readily decarboxylate in warm solvents to afford quantitative yields of the monocarboxylic acids (290 a-c). In contrast, the use of ethanolic sodium ethoxide as the catalyst in the cyclisation of the 2-nitrobenzylidene derivative (281b) gives, in addition to the diacid (286d), the corresponding 2-ethoxycarbonylquinoline-3-carboxylic acid 1-oxide (286b).

These cyclisation reactions are readily explained by a mechanism (Scheme 49) involving the direct aldol-type condensation of the reactive methylene group in (281) with the ortho-nitro group. Subsequent hydrolysis of the diester (293) in the alkaline medium, then accounts for the formation of the diacid products (286 d-f). Hydrolysis of the esters prior to cyclisation could also occur but this seems unlikely since the half-ester (286b) is isolated in the ethoxide-catalysed condensation.

Attempts to effect the base-catalysed cyclisation of 2,3-bis-(ethoxycarbonyl)-1-(2-nitrophenyl)propene (281b) using other basic catalysts was investigated in an attempt to isolate the quinoline diester (286a). Thus, heating the 2-nitrobenzylidene derivative (281b) with triethylamine for 0.5 h or 5 h, gave only unreacted starting

material and intractable mixtures. The use of piperidine in acetic acid as the catalyst again resulted, largely, in the isolation of starting material. However, treatment of the benzylidene derivative (281b) with ethanolic ammonia for 24 h was successful. A solid was isolated, in low yield, whose i.r. spectrum lacked bands due to a nitro group but showed the presence of N-H stretching bands at 3430, 3300 and 3180 cm^{-1} and two bands at 1740 and 1680 cm^{-1}, attributable to two distinct carbonyl groups. The mass spectrum of this solid showed a base peak at m/e 232 from which a molecular formula of $C_{11}H_9N_3O_3$ can be inferred. These data allow the structure, quinoline-2,3-dicarboxamide 1-oxide (295) to be tentatively assigned to this product. Formation of the dicarboxamide (295) from the nitro compound (281b) may either be the



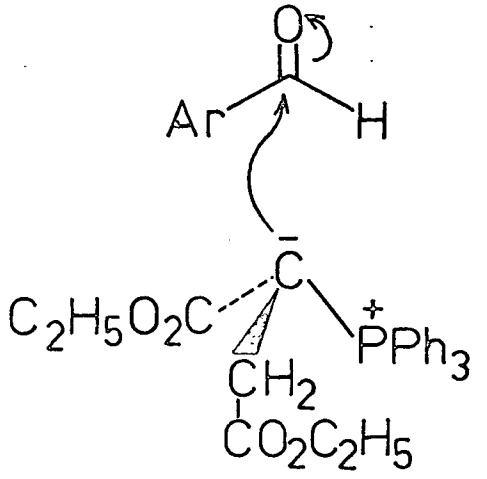
result of prior ammonolysis of the ester groups in (281b) to give the diamide (294) followed by cyclisation or of subsequent ammonolysis of the diester N-oxide (286a), produced by direct cyclisation of (281b).

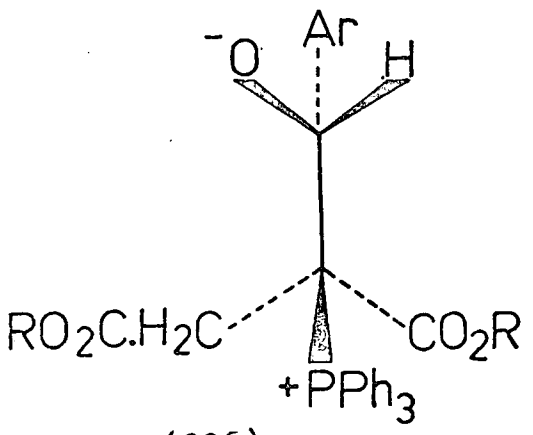
As the cyclisation of the 2-nitrobenzylidene derivatives (281 b-d) was successful, it may be inferred that the Wittig condensation[98] of the 2-nitrobenzaldehydes (279 a-c) with the bis-ethoxycarbonylethylidene-phosphorane (280b) produced only one of the two possible isomers,

Scheme 50

Ar= ortho-$NO_2C_6H_4$

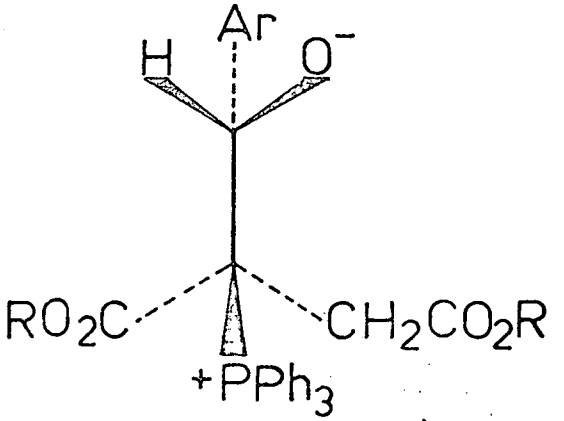
R = C_2H_5





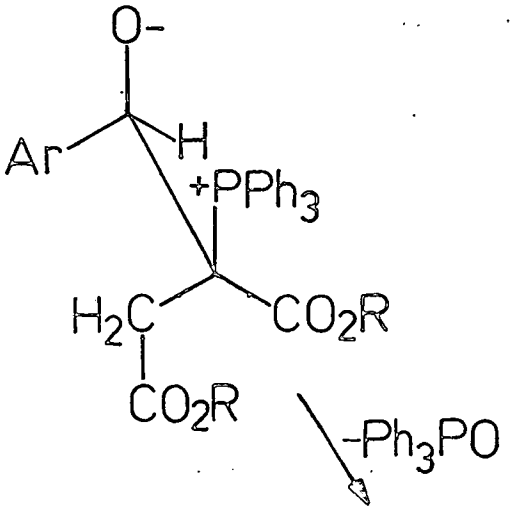
(296)

III

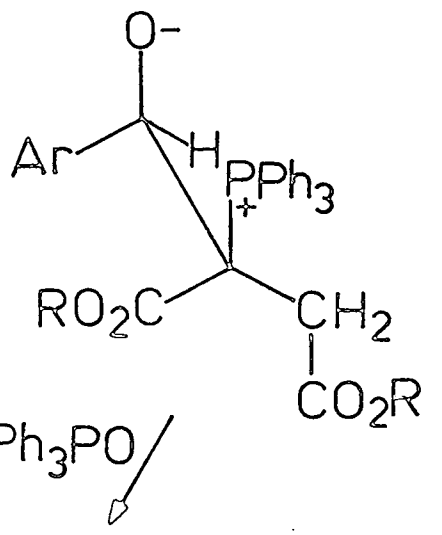


(297)

III

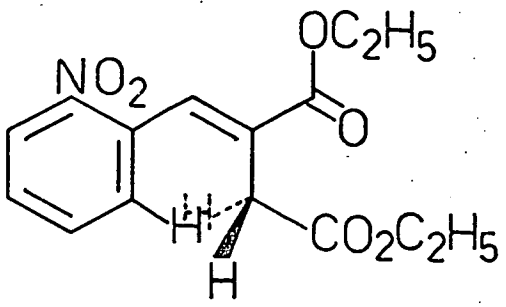


(298)

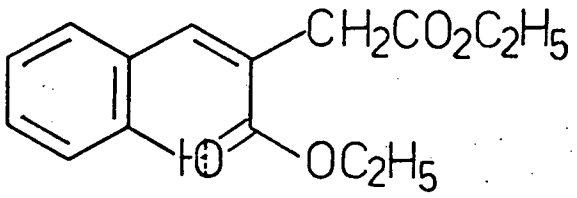


(299)

namely the E-isomer (298) which is structurally suited to cyclisation. The Z-isomer (299) is not structurally suited for successful cyclisation.



(298) (E)-isomer



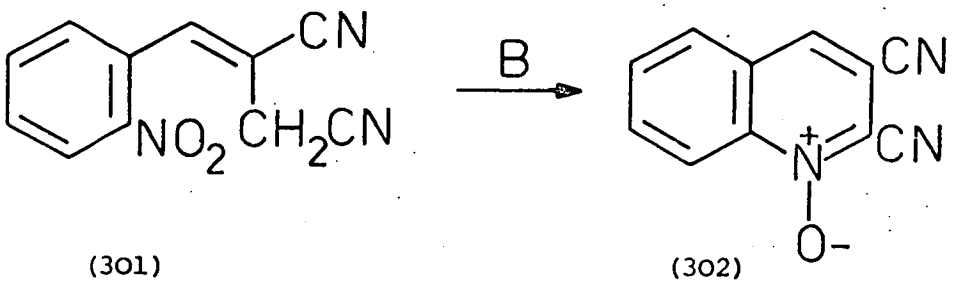
(299) (Z)-isomer

The mechanism of the Wittig condensation allows for the formation of both isomers. Thus, if the initial step of the Wittig condensation is nucleophilic attack by the α-carbon of the phosphorane on the 2-nitrobenzaldehyde carbonyl (Scheme 50), then the two enantiomeric intermediates (296) and (297) will be formed. In consequence, the preferential syn elimination of triphenylphosphine oxide undergone in non-solvolytic apolar media [105-107] by these enantiomeric intermediates, one (296) will give rise to the E-isomer (298) and the other (297) will give rise to the Z-isomer (299). The selective formation of the E-isomer (298) can then be explained[105-107] by postulating the reversible formation of the enantiomers (296) and (297). This will result in the more rapid formation of the olefin whose enantiomeric precursor can attain a more stable syn conformation for the elimination of triphenylphosphine oxide. Thus, the syn enantiomer, (296) suffers less steric repulsion between the aryl ring and the methylene group than the syn enantiomer, (297) suffers between the aryl group and the ethoxycarbonyl group. Therefore, the enantiomer (296) would be expected to be the predominant intermediate. Further, extrusion of triphenylphosphine oxide from the enantiomer (296) will lead to the more stable benzylidene

isomer (298). Due to the steric repulsion between the vinylic ethoxycarbonyl group and the benzene ring in the Z-isomer (299), there would be loss of conjugational stabilisation in this benzylidene derivative as a coplanar relationship between the nitrophenyl and vinylethoxycarbonyl moieties would not be favoured. This is not the case with the E-isomer (298) which suffers much less steric repulsion between the methylene group (the ethoxycarbonyl group attached can be held away from the ring) and the benzene ring. Thus, the trans benzylidene-ethoxycarbonyl moiety can assume a conjugation-stabilised coplanar relationship. However, the possibility does exist that the presence of a basic catalyst in the reaction medium may equilibrate the E- and Z-isomers by prototropic tautomerism[108] in which case the foregoing argument for the selective formation of the E-isomer, in the Wittig condensation, would be superfluous as reaction would occur whichever isomer was formed. But, as the prototropic tautomerism must occur over a carbon triad, which is energetically unfavourable,[108] it is unlikely to be of significance.

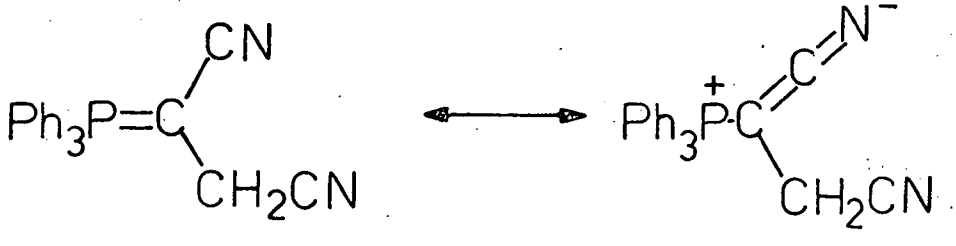
In view of the success of the Wittig condensation as a route to diethyl 2-nitrobenzylidenesuccinates (281 b-d) and their subsequent cyclisation to quinoline 1-oxide derivatives, further investigation of the scope of such synthetically useful cyclisations was undertaken. In particular, the synthesis and attempted cyclisation of 2,3-dicyano-1-(2'-nitrophenyl)propene (301) seemed worthy of investigation since the substrate, (301) would have a very reactive methylene centre in the ortho-side-chain and hence should undergo facile base-catalysed cyclisation to the unknown 2,3-dicyanoquinoline 1-oxide (302). The phosphorane precursor (300) of the benzylidene compound (301) was unknown but was readily prepared by the reaction of triphenylphosphine with fumaronitrile in acetic acid which performed the dual role of solvent and acid catalyst. The structure of the phosphorane (300) is supported

by its elemental analysis which is consistent with its molecular



(301) (302)

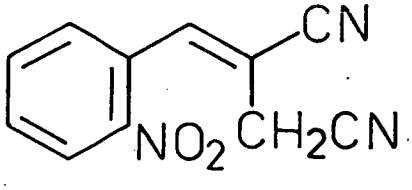
formula of $C_{22}H_{17}N_2P$. The mass spectrum however, did not show a parent ion and the base peak was attributable to triphenylphosphine oxide (m/e 278). This is in keeping with the behaviour of other authentic phosphoranes[109] which also show no parent ion and have a base peak corresponding to triphenylphosphine oxide. The i.r. spectrum of the phosphorane (300) showed two bands attributable to a cyano stretching mode. Thus, the higher band at 2240 cm^{-1} is weak as expected for a cyano group attached to a saturated carbon. The second band however, at 2140 cm^{-1}, is lowered due to conjugation reducing the triple bond character of the cyano group. This lower band at 2140 cm^{-1} is also the more intense and reflects the increase in dipole moment of the cyano group due to the contribution of a phosphobetaine structure (300b) to the overall electronic condition of the phosphorane (300).



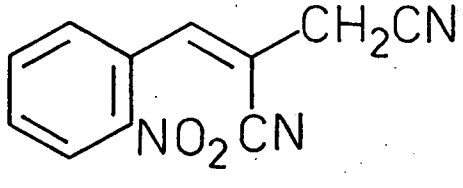
(a) (b)

(300)

The reaction of the phosphorane (300) with 2-nitrobenzaldehyde (279a) in refluxing benzene for 24 h, gave a moderate yield (54%) of 2,3-dicyano-1-(2'-nitrophenyl)propene (301a) (m.p. 126°). The structure of this benzylidene derivative is based on its elemental analysis and mass spectrum which has a parent ion at m/e 231. The i.r. spectrum of the dicyano compound (301a) shows a weak adsorption at 2250 cm^{-1} due to the non-conjugated 3-cyano group and the stronger band of 2200 cm^{-1}, is assigned to the conjugated 2-cyano group. Bands due to a nitro group and to a C=C were also present. However, when the same experiment was carried out at a temperature of 50°C for 48 h in attempt to improve the yield, the product that was isolated in 47% yield had a melting point of 80°C and was more soluble than the dicyano product (301a). The elemental analysis however, was consistent with a molecular formula $C_{11}H_7N_3O_2$, isomeric with the dicyano compound (301a). The i.r. spectrum of this isomeric material showed a weak cyano peak at 2265 cm^{-1} and a stronger band at 2115 cm^{-1}. The bands at 1525 and 1345 cm^{-1} are indicative of the presence of a nitro group. Hence, it was concluded that the isomeric material (301b) was simply a geometric isomer of the dicyano product (301a). Since conjugation is more strongly transmitted along



(301b)

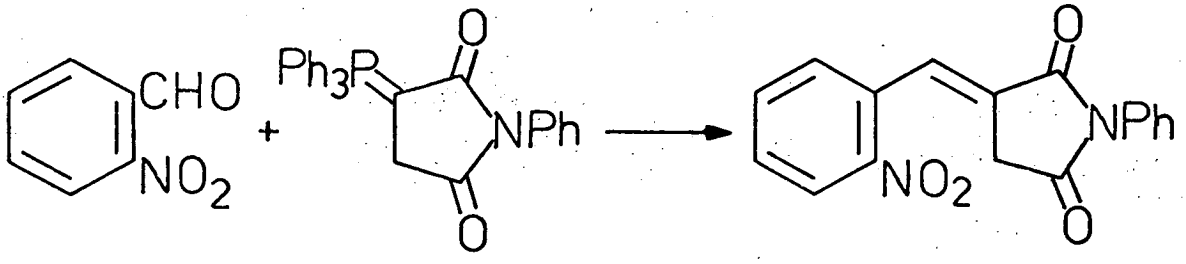


(301a)

a trans framework,[110] the isomer of the dicyano compound having the vinylic cyano group trans to the 2-nitrophenyl group will show a lower vinylic cyano group stretching frequency. Thus, the lower melting

isomer must have the configuration (cf. 301b) of an E-isomer.

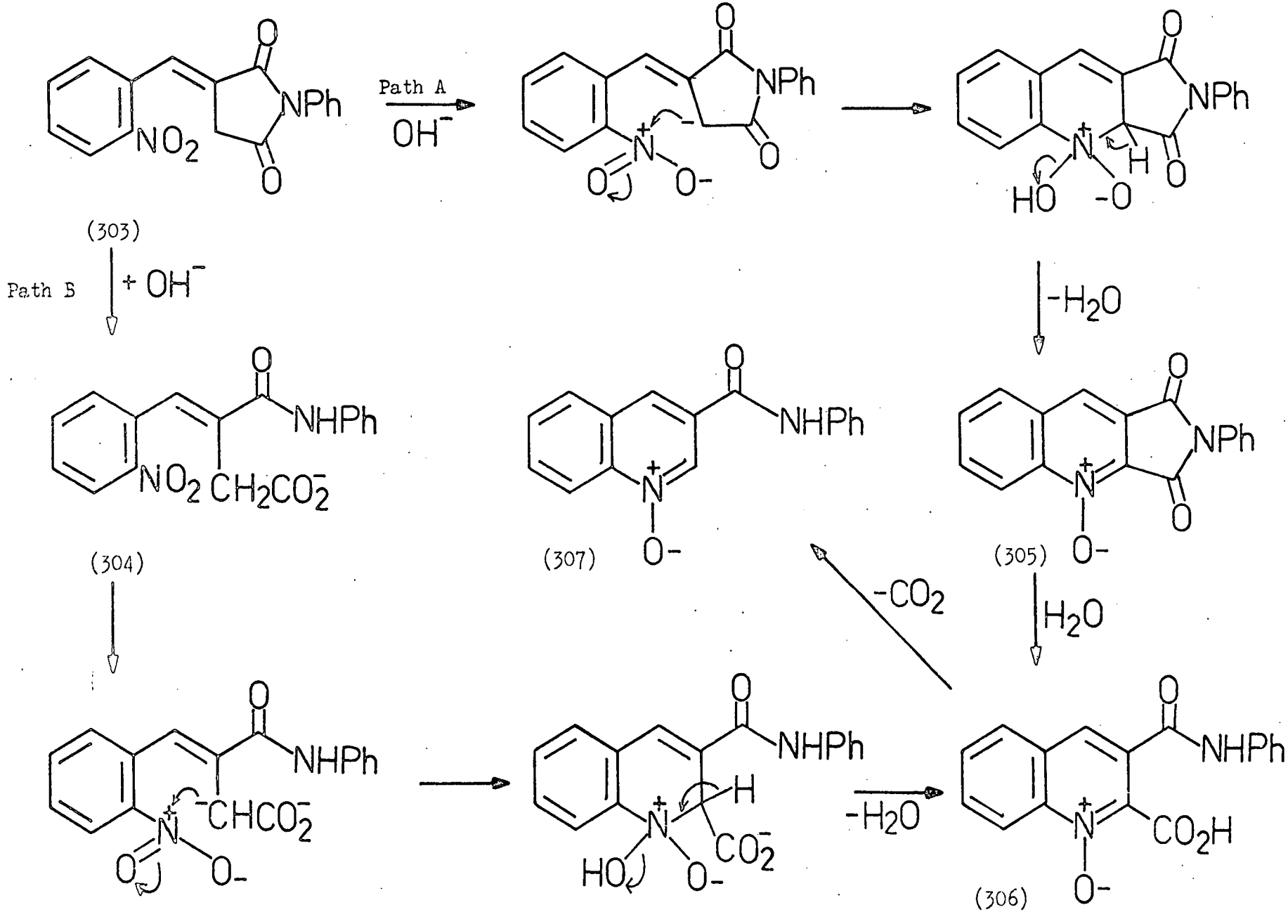
The attempted base-catalysed cyclisation of the two isomers (301a) and (301b) proved unsuccessful. Thus, when the Z-isomer (301a) was heated with ethanolic sodium hydroxide, the only isolated product was an amorphous solid which could not be fully characterised but whose i.r. spectrum showed the presence of a nitro group. Since there is hindered rotation about the carbon-carbon double bond, the Z-isomer (301a) is not structurally suited for nucleophilic interaction between the active methylene group and the ortho-nitro group due to the trans relationship between the cyanomethyl and the nitrobenzene ring. However, despite the more favourable steric situation in the E-isomer (301b), when it was heated with alkali the product was again an intractable solid whose i.r. spectrum showed the presence of a nitro group, indicating that the desired cyclisation had not occurred to any significant extent.



(302) (303)

In a further study of the scope of the Wittig condensation in this area, the reaction of the known N-phenyl-triphenylphosphoranylidenesuccinimide (302)[111] with 2-nitrobenzaldehyde in benzene under reflux for 24 h, gave 3-(2'-nitrobenzylidene)-1-phenylsuccinimide (303) in good yield. The latter product gave analytical and spectral data consistent with its formulation. In particular, its mass spectrum showed a parent ion at m/e 308 and its i.r. spectrum showed a strong

Scheme 51



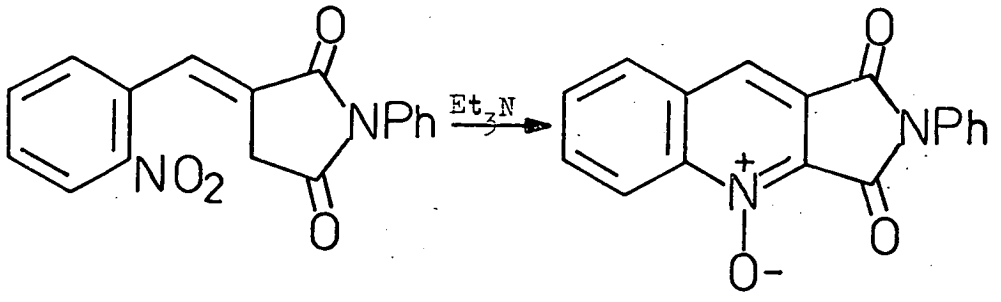
carbonyl band at 1715 cm^{-1} and a weak carbonyl band at 1775 cm^{-1}. The band at 1600 cm^{-1} is assigned to the C=C bond. The bands at 1530 and 1350 cm^{-1} are attributed to the nitro group stretching modes. The ^1H n.m.r. of the benzylidene derivative (303) was also consistent with the assigned structure. Thus the doublet at τ 1.87 is assigned to the H-(3') proton of the nitrobenzene ring which suffers deshielding by the 2'-nitro group. The triplet at τ 1.98 is assigned to the vinyl hydrogen which is coupled to the methylene group. This was confirmed by a decoupling experiment in which the methylene group, a doublet at τ 6.41, was irradiated and collapse of the triplet at τ 1.98 to a singlet, was observed. The signals in the region τ 2.20-2.68 are assigned to the remaining eight aromatic hydrogens.

The reaction of 3-(2'-nitrobenzylidene)-1-phenylsuccinimide (303) with aqueous ethanolic sodium hydroxide afforded an acidic solid whose i.r. spectrum showed an NH stretch at 3320 cm^{-1}, an acidic OH stretch at 2600 cm^{-1} and a broad carbonyl stretching mode at 1680 cm^{-1}. This solid is tentatively assigned the structure of 3-(N-phenylcarbamoyl) quinoline-2-carboxylic acid 1-oxide (306), (Scheme 51). As with the dicarboxylic acid analogues (286 b-d) it underwent decarboxylation on attempted recrystallisation from ethanol-acetic acid to afford a solid which is assigned the structure of quinoline-3-(N-phenylcarboxamide) 1-oxide (307) on the basis of its elemental analysis and its mass spectrum which showed a parent ion at m/e 264, in accord with a molecular formula of $C_{16}H_{12}N_2O_2$. Its i.r. spectrum showed bands due to an amide NH at 3250 and 3200 cm^{-1} and a band at 1680 cm^{-1} due to a carbonyl stretching mode.

The mechanism of the cyclisation of the benzylidenesuccinimide derivative (303) to the quinoline amide-carboxylic acid (306) may involve direct aldol-type condensation of the methylene group in the side-chain

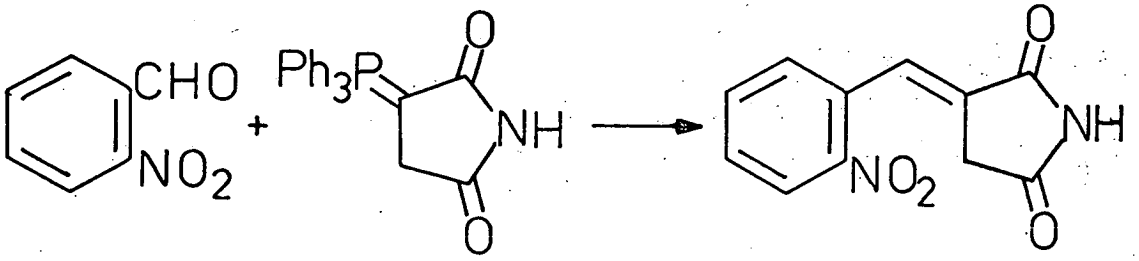
with the ortho-nitro group (Path A; Scheme 51) to give the tricyclic intermediate (305) which undergoes subsequent hydrolysis to afford the quinoline 1-oxide (306). An alternative route (Path B; Scheme 51) involving prior hydrolysis of the imide ring to give the carboxylic acid (304) seems unlikely. As the final product (306) has the carboxylic acid group on the 2-position of the quinoline nucleus, the mode of cleavage of the imide ring must occur as shown [(303) → (304); Scheme 51] and not by nucleophilic attack by hydroxide ion at the alternative amide carbonyl group which would result in a quinoline-3-carboxylic acid 1-oxide derivative on subsequent cyclisation. Thus, if the mechanism occurred as represented in path B (Scheme 51), the intermediate (304) would bear an ionised carboxylate group in the alkaline reaction medium and the presence of this negative charge would deactivate the methylene group making cyclisation unlikely.

An attempt to effect the base-catalysed cyclisation of the 2-nitrobenzylidenesuccinimide derivative (303) using ethanolic sodium ethoxide resulted only in the formation of intractable solids. With triethylamine as basic catalyst however, a small amount (10%) of a solid was isolated and identified as 2,3-dihydro-2-phenyl-1H-pyrrolo[3,4-b]-quinoline-1,3-dione (305) from its elemental analysis and its mass spectrum which showed a parent ion at m/e 290, consistent with a molecular formula of $C_{17}H_{10}N_2O_3$. Its i.r. spectrum lacked bands due to nitro group absorptions but did show two carbonyl stretching modes at 1780 and 1720 cm^{-1} which is consistent with the characteristic high frequency of five-membered cyclic imides. The isolation of this tricyclic N-oxide (305) is consistent with direct aldol-type condensation between the nitro group and the acidic methylene group in the side-chain and hence supports the mechanism postulated (Path A; Scheme 51) for the formation of the quinoline amide-acid 1-oxide (306) from the same benzylidene precursor (303).



(303) (305)

In similar fashion to the condensation of 2-nitrobenzaldehyde with the phosphorane derived from N-phenylsuccinimide, its condensation with the known 3-(triphenylphosphoranylidene)succinimide[111] (308) gave 3-(2'-nitrobenzylidene)succinimide (309) in good yield (72%). The benzylidene derivative (309) gave analytical and spectral data consistent with its formulation. In particular, its mass spectrum showed a base peak at m/e 186 which corresponds to the loss of the elements of nitrogen dioxide from the benzylidene parent ion, a known fragmentation[112] for some 2-nitrophenyl derivatives on electron impact.

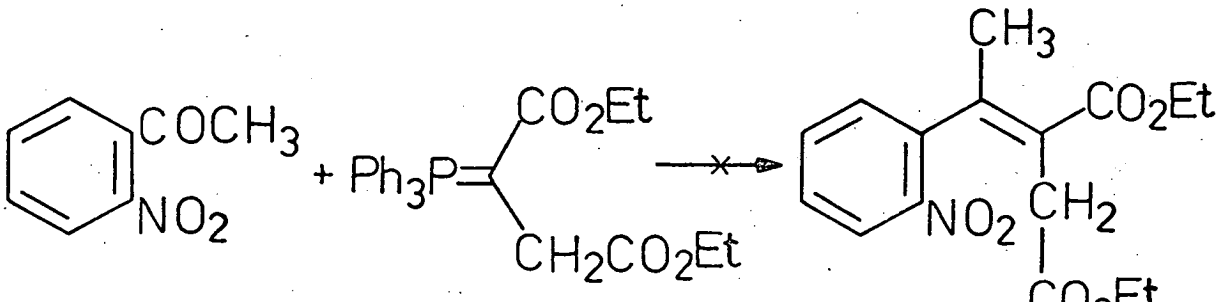


(308) (309)

Heating the benzylidene derivative (309) with ethanolic ethoxide afforded an unidentified solid in low yield (10%) whose elemental analysis and mass spectrum (m/e 261) are in accord with a molecular formula of $C_{16}H_{11}N_3O$. The i.r. spectrum of this solid showed absorption bands at 3340 and 3160 cm^{-1} which are attributed to NH stretching modes and the band at 1650 cm^{-1} indicates the presence of a carbonyl group. Bands

attributable to nitro group absorptions were absent. However, lack of material precluded further investigation of this solid. The use of triethylamine as the basic catalyst in the attempted cyclisation of (309) likewise gave a low yield (10%) of an unidentified solid.

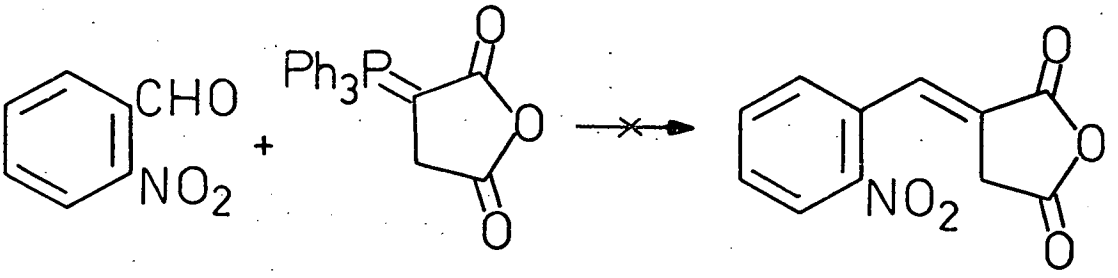
The possibility of synthesising the benzylidene precursor (311) with a view to effecting its base-catalysed cyclisation to a 4-substituted quinoline 1-N-oxide was envisaged. This extension to the quinoline 1-oxide synthesis was thwarted however, by the failure of 2-nitroacetophenone (310) to react with the phosphorane (280b) under the conditions



(310) (280b) (311)

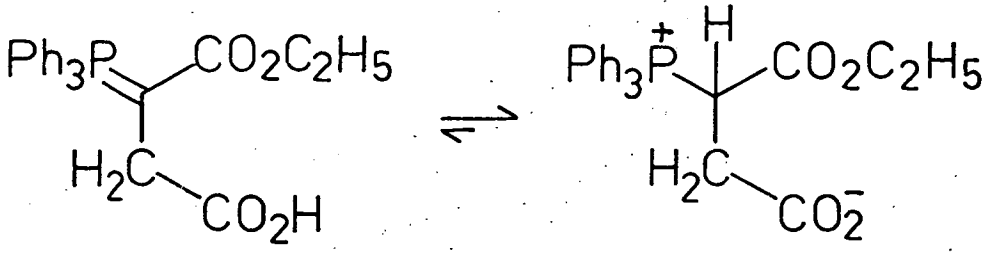
used for the successful 2-nitrobenzaldehyde condensations. The failure of the reaction between the ketone (310) and the phosphorane (280b) is explained by steric effects and the reduced electrophilicity of the ketonic carbonyl group (due to the inductive effect of the methyl group), in comparison to an aldehyde group.

The synthesis of other 2-nitrobenzylidene derivatives which contain an active methylene group suitable for nucleophilic interaction with an ortho-nitro group on a benzene ring was also investigated. Thus, 3-(triphenylphosphoranylidene)succinic anhydride[113] (312) was chosen as its successful condensation with 2-nitrobenzaldehyde would afford the benzylidene derivative (313) which would have an acidic methylene group capable of undergoing base-catalysed cyclisation to give a quinoline N-oxide. However, the attempted Wittig condensation of the phosphorane (312) with 2-nitrobenzaldehyde gave, as the only identified product, triphenylphosphine.



(312) (313)

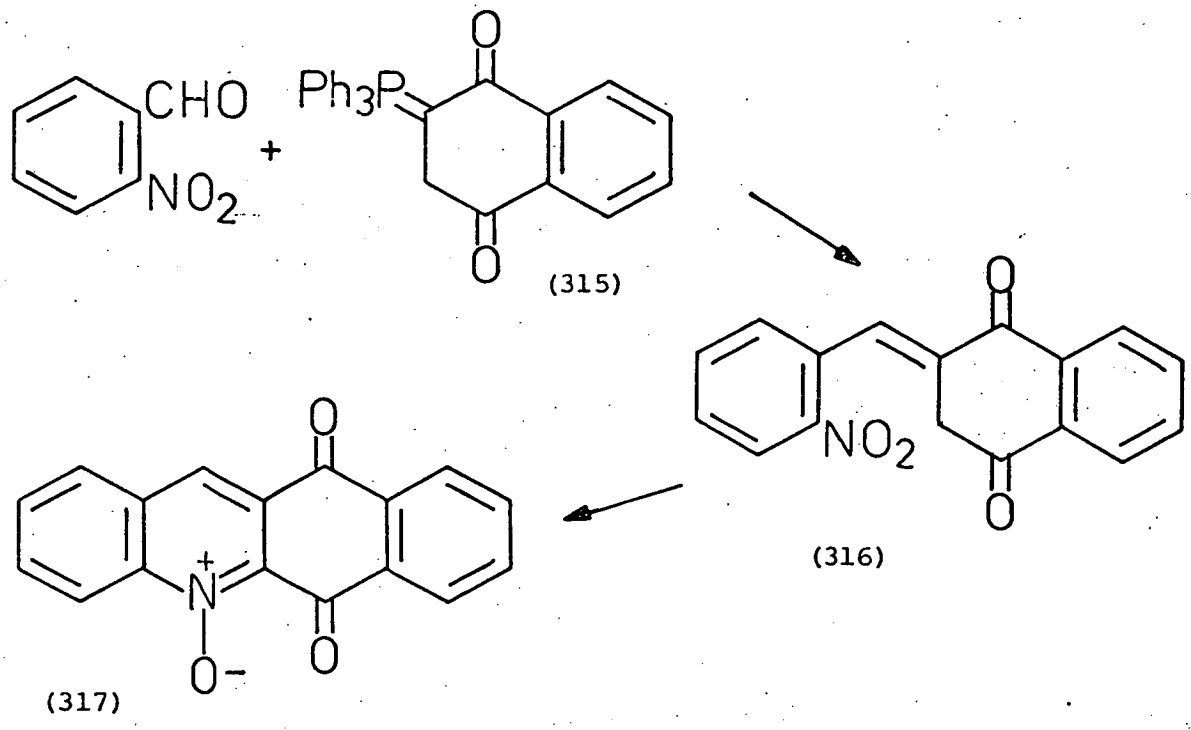
When 2-nitrobenzaldehyde was heated under reflux with 1-ethoxycarbonyl-ethylidenetriphenylphosphorane-2-carboxylate[113] (314), only a mixture of the starting materials was obtained. The failure of the reaction in this case may be attributed to the weakly nucleophilic nature of the α-carbon in the phosphorane (314), which is best represented by the phosphonium structure (314b).[113]



(a) (b)

(314)

The attempted extension of the scope of the Wittig condensation reaction of 2-nitrobenzaldehyde to the interesting possibility of synthesising a benzo-acridinequinone (317) was undertaken by attempting to condense the known phosphorane[114] (315) with the aldehyde (279a) to obtain the 2-nitrobenzylidene-naphthalene derivative (316) which would be expected to have an active methylene group. However, the only isolated material from the attempted Wittig condensation [(279a) + (315)] was a high return of unreacted phosphorane (315).

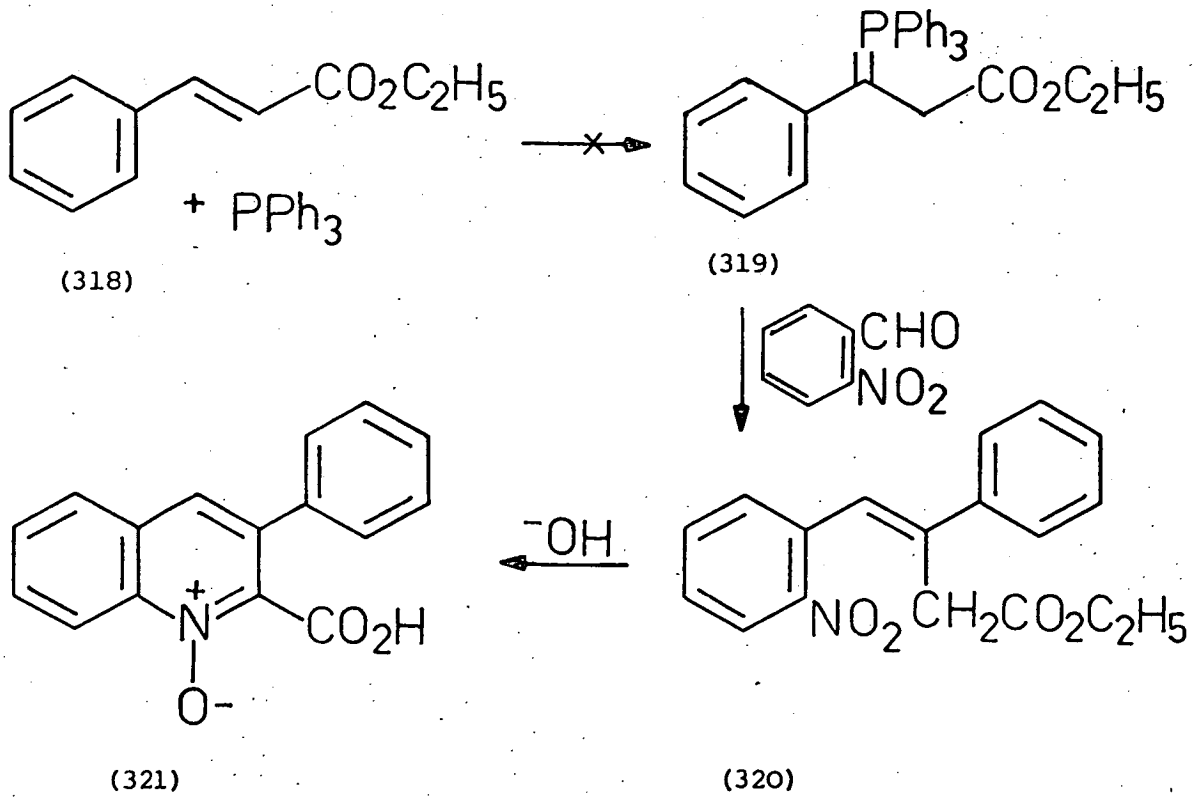


(315)

(316)

(317)

In one case, the proposed synthesis of the benzylidene derivative (320) was thwarted by the failure to obtain the phosphorane derivative. Thus triphenylphosphine failed to form an adduct (319) with ethyl cinnamate (318) and the subsequent cyclisation reaction could not be studied.



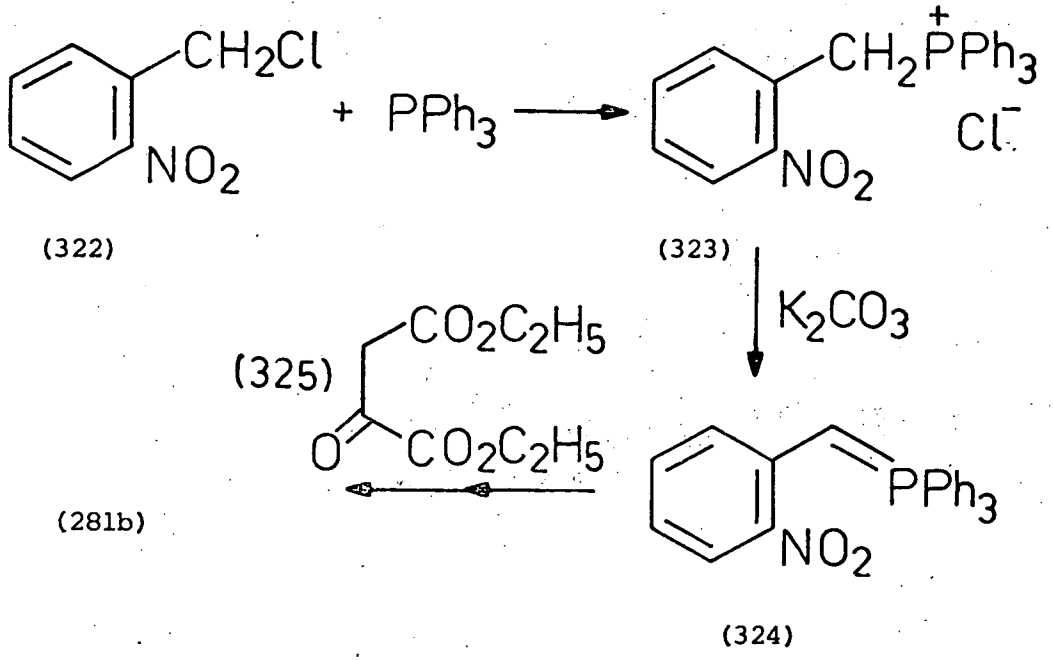
(318)

(319)

(320)

(321)

In all the successful syntheses of 2'-nitrobenzylidene derivatives so far reported in the present work, the common substrate has been a 2-nitrobenzaldehyde derivative which has been reacted with a phosphorane derived from an electron-deficient olefin. However, an alternative method of performing the Wittig reaction was envisaged in which the known phosphorane[115,116] (324) derived from 2-nitrobenzyl chloride (322) could be condensed with diethyl oxaloacetate (325) to again give the benzylidene derivative (281b). However, in practice, although the phosphorane (324) could be readily obtained, its reaction with the ester (325) proved unsuccessful, none of the benzylidene derivative (281b) being isolated



from the reaction mixture, although the purple colour of the phosphorane (324) disappeared readily. In the reaction of the phosphorane (324) with formalin solutions, Butcher et.al.[116] took the disappearance of the colour of the phosphorane as indicative of complete reaction. With the case in hand however, t.l.c. of the colourless reaction mixture showed

a mixture of starting materials to be present and the mixture was therefore heated under reflux for 24 h. Triphenylphosphine oxide was then isolated and this may be indicative of reaction. Nonetheless, it is apparent that the attempted Wittig condensation of the phosphorane (324) with diethyl oxaloacetate (325) does not provide an efficient, alternative route to the benzylidene derivative (281b).

EXPERIMENTAL

1,2-Dibenzoylethylidenetriphenylphosphorane[100] (280a).

a) The phosphorane (280a) was prepared by the method of Ramirez et. al.[100] (20%), m.p. 117° (lit.,[100] 122°).

b) Triphenylphosphine hydrobromide[117] (1.40 g) and dibenzoylethylene (0.94 g, 0.004 mol) were heated under reflux in acetonitrile (25.0 ml) for 15 min. The solution was treated with water (6.0 ml) and washed with ether (2 x 5.0 ml) and the aqueous phase was basified with dilute aqueous sodium hydroxide (4.0 ml) to give the insoluble phosphorane (280a) (0.76 g; 38%), m.p. 115° (lit.,[100] 122°), identical (i.r. spectrum) with a sample prepared as in (a).

1,2-Bis(ethoxycarbonyl)ethylidenetriphenylphosphorane[101] (280b)

The phosphorane (280b) was prepared[101] by the reaction of diethyl-fumarate with triphenylphosphine hydrobromide (83%) m.p. 104° (lit.,[101] 106°).

3-Triphenylphosphoranylidenesuccinic Anhydride[113] (312)

The phosphorane (312) was prepared by the reaction of maleic anhydride with triphenylphosphine (71%), m.p. 174° (decomp.) (lit.,[113] 174°).

1-Phenyl-3-triphenylphosphoranylidenesuccinimide[111] (302)

The phosphorane (302) was prepared by the method of Hedaya[111] with the modification that the acetic acid reaction mixture was evaporated and the residue was triturated with acetone to give the phosphorane (302) (63%), m.p. 172° (lit.,[111] 178°).

1-Ethoxycarbonylethylidenetriphenylphosphorane-2-carboxylate[113] (314)

The phosphorane (314) was prepared[113] by ethanolysis of the corresponding anhydride (312) (76%), m.p. 131° (lit.,[113] 127°).

2-Phosphoranylidene-1,2,3,4-tetrahydronaphthalene-1,4-dione[114] (315)

The phosphorane (315) was prepared by the method of M.A.A. Beg[114] (42%) m.p. 162° (lit.,[114] 163°).

3-Triphenylphosphoranylidenesuccinimide[111] (308)

The phosphorane (308) was prepared by the method of Hedaya[111] (70%), m.p. 270° (lit.,[111] 220°), $\nu_{max.}$ 2740 (NH) and 1740 and 1640 br(CO)cm^{-1}.

1,2-Dicyanoethylidenetriphenylphosphorane (300)

A mixture of triphenylphosphine (10.5 g, 0.04 mol) and fumaronitrile (3.2 g, 0.04 mol) in glacial acetic acid (130 ml) was stirred and heated on a steam bath at 100° for 1 h. The mixture was cooled and the solid was collected to give the phosphorane (300) (5.9 g; 43%), m.p. 146° (from ethyl acetate), $\nu_{max.}$ 2240 w and 2140 (CN).

Found: C, 77.9; H, 5.1; N, 8.4%; M^+, 278 (Ph_3PO).

$C_{22}H_{17}N_2P$ requires: C, 77.7; H, 5.0; N, 8.2%; M, 340.

Evaporation of the acetic acid filtrate afforded an oil (7.0 g) whose t.l.c. in ethyl acetate over silica showed it to contain three components one of which was the phosphorane (300). Dry column

chromatography of the oil (7.0 g) in ethyl acetate over silica afforded a further quantity of the phosphorane (0.2 g), identical (i.r. spectrum) with the previous crop. The attempted extraction of the more polar component from the silica using ethyl acetate and methanol afforded only an intractable black tar (0.8 g).

2'-Nitrobenzyltriphenylphosphonium Chloride[115] (323)

The phosphonium salt (323) was prepared by the method of Krohnke[115] with the modification that the filtrate from the first crop of product was evaporated and the residual gum was triturated with acetone to give a second crop of product (total 47%), m.p. 249° (lit.,[115] 230°).

2'-Nitrophenylmethylenetriphenylphosphorane (324)[115,116]

The phosphonium salt (323) (10.0 g) was stirred in 10% w/v aqueous sodium carbonate solution (300 ml) for 3 h at room temperature to give the deep purple ylide (324) (7.0 g; 80%), m.p. 163°.

The Attempted Synthesis of Ethyl 3-Phenyl-3-(triphenylphosphoranylidene) propionate (319)

A mixture of triphenylphosphine hydrobromide (1.4 g, 0.004 mol) and ethyl cinnamate (0.71 g, 0.004 mol) in analar acetonitrile (25.0 ml) was heated under reflux for 25 min. The mixture was cooled and poured into water (15.0 ml) and then washed with ether (3 x 5.0 ml). The aqueous phase was treated with dilute aqueous sodium hydroxide solution (3.0 ml) and then washed with ether (3 x 5.0 ml) to give an oil which was triturated with light petroleum to give triphenylphosphine (0.51 g), identical (m.p. and i.r. spectrum) with an authentic sample. The light petroleum filtrate was evaporated to leave an oil whose t.l.c. in ether over silica showed it to contain triphenylphosphine and ethyl cinnamate.

Evaporation of the original ether washings afforded an oil (0.29 g) whose t.l.c. in ether over silica showed it to contain ethyl cinnamate and one other minor component which was not identified.

Syntheses of 2-Nitrobenzylidene Derivatives

The Attempted Synthesis of 2,3-Dibenzoyl-1-(2'-nitrophenyl)propene (281a)

a) A suspension of 1,2-dibenzoylethylidenetriphenylphosphorane (280a) (1.3 g, 0.0025 mol) in dry benzene (30.0 ml) was added dropwise to a stirred solution of 2-nitrobenzaldehyde (0.38 g, 0.0025 mol) in dry benzene (5.0 ml). The mixture was then refluxed for 22 h. The resulting red solution was evaporated and the residue was extracted with hot light petroleum. The insoluble residue was recrystallised from ethanol to give 1,2-dibenzoylethylene[100] (0.2 g; 34%) m.p. 109° (lit.,[100] 111°) identical (m.p. and i.r. spectrum) with an authentic sample. Evaporation of the ethanol mother liquors gave a gum (0.07 g) whose t.l.c. in ether over silica showed it to contain 2-nitrobenzaldehyde and the phosphorane (280a).

Evaporation of the light petroleum extract and trituration of the residue with ethyl acetate afforded a solid (0.42 g), m.p. 115° whose t.l.c. in ether over silica showed it to contain the phosphorane (280a) and dibenzoylethylene. Evaporation of the ethyl acetate mother liquors left an oil (0.6 g) whose t.l.c. in ether over silica showed it to contain 2-nitrobenzaldehyde, dibenzoylethylene and the phosphorane (280a).

b) 2-Nitrobenzaldehyde (0.19 g, 0.13 mol) in dry benzene (5.0 ml) was added dropwise to the phosphorane (280a) (0.7 g) in dry benzene (25.0 ml) and the mixture was stirred at room temperature for 72 h. The resulting yellow solution was evaporated and the residue was triturated with ether to give a solid (0.11 g), m.p. 106°, whose t.l.c. in ether over silica showed it to contain only dibenzoylethylene and the unreacted phosphorane (280a).

Evaporation of the ether mother liquors left an oily solid (0.7 g) whose t.l.c. in ether over silica showed it to contain a mixture of debenzoylethylene, the phosphorane (280a) and 2-nitrobenzaldehyde.

2,3-Bis(ethoxycarbonyl)-1-(2'-nitrophenyl)propene (281b)

a) A solution of 1,2-bis(ethoxycarbonyl)ethylidenetriphenylphosphorane[101] (280b) (8.6 g, 0.02 mol) in dry benzene (60.0 ml) was added dropwise over a period of 15 min to a solution of 2-nitrobenzaldehyde (3.0 g, 0.02 mol) in benzene (15.0 ml) under an atmosphere of nitrogen. The mixture was heated under reflux for 24 h and then cooled and evaporated. The residue was extracted with ether and the insoluble triphenylphosphine oxide was collected (3.3 g; 68%) m.p. 157°, identical (i.r. spectrum) with an authentic sample.

The ether extract was evaporated and the residue (7.3 g) was recrystallised from 60% v/v ethanol-water to give the 2-nitrobenzylidene derivative (281b) as long colourless needles (5.5 g; 90%), m.p. 71°, $\nu_{max.}$ 1720 and 1710 (CO) and 1520 and 1340 (NO_2) cm^{-1}, $\tau(CCl_4)$ 1.86 (1H, d J 9Hz, ArH), 1.98 (1H, s, CH), 2.30-2.59 (3H, m, ArH) 5.76 (2H, q J 8Hz, CH_2), 5.90 (2H, q J 8Hz, CH_2), 6.86 (2H, s, CH_2), 8.67 (3H, t J 8Hz, CH_3), and 8.77 (3H, t J 8Hz, CH_3),

Found: C, 58.8; H, 5.5; N, 4.5%; M^+, 307.

$C_{15}H_{17}NO_6$ requires: C, 58.6; H, 5.6; N, 4.6%; M, 307.

b) 2'-Nitrophenylmethylenetriphenylphosphorane[115] (324) (0.79 g, 0.002 mol) in dry benzene (30.0 ml) was added dropwise over a period of 0.5 h with occasional mixing, to a solution of diethyl oxaloacetate (0.37 g) under an atmosphere of nitrogen. The purple colour of the phosphorane was discharged immediately. T.l.c. of the reaction mixture in ether over silica showed it to contain four components one of which was unreacted diethyl oxaloacetate. The solution was heated under reflux for 24 h

and then evaporated to leave an oil which was triturated with ether to give triphenylphosphine oxide (0.2 g) identical (i.r. spectrum) with an authentic sample. The filtrate was evaporated to give an oil (0.63 g), which was chromatographed over alumina. Elution with ether gave an unidentified oil (0.1 g), $\nu_{max.}$ 1750 (CO) and 1530 and 1350 (NO_2) cm^{-1}. Further elution with ethyl acetate afforded only triphenylphosphine oxide (0.24 g) identical (i.r. spectrum) with an authentic sample.

2,3-Bis(ethoxycarbonyl)-1-(5'-bromo-2'-nitrophenyl)propene (281c)

The nitrophenylpropene (281c) was prepared as in (a) above by the reaction of 5-bromo-2-nitrobenzaldehyde with 1,2-bis(ethoxycarbonyl) ethylidenetriphenylphosphorane[101] (280b) as colourless needles (70%), m.p. 85° (from 60% v/v ethanol-water), $\nu_{max.}$ 1715 (CO), and 1515 and 1340 (NO_2) cm^{-1}, τ($CDCl_3$; 60MHz) 2.06 (1H, d $J_{3,4}$ 8Hz ArH), 2.16 (1H, s, CH), 2.32-2.60 (2H, M, ArH), 5.66-6.18 (4H, m, CH_2), and 8.68-9.00 (6H, m, CH_3).

Found: C, 46.4; H, 4.1; N, 3.4%; M^+387/385

$C_{15}H_{16}BrNO_6$ requires: C, 46.6; H, 4.2; N, 3.6%; M,386.

Further work up yielded no more product.

2,3-Bis(ethoxycarbonyl)-1-(5'-chloro-2'-nitrophenyl)propene (281d)

The 2-nitrophenylpropene derivative (281d) was prepared as in (a) above by the reaction of 5-chloro-2-nitrobenzaldehyde with the phosphorane[101] (280d). It formed colourless needles (62%) m.p. 62° (from 60% v/v ethanol-water), $\nu_{max.}$ 1720 and 1710 (CO), and 1515 and 1340 (NO_2) cm^{-1}, τ($CDCl_3$) 1.86 (1H, d J 9Hz, ArH), 1.95 (1H, s, CH), 2.20-2.54 (2H, m, ArH), 5.60-5.94 (4H, m, CH_2), 6.72 (2H, s, CH_2) and 8.58-8.80 (6H, m, CH_3).

Found: C, 52.7; H, 4.7; N, 4.1%; M^+343/341

$C_{15}H_{16}ClNO_6$ requires: C, 52.7; H, 4.7; N, 4.1%; M,341.5.

Further work up yielded no more product.

3-(2'-Nitrobenzylidene)-1-phenylsuccinimide (303)

2-Nitrobenzaldehyde was reacted with the phosphorane[111] (302) in benzene as described for 1,2-bis(ethoxycarbonyl)ethylidenetriphenylphosphorane before. Evaporation of the reaction mixture gave a solid residue which was extracted with hot 50% v/v ethanol-water and hot-filtered. Recrystallisation of the insoluble solid from ethyl acetate afforded the colourless 2-nitrobenzylidene derivative (303) as a powder (73%), m.p. 183°, $\nu_{max.}$ 1775w, 1715 and 1680w (CO), and 1530 and 1350 (NO_2) cm^{-1}; τ $CDCl_3$-$(CD_3)_2SO$ 9.87 (1H, d J 9Hz, ArH), 9.98 (1H, t J 3Hz, ArH), 8.20-8.68 (8H, m, ArH), 6.41 (2H, d J 3Hz, CH_2).

Found: C, 66.1; H, 3.9; N, 8.8%; M^+308.

$C_{17}H_{12}N_2O_4$ requires: C, 66.2; H, 3.9; N, 9.1%; M,308.

Work up of the aqueous-ethanol mother liquors afforded only triphenylphosphine oxide (86%) identical (i.r. spectrum) with an authentic sample.

3-(2'-Nitrobenzylidene)succinimide (309)

2-Nitrobenzaldehyde was reacted with the phosphorane[111] (308) in acetonitrile as described for 1,2-bis(ethoxycarbonyl)ethylidenetriphenylphosphorane before. The reaction mixture was evaporated and the residue was extracted with hot 50% v/v ethanol-water. The insoluble solid was collected and recrystallised from ethanol-water to give the pure 2-nitrobenzylidene derivative (309) as colourless plates (72%), m.p. 172°, $\nu_{max.}$ 3190br (NH), 1775, 1715 and 1655 (CO) and 1525 and 1355 (NO_2) cm^{-1}. τ $(CD_3)_2SO$ -1.46 (1H, br s, NH), 1.90-2.52 (5H, m, ArH, CH) and 6.52 (2H, d J 3Hz, CH_2).

Found: C, 56.7; H, 3.4; N, 12.0%; p^+186 (M^+-NO_2)

$C_{11}H_8N_2O_4$ requires: C, 56.9; H, 3.5; N, 12.1%; M,232.

2,3-Dicyano-1-(2'-nitrophenyl)propene (301a and b)

a) 2-Nitrobenzaldehyde (0.002 mol) was reacted with the phosphorane (300) (0.002 mol) in benzene (15.0 ml) as described for 1,2-bis(ethoxycarbonyl)-ethylidenetriphenylphosphorane above. The reaction mixture was evaporated to give a gummy residue which was extracted with ether. Evaporation of the ether extract and trituration of the gummy residue with ethyl acetate gave triphenylphosphine oxide (0.47 g) identical (i.r. spectrum) with an authentic sample.

Evaporation of the ethyl acetate mother liquors and retrituration with methanol afforded the 2-nitrobenzylidene derivative (301a) (54%), m.p.126° (from ethanol-water), $\nu_{max.}$ 2250w and 2200 (CN), 1570 (C = C), and 1525 and 1345 (NO_2) cm^{-1}.

Found: C, 61.9; H, 3.4; N, 19.2%; M^+213.

$C_{11}H_7N_3O_2$ requires: C, 62.0; H, 3.3; N, 19.7%; M,213.

b) A solution of the phosphorane (300) (1.7 g, 0.005 mol) and 2-nitrobenzaldehyde (0.76 g, 0.005 mol) in dry benzene (100 ml) was heated at 50° for 48 h. The solution was evaporated and the residue was dissolved in chloroform and washed with saturated aqueous sodium hydrogen sulphite solution (2 x 5.0 ml) followed by dilute aqueous hydrochloric acid (5.0 ml). The chloroform layer was evaporated and the residue was triturated with ether-ethyl acetate to give triphenylphosphine oxide (0.44 g) identical (i.r. spectrum) with an authentic sample. The ether-ethyl acetate mother liquors were evaporated and the residue was triturated with ether-ethanol to give the 2-nitrobenzylidene derivative (301b) (0.5 g. 47%), m.p. 80° (from light petroleum-ethyl acetate), $\nu_{max.}$ 2265w and 2115 (CN), and 1525 and 1345 (NO_2) cm^{-1}.

Found: C, 61.8; H, 3.4; N, 19.8%; M^+ 213

$C_{11}H_7N_3O_2$ requires: C, 62.0; H, 3.3; N, 19.7%; M,213

The ether-ethanol mother liquors were evaporated to leave a gum (1.0 g) from which no further identifiable material could be isolated.

The Attempted Synthesis of 1,2-Bis(ethoxycarbonyl)-3-(2'-nitrophenyl)but-2-ene (311)

2-Nitroacetophenone (0.7 g, 0.004 mol) was reacted with the phosphorane[101] (280b) (1.8 g, 0.004 mol) in dry benzene (15.0 ml) as described before. Evaporation of the reaction mixture left an oil which was triturated with ether to afford the unreacted phosphorane (280b) (0.54 g), identical (m.p. and i.r. spectrum) with an authentic sample. The ether mother liquors were evaporated and the residual oil (1.65 g) was chromatographed over alumina. Elution with light petroleum afforded triphenylphosphine oxide (0.21 g) identical (m.p. and i.r. spectrum) with an authentic sample.

Elution with ether afforded unreacted 2-nitroacetophenone (0.67 g), identical (i.r. spectrum) with an authentic sample.

Further elution with ether afforded more unreacted phosphorane[101] (280b) (0.49 g) identical (i.r. spectrum) with an authentic sample. Finally, elution with methanol afforded no further material.

The Attempted Synthesis of 3-(2'-Nitrobenzylidene)succinic Anhydride (313)

a) 2-Nitrobenzaldehyde (0.75 g; 0.005 mol) was reacted with triphenylphosphoranylidene succinic anhydride[113] (312) (1.74 g, 0.005 mol) in benzene (40.0 ml) as described before. After 24 h the reaction mixture contained an insoluble gum. The supernatant liquid was decanted, evaporated and the resulting residue was triturated with methanol to afford triphenylphosphine (0.24 g), m.p. 78° (lit., 82°), identical (i.r. spectrum) with an authentic sample. T.l.c. over silica in ethyl acetate of the insoluble gum and of the methanol mother liquors showed them to consist of unresolvable multicomponent mixtures containing triphenylphosphine.

b) The reaction (a) above was repeated at room temperature for 48 h to give a dark solution whose t.l.c. in chloroform over silica showed it to contain largely 2-nitrobenzaldehyde and the phosphorane (312) plus a small amount of a highly coloured component. The mixture was not further investigated.

The Attempted Synthesis of 3-Ethoxycarbonyl-4-(2'-nitrophenyl)but-3-enoic Acid

2-Nitrobenzaldehyde was reacted with the phosphorane[113] (314) as described for the phosphorane (280b), before. Evaporation of the reaction mixture left an oily residue whose t.l.c. in chloroform over silica showed it to contain largely a mixture of the starting materials and two other minor components. The mixture was not further investigated.

The Attempted Synthesis of 2-(2'-Nitrobenzylidene)-1,2,3,4-tetrahydronaphthalene-1,4-dione (316)

2-Nitrobenzaldehyde was reacted with the phosphorane[114] (315) as described for the phosphorane (280b). Hot filtration of the reaction mixture gave the unreacted phosphorane[114] (315) a second crop of which was obtained by evaporating the filtrate and triturating the residue with ether-ethanol (total 77%) identical (m.p. and i.r. spectrum) with an authentic sample. T.l.c. of the residue from the ether-ethanol mother liquors in ether over silica showed it to contain largely 2-nitrobenzaldehyde and several other minor components.

The Base-Catalysed Cyclisations of 2-Nitrobenzylidene Derivatives

The Base-Catalysed Cyclisations of 2,3-Bis(ethoxycarbonyl)-1-(2'-nitrophenyl)propene (281b)

a) Using Ethanolic Sodium Ethoxide

The benzylidene derivative (281b) (0.6 g, 0.002 mol) in absolute ethanol (5.0 ml) was treated with a solution of sodium (0.18 g, 0.008 mol)

in absolute ethanol (10.0 ml) and the resulting solution was heated under reflux for 0.75 h during which time a solid precipitated. The mixture was evaporated, treated with water (10.0 ml) and extracted with chloroform. Evaporation of the chloroform extract gave no material. The aqueous phase was acidified with dilute aqueous sulphuric acid and extracted with chloroform to give 2-ethoxycarbonylquinoline-3-carboxylic acid 1-oxide (286b) (0.05 g; 10%), m.p. 200° (from ethanol-water), $\nu_{max.}$ 2720br and 2620br (OH), and 1740 and 1700br (CO) cm^{-1}.

Found: C, 59.9; H, 4.4; N, 5.4%; M^+ 261.

$C_{15}H_{15}NO_5$ requires: C, 59.8; H, 4.2; N, 5.4%; M, 261.

The aqueous filtrate on standing precipitated the monosodium salt of quinoline-2,3-dicarboxylic acid 1-oxide (0.2 g), $\nu_{max.}$ 3500br, 2500br (OH) and 1713 (CO) cm^{-1}, converted by stirring with concentrated aqueous hydrochloric acid for 20 min into quinoline-2,3-dicarboxylic acid 1-oxide (286d) (0.15 g, 32%) which decarboxylates at 130° and finally melts at 270°, $\nu_{max.}$ 2450br (OH) and 1760 and 1635 (CO) cm^{-1}, p^+ 189 (M^+-44). The dicarboxylic acid (286d) decarboxylated on recrystallisation from water to give quinoline-3-carboxylic acid 1-oxide (290a), m.p. 278°, $\nu_{max.}$ 2580br (OH) and 1720br (CO) cm^{-1}, $\lambda_{max.}$ 215, 237, 247 and 330 nm (log $\varepsilon_{max.}$ 3.67, 4.10, 3.97 and 3.38).

Found: C, 63.0; H, 3.8; N, 7.4%; M^+ 189.

$C_{10}H_7NO_3$ requires: C, 63.5; H, 3.7; N, 7.4%; M, 189.

b) Using Aqueous Ethanolic Sodium Hydroxide

The benzylidene derivative (281b) (1.2 g, 0.004 mol) in ethanol (20.0 ml) was treated with 10% w/v aqueous sodium hydroxide (10.0 ml) and the solution was heated under reflux for 45 min during which time a solid precipitated. The mixture was evaporated and the solid residue was treated with water (5.0 ml) and acidified with concentrated aqueous hydrochloric acid. The resulting precipitate (1.0 g) was collected and

acidified with concentrated aqueous hydrochloric acid to give the dicarboxylic acid (286d) (0.82 g; 89%) which decarboxylates at 130° and finally melts at 270°, $\nu_{max.}$ 2450br (OH) and 1760 and 1735 (CO) cm^{-1}, identical (m.p. and i.r. spectrum) with a sample prepared as in (a), before.

Extraction of the aqueous acidic mother liquors with chloroform gave no further material.

(c) Using Triethylamine

i) The benzylidene derivative (381b) (0.61 g, 0.002 mol) in absolute ethanol (10.0 ml) was treated with triethylamine (0.3 ml) and the mixture was heated under reflux for 0.5 h. The solution was then evaporated and the residual oil was triturated with a little methanol to give the starting material (281b) (0.2 g), m.p. 69°, identical (m.p. and i.r. spectrum) with an authentic sample. The methanol mother liquors were evaporated to give an oil (0.3 g) whose t.l.c. in ether over alumina showed it to contain two components one of which was the starting material. The oil was not further investigated.

ii) The reaction described in (i) was repeated with heating under reflux for 5 h. The solution was then evaporated to yield a gum (0.65 g) whose t.l.c. in ether over alumina showed it to be a multicomponent mixture containing the starting material, from which no identifiable material could be obtained.

d) Using Ethanolic Ammonia

The benzylidene derivative (281b) (1.23 g, 0.004 mol) was added to a saturated ethanolic solution of ammonia (10.0 ml) at 0° and the securely stoppered reaction vessel was left at room temperature for 24 h. The resulting red solution was evaporated to leave a gum which was triturated with ether-ethanol to give a solid. Treatment of the solid with dilute aqueous hydrochloric acid gave quinoline-2,3-dicarboxamide 1-oxide (295) (0.07 g), m.p. 250° (decomp.)(from ethanol-dimethylformamide), $\nu_{max.}$ 3430, 3300 and 3180 (NH_2), and 1740 and 1680 (CO) cm^{-1}, M^+232, $C_{11}H_9N_3O_3$ requires M, 232.

The ether-ethanol mother liquors were evaporated and the residue (0.9 g) was dissolved in chloroform (10.0 ml) and washed with water (2 x 4.0 ml). The red aqueous phase was acidified with dilute aqueous hydrochloric acid and was extracted with chloroform which on evaporation gave no material.

The original chloroform phase was evaporated to leave a gum (0.85 g) whose t.l.c. in ether over silica showed it to be a multicomponent mixture from which no identifiable material could be obtained.

(e) Using Piperidine in Acetic Acid

The benzylidene derivative (218b) (0.92 g, 0.003 mol) was dissolved in glacial acetic acid (7.0 ml) and treated with piperidine (2.0 ml). The reaction was stirred at 60° for 24 h and then cooled and poured into water (50.0 ml) to give the starting material (0.7 g), identical (m.p. and i.r. spectrum) with an authentic sample. Extraction of the aqueous filtrate with chloroform gave only a negligible amount of a brown oil.

6-Bromoquinoline-2,3-dicarboxylic Acid 1-Oxide (286e) and 6-Bromoquinoline-3-carboxylic Acid 1-Oxide (290b)

The benzylidene derivative (218b) (0.77 g, 0.002 mol) in ethanol (10.0 ml) was treated with 10% w/v aqueous sodium hydroxide (5.0 ml) and the solution was heated under reflux for 45 min and then cooled and evaporated. The residue was treated with water (5.0 ml) and extracted with chloroform. Evaporation of the chloroform extraction gave only a negligible amount of material. The aqueous phase was acidified with concentrated aqueous hydrochloric acid and the precipitate was collected and left in contact with concentrated aqueous hydrochloric acid for 15 min to afford the free dicarboxylic acid (286e) (0.5 g; 80%) which underwent decarboxylation without melting and finally melted at 283°, $\nu_{max.}$ 2480br (OH) and 1760 and 1730 (CO) cm^{-1}.

The attempted crystallisation of the diacid (286e) from ethanol-water resulted in its decarboxylation to give 6-bromoquinoline-3-carboxylic acid 1-oxide (290b) m.p. 284°, $\nu_{max.}$ 2710br (OH) and 1710br (CO) cm^{-1} $\lambda_{max.}$ 241, 253sh, 275sh and 335 nm (log $\varepsilon_{max.}$ 4.56, 4.63, 3.50 and 3.84).

Found: C, 44.2; H, 2.3; N, 5.0%; M^+ 269 and 267.

$C_{10}H_6BrNO_3$ requires: C, 44.5; H, 2.2; N, 5.2%; M, 268.

6-Chloroquinoline-2,3-dicarboxylic Acid 1-Oxide (286f) and 6-Chloroquinoline-3-carboxylic Acid 1-Oxide (290c)

The benzylidene derivative (281b) (0.68 g, 0.002 mol) in ethanol (10.0 ml) was treated with 10% w/v sodium hydroxide (5.0 ml) and the solution was heated under reflux for 45 min during which time a solid precipitated. The mixture was evaporated, treated with water (5.0 ml) and washed with chloroform. Evaporation of the chloroform extract gave no material. The aqueous phase was acidified with concentrated aqueous hydrochloric acid. The solid obtained was collected and left in contact with concentrated aqueous hydrochloric acid for 20 min to give the dicarboxylic acid (286f) (0.37 g; 70%) which decarboxylated at 140° without melting and finally melted at 277°, $\nu_{max.}$ 2400br (OH) and 1730 and 1700 (CO) cm^{-1}.

The diacid (286f) underwent decarboxylation on attempted crystallisation from ethanol-water, to give 6-chloroquinoline-3-carboxylic acid 1-oxide (290c), m.p. 287°, $\nu_{max.}$ 2570w (OH) and 1710br (CO) cm^{-1}, $\lambda_{max.}$ 216, 233, 250 and 339 nm (log $\varepsilon_{max.}$ 4.31, 4.61, 4.28, 3.77), τ $(CD_3)_2SO$ 1.29 (1H, d J 2Hz, ArH), 1.40-1.62 (3H, m, ArH) and 2.10 (1H, dd J 9Hz J 2Hz, ArH).

Found: C, 53.8; H, 2.7; N, 6.3%; M^+ 225/223.

$C_{10}H_6ClNO_3$ requires: C, 53.9; H, 2.7; N, 6.2%; M, 223.5.

Dimethyl Quinoline-2,3-dicarboxylate 1-Oxide (292a)

A suspension of the dicarboxylic acid (286d) (0.096 g) in acetonitrile (10.0 ml) was stirred and treated in one portion with a 1% w/v ethereal solution of diazomethane (8.0 ml, 0.002 mol). The solid dissolved after ca. 2 min and nitrogen was evolved. After the nitrogen evolution had subsided a few drops of acetic acid were added to decompose the excess of diazomethane and the solution was evaporated. The residue was triturated with ethyl acetate to give the diester (292a) (0.09 g, 82%), m.p. 180° (from ethyl acetate), $\nu_{max.}$ 1750 and 1728 (CO) cm^{-1}, $\tau(CDCl_3)$ 1.28 (1H, d J 9Hz, ArH), 1.59 (1H, s, ArH), 1.98-2.27 (3H, m, ArH), 5.91 (3H, s, CH_3), and 6.04 (3H, s, CH_3), $\lambda_{max.}$ 247, 257, and 340 nm, (log ε, 4.23, 4.12, and 3.51).

Found: C, 59.8; H, 4.4; N, 5.4%; M^+261

$C_{13}H_{11}NO_5$ requires: C, 59.8; H, 4.2; N, 5.4%; M,261.

Dimethyl 6-Bromoquinoline-2,3-dicarboxylate 1-Oxide (292b)

A suspension of the quinoline dicarboxylic acid (286e) (0.23 g, 0.008 mol) in acetonitrile (10.0 ml) was stirred and treated in one portion with a 2% w/v ethereal solution of diazomethane (10.0 ml). Stirring was continued for 5 min and then glacial acetic acid was added dropwise until effervescence ceased. The solution was evaporated and the residue was crystallised from ethyl acetate to give the diester (292b) (0.16 g, 63%), m.p. 175°, $\nu_{max.}$ 1755 and 1730 (CO) cm^{-1}, $\tau(CDCl_3)$ 1.42 (1H, d $J_{8,7}$ 9Hz, ArH), 1.71 (1H, s, ArH), 1.89 (1H, d $J_{5,7}$ 2Hz, ArH), 2.08 (1H, dd $J_{7,8}$ 9Hz $J_{7,5}$ 2Hz, ArH), 5.92 (3H, s, CH_3), and 6.04 (3H, s, CH_3), $\lambda_{max.}$ 247, 257 sh, 284 sh, and 338 nm, (log $\varepsilon_{max.}$ 4.63, 4.45, 3.92, and 3.81).

Found: C, 46.0; H, 3.0; N, 4.1%; M^+341 and 339.

$C_{13}H_{10}BrNO_5$ requires: C, 45.5; H, 2.8; N, 4.1%; M,340.

The Thermal Decarboxylation of Quinoline-2,3-dicarboxylic Acid 1-Oxide (286d) to Give Quinoline-3-carboxylic Acid 1-Oxide (290a)

The quinoline dicarboxylic acid 1-oxide (286d) (0.46 g, 0.002 mol) was heated under reflux in 20% v/v aqueous ethanol (5.0 ml) for 0.5 h. The solid was collected from the cooled solution to give quinoline-3-carboxylic acid 1-oxide (0.22 g; 57%), m.p. 280° (dec.), identical (m.p. and i.r. spectrum) with a sample prepared before. Evaporation of the filtrate gave only a negligible amount of a brown solid.

The Reduction of Quinoline-3-carboxylic Acid 1-Oxide (290a) by Triethylphosphite to Give Quinoline-3-carboxylic Acid[104] (291)

Quinoline-3-carboxylic acid 1-oxide (290a) (0.2 g) was treated with triethylphosphite (1.0 ml) and heated under reflux for 1 h. The excess of triethylphosphite was distilled off under reduced pressure and the residual gum was treated with saturated aqueous sodium hydrogen carbonate solution. No effervescence occurred and the oil remained insoluble. The aqueous phase was decanted and dilute aqueous sodium hydroxide (2.0 ml) was added to the residual gum which slowly dissolved. Acidification of the alkaline solution with dilute aqueous hydrochloric acid gave quinoline-3-carboxylic acid[104] (291) (0.1 g) m.p. 275° (dec.) (from ethanol-water) lit.,[104] 275° (decomp.), $\nu_{max.}$ 2500br (OH) and 1705br (CO), $\lambda_{max.}$ 214, 237 and 280 nm, (log $\varepsilon_{max.}$ 4.43, 4.67, and 3.73).

Found: C, 68.8; H, 4.0; N, 8.0%; M^+ 173.

Calc. for $C_{10}H_7NO_2$: C, 69.4; H, 4.1; N, 8.1%; M, 173.

The Attempted Catalytic Reduction of Quinoline-2,3-dicarboxylic Acid 1-Oxide (286d)

The dicarboxylic acid (286d) (0.2 g) in ethanol (50.0 ml) was hydrogenated at atmospheric pressure over 10% palladium-charcoal. 36 ml of hydrogen were taken up and the heterogeneous mixture was filtered and evaporated. The gummy residue was triturated with methanol to give a solid (0.16 g), m.p. 260° (decomp.), $\nu_{max.}$ 2570br (OH) and 1740 (CO) cm^{-1}, $M,^{+}$ 217 and 189, which recrystallised from ethanol-water with concomitant decarboxylation to give quinoline-3-carboxylic acid 1-oxide (290a), m.p. 278° (decomp.), $\nu_{max.}$ 2600br (OH) and 1730br (CO).

Found: C, 63.5; H, 3.9; N, 7.4%; M^{+}189

$C_{10}H_7NO_3$ requires: C, 63.5; H, 3.7; N, 7.4%; M,189.

identical (m.p. and i.r. spectrum) with a sample prepared before.

The Attempted Reduction of Quinoline-3-carboxylic 1-Oxide (290a) Acid Using Sodium Dithionite

The quinoline-1-oxide (290a) (0.19 g, 0.001 mol) in 70% v/v aqueous ethanol (5.0 ml) was treated with sodium dithionite (0.19 g)and heated under reflux for 1 h. More sodium dithionite (0.19 g) was added and heating under reflux was continued for a further 1 h after which time the mixture was hot filtered. The filtrate was evaporated and the residue was treated with water (2.0 ml) and made acidic with dilute aqueous sulphuric acid to give the starting material (0.14 g), m.p. 253°, $\nu_{max.}$ 2600br (OH) and 1740br(CO), $M,^{+}$ 189, $C_{10}H_7NO_3$ requires M, 189, identical (i.r. spectrum) with a sample prepared before.

The Attempted Base-Catalysed Cyclisation of 2,3-Dicyano-1-(2'-nitrophenyl) propene (301a and b)

a) Using Ethanolic Sodium Ethoxide

The benzylidene derivative (301a) (0.11 g, 0.0005 mol) was treated

with a solution of sodium (0.01 g) in absolute ethanol (5.0 ml) and the mixture was heated under reflux for 0.5 h. The solvent was evaporated and the residue was treated with water (5.0 ml) and extracted with chloroform to give a gum (0.05 g) from which no identifiable material could be obtained.

The aqueous phase was acidified with dilute aqueous hydrochloric acid and extracted with chloroform to give a brown amorphous solid (0.04 g), $\nu_{max.}$ 2240 (CN), 1650 (CO) and 1530 and 1350 (NO_2) cm^{-1}, which could not be characterised.

No further material was isolated from the reaction.

b) Using Aqueous Ethanolic Sodium Hydroxide

The benzylidene derivative (301b) (0.23 g, 0.001 mol) in ethanol (3.0 ml) was treated with 10% w/v aqueous sodium hydroxide (2.0 ml) and the solution was heated under reflux for 0.5 h. Evaporation of the solution left a dark residue which was treated with water (5.0 ml) and washed with chloroform. Evaporation of the chloroform extract gave only a negligible amount of material.

The aqueous phase was acidified with dilute aqueous hydrochloric acid to give an intractable brown solid (0.11 g), m.p. 215° (dec.) $\nu_{max.}$ 2200br (CN), 1625br (CO) and 1520 and 1340 (NO_2) cm^{-1}, which could not be characterised. Extraction of the aqueous acidic mother liquor with chloroform gave no material.

The Base-Catalysed Cyclisation of 3-(2'-Nitrobenzylidene)-1-phenylsuccinimide (303)

a) Using Aqueous Ethanolic Sodium Hydroxide

The benzylidene derivative (303) (0.6 g, 0.002 mol) in ethanol (10.0 ml) was treated with 10% w/v aqueous sodium hydroxide (5.0 ml) and the solution was heated under reflux for 35 min. The mixture was then

evaporated and the residue was treated with water (10.0 ml) to give on acidification with dilute aqueous sulphuric acid, 3-(N-phenylcarbamoyl) quinoline-2-carboxylic acid 1-oxide (306) (0.4 g; 65%), m.p. 220° (decomp.) $\nu_{max.}$ 3320br (NH), 2600br (OH) and 1680br (CO) cm^{-1}, which dissolved slowly in sodium hydrogen carbonate solution and on attempted crystallisation from ethanol-dimethylformamide or ethanol-acetic acid gave quinoline-3-(N-phenylcarboxamide) 1-oxide (307), m.p. 267°, $\nu_{max.}$ 3250 and 3200 (NH), and 1680 (CO) cm^{-1}, $\lambda_{max.}$ 212, 238, 254, and 315 nm (log $\varepsilon_{max.}$ 4.29, 4.54, 4.40, and 4.10), τ $(CD_3)SO$ -0.85 (1H, br s, NH), 1.04 (1H, d J 3Hz, Arh), 1.55 (1H, d J 3Hz, ArH) and 1.77-2.90 (9H, m, ArH).

Found: C, 73.0; H, 4.6; N, 10.3%; M^+ 264.

$C_{16}H_{12}N_2O_2$ requires: C, 72.7; H, 4.6; N, 10.6%; M, 264.

b) Using Ethanolic Sodium Ethoxide

The benzylidene derivative (303) (0.61 g, 0.002 mol) in absolute ethanol (5.0 ml) was treated with a solution of sodium (0.18 g) in absolute ethanol (10.0 ml) and heated under reflux for 20 min. The mixture was cooled to give a solid which was collected and treated with dilute aqueous hydrochloric acid. The resulting solid was combined with a second crop obtained by washing the filtrate with chloroform and then acidifying the aqueous phase with dilute aqueous hydrochloric acid to give an intractable product (total 0.15 g), m.p. 255° (dec.), $\nu_{max.}$ 3360br (OH) and 1640br (CO) which could not be characterised. Extraction of the aqueous phase with chloroform gave only a neglibible amount of gum.

The original chloroform layer was evaporated to give a gum which was triturated with ether to afford a brown intractable solid (0.25 g), m.p. 160° (dec.), $\nu_{max.}$ 3300br (OH) and 1650br(CO) cm^{-1}.

c) Using Triethylamine

The benzylidene derivative (303) (0.61 g, 0.002 mol) in ethanol (10.0 ml) was treated with triethylamine (0.3 ml) and the solution was heated under reflux for 5 h. The solution was evaporated and the residue was treated with water (10.0 ml) and extracted with chloroform. The insoluble solid (0.06 g) was collected and crystallised to give 2,3-dihydro-2-phenyl-1H-pyrrolo[3,4-b]quinoline-1,3-dione (305) m.p. 320° (from dimethylsulphoxide), $\nu_{max.}$ 1780w and 1720 (CO) cm^{-1}.

Found: C, 70.4; H, 3.6; N, 9.7%; M^+290.

$C_{17}H_{10}N_2O_3$ requires: C, 70.3; H, 3.5; N, 9.7%; M,290.

The chloroform layer was evaporated to leave a brown foam (0.55 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture from which no identifiable material could be isolated.

The Attempted Base-Catalysed Cyclisation of 3-(2'-Nitrobenzylidene) succinimide (309)

a) Using Aqueous Ethanolic Sodium Hydroxide

The benzylidene derivative (309) (0.7 g, 0.003 mol) in ethanol (10.0 ml) was treated with 10% w/v aqueous sodium hydroxide (5.0 ml) and the solution was heated under reflux for 0.5 h. The solution was then evaporated and the residue was treated with water (5.0 ml) and washed with chloroform. An unidentified insoluble solid (0.03 g) was collected, m.p. 342° (from water-dimethylformamide), $\nu_{max.}$ 3340 and 3160 (NH_2), and 1650 (CO) cm^{-1}.

Found: C, 73.0; H, 4.3; N, 16.2%; M^+261

$C_{16}H_{11}N_3O$ requires: C, 72.6; H, 4.2; N, 16.1%; M,261.

Evaporation of the chloroform extract gave no material.

The aqueous phase was acidified with dilute aqueous hydrochloric acid to give an intractable solid (0.1 g), m.p. 175° (dec.), $\nu_{max.}$ 3300br

and 3095br (NH) and 1715br and 1660br (CO) cm^{-1}, whose t.l.c. in ethyl acetate over silica showed it to be a mixture of several close-running components which was not further investigated.

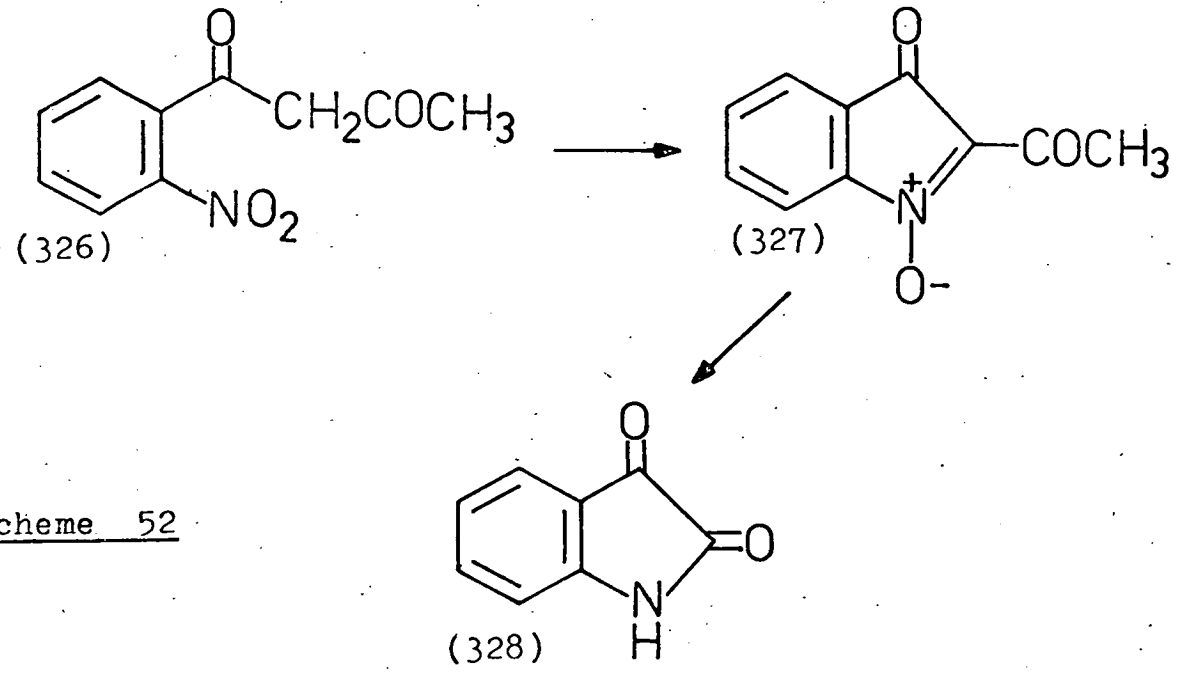
On standing, an unidentified solid (0.03 g) precipitated from the aqueous acidic mother liquors, m.p. 235°, $\nu_{max.}$ 3420 and 3300 (NH_2), and 1735 and 1675 (CO) cm^{-1}. Attempts to purify this solid for further investigation were unsuccessful. Neutralisation of the aqueous acidic phase with solid sodium acetate and extraction with chloroform gave no further material.

b) Using Triethylamine

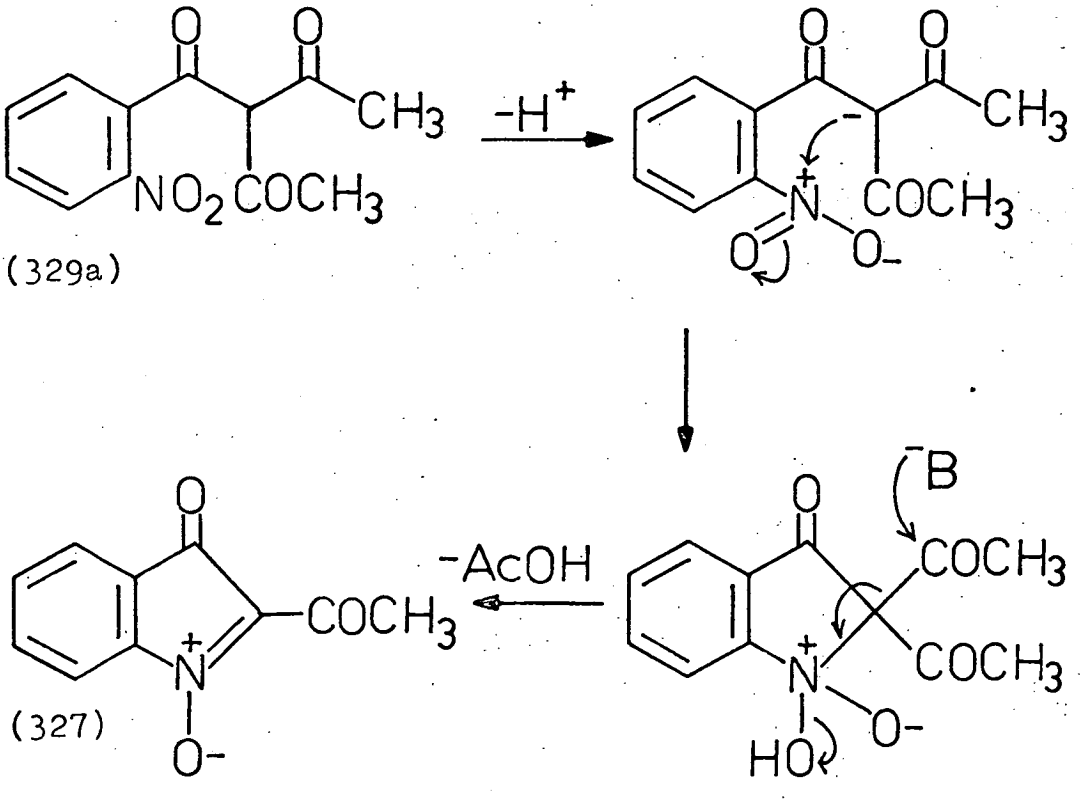
The benzylidene derivative (309) (0.32 g, 0.002 mol) in absolute ethanol (10.0 ml) was treated with triethylamine (0.3 ml) and the solution was heated under reflux for 1 h. The resulting red solution was then evaporated and the residual gum was triturated with methanol to give an unidentified yellow solid (0.03 g), m.p. 270° (decomp.) $\nu_{max.}$ 3180br (NH), and 1750w and 1700 (CO) cm^{-1}. The methanol mother liquors were evaporated to give an intractable foam (0.2 g) which decomposed to a tar on attempted purification.

Chapter 3

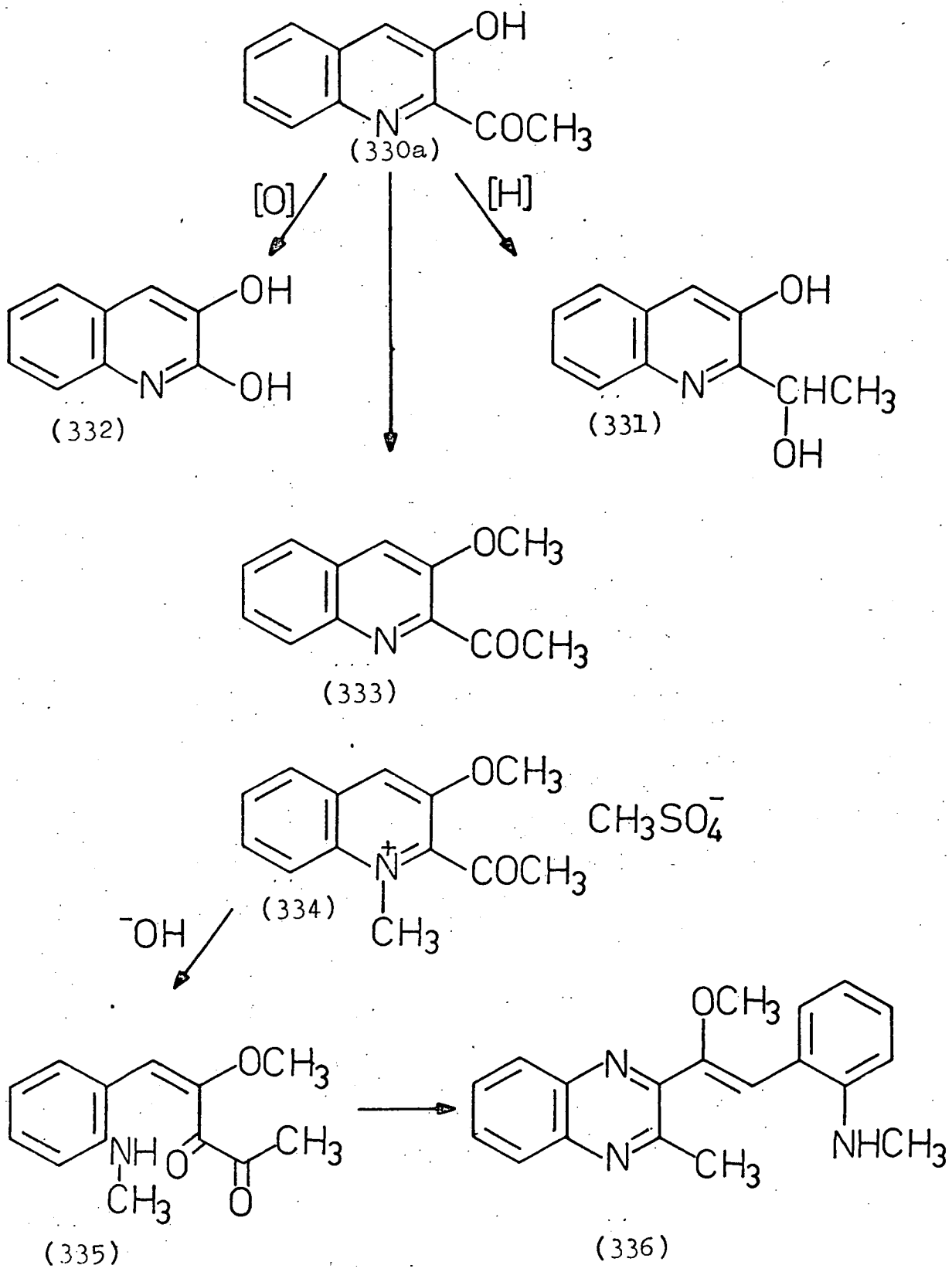
Extensions of the Base-Catalysed Cyclisation of 3-(2'-Nitrobenzoyl)pentane-2,4-dione to 2-Acetyl-3-hydroxyquinoline. - A Novel Variant of the Smiles Rearrangement



Scheme 52

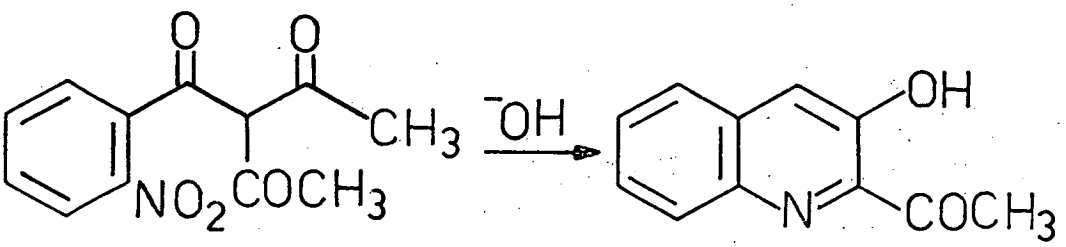


Scheme 53


OH
N
COCH3
(330a)
[O]
[H]
OH
N
OH
(332)
OH
N
CHCH3
OH
(331)
OCH3
N
COCH3
(333)
OCH3
CH3SO4
N+
COCH3
CH3
(334)
-OH
OCH3
NH
O
CH3
CH3
O
(335)
OCH3
N
N
CH3
NHCH3
(336)

Scheme 54

2-Nitrobenzoylacetone (326) has been shown[118] to undergo base-catalysed cyclisation to isatin [(328); Scheme 52] in a process which is readily explained[118] by the intermediate formation of 2-acetylisatogen (327). In a subsequent study designed to develop this type of cyclisation into a new synthesis of isatogens, Bayne[119] synthesised 3-(2'-nitrobenzoyl)pentane-2,4-dione (329a) and studied its base-catalysed cyclisation in the hope that the acidic methine centre present in the side-chain would permit the cyclisation to be carried out using mildly basic conditions under which the sensitive isatogen [(327); Scheme 53] could be isolated. In practice however, Bayne[119] found that the triketone (329a) was converted, not into the isatogen (327), but into a product which he subsequently identified as 2-acetyl-3-hydroxyquinoline (330a) on the basis of the following evidence (Scheme 54).

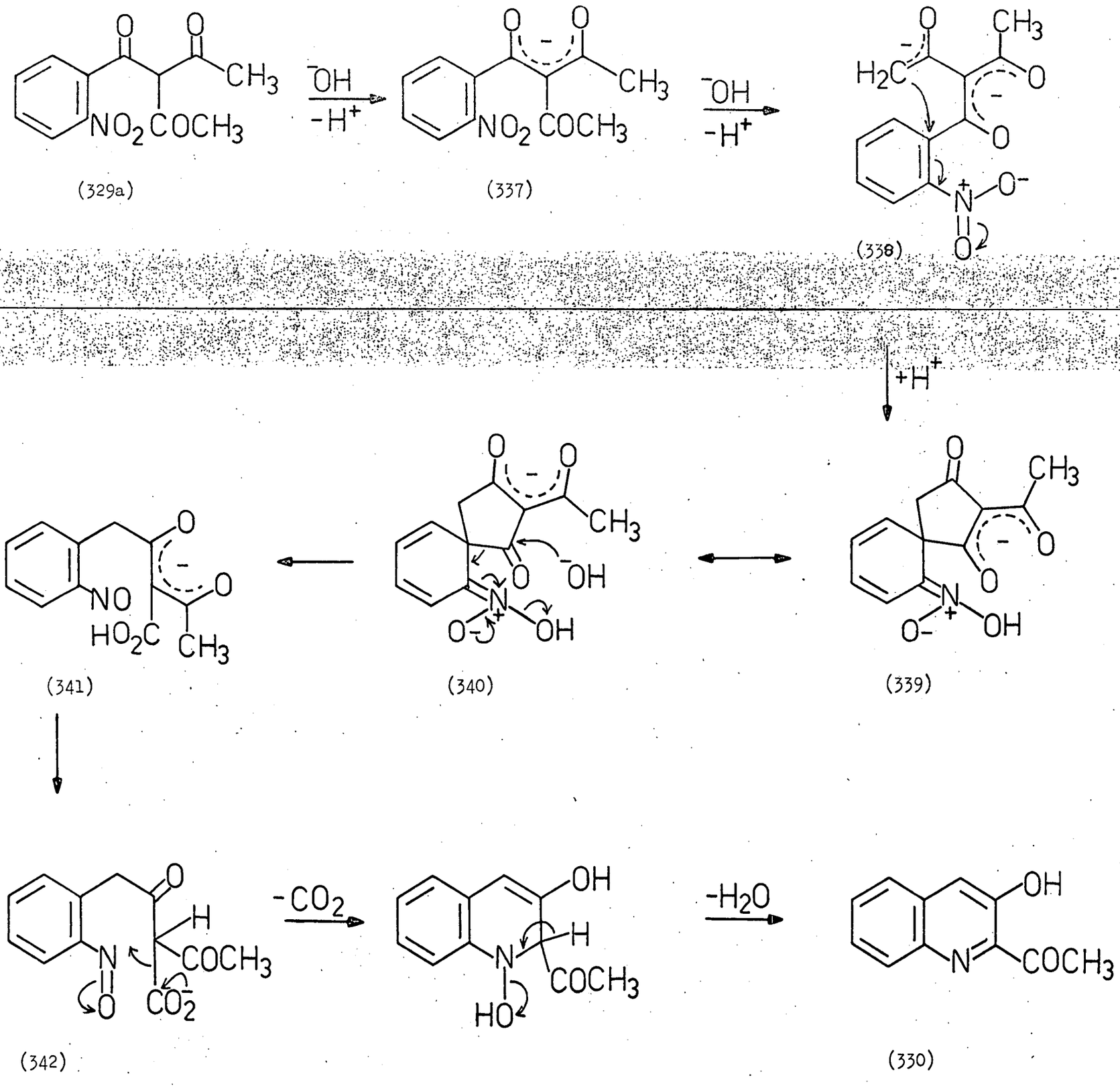


(329a) (330a)

(a) The product of the base-catalysed cyclisation of the triketone (329a) gave analytical, i.r., u.v., ^{1}H n.m.r., and mass spectral data consistent with the structure (330a)

(b) Its acidity and formation of an acetoxy-derivative were consistent with the presence of the 3-hydroxyl group.

(c) Its formation of a hydrazone derivative and its reduction to an ethanol derivative (331) were consistent with the presence of an acetyl group.



Scheme 55

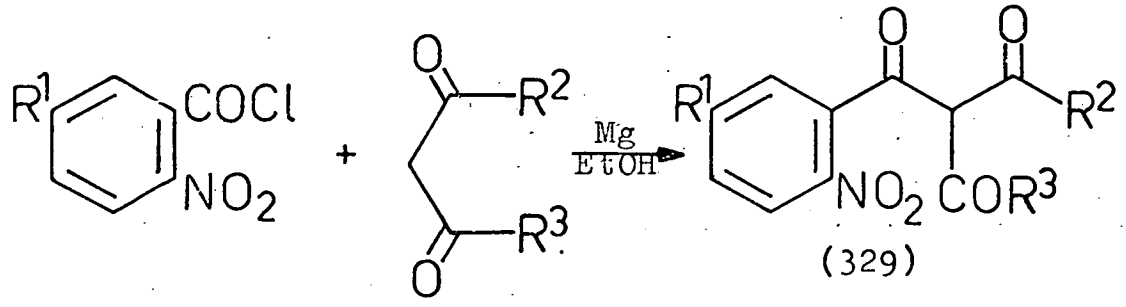
(d) Its oxidation to 2,3-dihydroxyquinoline (332) established the presence of the quinoline nucleus.

(e) On methylation, a mixture of a mono-methoxy derivative (333) and a methoxy-N-methylquinolinium methosulphate (334) was obtained. The latter underwent ring-opening to the diketone (335) which was characterised as the quinoxaline derivative (336).

The mechanism proposed[119] for the transformation of 3-(2'-nitrobenzoyl)pentane-2,4-dione (329a) into 2-acetyl-3-hydroxyquinoline (330a) is shown in Scheme 55. The enolate anion (337) is initially formed but nucleophilic attack on the nitro group does not occur because the anion is too stable to react, being delocalised throughout the tricarbonyl system. However, under the strongly basic conditions present, formation of the dianionic intermediate (338) is postulated. Attack at the nitro group by the more localised enolate anionic centre in (338) is not sterically favourable as this would involve the formation of a seven-membered cyclic intermediate. Consequently, alternative nucleophilic attack at the C-(1) position of the ring occurs to give the spiro intermediate (339) in an analogous fashion to the well known Smiles rearrangement.[120] However, unlike the usual intermediate in a Smiles rearrangement,[120] the spiro intermediate (339) has no suitable leaving group available to allow rearomatisation with retention of the intact nitro group. Consequently, nucleophilic attack by hydroxide ion at the benzoyl carbonyl group occurs with subsequent ring-opening and concomitant reduction of the nitro group to nitroso [Scheme 55; (339) → (340) → (341)] to give the carboxylate intermediate (342). This then undergoes decarboxylation and cyclisation to afford the quinoline (330a).

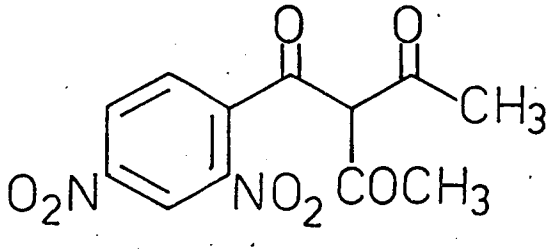
The conversion of the tricarbonyl compound (329a) in high yield, into the quinoline (330a) represents a new and potentially general route

Scheme 56

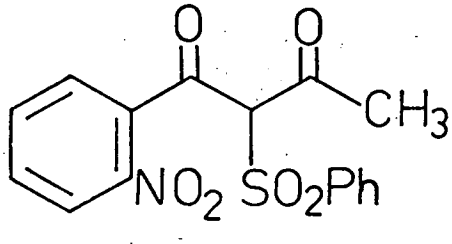


(329)

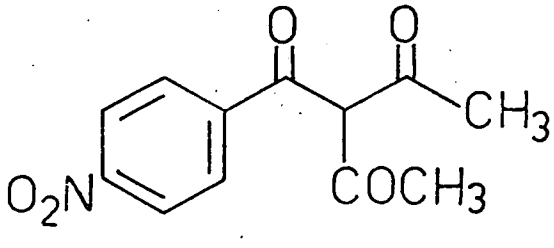
(329)	R^1	R^2	R^3	Yield %
a;	H	CH_3	CH_3	62
b;	CH_3	CH_3	CH_3	69
c;	Cl	CH_3	CH_3	47
d;	H	CH_3	Ph	72
e;	H	CH_3	NHPh	42
f;	H	CH_3	OC_2H_5	49
g;	H	C_2H_5	C_2H_5	32



(343)



(344)

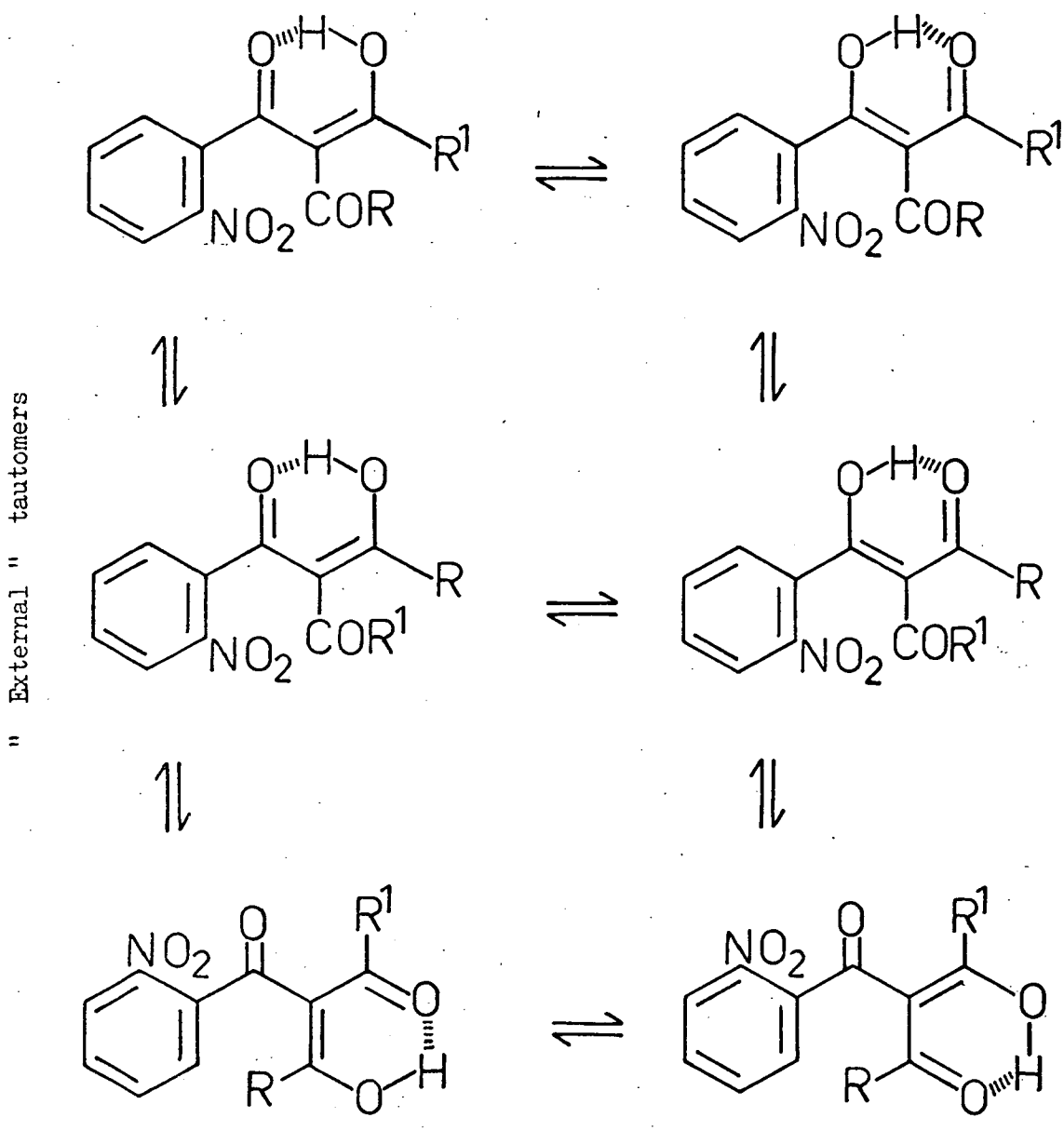


(345)

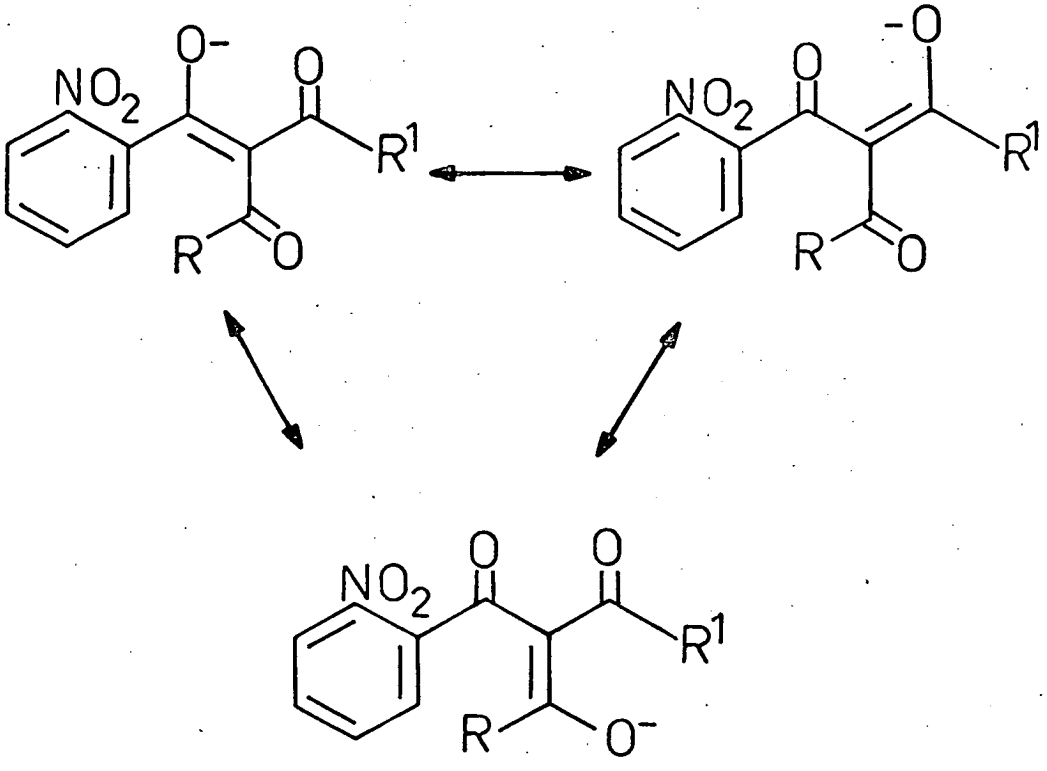
to otherwise inaccessible 3-hydroxyquinoline derivatives[121] as well as an entirely new and interesting mechanistic variant of the Smiles rearrangement. Consequently, it was of interest to investigate further, the scope of such cyclisations and to seek evidence for their detailed mechanism.

The synthesis of the 2-nitrobenzoylacetone derivatives (329 a, b and d) was initially approached using the method of Louden and Wellings.[122] However, the present author found this method - (involving the sodium ethoxide-catalysed condensation of 2-nitrobenzoyl chloride with β-dicarbonyl compounds) - unsatisfactory due to ethanolysis of the acid chlorides with consequent low yields of the desired products. In contrast to the result reported by Bayne,[119] a reinvestigation of the method of Reynolds and Hauser[123] proved it readily applicable to the synthesis of a variety of 2-nitrophenyl-tricarbonyl compounds. This method was found to be more convenient than the Loudon-Wellings method[122] giving comparatively better yields of the tricarbonyl derivatives which were obtained directly from the reaction mixtures, in a pure crystalline state. The reduced formation of undesirable ester derivatives in these magnesium enolate reactions adapted from the method of Reynolds and Hauser,[123] is in part due to the smaller quantities of ethanol, in proportion to acid chloride, present in the mixtures. Thus the 2'-nitrobenzoylacetone derivatives (329a-f) and (343)-(345) (Scheme 56) were obtained in moderate to good yield using the magnesium enolate method.[123] The magnesium enolate of heptane-3,5-dione was also condensed with 2-nitrobenzoyl chloride to give 4-(2'-nitrobenzoyl)heptane-3,5-dione (329g) in moderate yield.

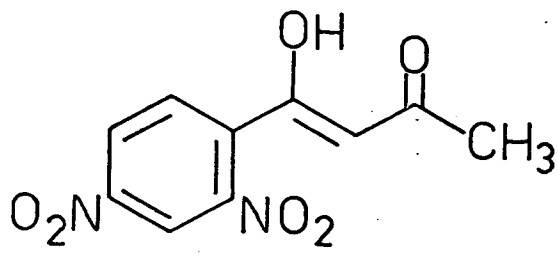
Although the synthesis of 3-(2',4'-dinitrobenzoyl)pentane-2,4-dione (343) was successful using the magnesium enolate method,[123] the cyclisation of this compound could not be studied as it was found to undergo facile solvolysis of an acetyl group on attempted recrystallisation to afford 2,4-dinitrobenzoylacetone (346).



Scheme 57

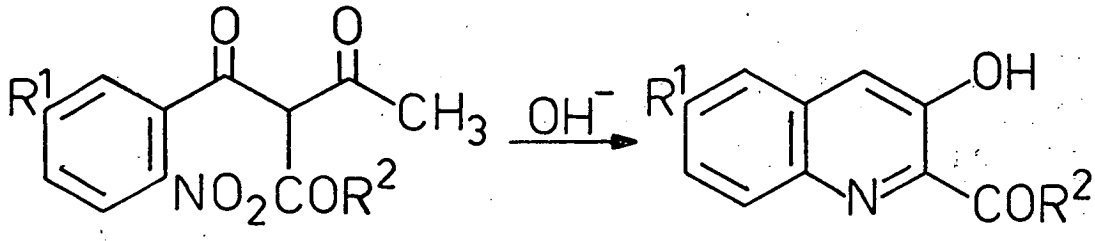


Scheme 58



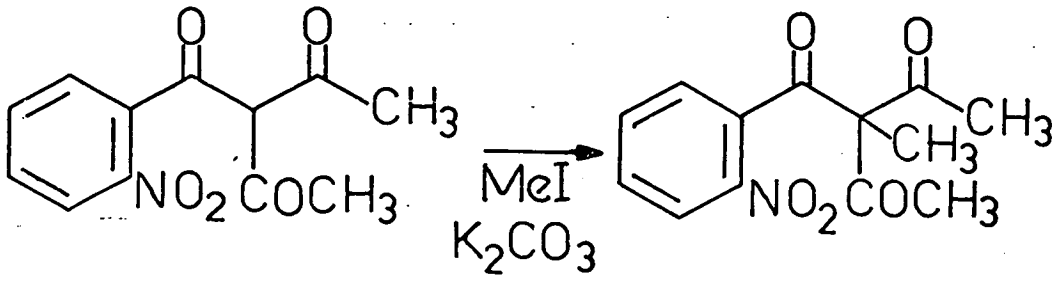
(346)

Characteristically,[124] the β,β'-tricarbonyl derivatives in question and the benzenesulphonyldicarbonyl derivative (344) showed a very low field resonance in their ^{1}H n.m.r. spectra (ca τ-7.5; δ 17.5), attributed to the formal methine proton. This would indicate that, in solution at least, the tricarbonyl derivatives (329) and the benzenesulphonyl derivative (344) exist in one or more of the six possible tautomeric, hydrogen-bonded, enolic forms (Scheme 57). Thus, the low chemical shift of the methine proton reflects to some extent, its acidity. This observation supports the hypothesis that the anion (337) of the tricarbonyl derivative (329a) would not be very nucleophilic as it would be greatly stabilised by delocalisation throughout the tricarbonyl system (Scheme 58). However, 3-(2'-nitrobenzoyl)pentane-2,4-dione (329a) did show a degree of nucleophilicity at the tertiary carbon atom towards methyl iodide in the presence of carbonate ion and afforded 3-methyl-3-(2'-nitrobenzoyl) pentane-2,4-dione (347) in high yield (83%). The ^{1}H n.m.r. spectrum of the methylated derivative (347) showed a high field methyl resonance a τ 8.35 which excludes the possibility of methylation having occurred at oxygen as the signal is higher than the typical values for a methoxyl resonance.



(329)	R^1	R^2	(330)	R^1	R^2	Yield%
a;	H	CH_3	a;	H	CH_3	73
b;	CH_3	CH_3	b;	CH_3	CH_3	59
c;	Cl	CH_3	c;	Cl	CH_3	65
d;	H	Ph	d;	H	Ph	12.5

Scheme 59

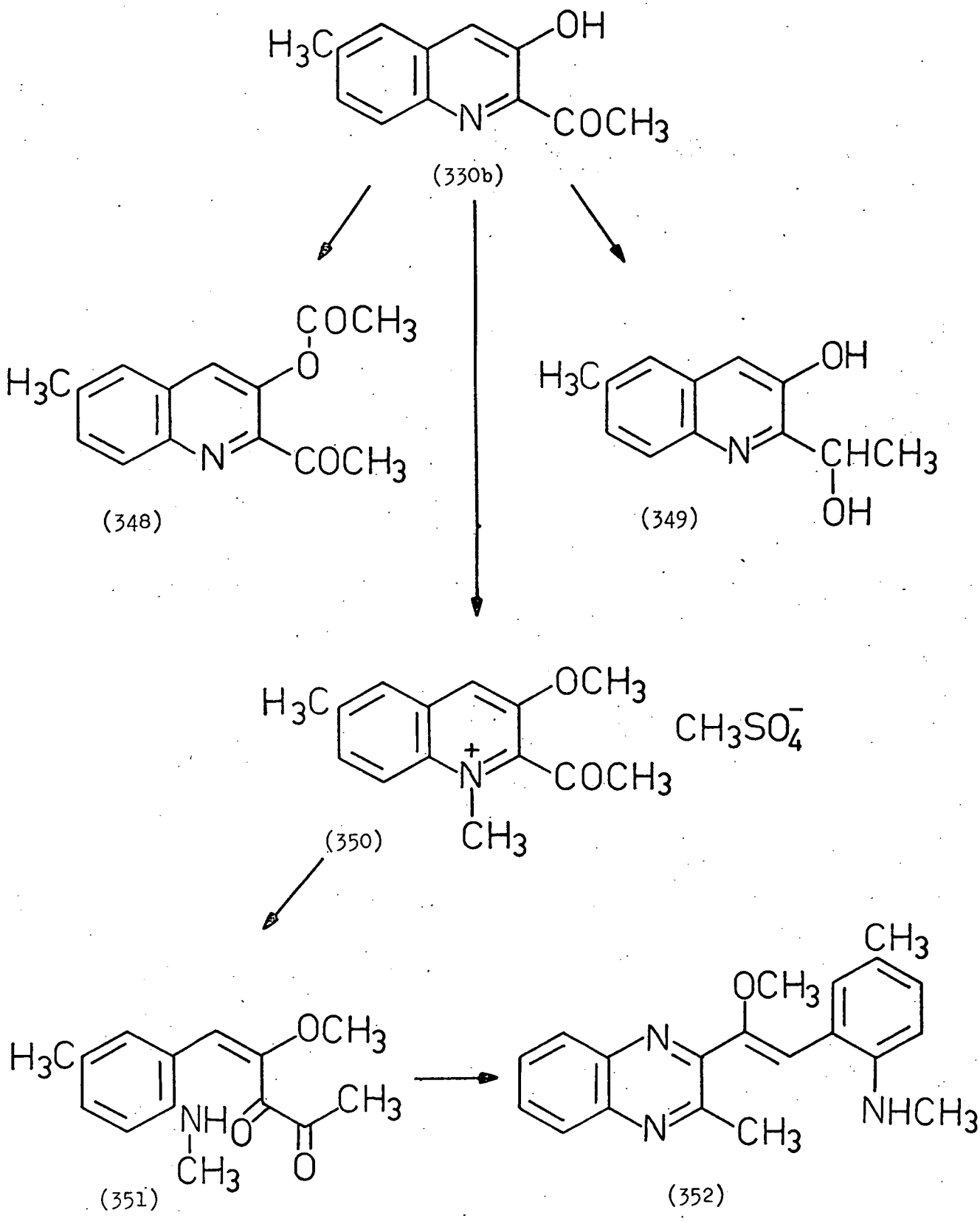


(329a) (347)

The base-catalysed formation of 2-acyl-3-hydroxyquinolines was initially extended to the cyclisation of the 2'-nitrobenzoylpentanedione (329b) to 2-acetyl-3-hydroxy-6-methylquinoline [Scheme 59; (330b)] and the cyclisation of the 2-nitrobenzoylpentanedione (329a) to 2-acetyl-3-hydroxyquinoline (330a) was also reinvestigated. The present author found that upon acidification of the reaction mixtures, effervescence of carbon dioxide occurred and the quinolines (330 a and b) were obtained as amorphous solids which contained inorganic material and from which the quinolines were obtained in good yields, and in a relatively pure form, by virtue of their solubility in light petroleum. The 6-methylquinoline derivative (330b) gave elemental and spectral data in accord with the assigned structure. In particular its ^{1}H n.m.r. spectrum showed a phenolic hydroxyl resonance at τ-1.00. The signal at τ 2.15 which shows ortho coupling (J 7Hz) is assigned to the H-(8) protons and the multiplet centred at τ 2.62 is assigned to the remaining three aromatic protons. Two resonances at τ 7.16 and τ 7.15 are assigned to the acetyl and aromatic methyl groups respectively.

Analogous to the reactions of 2-acetyl-3-hydroxyquinoline (330a) described by Bayne,[118] 2-acetyl-3-hydroxy-6-methylquinoline (330b) underwent; (i) - monoacetylation in acetic anhydride to give 3-acetoxy-2-acetyl-6-methylquinoline (348), (ii) - reduction by sodium dithionite to afford 3-hydroxy-2-(α-hydroxyethyl)-6-methylquinoline (349), and

Scheme 60



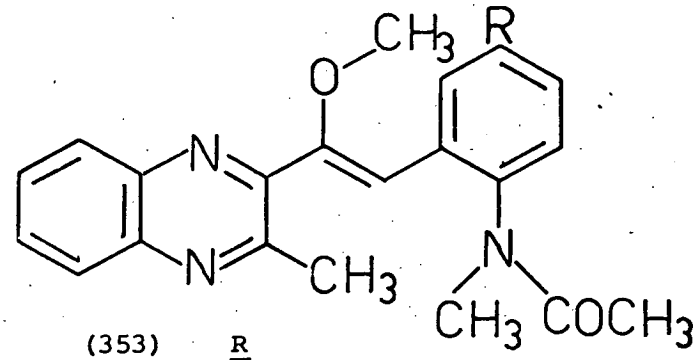
(iii)-methylation in the presence of dimethyl sulphate to give 1,6-dimethyl-3-methoxyquinolinium methosulphate (350) (cf. Scheme 60). The derivatives (348)-(350) gave analytical and spectral data consistent with their assigned structures.

The degradation of the methosulphate salt (350) by cold aqueous alkali afforded a foam which is assigned the α-dicarbonyl structure (351) on the basis of its i.r. spectrum. Whereas Bayne[119] reported the α-diketone derivative (335)[119] to show a ^{1}H n.m.r. spectrum consistent with its assigned structure, that of the α-diketone derivative (351) showed an ambiguous ^{1}H n.m.r. spectrum from which no specific structural inferences could be made. Since the structures of these α-diketones (335) and (351) are important in relation to providing further support for the structures of the 2-acyl-3-hydroxyquinolines (330a and b), it was decided to seek chemical evidence for their constitution. An attempt to acetylate the N-methylamino function of the α-dicarbonyl derivative (335) proved unsuccessful and the reaction of both (335) and (351) with aqueous acids failed to produce any characterisable material which might have been expected from cleavage of the enol-ether function of these α-dicarbonyl compounds. However, the α-dicarbonyl compound (351) was characterised by its reaction with ortho-phenylenediamine to give the quinoxaline derivative (352). As in the case of the quinoxaline derivative (336) obtained from the α-diketone derivative (335) by Bayne[119] and the present author, the ^{1}H n.m.r. spectrum of the quinoxaline derivative (352) showed it to be a mixture of two isomers. This isomerism was attributed, by Bayne[119] to the existence of two conformers resulting from steric crowding within the molecule. However, variable temperature ^{1}H n.m.r. spectroscopy of the quinoxaline derivative (336) showed a change in the ratio of isomers from 2:1 at 25° to 5:1 at 60° in favour of the conformer having the methyl signals at τ6.14, 7.22 and 7.48. No changes in the

chemical shifts of the individual methyl signals were observed on heating from 25° to 60°. This absence of any coalescence or broadening of the methyl signals on heating from 25° to 60°, is inconsistent with a simple conformational change. On cooling the solution at 60° to 25° the isomer ratio of 2:1 was restored showing that no chemical change had occurred on heating the quinoxaline derivative (336).

In accord with the presence of a methylamino function, both quinoxaline derivatives (336) and (352) underwent reaction with acetic anhydride to give the mono-acetylated quinoxaline derivatives (353 a and b), respectively.

(336) or (352) $\xrightarrow{Ac_2O}$



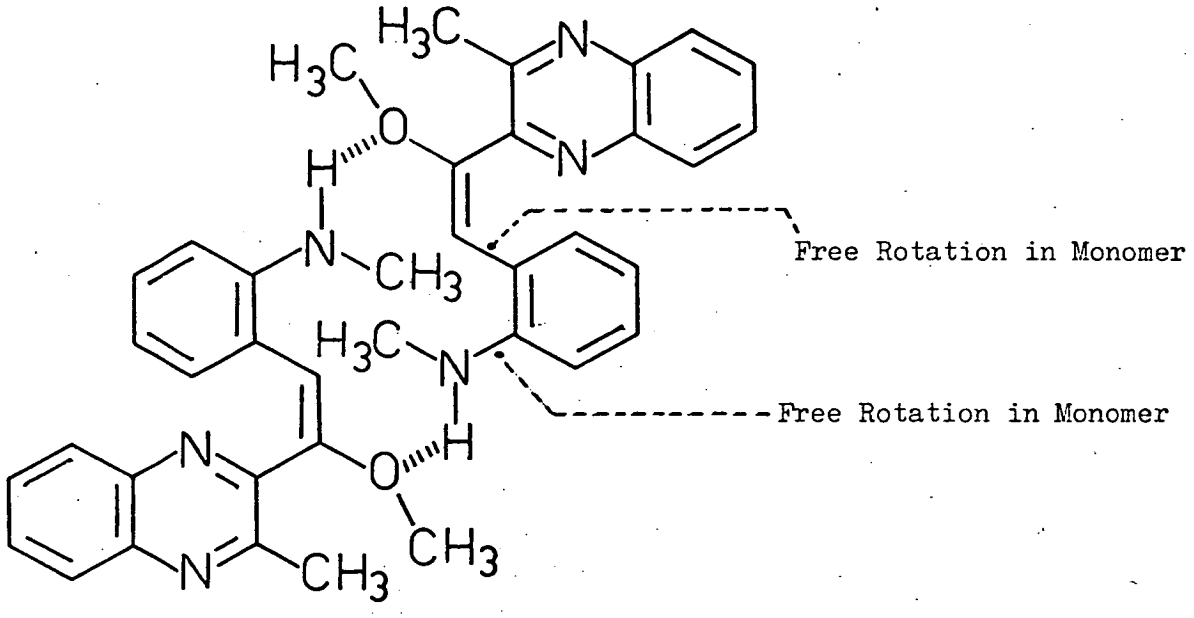
(353) R

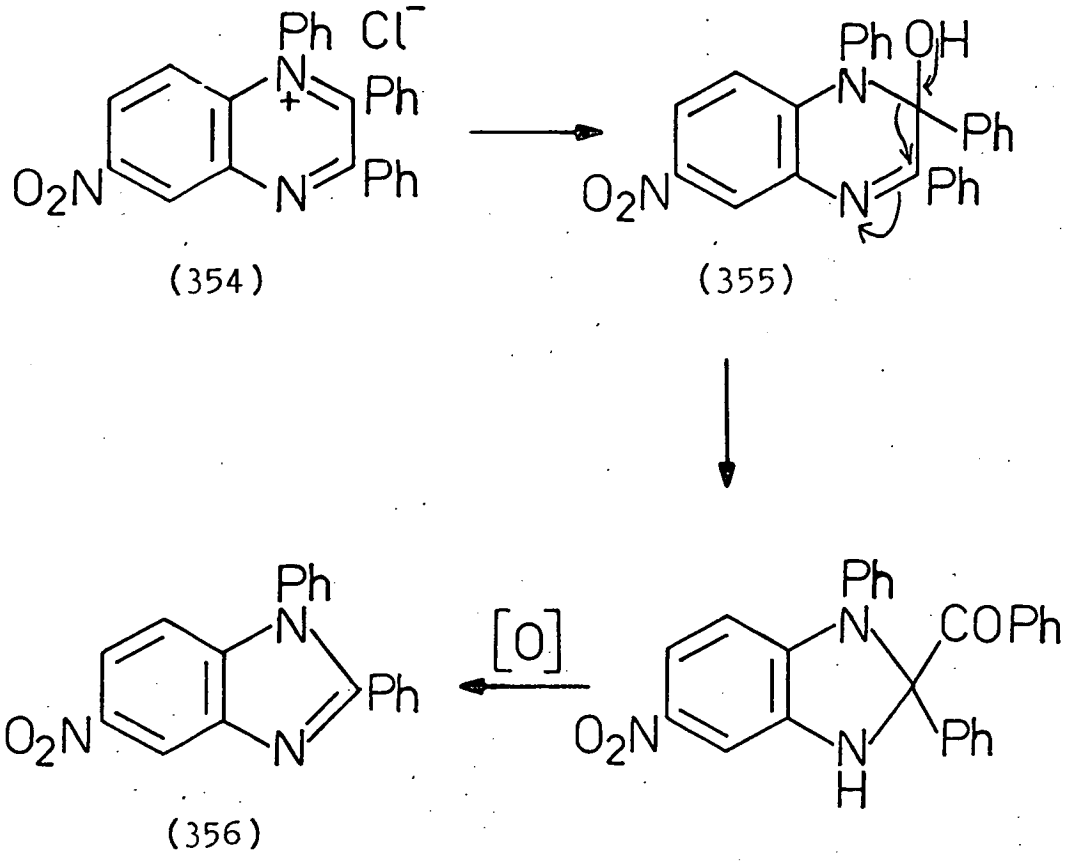
a; H

b; CH_3

These products gave analytical and mass spectral data in accord with their assigned formulae. The i.r. spectra of the acetylated quinoxaline derivatives (353) showed an absence of bands attributable to NH stretching modes but did show bands attributable to amide carbonyl absorptions. In contrast to the ^1H n.m.r. spectrum of the quinoxaline derivatives (336) and (352) that of the acetylated quinoxaline derivatives (353a) and (353b) showed only the presence of a single isomer having four methyl group singlet resonances at τ 6.11,6.70,7.33, and 8.06 and five methyl signals at τ 6.15, 6.85, 7.40, 8.16 and 8.23, respectively. This would suggest that in the non-acetylated quinoxaline derivatives (336) and (352) intramolecular hydrogen-bonding between the amine and methoxy

Scheme 61

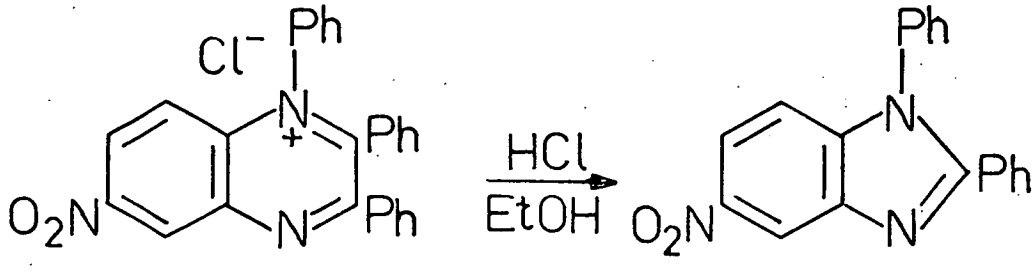



Ph Cl⁻
N⁺
Ph
O₂N
N
Ph
(354)
Ph OH
N
Ph
O₂N
N
Ph
(355)
Ph
N
CO Ph
O₂N
N
H
Ph
[O]
Ph
N
Ph
O₂N
N
(356)

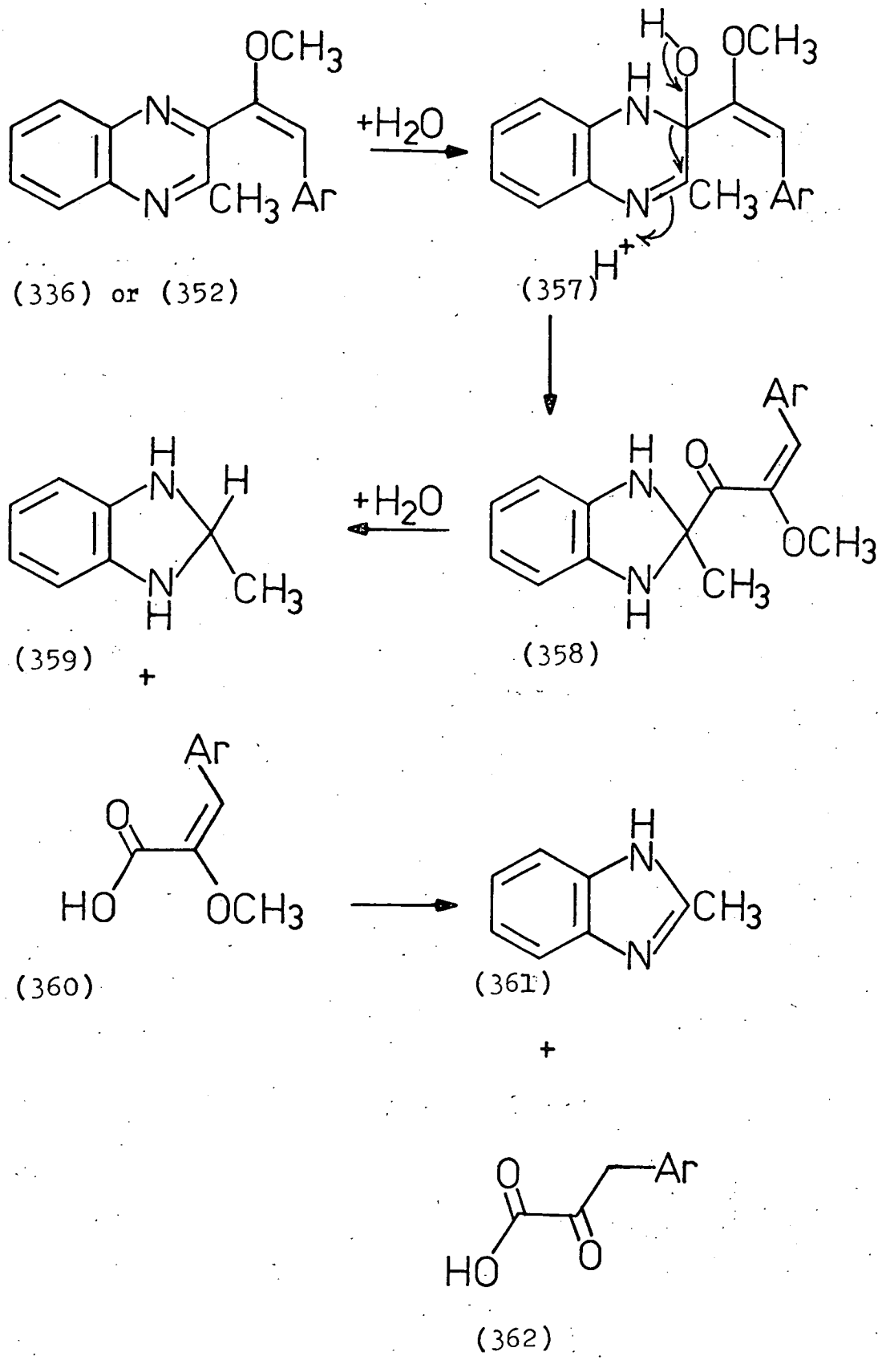
Scheme 62

groups, contributes to the stabilisation of a single conformer existing in equilibrium with other conformers which are not hydrogen-bonded and can thus exhibit free rotation about the bonds indicated in Scheme 61. Since the capacity for hydrogen-bonding is removed upon acetylation of the amine functions, the acetylated quinoxaline derivatives (353a and b) exist in any number of conformers produced by free rotation about the C-C and C-N single bonds in the molecule and thus, only one averaged structure is observed in their ^{1}H n.m.r. spectra.

In an attempt to further establish the structures of the quinoxaline derivatives (336) and (352), it was decided initially, to investigate their acid-catalysed degradation. Thus, in hot 20% w/v aqueous sulphuric acid both quinoxaline derivatives (336) and (352) unexpectedly afforded the same product which gave analytical and mass spectral data and showed properties consistent with the known compound[125] 2-methylbenzimidazole (361). The benzimidazole (361) must arise by a ring-contraction of the quinoxaline moiety of the quinoxaline derivatives (336) and (352). Although ring-contractions of quinoxalines to benzimidazoles are rare, a few examples[126] are known. Thus, (Scheme 62) the quinoxaline derivative (354) is converted, in ethanolic hydrogen chloride solution into 1,2-diphenylbenzimidazole (356).[127] A similar transformation (Scheme 63) may be envisaged for the



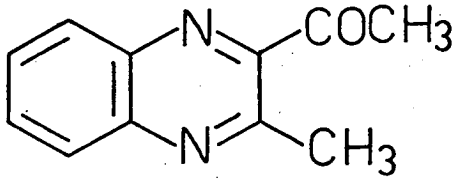
(354) (356)


OCH3
N
N
CH3 Ar
+H2O
H
O
OCH3
H
N
N
CH3 Ar
H+
(336) or (352)
(357)
Ar
H
N
O
OCH3
N
CH3
H
+H2O
H
N
H
N
CH3
H
(359)
+
(358)
Ar
O
HO
OCH3
(360)
H
N
CH3
N
(361)
+
O
Ar
HO
O
(362)

Scheme 63

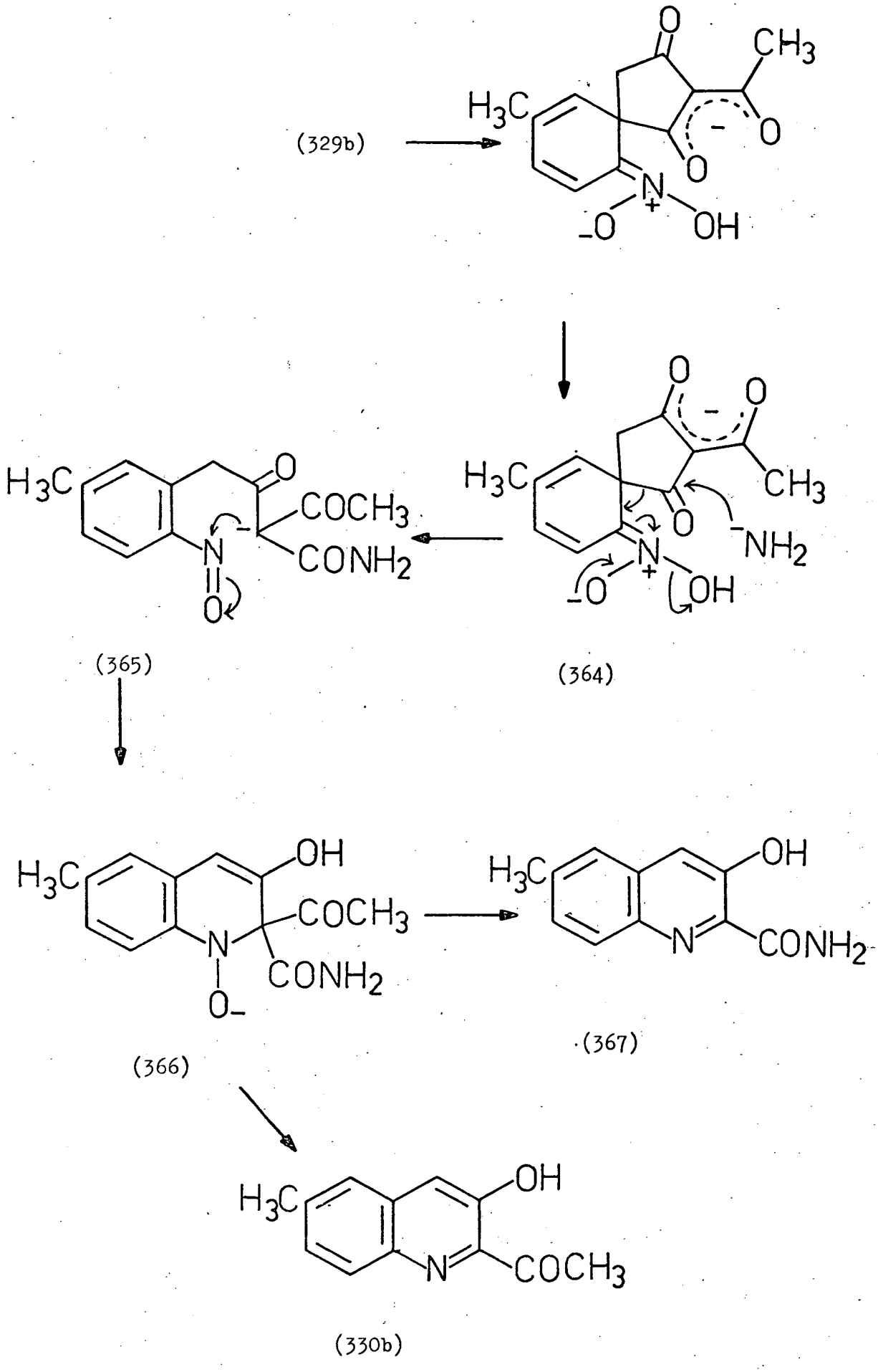
conversion of the quinoxaline derivatives (336) and (352) into 2-methylbenzimidazole (361). Initial hydration of the C=N in the quinoxaline ring to give the intermediate (357), followed by ring contraction would afford the dihydrobenzimidazole derivative (358). Loss of the side-chain by solvolysis (akin to the loss of the benzoyl group as ethyl benzoate in the analogous case depicted in Scheme 63) followed by oxidation, either aerially or perhaps by sulphate ion, would afford 2-methylbenzimidazole (361). However, the other fragment (362) produced in this process, could not be isolated. An attempt to effect the degradation of the quinoxaline (336) in a mixture of acetyl chloride and acetic acid and hence to trap any fragment of the type (362) by acetylation failed, only intractable gums being isolated. The attempted degradation of the quinoxaline derivative (336) using aqueous hydrochloric acid gave only unreacted starting material.

In an attempt to simulate the acid-catalysed ring contraction of the quinoxalines (336) and (352) to 2-methylbenzimidazole[125] (361), the effect of hot aqueous acid on the known compound[128] 2-acetyl-3-methyl-quinoxaline (363) was investigated. This substrate was chosen as a model because of its formal structural similarity to the more complex quinoxalines (336) and (352). In practice however, the model quinoxaline (363) was unaffected by heating with 20% w/v aqueous sulphuric acid.



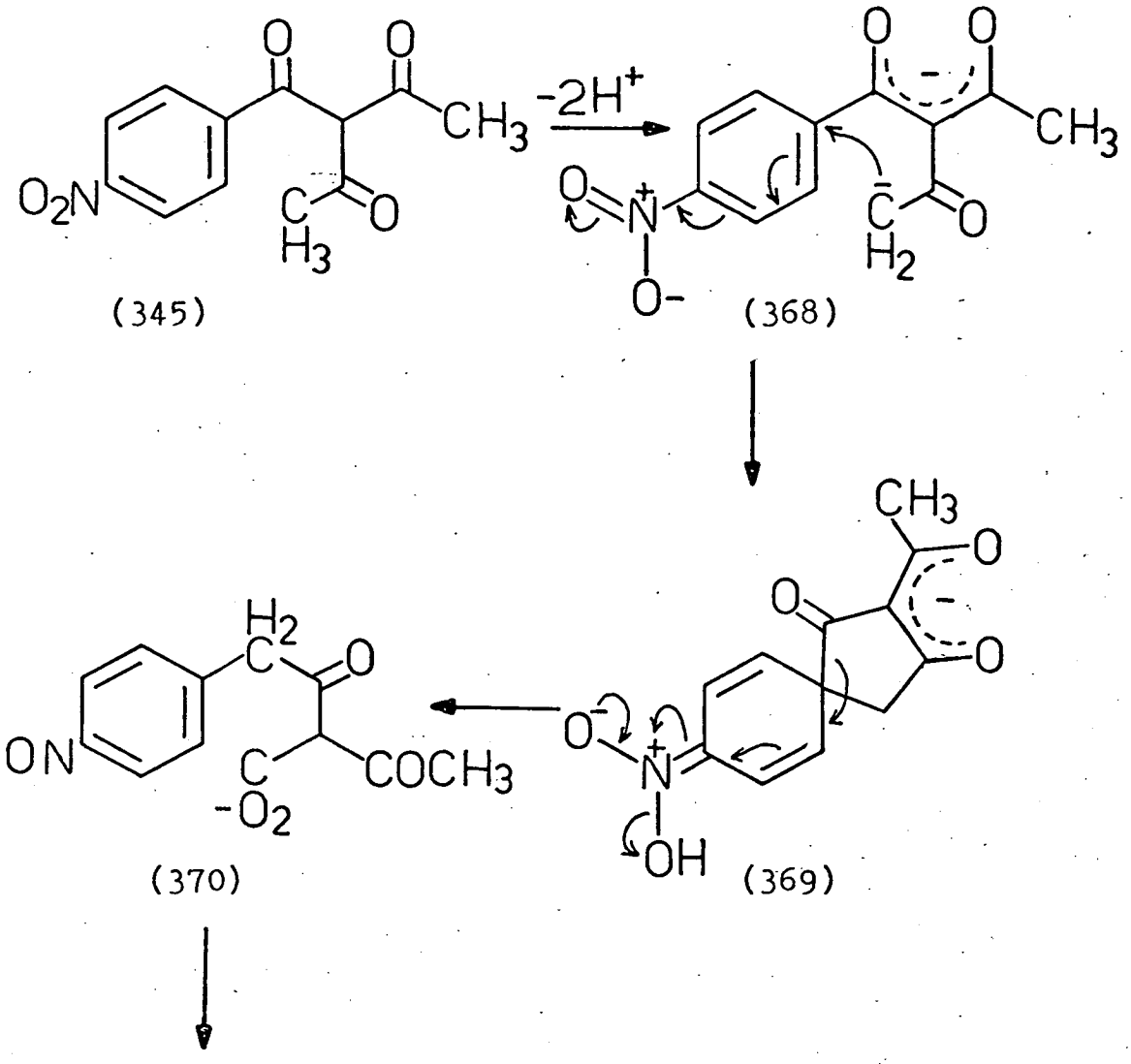
(363)

Scheme 64

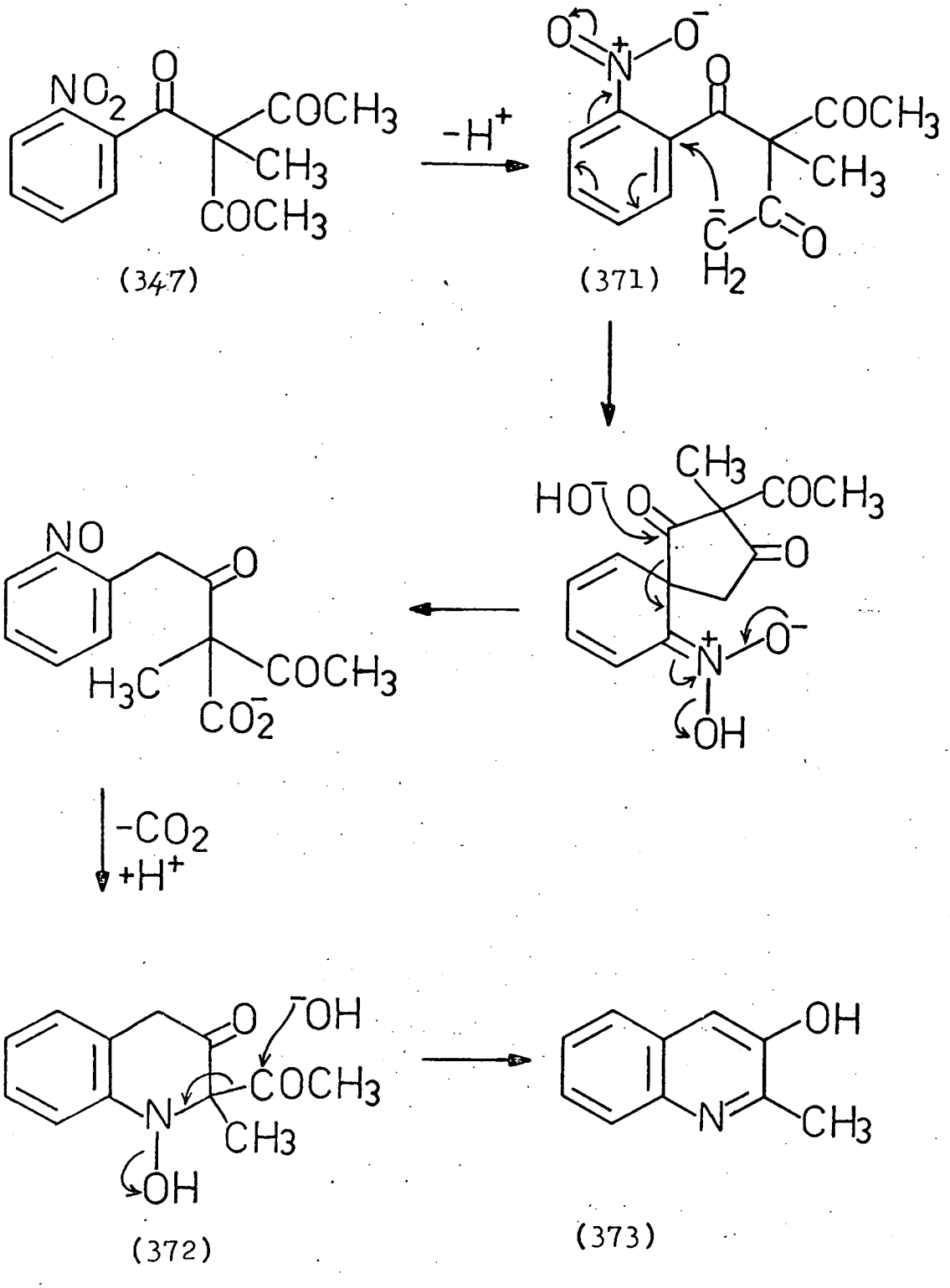


In a further attempt to degrade the complex quinoxaline derivative (352) into a simpler quinoxaline, its behaviour towards oxidation was studied. However, the attempted chromic acid or peracid oxidation of (352) led to ill-defined solids which could not be characterised.

As already discussed, the mechanism (Scheme 55) proposed for the base-catalysed cyclisation of the 3-(2'-nitrobenzoyl)pentane-2,4-dione derivatives (329a and b) involves the generation of a dianion (338) as the reactive intermediate. Consequently, it was decided to investigate the use of sodamide as the basic catalyst. Since it is known[129] that sodamide deprotonates acetylacetone to give the corresponding dianion it was reasonable to expect that sodamide would generate the dianion of the more acidic tricarbonyl system in (329b) and hence allow subsequent cyclisation (Scheme 64) thus supporting the proposal that a dianionic species is involved in the mechanism. In practice, when 3-(5'-methyl-2'-nitrobenzoyl)pentane-2,4-dione (329b) was treated with sodamide in liquid ammonia at -78° to form the dianionic salt which was then heated under reflux in tetrahydrofuran for 1 h, a 35% yield of the quinoline (330b) was obtained. The reduced yield under these conditions compared with the hydroxide-catalysed process, may be attributed to the fact that, being a more potent nucleophile, amide ion will be less selective in its attack on the spiro intermediate [Scheme 64; (364)] and so will produce side-reactions with consequent lowering of the yield of quinoline. Loss of the acetyl group in place of the carbamoyl group from the expected intermediate [(366); Scheme 64] would be expected to produce 2-carbamoyl-3-hydroxyquinoline (367). However, none of this product was isolated from the reaction mixture.



Scheme 65


NO2
COCH3
CH3
COCH3
-H+
(347)
(371)
HO
CH3
COCH3
NO
H3C
CO2
-CO2
+H+
OH
(372)
(373)

Scheme 66

By way of further probing the mechanism of the base-catalysed cyclisation of the 2-nitrobenzoylpentane-2,4-diones (329a and b), it was decided by using the 4-nitrobenzoyl derivative (345)[130] to attempt to demonstrate the rearrangement of the side-chain (Scheme 65) without the possibility of cyclisation onto a nitro group, thus permitting the isolation of a nitroso species derived from the intermediate (370) (Scheme 65). However, the only identified product of the base-catalysed reaction of 3-(4'-nitrobenzoyl)pentane-2,4-dione (345) was a low yield of p-aminoacetophenone. The origin of this product is not clear but it may arise by solvolysis[130] of the substrate (345) to <u>para</u>-nitroacetophenone followed by reduction in the aqueous ethanolic alkaline medium.

In another attempt to gain information about the mechanism of the base-catalysed cyclisation of the 2-nitrobenzoylpentanedione derivatives (329a and b), the reaction of 3-methyl-3(2'-nitrobenzoyl)pentane-2,4-dione (347) with aqueous ethanolic alkali was investigated. The presence of the 3-methyl group will not allow formation of a mono-anion of the type (337) (cf. Scheme 55) but abstraction of a hydrogen atom from an acetyl group to give an enolate ion of the type [(371)- Scheme 66] can still occur and consequently cyclisation (cf. Scheme 66) is possible to give an intermediate of the type (372) which would be expected to aromatise by loss of the elements of acetic acid, as shown, to give as the predicted product, 3-hydroxy-2-methylquinoline (373). However, in practice the substrate (337) when treated with hot aqueous ethanolic alkali, produced only intractable gums.

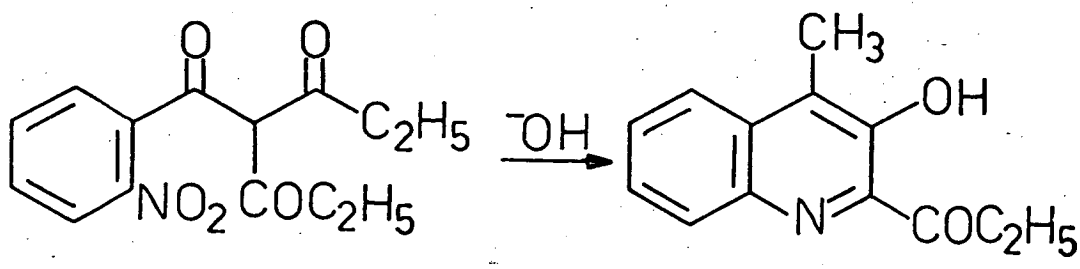
It was also thought that if 2-nitrobenzoylacetone (326) could be induced to form a dianion by its treatment with strong aqueous ethanolic alkali, then cyclisation akin to that found in the tricarbonyl cases, might occur. However, in practice only isatin (328) was formed. The formation of this product (328) by the base-catalysed cyclisation of 2-nitrobenzoylacetone (326) has been reported in the literature[118] and need only involve a mono-anion intermediate (see Scheme 52).

The chloroquinoline [(330c); Scheme 59] was formed in good yield by the cyclisation of the triketone (329c) in aqueous ethanolic alkali. In accord with its assigned structure its ^{1}H n.m.r. spectrum showed a hydroxyl group resonance at τ 1.20 while the ortho coupled doublet at τ 2.07 is assigned to the H-(8) nucleus which is deshielded due to the electron-withdrawing effect of the quinoline nitrogen atom. The signal at τ 2.39 is assignable either to the H-(4) nucleus or the H-(5) nucleus as it shows only meta coupling. However, it can be positively assigned to the H-(4) atom on the basis that the combined deshielding effect of the hydroxyl and acetyl substituents and the nitrogen atom in the pyridine ring will have a greater effect on the H-(4) nucleus than the chloro substituent will have on the H-(5) nucleus.

In an attempt to extend the scope of the base-catalysed formation of 2-acyl-3-hydroxyquinolines to systems other than 3-(2'-nitrobenzoyl)pentane-2,4-diones already discussed, the cyclisation of 2-(2'-nitrobenzoyl)-1-phenylbutane-1,3-dione [(329d); Scheme 59] was investigated. This substrate showed less reactivity towards cyclisation in aqueous ethanolic alkali than the pentane-2,4-dione derivatives (329a-c). Only a low yield (12.5%) of 2-benzoyl-3-hydroxquinoline (330d) was obtained and starting material was recovered. This reduced yield may be attributable to the electron-releasing property of the phenyl group which will inhibit the stabilising effect of the tricarbonyl system thus making formation of the dianionic intermediate necessary for cyclisation, difficult. Further, the reduced yield may be due to the difficulty the substrate has in assuming the planar configuration implicit in charge stabilisation by delocalisation due to the steric compression suffered by the acetyl group which would be constrained to lie between the two benzene rings.

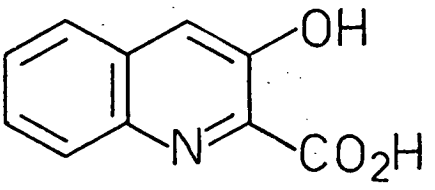
As a further extension of the 3-hydroxyquinoline synthesis it was decided to attempt the base-catalysed cyclisation of 4-(2'-nitrobenzoyl) heptane-3,5-dione (329g). The expected product of this cyclisation is

3-hydroxy-4-methyl-2-propionylquinoline (374). In practice, the yellow product, formed in good yield, gave the required elemental and mass spectral data (m/e 215) for the expected product (374). Its i.r. spectrum showed a single carbonyl absorption at 1670 cm^{-1} and its ^1H n.m.r. spectrum showed a signal attributable to a phenolic hydrogen at τ -1.45. The four aromatic protons appeared as a multiplet in the range τ 2.00-2.55. The methylene group of the ethyl moiety appeared as a quartet (J 8 Hz) at τ 6.55 and the methyl group of the ethyl moiety appeared as a triplet (J 8 Hz) at τ 8.76. The singlet at τ 7.53, due to three protons, is assigned to the methyl group in the 4-position of the quinoline ring.



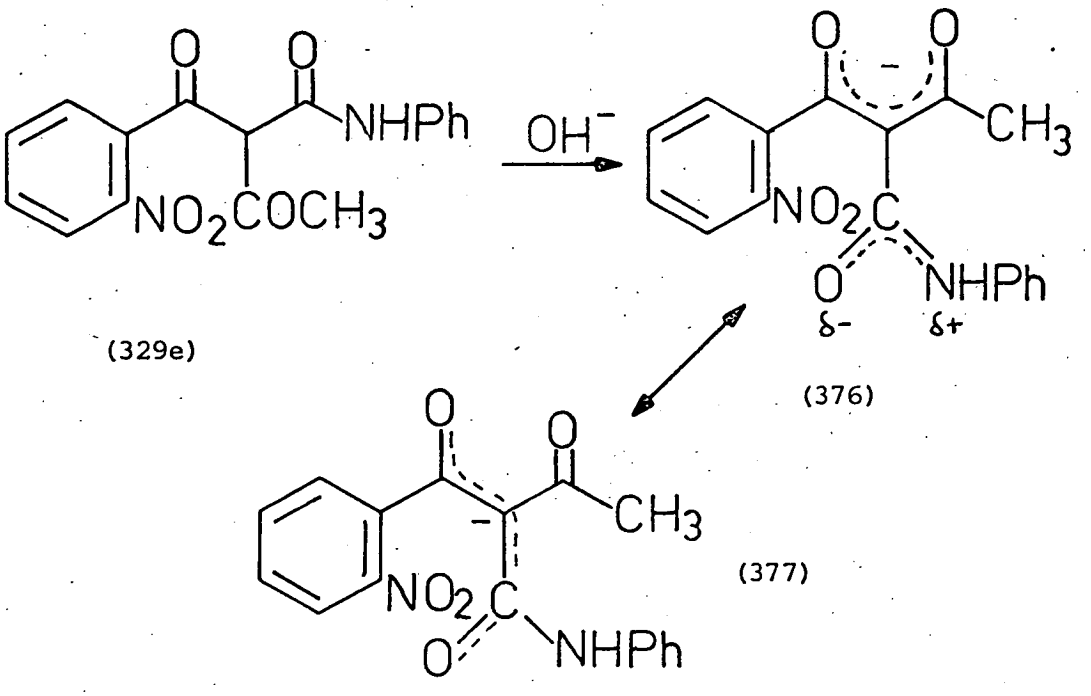
(329g) (374)

The possible extension of the base-catalysed cyclisation of the 3-(2'-nitrobenzoyl)pentane-2,4-diones to other substrates which were not purely ketonic, was also studied. Thus the behaviour of the diketo-ester (329f) towards hot aqueous ethanolic alkali was investigated in the hope that the expected product 3-hydroxyquinoline-2-carboxylic acid (375) would be isolated. In practice however, the reaction yielded only intractable tars. The failure of the ester (329f) to cyclise in a similar manner to the triketones (329a-d and g) may be attributed to its ease of hydrolysis and hence to the ready degradation of the side-chain before cyclisation can occur.



(375)

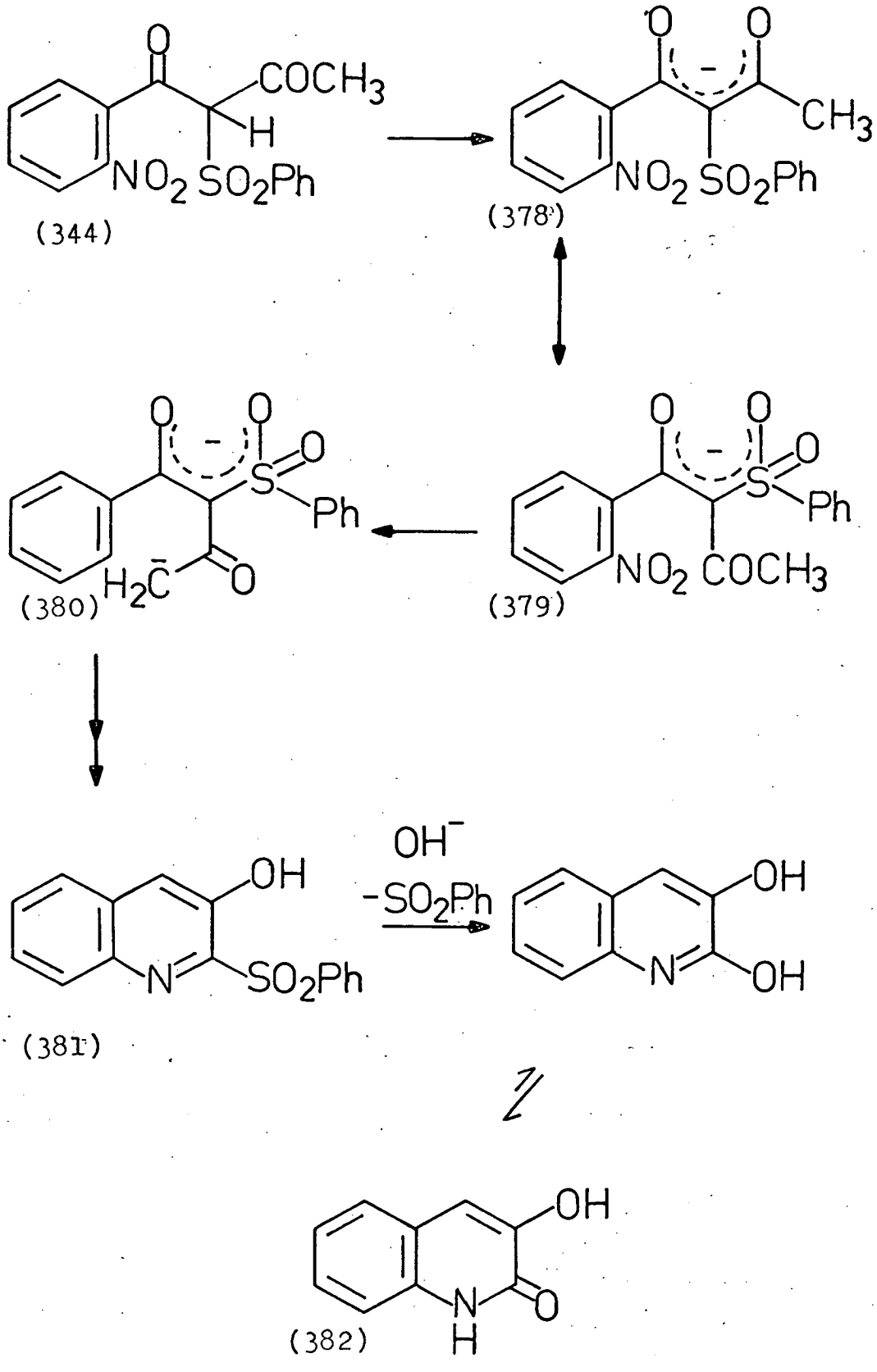
In contrast to the ready decomposition of the ester (329f) by alkali, the anilide derivative (329e) proved to be stable to heating in 20% or 40% aqueous potassium hydroxide and was recovered unchanged in high yield, by acidification of the reaction mixture. The resistance of the anilide (329e) to cyclisation may be attributed to preferential delocalisation of its mono-anion towards the acetyl group due to the destabilisation of the enolate structure (377) because of the electron-releasing capacity of the amide nitrogen. Thus abstraction of a second hydrogen from the acetyl methyl group in (376) will be hindered by the more localised negative charge already present in the molecule and



(329e)

(376)

(377)


COCH3
H
NO2 SO2Ph
(344)
CH3
(378)
Ph
(379)
(380)
H2C
OH
-SO2Ph
OH
N
SO2Ph
(381)
OH
N
H
(382)

Scheme 67

consequently, cyclisation cannot proceed. This effect is similar to that proposed to explain resistance of the benzoyl derivative (329d) to cyclisation. In order to gain some support for these suggestions, the base-catalysed cyclisation of the benzenesulphonyl diketone (344) was investigated. It was hoped that in this molecule, preferential delocalisation of the anion would be towards the benzenesulphonyl group [cf. (379); Scheme 67)] rather than towards the acetyl group, thus allowing deprotonation of the acetyl group to give the anionic intermediate (380) which could then undergo cyclisation to 2-benzenesulphonyl-3-hydroxyquinoline (381) or (by subsequent reaction with hydroxide ion) 3-hydroxyquinoline-2(1H)-one (382). However, treatment of the benzenesulphonyl derivative (344) with hot aqueous alkali gave only intractable tars.

In summary it has been shown that the novel base-catalysed formation of 2-acyl-3-hydroxyquinolines from 2-nitrobenzoylalkanone is a fairly general process but appears to be restricted to purely ketonic substrates. The initial formation of a dianionic intermediate in such reactions is tentatively supported by the ability of sodamide to catalyse cyclisation. However, further extensive studies are required in order to produce more conclusive evidence for the actual mechanism involved in these cyclisations.

EXPERIMENTAL

1.

4-Nitrobenzoyl chloride[131] was prepared (83%) by the standard reaction[132] of 4-nitrobenzoic acid with phosphorus pentachloride, b.p. 88-94° at 0.5 mm.

5-Chloro-2-nitrobenzoyl chloride was prepared[132] (81%) by the standard reaction of 5-chloro-2-nitrobenzoic acid with phosphorus pentachloride, $\nu_{max.}$ 1790(CO) and 1540 and 1350 (NO_2) cm^{-1}.

2,4-Dinitrobenzoyl chloride was prepared (96%) by the standard reaction[132] of 2,4-dinitrobenzoic acid with phosphorus pentachloride, m.p. 42° (lit.,[133] 45°), $\nu_{max.}$ 1790 (CO) and 1550 and 1350 (NO_2) cm^{-1}.

5-Methyl-2-nitrobenzoyl chloride was prepared (88%) by the standard reaction[133] of 5-methyl-2-nitrobenzoic acid with phosphorus pentachloride, m.p. 38° (lit.,[134] 46°).

2-Nitrobenzoyl chloride was prepared[132] (85%) by the standard reaction of 2-nitrobenzoic acid with thionyl chloride.

2. The Preparation of 5-Chloro-2-nitrobenzoic Acid was carried out by the method of Hollemann[135] (yield 70%), m.p. 134°(from benzene-light petroleum) (lit.,[135] 138°).

3. The Condensation of Nitrobenzoyl Chlorides with Acetylacetone in the Presence of Sodium Ethoxide.

General Method:

A mixture of acetylacetone (15.0 g, 14.6 ml, 0.15 mol) and 62.5 ml of a solution of sodium (7.79 g) in absolute ethanol (125 ml) was cooled to 0° (ice-salt bath) and treated in portions with stirring, with the acid chloride (0.075 mol). After stirring at 0° for 0.5 h, further sodium ethoxide solution (31.5 ml) was added followed in portions with

stirring by further acid chloride (0.033 mol). The mixture was again stirred at 0° for 0.5 h and the remaining ethoxide solution was then added followed by the acid chloride (0.032 mol) as before. The reaction mixture was stirred overnight in the melting ice-bath and then filtered to give the salt of the product and an organic filtrate which were worked up as described for the individual reactions below.

a) 3-(4'-Nitrobenzoyl)pentane-2,4-dione[130] (345)

The reaction of acetylacetone and 4-nitrobenzoyl chloride[131] as described above gave a salt which was acidified with dilute aqueous sulphuric acid to afford 4-Nitrobenzoic acid m.p. 239° (from ethanol-water) (lit.,[136] 241°), $\nu_{max.}$ 2660, 2550 (OH), 1700 (CO) and 1530 and 1350 (NO_2) cm^{-1}.

The ethanolic organic filtrate was concentrated to ca. one third of its original volume and the solid was collected and dissolved in water. The aqueous solution was acidified with concentrated aqueous hydrochloric acid, while cooling ice, and was then extracted with chloroform (2 x 75.0 ml) to give a brown oil which was triturated with light petroleum to afford the 2-nitrobenzoyl derivative (345) (13.5%), m.p. 113° (from 1:1 ethanol-light petroleum) (Lit.,[130] 103°), $\nu_{max.}$ 1670 and 1600br (CO), and 1530 and 1350 (NO_2) cm^{-1}.

b) 3-(5'-Methyl-2'-nitrobenzoyl)pentane-2,4-dione (329b)

The reaction of acetylacetone with 5'-methyl-2'-nitrobenzoyl chloride as described in the general method gave a salt which was combined with a second crop obtained by concentrating the ethanol filtrate to one-third of its original volume (total 31.8 g). This salt was dissolved in water (350 ml) and washed with chloroform to remove an unidentified oil (2.4 g). Acidification of the aqueous solution with dilute aqueous sulphuric acid and extraction with chloroform gave an unidentified oil (8.6g).

The original ethanolic mother liquor was evaporated and the residue was treated with water (50.0 ml). The aqueous phase was decanted from an insoluble oil, acidified with dilute aqueous sulphuric acid and extracted with chloroform to give an oil which was triturated with light petroleum to yield the 2-nitrobenzoyl derivative (329b) (0.52 g; 1%) m.p. 118°, $\nu_{max.}$ 1670 (CO) and 1527 and 1360 (NO_2) cm^{-1}, identical (i.r. spectrum) with a sample prepared later. The insoluble oil was dissolved in chloroform and washed with saturated aqueous sodium hydrogen carbonate solution. Evaporation of the chloroform layer gave ethyl 5-methyl-2-nitrobenzoate as a crystalline solid (17.5 g; 56%), $\tau(CDCl_3)$ (60 MHz) 2.15 (1H, d J 8Hz, ArH), 2.55 (1H, s, ArH), 2.64 (1H, d J 8Hz, ArH), 5.62 (2H, q J 6Hz, CH_2) 7.54 (3H, s, CH_3) and 8.64 (3H, t J 6Hz, CH_3).

Acidification of the aqueous sodium hydrogen carbonate extract and extraction with chloroform gave only a negligible amount of dark oil.

4. The Condensation of Nitrobenzoyl Chlorides with Active Methylene Compounds in the Presence of Magnesium Ethoxide

General Method:[123]

Magnesium turnings (0.11 mol), absolute ethanol (2.5 ml) and carbon tetrachloride (0.25 ml) were mixed and after the initial vigorous reaction had subsided, the mixture was treated cautiously with dry ether (75.0 ml). The mixture was then mechanically stirred and treated dropwise with a solution of the β-dicarbonyl compound (0.11 mol) in dry ether (12.5 ml) and absolute ethanol (10.0 ml) at such a rate that refluxing was maintained. When all of the magnesium was consumed (4-7.5 h), the stirred magnesium enolate solution was treated with the respective acid chloride (0.11 mol) in ether (25.0-40.0 ml) and the mixture was stirred until it solidfied

(ca. 10 min). Dilute aqueous sulphuric acid (100 ml) was then added to decompose the magnesium complex and the various reaction mixtures were then worked up as described below 4(a)-4(j).

(a) 3-(2'-Nitrobenzoyl)pentane-2,4-dione (329a)[119]

The ethereal phase of the reaction mixture from the condensation of 2-nitrobenzoyl chloride and acetylacetone was washed with water and evaporated to leave an oil which was triturated with a little ether to afford 3-(2'-nitrobenzoyl)pentane-2,4-dione (329a) (62%) as a crystalline solid, m.p. 72° (lit.,[119] 72°). Evaporation of the ether mother liquors gave a heavy oil from which no identifiable material could be obtained.

(b) 3-(5'-Methyl-2'-nitrobenzoyl)pentane-2,4-dione (329b)

The reaction mixture from the condensation of 5-methyl-2-nitrobenzoyl chloride and acetylacetone was filtered and the salt obtained was acidifed with dilute aqueous sulphuric acid. The resulting solid was combined with a second crop obtained by evaporating the ethereal phase of the filtrate and triturating the residue with a little ether to give 3-(5'-methyl-2'-nitrobenzoyl)pentane-2,4-dione (329b) (69%) as a crystalline solid, m.p. 98° (from ethanol), $\nu_{max.}$ 1660 and 1600br (CO), and 1530 and 1350 (NO_2) cm^{-1}, $\tau(CDCl_3)$ 2.12 (1H, d J 8Hz, ArH), 2.60-2.75 (2H, m, ArH), 7.54 (3H, s, CH_3) and 7.85 (6H, s, CH_3).

Found: C, 59.0; H, 5.0; N, 5.2%; p^+, 217(M^+-NO_2)

$C_{13}H_{13}NO_5$ requires: C, 59.3; H, 5.0; N, 5.3%; M, 263.

(c) 3-(5'-Chloro-2'-nitrobenzoyl)pentane-2,4-dione (329c)

The reaction mixture from the condensation of 5'-chloro-2'-nitrobenzoyl chloride and acetylacetone was filtered to give a solid which was combined with a second crop obtained by evaporating the ether layer and triturating the oily residue with ether to give 3-(5'-chloro-2'-nitrobenzoyl)pentane-2,4-dione (329c)(47%) as a colourless

crystalline solid, $\nu_{max.}$ 1675 and 1600br (CO), and 1540 and 1350 (NO_2) cm^{-1}, $\tau(CDCl_3)$-7.00 (1H, s, OH), 2.07 (1H, d J 12Hz, ArH), 2.45 (1H, d J 12Hz, ArH), 2.54 (1H, s, ArH) and 7.80 (6H, s, CH_3).

Found: C, 50.7; H, 3.6; N, 5.0%; p^+, 239/7(M^+-NO_2)

$C_{12}H_{10}ClNO_5$ requires: C, 50.7; H, 3.7; N, 4.7%; M, 283.5.

(d) 3-(2',4'-Dinitrobenzoyl)pentane-2,4-dione (343)

The condensation of acetylacetone and 2,4-dinitrobenzoyl chloride (which was added as a slurry in ether) gave an insoluble solid which was collected and combined with a second crop obtained by evaporating the ether layer and triturating the residual oil with ether to give 3-(2',4'-dinitrobenzoyl)pentane-2,4-dione (343)(71%) m.p. 115°, as a colourless solid. A sample prepared for elemental analysis had m.p. 141° (from ethanol), $\nu_{max.}$ 1650 (CO), and 1535br and 1350 (NO_2) cm^{-1}, $\tau(CDCl_3)$-8.30 (1H, s, OH), 1.20 (1H, d J 3Hz, ArH), 1.48 (1H, d J 9Hz, ArH), 2.30 (1H, d J 9Hz, ArH), and 7.78 (6H, s, CH_3).

Found: C, 48.9; H, 3.4; N, 9.3%; M^+, 294.

$C_{12}H_{10}N_2O_7$ requires: C, 49.0; H, 3.4; N, 9.5%; M, 294.

Attempted recrystallisation of the bulk of the triketone (343) (7.17g) from ethanol with prolonged heating under reflux resulted in its deacetylation to give 2,4-dinitrobenzoylacetone (5.0 g) as yellow needles, m.p. 78°, $\nu_{max.}$ 1610br (CO), and 1530 and 1350 (NO_2) cm^{-1}, $\tau(CDCl_3)$ 1.26 (1H, d $J_{3,5}$ 3Hz, ArH), 1.50 (1H, dd $J_{5,6}$ 8Hz $J_{5,3}$ 2Hz, ArH), 2.26 (1H, d $J_{6,5}$ 8Hz, ArH), 4.18 (1H, s, CH) and 7.82 (3H, s, CH_3).

Found: C, 48.2; H, 3.3; N, 10.8%: M^+, 252.

Calculated for $C_{10}H_8N_2O_6$: C, 47.6; H, 3.2; N, 11.1%; M, 252.

(e) 3-(4'-Nitrobenzoyl)pentane-2,4-dione (345)

The reaction mixture from the condensation of acetylacetone and 4-nitrobenzoyl chloride was filtered and the solid was combined with a second crop obtained by evaporating the ether layer and triturating

the residual oil with ether to give 3-(4'-nitrobenzoyl)pentane-2,4-dione (345) (82%) m.p. 78° (from ethanol) (lit.,[130] 103°), $\nu_{max.}$ 1670 and 1600br (CO), and 1530 and 1350 (NO_2) cm^{-1}, $\tau(CDCl_3)$ (60 MHz) 1.72 (2H, d J 9Hz, ArH), 2.04 (2H, d J 9Hz, ArH), and 7.88 and 8.00 (6H, s, CH_3).

Found: C, 57.8; H, 4.3; N, 6.1%; M^+, 249.

Calculated for $C_{12}H_{11}NO_5$: C, 57.8; H, 4.5; N, 5.6%; M, 249.

(f) 2-(2'-Nitrobenzoyl)-1-phenylbutane-1,3-dione (329d)

The reaction mixture from the condensation of benzoyacetone and 2-nitrobenzoyl chloride was filtered and the solid was combined with a second crop obtained by evaporating the ether phase and triturating the residual oil with methanol to give 2-(2'-nitrobenzoyl)-1-phenylbutane-1,3-dione (329d) (72%) m.p. 104° (from ethanol), $_{max.}$ 1650 and 1600br (CO), and 1533 and 1350 (NO_2) cm^{-1}, $(CDCl_3)$-6.65 (1H, br s, OH), 2.00-3.10 (9H, m, ArH) and 7.74 (3H, s, CH_3).

Found: C, 65.6; H, 4.1; N, 4.9%; p^+, 265 (M^+-NO_2).

$C_{17}H_{13}NO_5$ requires: C, 65.7; H, 4.2; N, 4.5%; M, 311.

(g) 4-(2'-Nitrobenzoyl)heptan-3,5-dione (329g)

The reaction mixture from the condensation of 2-nitrobenzoyl chloride and heptane-3,5-dione was separated and the ether layer was evaporated to leave an oil which crystallised on standing. The resulting solid was collected and washed with ether to give 4-(2'-nitrobenzoyl)heptane-3,5-dione (329 g) (32%) m.p. 54° (from benzene-light petroleum), $_{max.}$ 1640 (CO) and 1540 and 1320 (NO_2) cm^{-1}, $(CDCl_3)$-8.03 (1H, s, OH), 1.80-2.40 (4H, m, ArH), 7.54 (4H, m, CH_2) and 8.95 (6H, m, CH_3),

Found: C, 60.3; H, 5.4; N, 5.1%; p^+, 248 (M^+-CH_3CH_2).

$C_{14}H_{15}NO_5$ requires: C, 60.6; H, 5.5; N, 5.1%; M, 277.

(h) 2-Benzenesulphonyl-1-(2'-nitrophenyl)butane-1,3-dione (344)

The condensation of benzenesulphonylacetone with 2-nitrobenzoyl chloride was carried out as described in the general method above, with the exception that the formation of the magnesium enolate solution required 18 h at room temperature. The resulting reaction mixture, (after work-up as described in the general method) was separated and the ether layer was left in contact with saturated aqueous sodium hydrogen carbonate solution for 5 h. The ether layer was then evaporated to give an oil from which benzenesulphonylacetone (15%) separated, identical (m.p. and i.r. spectrum) with an authentic sample. The remaining oil was a mixture of unreacted acid chloride and benzenesulphonylacetone as shown by its i.r. spectrum.

The saturated aqueous sodium hydrogen carbonate extract was acidified with dilute aqueous sulphuric acid to give 2-benzenesulphonyl-1-(2'-nitrophenyl)butane-1,3-dione (344)(18%), m.p. 123° (from ethanol), $\nu_{max.}$ 1680 (CO) and 1540 and 1350 (NO_2) cm^{-1}, $\tau(CDCl_3)$-7.75 (1H, s, OH), 1.8-2.9 (9H, m, ArH) and 7.43 (3H, s, CH_3).

Found: C, 55.0; H, 3.7; N, 4.0%; p^+, 301 (M^+-NO_2)

$C_{16}H_{13}NO_6S$ requires: C, 55.3; H, 3.7; N, 4.2%; M, 347.

(i) 2-(N-Phenylcarbamoyl)-1-(2'-nitrophenyl)butane-1,3-dione (329e).

The condensation of 2-nitrobenzoyl chloride and acetoacetanilide was carried out as described in the general method with the exception that the acetoacetanilide was dissolved in tetrahydrofuran and the mixture was stirred overnight to allow formation of the magnesium enolate. The resulting reaction mixture, after the condensation was complete, was separated and the organic layer was evaporated and the residue was triturated with ether to give 2-(N-phenylcarbamoyl)-1-(2'-nitrophenyl)-butane-1,3-dione (329e) (42%), m.p. 122° from ethanol), $\nu_{max.}$ 1630 br (CO), and 1540 and 1360 (NO_2) cm^{-1}, $\tau(CDCl_3)$(60 MHz)-8.73 (1H, s, OH),

-1.6(1H, br s, NH), 1.90-3.00 (9H, m, ArH) and 8.2 (3H, s, CH_3)

Found: C, 62.9; H, 4.5; N, 8.6%; M^+, 326.

$C_{17}H_{14}N_2O_5$ requires: C, 62.6; H, 4.3; N, 8.6%; M, 326.

(j) 2-Ethoxycarbonyl-1-(2'-nitrophenyl)butane-1,3-dione (329f)

The reaction mixture from the condensation of ethyl acetoacetate with 2-nitrobenzoyl chloride was separated and the ether layer was evaporated to leave an oil which was distilled under reduced pressure to give two volatile fractions; namely, ethyl acetoacetate (21%), b.p. 34° at 0.1 mm, identical (i.r. spectrum) with an authentic sample, and ethyl 2-nitrobenzoate (19%), b.p. 120° at 0.2 mm, identical (i.r. spectrum) with an authentic sample, τ($CDCl_3$) (60 MHz) 2.22 (4H, m, ArH), 5.46 (2H, q J 8Hz, CH_2) and 8.68 (3H, t J 8Hz, CH_3).

The non-volatile residue was dissolved in ether and washed with dilute aqueous sodium hydroxide (2 x 20 ml). The aqueous sodium hydroxide extract was then acidified with dilute aqueous sulphuric acid and extracted with ether to give 2-ethoxycarbonyl-1-(2'-nitrophenyl)butane-1,3-dione (329f)[137] (49%) as a dark oil, τ(CCl_4) (60 MHz) 2.02 (1H, dd J 8Hz J 3Hz, ArH), 2.40-3.00 (3H, m, ArH), 6.22 and 6.70 (2H, q J 8Hz, CH_2), 7.66 and 8.02 (3H, s, CH_3) and 8.98 and 9.42 (3H, t J 8Hz, CH_3).

5. 3-Methyl-3-(2'-nitrobenzoyl)pentane-2,4-dione. (347)

A mixture of 3-(2'-nitrobenzoyl)pentane-2,4-dione (329a) (3.0 g, 0.012 mol), methyl iodide (3.6 g, 0.024 mol), analar acetone (60.0 ml), and anhydrous potassium carbonate (6.0 g) was heated under reflux for 8 h. The mixture was hot filtered to remove inorganic material and evaporated. The resulting residue was dissolved in chloroform and washed with water. Evaporation of the organic phase afforded 3-methyl-3-(2'-nitrobenzoyl)pentane-2,4-dione (347) (2.6g; 83%), m.p. 95° (from ethanol), $\nu_{max.}$ 1720 and 1695 (CO) and 1535 and 1350 (NO_2) cm^{-1}, τ($CDCl_3$)

1.88 (1H, m, ArH), 2.35 (2H, m, ArH), 2.63 (1H, m, ArH), 7.68 (6H, s, CH_3) and 8.35 (3H, s, CH_3).

Found: C, 59.5; H, 5.0; N, 5.3%; p^+, 178.

$C_{13}H_{13}NO_5$ requires: C, 59.3; H, 5.0; N, 5.3%; M, 263.

6. Cyclisation Reactions of 2-Nitrobenzoyl Derivatives (329 a-d and g) to 2-Acyl-3-hydroxyquinolines (330 a-d and 374) in the Presence of Aqueous Ethanolic Potassium Hydroxide.

General Method:

A solution of the 2-nitrobenzoyl derivative (0.01) in ethanol (30.0 ml) was treated with 20% w/v aqueous potassium hydroxide (15.0 ml) and the mixture was heated under reflux for 0.5 h. The mixture was evaporated, treated with water and washed with chloroform. In all cases 6a-d below , evaporation of the chloroform extract gave either a negligible amount of material or no material. The aqueous phase was then cooled in ice and acidified with dilute aqueous sulphuric acid, and effervescence of a gas (presumably carbon dioxide) was observed. The acidified aqueous phase was then worked up as described for the individual reactions below.

(a) 2-Acetyl-3-hydroxyquinoline (330a)[119]

The acidified aqueous phase from the reaction of 3-(2'-nitrobenzoyl) pentane-2,4-dione (329a) with potassium hydroxide, was filtered to give a brown solid which was subjected to Soxhlet extraction using light petroleum (b.p. 80-100°). The insoluble fraction was an intractable brown solid. Evaporation of the petroleum extract gave 2-acetyl-3-hydroxyquinoline (330a) (73%), m.p. 100° (from ethanol)(lit.,[119] 118°), $\nu_{max.}$ 1660 (CO) cm^{-1}, identical (i.r.spectrum) with an authentic sample.

(b) 2-Acetyl-3-hydroxy-6-methylquinoline (330b)

The acidified aqueous phase from the reaction of 3-(5'-methyl-2'-nitrobenzoyl)pentane-2,4-dione (329b) with potassium hydroxide was filtered to give a brown solid which was subjected to Soxhlet extraction using light petroleum (b.p. 80-100°) to yield 2-acetyl-3-hydroxy-6-methylquinoline (330b)(59%), m.p. 126° (from ethanol), $\nu_{max.}$ 1665 (CO) cm^{-1}, $\tau(CCl_4)$-1.00 (1H, s, OH), 2.15 (1H, d $J_{8,7}$ 7Hz, ArH), 2.62 (3H, m, ArH), 7.16 (3H, s, CH_3) and 7.50 (3H, s, CH_3), $\lambda_{max.}$ 216, 246, 261 sh, 319 and 359 nm, (log $\varepsilon_{max.}$ 4.21, 4.53, 4.24, 3.99 and 3.29).

Found : C, 71.6; H, 5.5; N, 7.0%; M^+, 201.

$C_{12}H_{11}NO_2$ requires: C, 71.6; H, 5.5; N, 6.9%; M, 201.

(c) 2-Acetyl-6-chloro-3-hydroxyquinoline (330c)

The acidified aqueous phase from the reaction of 3-(5'-chloro-2'-nitrobenzoyl)pentane-2,4-dione (329c) with potassium hydroxide was filtered and the brown solid was subjected to Soxhlet extraction using light petroleum to give 2-acetyl-6-chloro-3-hydroxyquinoline (330c) (65%), m.p. 149° (from ethanol), $\nu_{max.}$ 1665 (CO) cm^{-1}, $\tau(CDCl_3)$-1.20 (1H, s, OH), 2.07 (1H, d $J_{8,7}$ 10Hz, ArH) 2.39 (1H, d $J_{5,7}$ 3Hz, ArH), 2.56 (2H, m, ArH) and 7.15 (3H, s, CH_3), $\lambda_{max.}$ 219, 245, 311 and 382 nm, (log $\varepsilon_{max.}$ 4.26, 4.60, 3.92 and 3.51).

Found: C, 59.6; H, 3.7; N, 6.3%; M^+, 221/3.

$C_{11}H_8ClNO_2$ requires: C, 59.6; H, 3.6; N, 6.3%; M, 221.5.

The material, insoluble in light petroleum was an intractable brown solid.

(d) 2-Benzoyl-3-hydroxyquinoline (330d)

The acidic aqueous phase from the reaction of 2-(2'-nitrobenzoyl)-1-phenylbutane-1,3-dione (329d) with potassium hydroxide for 2 h, as described in the general method, was extracted with chloroform to afford an oil which was extracted with light petroleum to give the crude product.

Crystallisation gave the pure 2-benzoyl-3-hydroxyquinoline (330d) (12.5%) m.p. 95° (from ethanol), $\nu_{max.}$ 1640 (CO) cm^{-1}, $\tau(CDCl_3)$-1.25 (1H, s, OH), 1.67 (2H, m, ArH), 1.99 (1H, m, ArH), 2.32 (1H, s, ArH) and 2.46 (6H, m, ArH), $\lambda_{max.}$ 217, 248 and 319 nm, (log $\varepsilon_{max.}$ 4.49, 4.38 and 3.80).

Found: C, 76.8; H, 4.5; N, 5.5%; M^+, 249.

$C_{16}H_{11}NO_2$ requires: C, 77.1; H, 4.5; N, 5.6%; M, 249.

Evaporation of the ethanol recrystallisation mother liquors left a solid (0.6 g), m.p. 51-80°, $\nu_{max.}$ 1690 and 1640 (CO) cm^{-1}. Attempts to purify this solid for further investigation were unsuccessful.

The petroleum insoluble residue was triturated with methanol to afford a solid (15%) identical (m.p. and i.r. spectrum) with the starting material. Evaporation of the methanol mother liquors left a gum (37.5% by weight) whose t.l.c. in ether over silica showed it to be a multicomponent mixture.

(e) 3-Hydroxy-4-methyl-2-propionylquinoline (374)

The acidified aqueous phase from the reaction of 4-(2'-nitrobenzoyl) heptane-3,5-dione (329g) with potassium hydroxide was filtered and the solid dissolved in chloroform and filtered to remove inorganic material. Evaporation of the chloroform extract afforded the crude product which was crystallised from ethanol to give the pure 3-hydroxy-4-methyl-2-propionylquinoline (374) (84%), m.p. 82°, $\nu_{max.}$ 1670 (CO) cm^{-1}, $\lambda_{max.}$ 219, 245, 311 and 382 nm, (log $\varepsilon_{max.}$ 4.26, 4.60, 3.92 and 3.51), $\tau(CDCl_3)$-1.45 (1H, s, OH), 2.00-2.55 (4H, m, ArH), 6.55 (2H, q J Hz, CH_2), 7.53 (3H, s, CH_3) and 8.76 (3H, t, CH_3).

Found: C, 72.1; H, 6.1; N, 6.5%; M^+, 215.

$C_{13}H_{13}NO_2$ requires: C, 72.5; H, 6.1; N, 6.5%; M, 215.

7. The Cyclisation Reaction of 3-(5'-Methyl-2'-nitrobenzoyl)pentane-2-4-dione (329b) with Sodamide in Liquid Ammonia.

Liquid ammonia (ca. 30 ml) was cooled to -78° (acetone-solid CO_2 bath) and the flask was flushed with nitrogen. Sodium metal (0.23 g, 0.01 mol) was added and the mixture was stirred until the blue colour was discharged. The 2-nitrobenzoyl derivative (329b) (1.32 g, 0.005 mol) in dry tetrahydrofuran (10.0 ml) was then added to the stirred sodamide solution at -78° and the cooling bath was then removed and the reaction mixture allowed to warm up to room temperature. Further dry tetrahydrofuran (15.0 ml) was then added and the mixture was stirred and heated under reflux for 1 h. The mixture was then evaporated and the solid residue was dissolved in water (20.0 ml) and was extracted with chloroform to remove an unidentified orange solid (0.09 g). The aqueous phase was acidified with dilute aqueous sulphuric acid and was then extracted with chloroform. The chloroform layer was washed with saturated aqueous sodium hydrogen carbonate solution and was evaporated to give a gummy residue (1.0 g) which was extracted with hot light petroleum to afford 2-acetyl-3-hydroxy-6-methylquinoline (330b) (0.35 g, 35%), m.p. 126° (from ethanol) identical (m.p. and i.r. spectrum) with a sample prepared before. The petrol insoluble residue (0.23 g) was a tar whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture.

The aqueous sodium hydrogen carbonate extract was acidified with silute aqueous sulphuric acid to give an unidentified solid (0.15 g), $\nu_{max.}$ 2660w (OH) and 1690 (CO) cm^{-1}. Attempts to purify the solid for further investigation were unsuccessful.

8. 2-Acetyl-3-acetoxy-6-methylquinoline (348)

The quinoline (330b) (0.40 g) in acetic anhydride (2.0 ml) was heated under reflux for 2h. The solution was evaporated and the residue

was triturated with water to give 3-acetoxy-2-acetyl-6-methylquinoline (348) (0.23 g), m.p. 63° (from light petroleum), $\nu_{max.}$ 1755 and 1690 (CO) cm^{-1}, $\lambda_{max.}$ 217, 247 and 304 nm (log $\varepsilon_{max.}$ 4.36, 4.57 and 3.83) τ($CDCl_3$; 60 MHz), 1.88-2.69(4H, m, ArH), 7.19 (3H, s, ArCOMe), 7.48 (3H, s, ArMe) and 7.60 (3H, s, CH_3)

Found: C, 68.9; H, 5.7; N, 5.6%; M^+, 243.

$C_{14}H_{13}NO_3$ requires: C, 69.2; H, 5.4; N, 5.8%; M, 243.

9. 3-Hydroxy-2-(α-hydroxyethyl)-6-methylquinoline (349)

The quinoline (330b)(0.40 g) was heated under reflux with sodium dithionite (0.8 g) (added in two portions, the second after 0.5 h) in 70% v/v aqueous ethanol (25.0 ml) for 1 h. The mixture was evaporated and the residue treated with water to give 3-hydroxy-2-(α-hydroxyethyl)-6-methylquinoline (349) (0.35 g, 88%), m.p. 169° (from ethanol-water), $\nu_{max.}$ 3300br (OH) cm^{-1}, $\lambda_{max.}$ 219, 238, 262 sh, 320 and 331 nm (log $\varepsilon_{max.}$ 4.48, 4.46, 3.84, 3.78 and 3.81), τ[$CDCl_3$-$(CD_3)_2SO$] 2.18 (1H, d J 9Hz, ArH), 2.63 (3H, m, ArH), 4.76 (1H, q J 7Hz, CH), 7.55 (3H, s, CH_3), and 8.43 (3H, d J 7Hz, CH_3).

Found: C, 70.0; H, 6.4; N, 6.7%; M^+, 203.

$C_{12}H_{13}NO_2$ requires: C, 70.9; H, 6.5; N, 6.9%; M, 203.

10. The Methylation of the Quinolines (330a and b) Using Dimethyl Sulphate in the Presence of Potassium Carbonate

2-Acetyl-3-methoxy-1,6-dimethylquinolinium Methosulphate (350)

The quinoline (330b) (10.0 g, 0.05 mol) and dimethyl sulphate (30.0 ml) were heated under reflux in analar acetone in the presence of anhydrous potassium carbonate (52.5 g), for 5 h and the mixture was filtered and evaporated. The residue from evaporation of the filtrate was left in contact with water (35.0 ml) for 0.5 h and then extracted with

chloroform to give 2-acetyl-3-methoxy-1,6-dimethylquinolinium methosulphate (350) as a pale yellow solid (8.7 g; 51%), m.p. 235° (from ethanol), $\nu_{max.}$ 1720 (CO) cm^{-1}, τ(D_2O) 1.43 (1H, s, ArH), 1.80 (1H, d J 10Hz, ArH), 2.03 (1H, s, ArH), 2.08 (1H, d J 10Hz, ArH), 5.60 (3H, s, CH_3), 5.83 (3H, s, CH_3), 6.28 (3H, s, CH_3), 7.12 (3H, s, CH_3) and 7.38 (3H, s, CH_3).

Found: C, 52.7; H, 5.7; N, 4.1%; M^+, 230.

$C_{15}H_9NO_6S$ requires: C, 52.7; H, 5.6; N, 4.1%; M (cation), 230.

2-Acetyl-3-methoxy-1-methylquinolinium Methosulphate (334).

The methosulphate (334) was prepared as described by Bayne[119] (59%), m.p. 217° (from ethanol) identical (i.r. spectrum) with an authentic sample.[119]

11. 1-Methoxy-2-(5'-methyl-2'-methylaminophenyl)-1-pyruvoylethylene (351) and 2-[α-(β'-methoxy-5'-methyl-2'-methylaminostyryl)]-3-methylquinoxaline (352)

The methosulphate salt (350) (1.03 g, 0.003 mol) was stirred for 20 min. in dilute aqueous sodium hydroxide (10.0 ml) and was then extracted with chloroform to give the α-dicarbonyl derivative (351) as a foam (0.51 g), $\nu_{max.}$ 3400w (NH) and 1720 and 1670 (CO) cm^{-1}. The α-dicarbonyl derivative was characterised as the quinoxaline derivative (352) prepared by heating a mixture of the α-dicarbonyl derivative (351) (0.25 g) and ortho-phenylenediamine (0.12 g) in ethanol (10.0 ml), under reflux for 2 h. The solution was cooled to give the quinoxaline derivative (352) (0.22 g, 69%) as a yellow crystalline solid, m.p. 118° (from benzene), $\nu_{max.}$ 3210 and 1650w (NH), $\lambda_{max.}$ 237, 252 inf., 279 and 330 nm (log $\varepsilon_{max.}$ 4.65, 4.47, 4.09 and 3.76), τ($CDCl_3$; 60 MHz) 1.98-2.50 (4H, m, ArH), 3.00-3.80 (4H, m, ArH), 4.10 and 4.30 (1H, s, CH), 6.03 and 6.32 (3H, s and s, OMe) and 7.20, 7.26, 7.43, 7.72, 7.80 and 8.15 (9H, s, CH_3).

Found: C, 75.2; H, 6.6; N, 13.1%; M^+, 319.

$C_{22}H_{23}N_3O_2$ requires: C, 75.2; H, 6.7; N, 12.5%; M, 319.

1-Methoxy-2-(2'-methylaminophenyl)-1-pyruvoylethylene (335) and 2-[α-(β'-methoxy-2'-methylaminostyryl)]-3-methylquinoxaline (336)

The α-dicarbonyl derivative (335) was prepared by the method described by Bayne,[119] as a foam (95%), $\nu_{max.}$ 3410 (NH), 1720 and 1660 (CO) cm^{-1}.

The quinoxaline derivative (336) was prepared by the method described by Bayne[119] (36%), m.p. 176°, identical m.p. and i.r. spectrum) with an authentic sample.

The Attempted Acetylation of the α-Dicarbonyl Derivative (335)

The α-diketone (335) (0.44 g, 0.002 mol) was heated under reflux in acetic anhydride (1.0 ml) for 10 min. The mixture was then cooled and evaporated to give an intractable tar whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture containing starting material.

12. The Acetylation of the Quinoxaline Derivatives (336 and 352)

The quinoxaline derivative (336) (0.60 g, 0.002 mol) was heated under reflux in acetic anhydride (2.0 ml) for 0.5 h. Evaporation of the solution gave a gum which was triturated under methanol-water to give the acetyl derivative of the quinoxaline (353a) (0.53 g; 77%), m.p. 129° (from benzene-light petroleum), $\nu_{max.}$ 1660 (CO) cm^{-1}, $\lambda_{max.}$ 211, 239, 256, and 325 nm (log $\varepsilon_{max.}$ 4.52, 4.55, 4.19 and 3.83), τ($CDCl_3$) 2.05 (2H, m, ArH), 2.30 (2H, m, ArH), 2.90 (2H, m, ArH), 3.20 (1H, m, ArH), 3.50 (1H, d J 8Hz, ArH), 4.03 (1H, s, CH), 6.11 (3H, s, CH_3), 6.70 (3H, s, CH_3), 7.33 (3H, s, CH_3) and 8.06 (3H, s, CH_3).

Found: C, 72.7; H, 6.1; N, 12.1%; M^+, 347.

$C_{21}H_{21}N_3O_2$ requires: C, 72.6; H, 6.1; N, 12.1%; M, 347.

The quinoxaline derivative (352) (0.4 g) was heated under reflux in acetic anhydride (1.5 ml) for 0.5 h. The solution was evaporated and the residue was triturated with aqueous methanol to give the acetylated quinoxaline derivative (353b) (0.37 g, 82%), m.p. 135° (from ethanol-light petroleum), $\nu_{max.}$ 1640 (CO) cm^{-1} τ($CDCl_3$; 60 MHz) 1.90-2.52 (4H, m, ArH), 2.28 (2H, m, ArH), 3.70 (1H, s, ArH), 4.90 (1H, s, CH), 6.15 (3H, s, OCH_3), 6.85 (3H, s, CH_3), 7.40 (3H, s, CH_3), 8.16 (3H, s, CH_3) and 8.23 (3H, s, CH_3).

Found: C, 72.5; H, 6.5; N, 11.4; M^+, 361.

$C_{22}H_{23}N_3O_2$ requires: C, 73.1; H, 6.4; N, 11.6; M, 361.

13. The Attempted Acid-Catalysed Degradation of the α-Diketone Derivatives (335 and 351)

(a) The α-diketone derivative (335) (0.44 g) was stirred with dilute aqueous hydrochloric acid (10.0 ml) at room temperature for 2 h, throughout which time, a gum remained insoluble in the acid. The mixture was then extracted with chloroform to give on evaporation, a gum (0.09 g) whose t.l.c. in chloroform over silica showed it to be a multicomponent mixture. The aqueous phase was basified by the dropwise addition of dilute aqueous sodium hydroxide solution and then extracted with chloroform. Evaporation of the chloroform extract gave a gum which was triturated with ether-ethyl acetate to afford an unidentified yellow solid (0.02 g). Evaporation of the ether-ethyl acetate mother liquors gave a gum (0.22 g) whose t.l.c. in chloroform over silica showed it to be a multicomponent mixture containing starting material.

(b) The α-diketone derivative (351) (0.9 g) was dissolved in dilute aqueous sulphuric acid (15.0 ml) and the solution was heated under reflux for 1 h, cooled, and then extracted with chloroform to give a gum (0.27 g) whose t.l.c. in ether or chloroform over silica showed it to be a multi-component mixture. The aqueous phase was neutralised with solid sodium hydrogen carbonate and extracted with chloroform to give a light brown solid (0.2 g) which decomposed on standing to give an intractable tar.

14. The Acid-Catalysed Degradation of the Quinoxaline Derivatives (336 and 352)

a) Using Aqueous Sulphuric Acid

i) A solution of the quinoxaline derivative (336) (0.6 g, 0.002 mol) in 20% w/v aqueous sulphuric acid was heated under reflux for 0.5 h, hot filtered to remove a negligible amount of solid and then neutralised with solid sodium hydrogen carbonate to give a precipitate of 2-methylbenzimidazole (361) (0.21 g; 80%), m.p. 176° (from benzene) (lit.,[125] 176°),

Found: C, 72.6; H, 6.1; N, 21.0%; M^+, 132.

Calculated for $C_8H_8N_2$: C, 72.7; H, 6.1; N, 21.2%; M, 132,

which was converted in ethanolic picric acid into the picrate, m.p. 210° (from ethanol), (lit.,[125] 208°).

The neutral aqueous filtrate was concentrated and extracted with chloroform to give a gum (0.18 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture from which no identifiable material could be obtained.

i)) A solution of the quinoxaline derivative (352) (0.4 g) in 20% w/v aqueous sulphuric acid (6.0 ml) was heated under reflux for 0.5 h and then filtered to remove a negligible amount of material. The solid that precipitated on cooling was dissolved in water and the aqueous solution adjusted to pH7-8 by the addition of solid sodium hydrogen carbonate. Extraction of the neutral aqueous phase gave no material.

The original acidic aqueous mother liquor was neutralised with solid sodium acetate and extracted with chloroform to give 2-methylbenzimidazole (361) (0.08 g; 50%), identical (m.p. and i.r. spectrum) with a sample obtained before.

b) Using Aqueous Hydrochloric Acid

i) The quinoxaline derivative (336) (0.35 g; 0.001 mol) stirred in dilute aqueous hydrochloric acid (4.0 ml) for 1 h at room temperature. The solution was then made alkaline by the dropwise addition of dilute aqueous sodium hydroxide solution to give a solid (quantitative) identical (m.p. and i.r. spectrum) with the starting material.

ii) Reaction (i) was repeated at 60° for 0.5 h and the resulting red solution was extracted with chloroform to give a gum which was triturated with ether to yield an unidentified solid (0.05 g), m.p. 156°, $\nu_{max.}$ 3330br (OH).

The aqueous mother liquor was basified by the dropwise addition of dilute aqueous sodium hydroxide solution. Extraction with chloroform gave a gum (0.2 g) which was triturated with ether-ethyl acetate to give the starting material more of which was obtained by evaporating the trituration mother liquor and retriturating the residue with methanol (total 0.06 g), identical (m.p. and i.r. spectrum) with an authentic sample.

c) Using Acetyl Chloride in Acetic Acid

The quinoxaline derivative (336) (0.31 g, 0.001 mol) was dissolved in acetic acid (2.0 ml) and acetyl chloride (3.0 ml) was added and the solution was heated under reflux for 1 h. The mixture was evaporated, treated with chloroform, and washed with saturated aqueous sodium hydrogen carbonate solution (2 x 5.0 ml). Evaporation of the chloroform extract afforded an intractable gum (0.26 g) whose t.l.c. in ethyl acetate over silica showed it to contain several close-running components one of which was the starting material.

The Attempted Acid-Catalysed Rearrangement of 2-Acetyl-3-methylquinoxaline (363).

A solution of the quinoxaline (363) (0.75 g, 4 mM) in 20% w/v aqueous sulphuric acid (12.0 ml) was heated under reflux for 0.5 h. The green solution was cooled and neutralised with solid sodium hydrogen carbonate to give a solid (0.68 g; 91%) identical (m.p. and i.r. spectrum) with the starting material (363).

15. The Attempted Oxidative Degradation of the Quinoxaline Derivatives (336 and 352)

a) Using Chromium(VI)Trioxide

A solution of the quinoxaline (336)(0.6 g) in 70% v/v aqueous acetic acid (10.0 ml) was treated with chromium (VI) oxide (0.6 g) and the mixture was heated under reflux for 1 h. The solution was evaporated to leave a dark oil which was dissolved in chloroform and water (10.0 ml). The chloroform layer was evaporated and the residue was triturated with methanol to give an intractable dark brown solid. Attempts to crystallise this solid for further investigation were unsuccessful. The methanol mother liquors were evaporated to leave another amount of an intractable solid (0.22 g) which could not be characterised.

b) Using Hydrogen Peroxide in Acetic Acid

A solution of the quinoxaline (352) (0.54 g) in glacial acetic acid (10.0 ml) was treated with 30% v/v aqueous hydrogen peroxide (4.5 ml) and stirred at 50^{o} for 17 h. The mixture was diluted with water (15.0 ml) and extracted with chloroform. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (2 x 15.0 ml) and evaporated to give a gum (0.21 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture. Acidification of the sodium hydrogen carbonate washings with dilute aqueous sulphuric acid and extraction with chloroform afforded an intractable gummy solid (0.06 g).

16. The Attempted Cyclisation Reactions of the 2-Nitrobenzoyl Derivatives (329 e,f,344 and 347) in the Presence of Potassium Hydroxide

The 2-nitrobenzoyl derivatives were heated under reflux with 20% w/v aqueous potassium hydroxide as described in the General Method described before for the successful cyclisations of the 2-nitrobenzoyl derivatives. The acidified aqueous phase was then worked up as described for the individual reactions below.

a) The Attempted Cyclisation of 2-Ethoxycarbonyl-1-(2'-nitrobenzoyl) butane-1,3-dione (329f)

The acidified aqueous phase was extracted with chloroform and washed with saturated aqueous sodium hydrogen carbonate solution (2 x 10.0 ml). Evaporation of the chloroform layer gave an oil (49% by weight of starting material) whose t.l.c. in ethyl acetate over silica showed it to be a mixture containing several close-running components from which no identifiable material could be obtained. The sodium hydrogen carbonate washings were acidified with dilute aqueous sulphuric acid and extracted with chloroform to give a dark oil (20% by weight of starting material) whose t.l.c. in chloroform over silica showed it to be a multicomponent mixture.

b) The Attempted Cyclisation of 3-Methyl-3-(2'-nitrobenzoyl)pentane-2, 4-dione (347)

The acidified aqueous phase was extracted with chloroform. The chloroform phase was then washed with saturated aqueous sodium hydrogen carbonate solution (2 x 25.0 ml) and evaporated to give an intractable black tar (20% by weight of starting material). The sodium hydrogen carbonate washings were acidified with dilute aqueous sulphuric acid and extracted with chloroform to give a further intractable black tar (62% by weight of starting material).

c) The Attempted Cyclisation of 1-(2'-Nitrobenzoyl)-2-(N-phenylcarbamoyl) butane-1,3-dione (329e)

i) The acidified aqueous phase was filtered to give a solid (94%) identical, (m.p. and i.r. spectrum) with the starting material.

ii) The experiment (i) above was repeated using 40% w/v aqueous potassium hydroxide instead of 20% w/v aqueous potassium hydroxide as described in the General Method. Again the acidified aqueous phase was filtered to give a solid (quantitative) identical (m.p. and i.r. spectrum) with the starting material.

d) The Attempted Cyclisation of 2-Benzenesulphonyl-1-(2'-nitrobenzoyl) butane-1,3-dione (344)

The acidified aqueous phase was extracted with chloroform and the organic layer was washed with saturated aqueous sodium hydrogen sulphate solution (2 x 10 ml). The chloroform layer was then evaporated to give an intractable black tar (55% by weight of starting material) whose t.l.c. in chloroform over alumina showed it to be a multicomponent mixture. Acidification of the sodium hydrogen carbonate extract and extraction with chloroform afforded only a negligible amount of material.

The Attempted Reaction of 3-(4'-Nitrobenzoyl)pentane-2,4-dione (345) in the Presence of Potassium Hydroxide

The 4-nitrobenzoyl derivative (345) (5.0 g) in ethanol (50.0 ml) was heated under reflux with 20% w/v aqueous potassium hydroxide (25.0 ml) for 0.5 h. The mixture was evaporated, treated with water (30.0 ml) and the resulting solution was washed with chloroform to give, on evaporation of the organic layer, p-aminoacetophenone (0.09 g), m.p. 106° (from water) (lit., 106°), $\nu_{max.}$ 3400w, 3340 and 3220 (NH_2), and 1650 (CO) cm^{-1}, ($CDCl_3$) (60 MHz) 2.34 (2H, d J 9Hz, ArH), 3.50 (2H, d J 9Hz, ArH), 5.87 (2H, br s, NH_2) and 7.60 (3H, s, CH_3).

The aqueous mother liquor was acidified with dilute aqueous sulphuric acid to give an intractable semi-solid from which no identifiable material could be obtained.

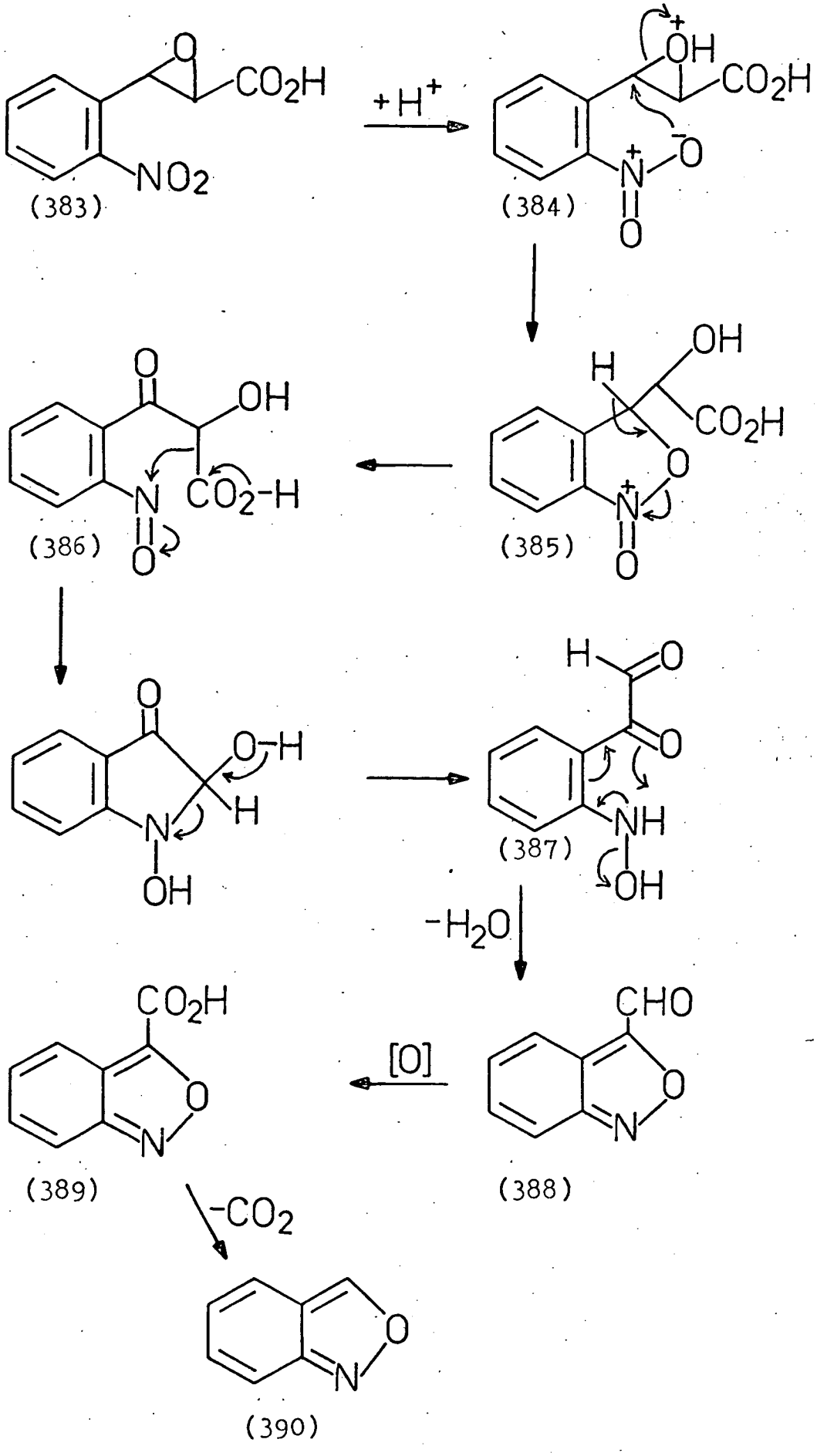
17. The Attempted Cyclisation Reaction of the 2-Nitrobenzoylacetone[118] (326) in the Presence of Potassium Hydroxide

2-Nitrobenzoylacetone[118] (2 g, 0.01 mol) in ethanol (30.0 ml) was treated with 20% w/v aqueous potassium hydroxide (15.0 ml) and the mixture was heated under reflux for 0.5 h and evaporated and treated with water (20.0 ml). The aqueous phase was extracted with chloroform evaporation of which, gave no material. The aqueous phase was acidified with dilute aqueous sulphuric acid and was extracted with chloroform. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (2 x 20.0 ml) and then evaporated to give isatin (328) (0.23 g) m.p. 203° (lit.[118], 203°) $\nu_{max.}$ 3,200w (NH), and 1740 (CO) cm^{-1}, identical (m.p. and i.r. spectrum) with an authentic sample. The sodium hydrogen carbonate extract was acidified with dilute aqueous sulphuric acid and extracted with chloroform to give a gum (0.22 g) from which no identifiable material could be isolated. The acidified sodium hydrogen carbonate extract was neutralised with anhydrous solid sodium acetate and extracted with chloroform to give a red solid (0.1 g) whose t.l.c. in chloroform over silica showed to to be a mixture of three close-running components.

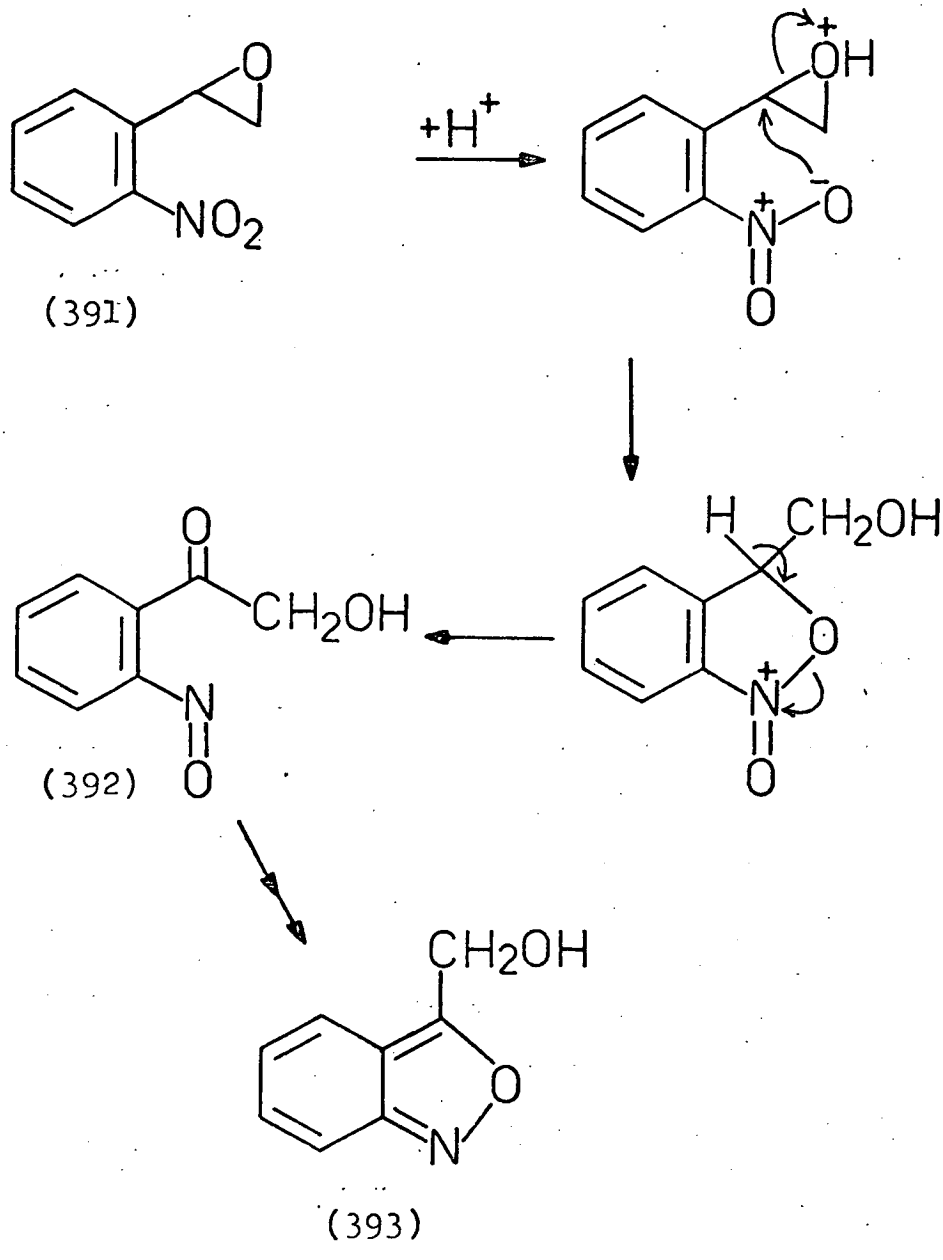
The original acidic aqueous phase was evaporated and the residue extracted with ethanol to give a gum (0.12 g) which was triturated with ethanol-light petroleum to give an unidentified solid (0.04 g).

Chapter 4

"The Acid-Catalysed Transformations of Some 2-Acyl-3-(2'-nitrophenyl)oxiranes"



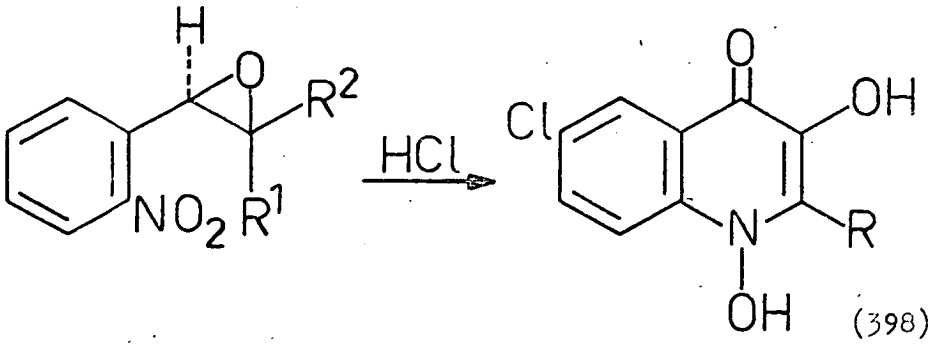
Scheme 68



Scheme 69

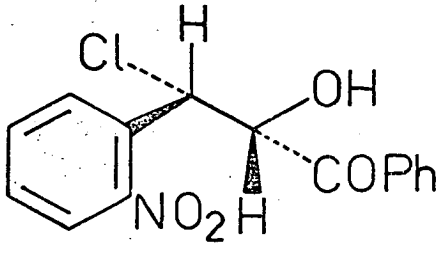
As discussed previously (see Introduction) it has been shown that the ortho-nitro group can anchimerically assist the solvolysis of 2-nitrobenzyl bromides. Participation by the ortho-nitro group is also proposed to account for the facile ring-opening reactions of certain 2'-nitrophenyloxirane derivatives. One of the earliest examples of such an interaction between a nitro group and a neighbouring epoxide substituent is that which is involved in the conversion[138] of ortho-nitrophenylglycidic acid (383) in hot glacial acetic acid or water, into a mixture of anthranil (390) and anthranil-3-carboxaldehyde (388). This transformation can be explained by intramolecular nucleophilic attack on the protonated epoxide [Scheme 68; (384)] (presumably in water the glycidic acid acts as its own acid catalyst) by an oxygen atom of the ortho-nitro group to give the cyclic intermediate (385) which then rearranges to the nitrosoketone (386). Decarboxylation of the latter and internal oxidation-reduction then gives the hydroxylamine derivative (387), cyclisation of which affords the aldehyde (388). The formation of the anthranil (390) can then be accounted for by oxidation[138] of the aldehyde (388) to anthroxanic acid (389) with subsequent decarboxylation.[139] Evidence for a nitroso intermediate in the acid-catalysed interaction between ortho-nitro groups and epoxide side-chains is provided[140] by the isolation of the nitrosoketone (392) from the reaction of 2-nitrophenyloxirane (391) with formic acid (Scheme 69). This reaction can be explained by a similar course to that proposed for 2-nitrophenylglycidic acid (383) previously discussed and indeed, the nitroso intermediate (392) reacts further, under acid conditions to afford the benzisoxazole (393).

More recently,[141,119] the reactions of the oxiranes (394 a-e) with hydrogen chloride in ether have been shown to afford the 6-chloro-N-hydroxyquinolones (398 a and b: Scheme 70) in varying yields.

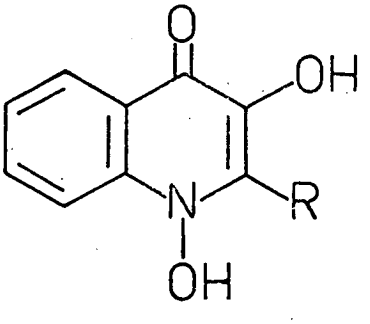


(398) R
a; Ph
b; CH_3

SUBSTRATE			PRODUCT	
(394)	R^1	R^2	(398)	Yield%
a;	H	Bz	a	43
b;	H	Ac	b	20
c;	Ac	Ac	b	85
d;	Bz	H	a	90
e;	Ac	Bz	b	85
f;	Bz	Bz	a	82



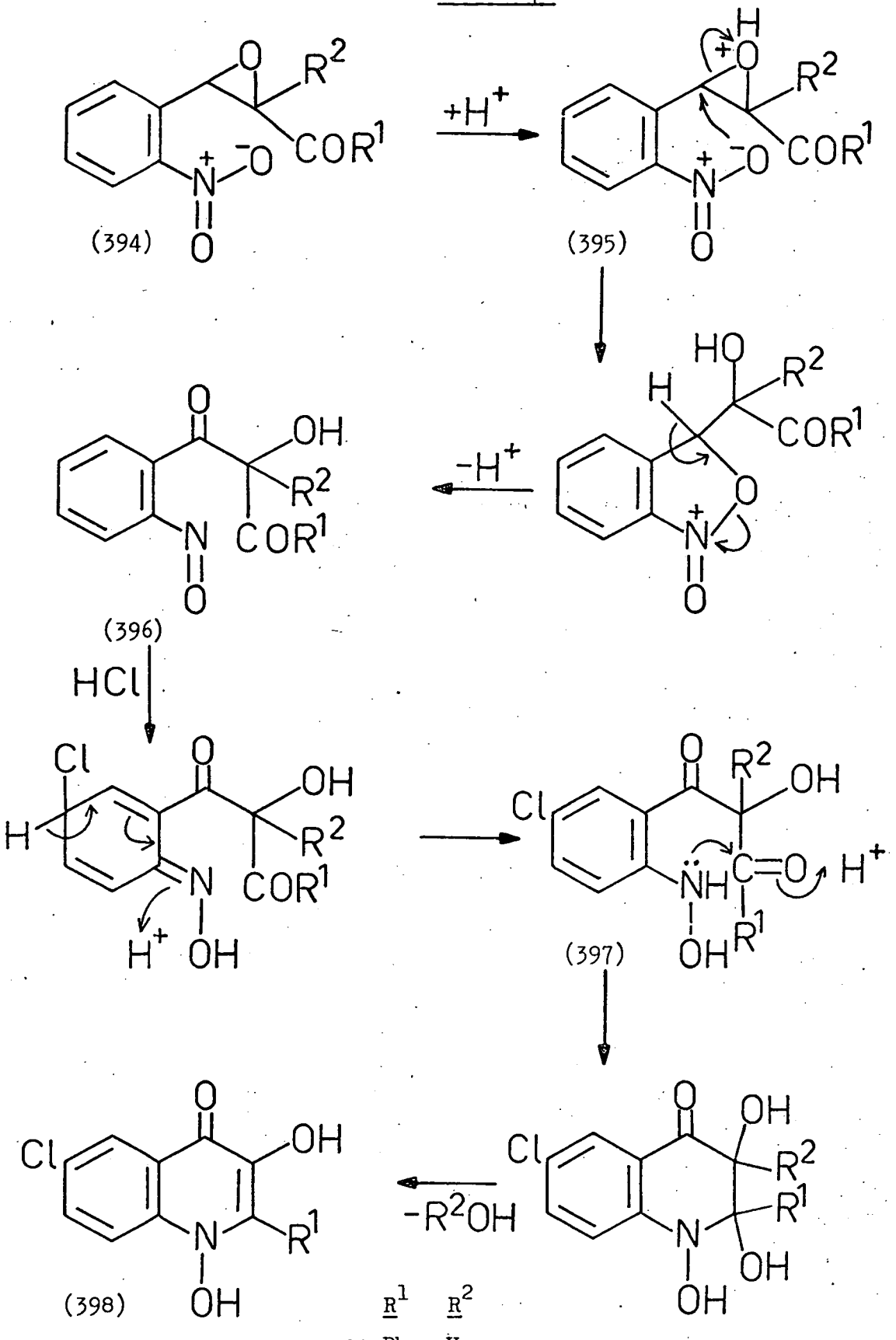
(399)



(400) R
a; Ph
b; CH_3

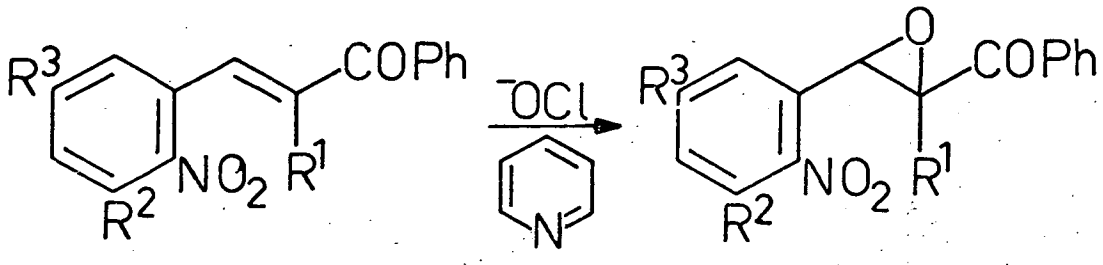
Scheme 70

Scheme 71



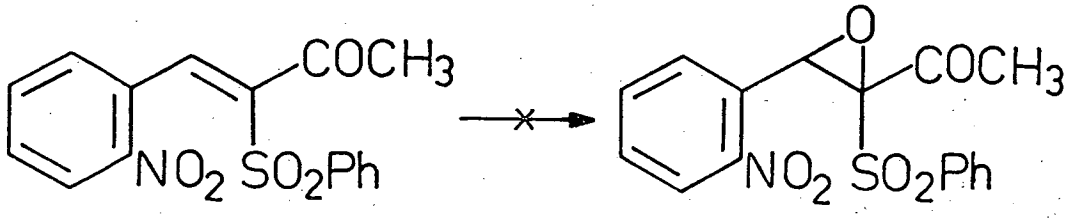
	R^1	R^2
a;	Ph	H
b;	CH_3	H
c;	CH_3	$COCH_3$
e;	CH_3	COPh
f;	Ph	COPh

Whereas the trans oxiranes (394a and b) afford only low yields of the N-hydroxyquinolones (398 a and b) respectively, accompanied in one case by the chlorohydrin adduct (399), the cis oxirane (394d) and the trisubstituted oxirane (394 c, e and f) afford high yields of the corresponding 6-chloro-N-hydroxyquinolones (398 a and b). This variation in yield of the N-hydroxyquinolone product between the cis and trans isomers is attributed[141] to the steric effect of the acyl substituents. In the cis oxirane the nitro group is presumed to be constrained by a buttressing effect of the acyl substituents, to a favourable position for nucleophilic attack upon the conjugate acid (395) of the oxirane (cf. Scheme 71). The absence of any chlorohydrin products from the reaction of the nitrophenyloxiranes (394 c-f) implies that the nitro group participates in the actual ring-opening of the oxirane thus blocking competitive nucleophilic attack on the oxirane ring by chloride ion since the approach of the nucleophile must be colinear with the bond being broken. This line of approach is not blocked in the trans oxiranes and consequently,in the presence of a high concentration of hydrogen chloride, the competitive nucleophilic attack by chloride ion on the conjugate acid of the oxirane, prevails. The initial stages of the mechanism[141] proposed for the formation of the chloroquinolones (Scheme 71) are analogous to those invoked to account for the formation of anthranil-3-carboxaldehyde (388) and 2-nitrosophenylmethanol (392) from other 2'-nitrophenyloxirane derivatives discussed before. However, in the presence of hydrogen chloride the nitroso intermediate [(396); Scheme 71] can undergo reduction to a hydroxylamino intermediate (397) with simultaneous introduction of a chlorine atom at the 5-position of the benzene ring. Cyclisation of the hydroxylamino intermediate (397) then yields the chlorinated N-hydroxyquinolone product (398). The dehalogenated quinolones (400 a and b)

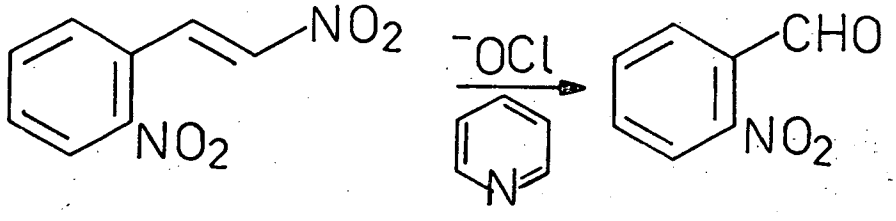


(402) (403)

	$\underline{R}^1$	$\underline{R}^2$	$\underline{R}^3$
a;	COPh	H	Cl
b;	COPh	H	Br
c;	COPh	Cl	Cl
d;	$CONH_2$	H	H



(404) (405)

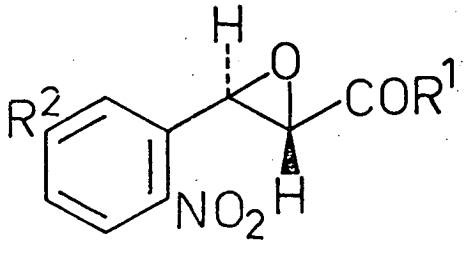


(406)

Scheme 72

may be formed by the addition of hydroquinone in the hydrogen chloride catalysed reaction or by the use of hydrogen bromide as an alternative catalyst in which cases the reduction step, involving conversion of the nitroso intermediate (396) into a hydroxylamino intermediate in the proposed reaction pathway, is effected without introduction of a halogen atom at the 5-position of the benzene ring.

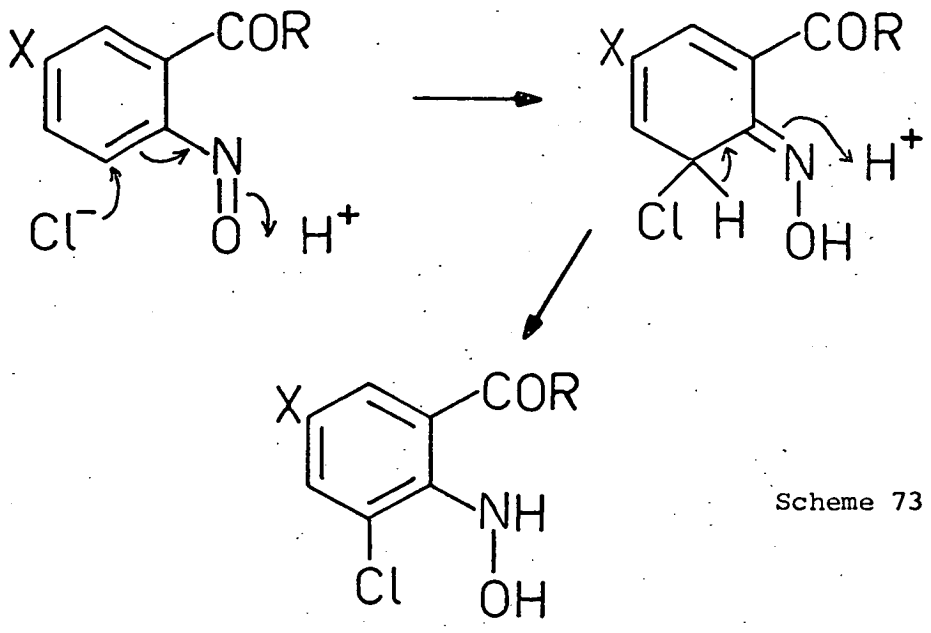
It was thought that by changing the nature of the acidic catalyst and examining the scope of the reactions of 3-acyl-2-(2'-nitrophenyl) oxiranes that additional information about the mechanism of these reactions could be obtained. It was also hoped to demonstrate the synthetic value of such reactions. The 2-acyl-3-(2'-nitrophenyl)oxiranes (394 a and 401 a-d) required for study were prepared by Darzens condensation[142] of 2-nitrobenzaldehydes with α-halocarbonyl compounds, in moderate to excellent yields. The 2,2-diacyl-3-(2'-nitrophenyl)oxiranes [(403 a-c); Scheme 72] were prepared in excellent yield by the oxidation of the corresponding benzylidene derivatives (402 a-c) using aqueous sodium hypochlorite



(401)	R^1	R^2
a;	NH_2	H
b;	Ph	Br
c;	Ph	H
d;	CH_3	H
e;	OEt	H

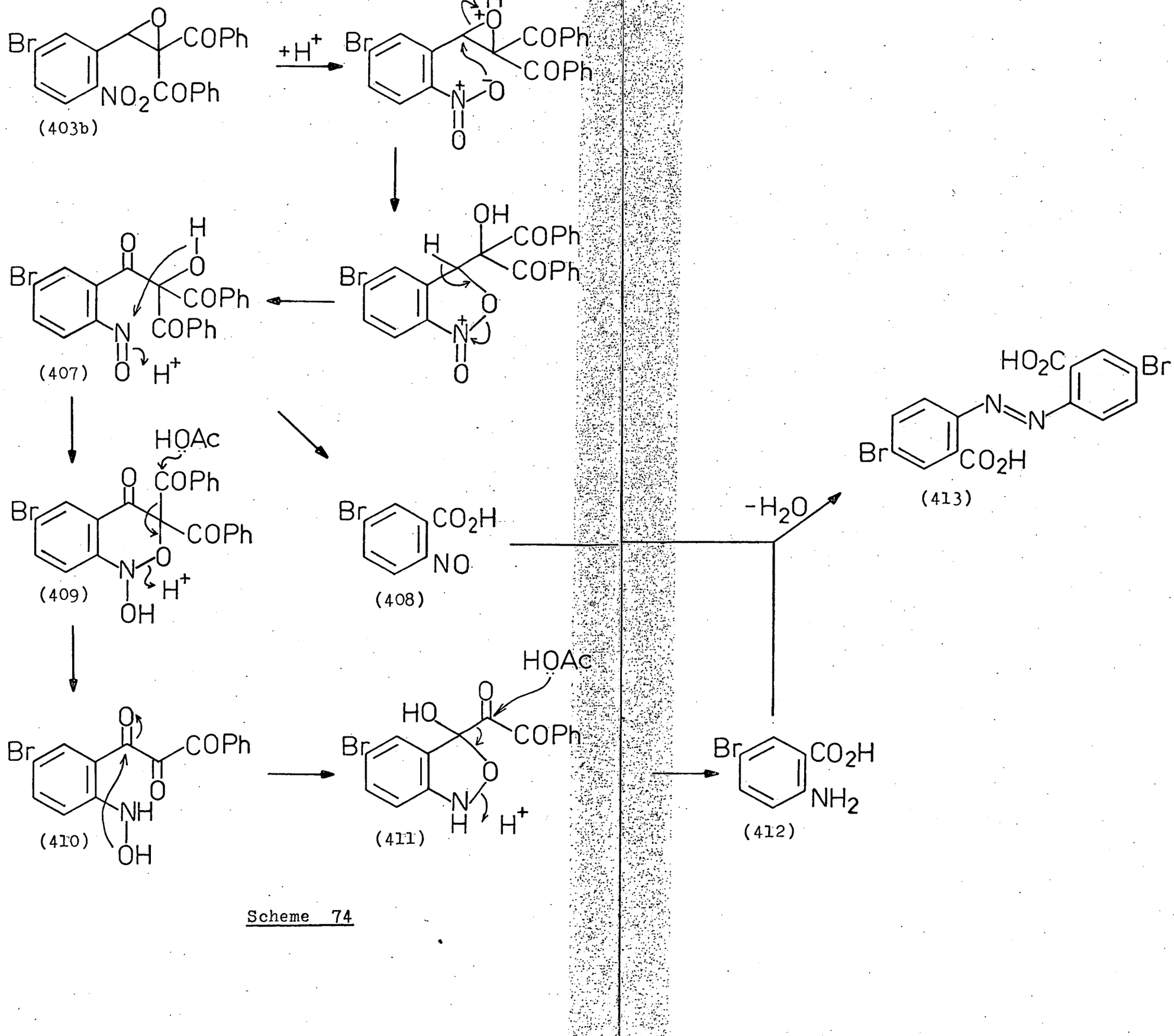
in pyridine, a method developed by Bayne.[119] However, this method failed to epoxidise the benzylidine derivative (402d) and the sulphone derivative (404). A similar attempt to epoxidise the known 2,2'-dinitrostyrene (406) resulted in its decomposition, the only product isolated being 2-nitrobenzaldehyde. The 2-nitrobenzylidene derivatives (402 a-d) required for epoxidation, were readily obtained in high yield by a modification of the method of Loudon and Sword,[143] namely condensation of 2-nitrobenzaldehydes with suitable β-dicarbonyl compounds in the presence of piperidine acetate as catalyst at a temperature of 60° for 24 h as opposed to the conditions recommended,[143] namely, room temperature for 4 days. The benzenesulphonyl derivative (404) was obtained by the condensation of benzenesulphonylacetone with 2-nitrobenzaldehyde in the presence of piperidinium toluene-p-sulphonate as catalyst.

It has been proposed, in the mechanism of quinolone formation from 2-acetyl-3-(2'-nitrophenyl)oxirane derivatives (cf. Scheme 71) that reduction of the nitroso intermediate is effected by hydrogen chloride with the introduction of chloride ion into the ring. The question therefore arose as to what would happen if the 5-position in the nitrosophenyl ring was blocked thus preventing chloride ion introduction at this position. If the assumption that reduction is achieved by nucleophilic attack by chloride ion on the nitrosophenyl ring is correct then it may be predicted, in this case, that the reduction step could still be effected by entry of chloride ion at the 3-position. (Scheme 73). The observation of such alternative substitution would provide some indirect evidence for the mechanism proposed for N-hydroxyquinolone formation. Conversely, if it was observed that blocking chloride entry at the 5-position prevented formation of N-hydroxyquinoline, then this would be positive evidence that reduction is affected by hydrogen chloride and not by any other means.



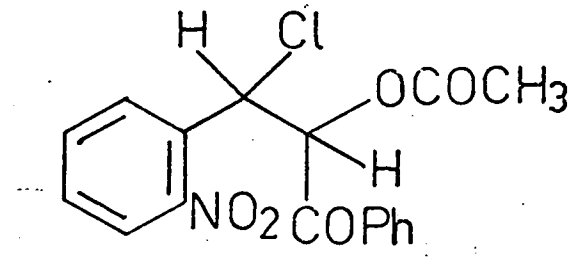
Scheme 73

In practice treatment of 3-(5'-bromo-2'-nitrophenyl)-2,2-dibenzoyloxirane (403b) with hydrogen chloride in either acetic acid or dioxan at room temperature, the conditions under which N-hydroxyquinolone formation from the parent oxirane (394f) was successful[119], afforded only a high return of unreacted starting material. Thus it is not unexpected that the 3',5'-dichloro-2'-nitrophenyloxirane (403c) when treated with hydrogen chloride in dioxan at room temperature for 48 h, also afforded only a high return of the unreacted starting material. The failure of both oxiranes (403 b and c) to react at all to any great extent, even to the extent of yielding the corresponding chlorohydrins, is surprising although the parent oxirane (394f) is itself slow to react, some starting material being recovered after even 80 h. The inertness of these dibenzoyloxiranes (394f) and (403b and c) may be attributed to the electron-deficiency of the oxirane ring due to the electron-withdrawing groups attached inhibiting protonation of the oxygen atom and consequently inhibiting ring-opening. The failure of chlorohydrin formation would thus arise from the reduced efficiency of acid-catalysis and from a steric blocking effect on chloride ion attack akin to that described in the quinolinone formation from the cis-disubstituted oxirane (394d) earlier.

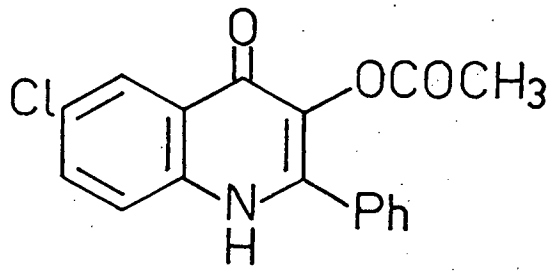

Br
O
COPh
NO2COPh
(403b)
+H+
H
+O
COPh
COPh
N+
O
O
OH
H
(407)
H+
HOAc
(409)
(408)
(410)
(411)
(412)
-H2O
HO2C
N=N
CO2H
(413)
NH
NH2

Scheme 74

In an attempt to force the bromonitrophenyloxirane (403b) to undergo acid-catalysed rearrangement, it was heated under reflux for 3 h with hydrogen chloride in acetic acid. Despite these forcing conditions the oxirane (403b) was recovered unchanged in 45% yield. However, a solid whose properties are consistent with it being 4,4'-dibromoazobenzene-2,2'-dicarboxylic acid (413) was isolated. In particular, it was acidic and its i.r. spectrum showed acidic hydroxyl bands at 2650 and 2550 cm^{-1} and a carbonyl band at 1695 cm^{-1}. Its mass spectrum showed a parent ion in 1:2:1 isotope ratio, consistent with the inclusion of two bromine atoms in the molecule. When 2,2-dibenzoyl-3-(2'-nitrophenyl)oxirane(394f) was subjected to heating with hydrogen chloride in glacial acetic acid the only identified product, obtained in low yield was benzoic acid. Since it appears that hydrogen chloride cannot effect reduction of a nitroso intermediate without the incorporation of chlorine into the nitrosophenyl ring, and since no chlorine was incorporated into the azobenzene product (413), the mechanism proposed (Scheme 74) for the formation of the azo compound (413) involves only internal oxidation-reduction processes. Thus, acid-catalysed ring-opening of the oxirane (403b) with participation of the nitro group, gives rise to the nitroso intermediate (407) as in the mechanism proposed for quinolone formation. Solvolytic cleavage of side-chain of the nitrosophenyl ring then produces the 2-nitrosobenzoic acid derivative (408). Alternatively, the nitrosophenyl intermediate (407) can rearrange to the hydroxylaminotriketone intermediate (410) by an internal oxidation-reduction with solvolysis of a benzoyl group. This intermediate (410) may then undergo further internal oxidation-reduction, again with solvolytic cleavage of the remaining benzoyl group, to give the anthranilic acid derivative (412), condensation of which with the nitrosobenzoic acid intermediate (408) explains the formation of the dibromoazobenzene derivative (413).



(414)



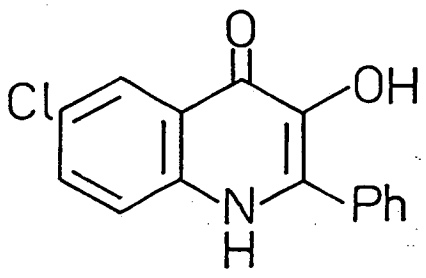
(415)

In a further attempt to effect the acid-catalysed rearrangement of 2,2-diacyl-3-(2'-nitrophenyl)oxiranes to chlorinated N-hydroxyquinolones under conditions which might be applicable to apparently unreactive substrates such as 2,2-dibenzoyl-3-(5'-bromo-2'-nitrophenyl)oxirane (403b), the use of concentrated aqueous hydrochloric acid as the catalyst in such transformations was investigated. Thus, heating the parent dibenzoyloxirane (394f) under reflux with concentrated aqueous hydrochloric acid in glacial acetic acid for only 1 h, gave a 91% yield of the N-hydroxyquinolone (398 a), a marked improvement on the room temperature hydrogen chloride catalysed cyclisation.[119] Benzoic acid (50%) was also isolated. Despite the success of this method, the attempted rearrangement of the 5-chloro-substituted oxirane (403 a) using hot concentrated aqueous hydrochloric acid in glacial acetic acid, gave a 47% recovery of starting material. Benzoic acid (50%) was however, also isolated.

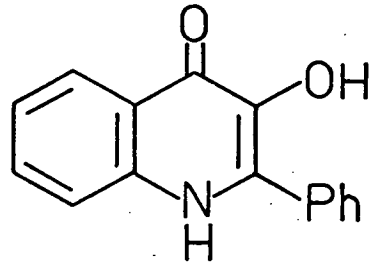
In an attempt to further probe the mechanism of the hydrogen chloride catalysed reactions of 2-acyl-3-(2'-nitrophenyl)oxiranes, their reactions in a hot mixture of acetyl chloride and acetic acid were investigated. This medium was chosen in the expectation that it would provide both the necessary hydrogen chloride catalyst and an acetylating reagent which might permit the trapping of one or more of the reactive intermediates [e.g. the hydroxylamino intermediate (397); (Scheme 71)] as their acetyl derivatives. Thus, heating trans 2-benzoyl-3-(2'-nitrophenyl)oxirane (394a) in a mixture of acetyl chloride and acetic acid afforded two products in low yield. These were subsequently identified as the acetylated chlorohydrin (414) and 3-acetoxy-6-chloro-2-phenylquinolin-4(1H)-one (415). The structure of the acetylated chlorohydrin (414) is based on its elemental analysis and its i.r. spectrum which showed bands attributable to nitro group absorptions. Its ^{1}H n.m.r. spectrum showed nine aromatic

protons and two mutually coupled (J 9Hz) signals at τ3.26 and τ3.80 which are assigned to the two methine hydrogen atoms. The peak due to three protons at τ8.12 is assigned to the acetoxy methyl group. Its mass spectrum did not show a parent ion and the base peak appeared at m/e 204. The quinolone (415) showed an identical i.r. spectrum of an authentic sample.[141] The structure of the quinolone (415) was further established by its hydrolysis to the known[141] compound, 6-chloro-3-hydroxy-2-phenyl-quinolin-4(1H)-one (416) which gave identical spectral data to that of an authentic sample. Its elemental analysis, however, showed it to be a mono-hydrate.

The attempted reaction of the bromo-nitrophenyloxirane (401b) with hot acetyl chloride in acetic acid, gave largely starting material.



(416)



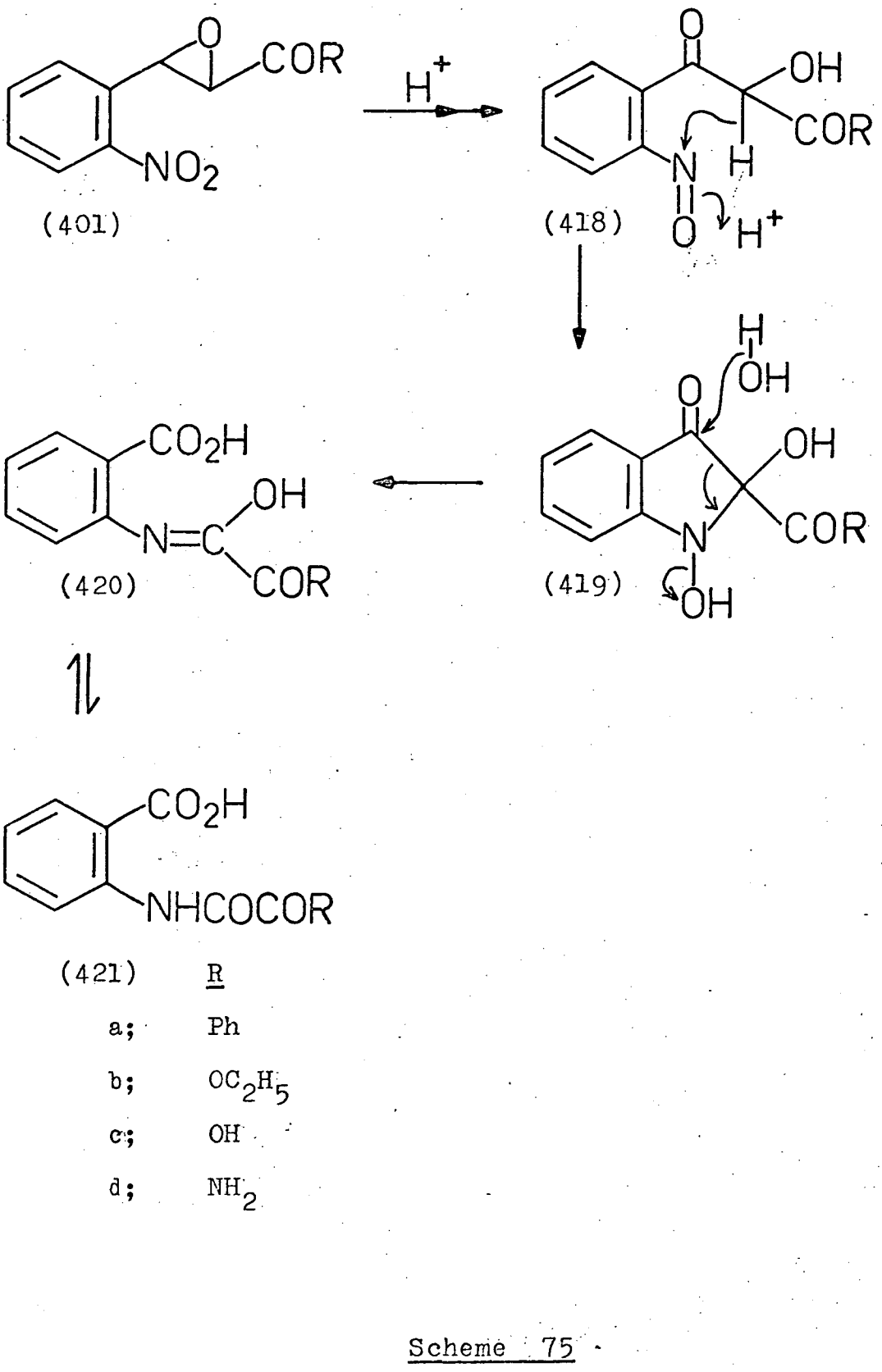
(417)

The inertness of the bromo compound (401b), even to chlorohydrin formation again shows that an electron-withdrawing substituent on the nitrophenyl ring has a marked effect upon the ability of the oxirane to undergo ring-opening. Thus, it is possible that the additional electron-withdrawing effect of the bromo substituent inhibits formation of the conjugate acid of the type (395) (cf. Scheme 71), hence inhibiting acid-catalysis of the ring-opening reaction. Alternatively, the effect of the electron-withdrawing substituent may be to decrease the nucleophilicity of the nitro group thus removing the participation of the nitro group in the ring-opening of a conjugate acid of the type (395). This implies however, that it is necessary for the nitro group to interact with the

oxirane for ring-opening to occur at all and that chloride ion cannot effect ring-opening of a conjugate acid of the type (395) since no chlorohydrin was formed in the reaction of the bromo-oxirane derivative (401b) with hot acetyl chloride-acetic acid, or with hydrogen chloride in acetic acid. However, it is difficult to reconcile this implication with the reason proposed for the variation in the yields of product from cis and trans isomers of the disubstituted oxiranes (cf. Scheme 70). When the benzoyloxirane (394a) was heated in a mixture of acetyl bromide and glacial acetic acid, the isolated product formed in moderate yield, was the 3-hydroxy-2-phenylquinolin-4(1H)-one (417) which was identical to an authentic sample.[141] This was the expected product by analogy with the acetyl chloride-acetic acid reaction but in this case the reduction of the nitroso intermediate [(396); Scheme 71] is effected by hydrogen bromide without incorporation of bromine into the product.

The attempted reactions of other 2-acyl-3(2'-nitrophenyl)oxiranes with hot acetyl chloride in acetic acid were largely unsuccessful. Thus, the acetyl-oxirane (401d) and the ester (401e) gave intractable products from which no identifiable material could be obtained. On the other hand, similar treatment of the dibenzoyl-oxirane (394f) gave a high return of the starting material.

The results obtained from the reactions of the oxiranes (401c-e and 394f) with acetyl chloride or acetyl bromide are difficult to explain in view of those obtained in the hydrogen chloride catalysed reactions of the same oxiranes (401 c-e and 394f) since the acetyl halide reactions give products that are reduced with respect to the 1,3-dihydroxyquinolinones (398 a and b) obtained from the hydrogen halide reactions. However, it was shown that the 1,3-dihydroxyquinolinone (398a) could be converted under the acetyl chloride-acetic acid conditions, into the 3-acetoxyquinolone (415). The mechanism of this reaction is not clear but obviously a reduction is involved at some stage.



(401) (418) (419) (420)

(421) R

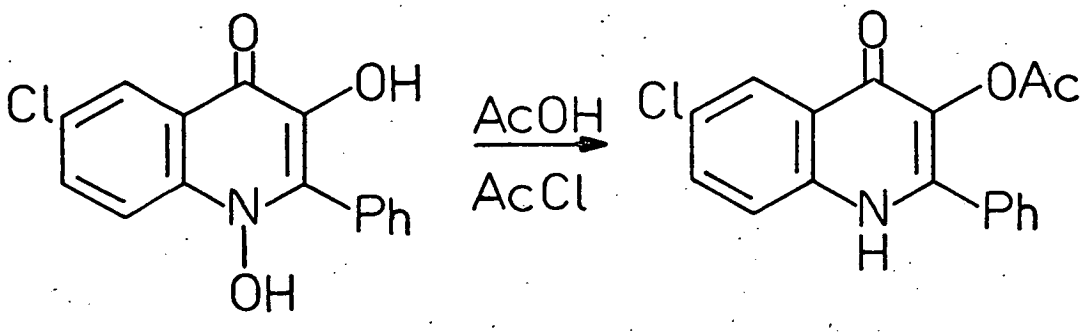
a; Ph

b; OC_2H_5

c; OH

d; NH_2

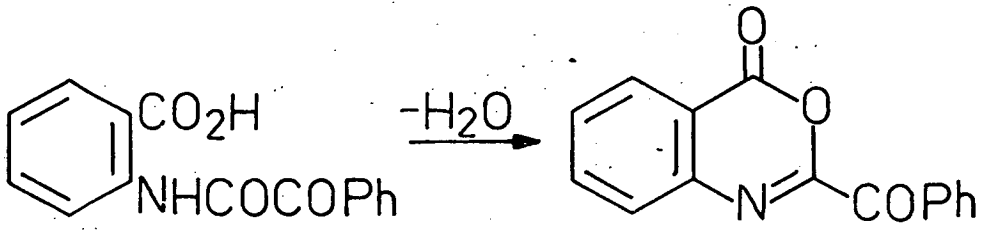
Scheme 75



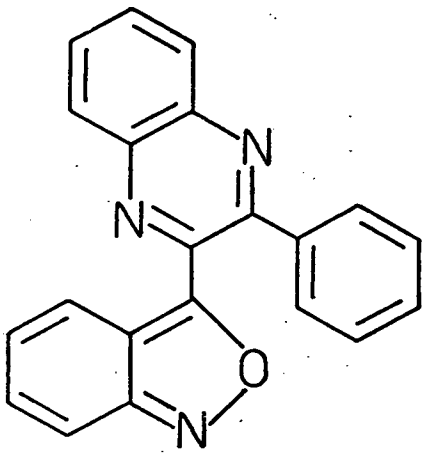
(398a) (415)

Attention was next turned to the study of the acid-catalysed reactions of 2-acyl-3-(2'-nitrophenyl)oxirane derivatives using acidic catalysts which cannot effect reduction in the hope that the acid-catalysed rearrangement would be halted at the nitroso stage, thereby providing information about the overall mechanism of the ortho-nitro group-side-chain rearrangement. Concentrated sulphuric acid has been used as the catalyst in transformations of 2-nitrobenzylidene derivatives (cf. Introduction) but in the present studies, this reagent was considered to be too severe and the milder polyphosphoric acid was chosen instead.

Thus, stirring 2-benzoyl-3-(2'-nitrophenyl)oxirane (401c) with polyphosphoric acid at room temperature or at 80° afforded moderate yields of a product identical in all respects to an authentic[144] sample of N-(phenylglyoxyloyl)anthranilic acid [(421a); Scheme 75]. The structure of the anthranilic acid derivative (421a) was further established by its reaction with acetic anhydride to afford 2-benzoyl-4H-3,1-benzoxazin-4-one (422) which was identical to an authentic sample[144] and on hydrolysis was reconverted into the anthranilic

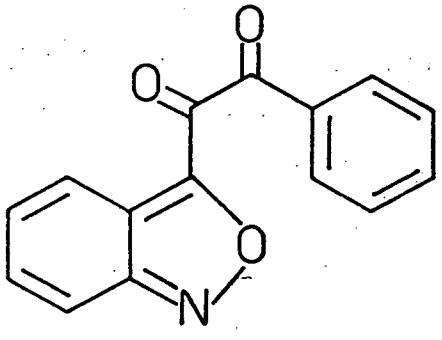


(421a) (422)

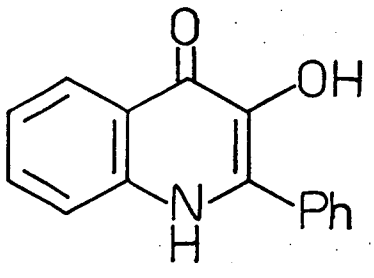


(427)

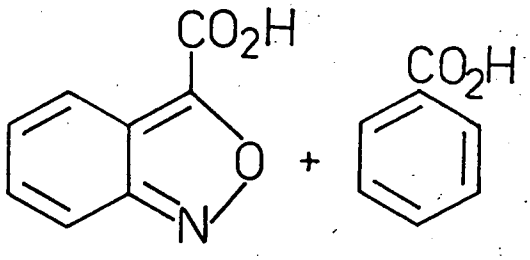
OPDA



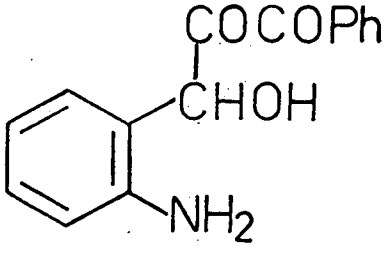
(426a)



(417)



(429) (430)



(428)

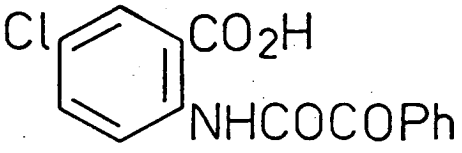
Scheme 76

acid derivative (421a). 2-Ethoxycarbonyl-3-(2'-nitrophenyl)oxirane (401e) reacted similarly with polyphosphoric acid to afford a high yield (75%) of the known[145] N-ethoxalylanthranilic acid (421b). When the carbamoyl-oxirane (401a) was treated with polyphosphoric acid at 80°, however, a vigorous reaction ensued and a low yield of N-oxalylanthranilic acid (421c) was isolated. This product, which was identical to the acidic product from the solvolysis of the ester (421b) obtained before, was identified by comparison with an authentic sample.[144] In contrast, treatment of the carbamoyl-oxirane (401a) with polyphosphoric acid at room temperature, afforded the expected N-oxamoylanthranilic acid (421d)[144] in near quantitative yield.

The acid-catalysed reactions of 2,2-dibenzoyl-3-(2'-nitrophenyl)-oxiranes (394f and 403a-c) with polyphosphoric acid were also investigated. Thus, heating the parent 2,2-dibenzoyl-3-(2'-nitrophenyl)oxirane (394f) with polyphosphoric acid at 80° afforded a neutral yellow solid, in contrast to the colourless acidic products obtained from the disubstituted oxiranes (401) discussed before. Its elemental and mass spectral (m/e 251) data suggested a molecular formula $C_{15}H_9NO_3$ and its i.r. spectrum lacked bands due to nitro group absorption but contained carbonyl absorption at 1665 cm^{-1}. The loss of a seven-carbon fragment from the starting oxirane (394f) to give a fifteen carbon compound was further indicated by the isolation of benzoic acid in high yield (83%) as a by-product of the reaction. The structure of the yellow product was firmly established as the 2,1-benzisoxazole (anthranil) (426a) derivative on the basis of its reaction with ortho-phenylenediamine (OPDA) to give the quinoxaline derivative (427) (Scheme 76). Its reduction by dithionite to afford a compound identical in all respects with an authentic sample[141] of 3-hydroxy-2-phenylquinolin-4(1H)-one (417) further supports the structure (426a) of the product. This reduction product may be

rationalised (Scheme 76) on the basis of reductive ring-opening of the anthranil derivative (426a) to the amine (428) followed by ring-closure to the quinolinone (417). The presence of the anthranil nucleus in the yellow product was established by its oxidation with potassium dichromate to give anthranil-3-carboxylic acid (429) identical in all respects with an authentic[141] sample. Benzoic acid (430) was also isolated from the oxidation of the yellow product (426a).

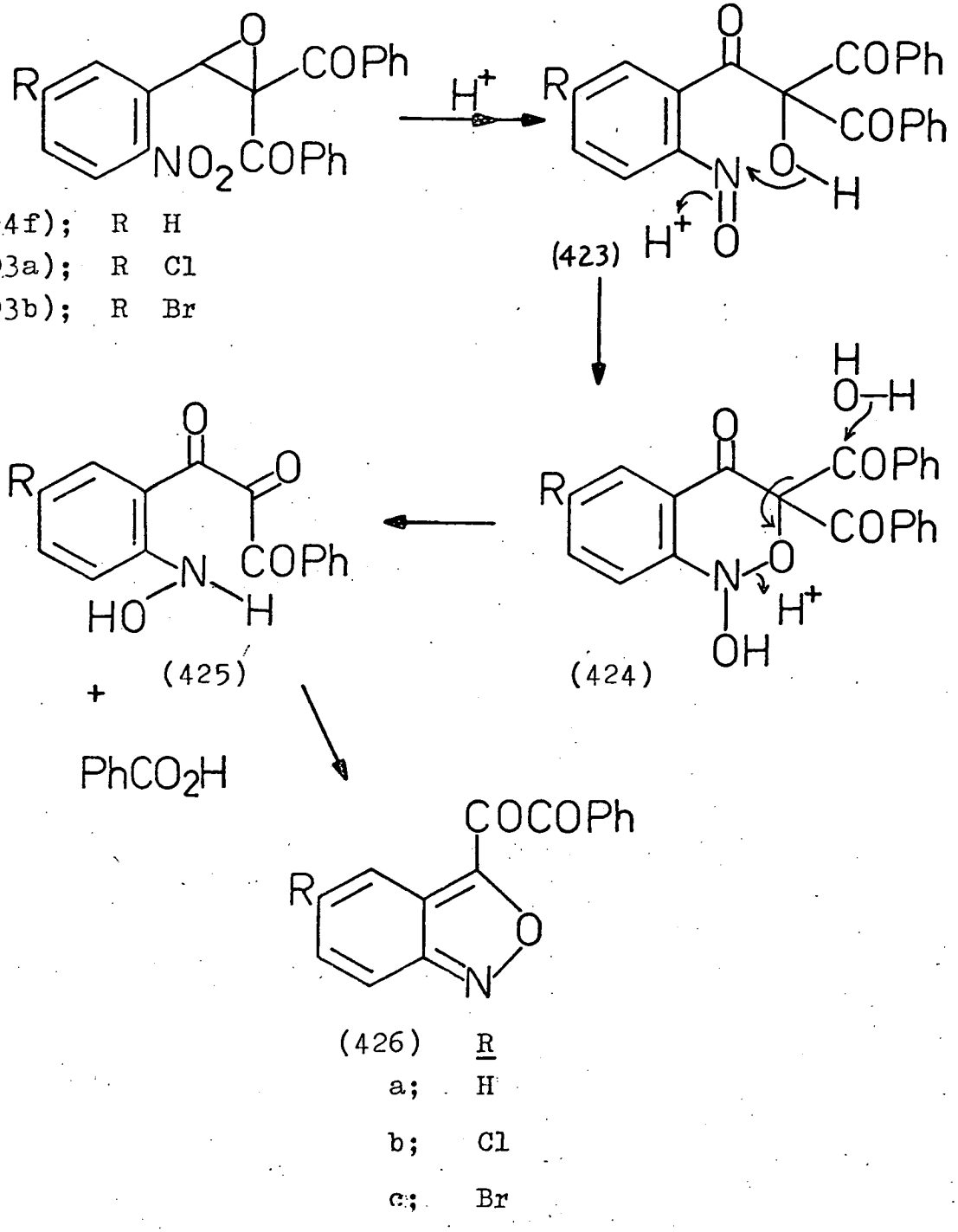
Anthranil formation was also observed with the chlorinated and brominated dibenzoyloxiranes (403 b and c) when they were reacted with hot polyphosphoric acid. Benzoic acid was also isolated as a by-product in these reactions and in one case, that of the chlorinated derivative (403a), a small amount of an acidic solid whose elemental analysis was consistent with the anthranilic acid derivative (431) was isolated.



(431)

Its i.r. spectrum showed a band at 3190 cm^{-1} attributable to an amide NH stretch and carbonyl adsorption at 1695 and 1660 cm^{-1} were also present.

However, as already observed in the hydrogen chloride catalysed processes, the presence of the halogen substituents imparted a degree of inertness in the case of the conversions of the halogenated-2,2-dibenzoyloxiranes (403 a and b) into the anthranils (426 b and c) as compared with the formation of the anthranil (426a) from the parent oxirane (394f). Thus, the latter transformation was complete within 3 h at 80° but the bromo-oxirane (403b) required 6 h at 80° and the



(394f); R H
(403a); R Cl
(403b); R Br

(426) R
a; H
b; Cl
c; Br

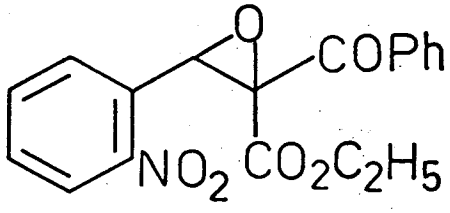
Scheme 77

chloro-oxirane (403a) required 20 h at 80° for complete reactions. This inertness again may be attributed to the effect of the electron-withdrawing effect of the halogen-substituent reducing the basicity of the oxirane ring towards protonation and perhaps to the decreased nucleophilicity of the nitro group, thus inhibiting the acid-catalysed ring-opening reaction. This effect was even more apparent with the dichloro-oxirane (403c) which was recovered essentially unchanged after heating at 100° for 6 h.

The course of the polyphosphoric acid catalysed reactions of the 2-acyl-3-(2'-nitrophenyl)oxiranes (401 a,c and e) and of the 2,2-dibenzoyl-3-(2'-nitrophenyl)oxiranes (394f and 403 a and b) can be postulated to have a common course as far as formation of the respective nitroso intermediates [(418) and (423); Schemes 75 and 77]. The difference then between these two intermediates, is the presence of an acidic methine proton in the nitroso intermediate (418) derived from the disubstituted oxiranes (401). Thus, the nitroso intermediate [(418); Scheme 75] may be postulated to suffer intramolecular nucleophilic attack at the nitroso group to give the cyclic intermediate (419) which is presumably stable until aqueous work-up causes ring opening as shown [(419) → (420)] to give the N-acyl-anthranilic acid derivatives (421 a-d). However, the nitroso intermediate (423) derived from the 2,2-dibenzoyl-3-(2'-nitrophenyl)oxiranes (394 f and 403) does not possess such an acidic methine proton and alternative nucleophilic attack on the nitroso group by the acid hydroxyl group occurs to give the cyclic intermediate (424) which can loose benzoic acid to afford the 1,2,3-tricarbonyl-hydroxylamino derivative (425). This then cyclises in a fashion analogous to that proposed for the hydroxylamino derivative [(387); Scheme 68] in the final step of formation of anthranil-3-carboxaldehyde [(388); Scheme 68]. The high yields of cyclised products obtained from nitro group side chain

interactions in the case of the trans 2-acyl-3-(2'-nitrophenyl)oxiranes (401) in the polyphosphoric acid-catalysed reactions is attributable to the absence of any competing nucleophile (i.e. chloride ion) as is the case with the hydrogen chloride-catalysed reactions.

In an attempt to extend the polyphosphoric acid-catalysed cyclisation of trisubstituted oxiranes to 2,1-benzisoxazole derivatives, 2-benzoyl-2-ethoxycarbonyl-3-(2'-nitrophenyl)oxirane (432) was treated with polyphosphoric acid at 50° for 3 h. On work-up however, no identifiable products were obtained.



(432)

In summary it has been demonstrated that the capacity of the 2-acyloxiranes (401) and the 2,2-dibenzoyloxiranes (403) to form quinolinone derivatives requires the presence of an added reducing agent. In the absence of any such reducing agent the 2,2-dibenzoyloxiranes (403) and the 2-acyloxirane (401) give different types of products but these can both be rationalised in terms of initial formation of a nitroso intermediate arising from nitro group-side-chain interaction. It was also shown that in general, the reactivity of the oxiranes (401 and 403 etc.) was very sensitive to the presence of electron-withdrawing substituents in the nitrophenyl ring, but it is largely unclear how this effect operates in the detailed mechanism of the reactions described.

EXPERIMENTAL

The Condensation of 2-Nitrobenzaldehydes with Active Methylene Compounds in the Presence of Piperidine in Acetic Acid.

1. General Method:

A mixture of the aldehyde (0.02 mol) and dibenzoylmethane (0.025 mol) in glacial acetic acid (40.0 ml) was treated with piperidine (10.0 ml) and the mixture was stirred at 60° for 48 h except in case (a) where the duration of stirring and heating was 24 h. The mixtures were then cooled and the insoluble solid was collected and washed with water and ethanol to give the benzylidene derivatives as described below

(a) 1,1-Dibenzoyl-2-(2'-nitrophenyl)ethylene[143] (394f) was prepared by the reaction of 2-nitrobenzaldehyde with dibenzoylmethane as colourless needles (63%), m.p. 136° (lit.,[143] 137°), $\nu_{max.}$ 1685 and 1640 (CO) cm^{-1}.

Evaporation of the combined filtrate and washings afforded only a mixture of unreacted starting materials.

(b) 1,1-Dibenzoyl-2-(5'-chloro-2'-nitrophenyl)ethylene (402a) was prepared by the reaction of 5-chloro-2-nitrobenzaldehyde with dibenzoylmethane as colourless needles (90%), m.p. 124° (from ethanol), $\nu_{max.}$ 1670 and 1630 (CO) and 1530 and 1340 (NO_2) cm^{-1},

Found: C, 67.4; H, 3.6; N, 3.4; p^+, 392/391(M^+-H)

$C_{22}H_{14}ClNO_4$ requires: C, 67.4; H, 3.6; N, 3.6; M, 392.5.

(c) 1,1-Dibenzoyl-2-(5'-bromo-2'-nitrophenyl)ethylene (402b) was prepared by the reaction of 5-bromo-2-nitrobenzaldehyde with dibenzoylmethane as colourless needles (65%), m.p. 147° (from ethanol-dimethylformamide), $\nu_{max.}$ 1680 and 1645 (CO) and 1530 and 1350 (NO_2) cm^{-1}

Found: C, 60.8; H, 3.3; N, 3.1%; M^+, 437/435.

$C_{22}H_{14}BrNO_4$ requires: C, 60.6; H, 3.2; N, 3.2%; M, 436.

Further work-up of the filtrate and washings gave no more product.

(d) 1,1-Dibenzoyl-2-(3',5'-dichloro-2'-nitrobenzoyl)ethylene (402c) was prepared by the reaction of 3,5-dichloro-2-nitrobenzaldehyde with dibenzoylmethane but the reaction was prolonged for a further 20 h. The 2-nitrobenzoylethylene derivative (402c) (53%) formed colourless needles, m.p. 99° (from ethanol), $\nu_{max.}$ 1665 and 1647 (CO) and 1525 and 1355 (NO_2) cm^{-1}.

Found: C, 62.2; H, 3.1; N, 3.2%; p^+, 381/379(M^+-NO_2)

$C_{22}H_{13}ClNO_4$ requires: C, 62.0; H, 3.1; N, 3.3%; M, 426.

The filtrate and washings were diluted with water (20.0 ml) and extracted with chloroform. The chloroform phase was washed with saturated aqueous sodium hydrogen carbonate solution (2 x 20.0 ml) and evaporated to give an oil (1.5 g) which was redissolved in ether and washed with saturated aqueous sodium hydrogen sulphite solution (2 x 10.0 ml). Evaporating the ether phase and triturating the residue with a little ether afforded an unidentified colourless solid (0.11 g), m.p. 142°, $\nu_{max.}$ 1660 and 1530 and 1360 (NO_2) cm^{-1}.

The trituration mother liquor was evaporated to give an oil (1.2 g) whose t.l.c. in chloroform over silica showed it to be a multicomponent mixture containing none of the desired product.

Acidification of the sodium hydrogen sulphite extract with dilute aqueous sulphuric acid, and extraction with chloroform gave no material.

(e) 1-Benzoyl-1-carbamoyl-2-(2'-nitrophenyl)ethylene (402d) was prepared by the reaction of 2-nitrobenzaldehyde with benzoylacetamide[147] as described for dibenzoylmethane before. The amide (402d) formed colourless needles (78%) m.p. 181° (from ethanol), $\nu_{max.}$ 3410, 3390 and 3160 (NH_2), 1680 and 1640 (CO), and 1520 and 1345 (NO_2) cm^{-1}

Found: C, 65.4; H, 4.1; N, 9.5%; M^+ 296.

$C_{16}H_{12}N_2O_4$ requires: C, 64.9; H, 4.1; N, 9.5%; M, 296.

2. 1-Acetyl-1-benzenesulphonyl-2-(2'-nitrophenyl)ethylene (404)

A mixture of benzenesulphonylacetone (4.0 g, 0.02 mol) and 2-nitrobenzaldehyde (3.0 g, 0.02 mol) in dry dimethylformamide (10.0 ml) and dry benzene (20.0 ml) was treated with piperidine (0.2 ml) followed by a little toluene-p-sulphonic acid and was heated under reflux for 3h with provision for the azeotropic distillation of water formed in the reaction (Dean and Stark apparatus). The mixture was evaporated under reduced pressure and the resulting black solid was successively triturated with methanol to give the olefin (404) (total 4.6 g, 70%), m.p. 117° (from ethanol), $\nu_{max.}$ 1700 (CO), 1570 (C=C), 1525 and 1350 (NO_2), and 1150 (SO) cm^{-1}.

Found: C, 58.0; H, 4.0; N, 3.9%; p^+, 285 (M^+-NO_2)

$C_{16}H_{13}NO_5S$ requires: C, 58.0; H, 3.9; N, 4.2%; M, 331.

3. 1-Nitro-2-(2'-nitrophenyl)ethylene[148]

The 2-nitrophenylalkene (406) was prepared by the method of Fieser et.al.[148] as an orange solid (42%) m.p. 105° (from ethanol) (lit.,[148] 108°).

4. The Epoxidation of the 2-Nitrophenylethylene Derivatives (402 a-c) to Give the 2-Nitrophenyloxiranes (394 f and 403 a-c) Using Aqueous Sodium Hypochlorite in Pyridine

General Method:

The 2-nitrophenylethylene derivative (0.005 mol) in pyridine (7.5 ml) was stirred and treated in one portion with 8% aqueous sodium hypochlorite solution (11.0 ml). After 10-15 min the mixture was poured into water (ca. 20.0 ml) to give the 2-nitrophenyloxirane derivative.

a) 2,2-Dibenzoyl-3-(5'-chloro-2'-nitrophenyl)oxirane (403a) was prepared from the corresponding olefin (402a) by the method described above as colourless needles (92%), m.p. 184°(from dioxan-ethanol), $\nu_{max.}$ 1690 (CO) and 1530 and 1350 (NO_2) cm^{-1}, τ $(CD_3)_2SO$ 1.71-2.58 (13H, m, ArH) and 4.50 (1H, s, CH).

Found: C, 64.8; H, 3.5; N, 3.5%; p^+304/302(M^+-COPh)

$C_{22}H_{14}ClNO_5$ requires: C, 64.8; H, 3.4; N, 3.4%; M, 408.5.

(b) 2,2-Dibenzoyl-3-(5'-bromo-2'-nitrophenyl)oxirane (403b) was obtained from the corresponding olefin (402b) by the method described above, as colourless needles (95%), m.p. 199° (from ethanol-dimethylformamide), $\nu_{max.}$ 1690 (CO) and 1530 and 1350 (NO_2) cm^{-1}.

Found: C, 58.2; H, 3.2; N, 3.3%; M^+453/451.

$C_{22}H_{14}BrNO_5$ requires: C, 58.4; H, 3.1; N, 3.1%; M, 452.

(c) 2,2-Dibenzoyl-3-(3',5'-dichloro-2-nitrophenyl)oxiranes (403c) was obtained from the corresponding olefin (402c) as colourless needles (92%) m.p. 170° (from ethanol-dimethylformamide), $\nu_{max.}$ 1680 (CO) and 1530 and 1360 (NO_2) cm^{-1}.

Found: C, 59.8; H, 3.0; N, 3.3%; p^+ 293/291

($M-\underline{O}-NO_2C_6H_4.CO$)

$C_{22}H_{13}Cl_2NO_5$ requires: C, 59.7; H, 2.9; N, 3.2%; M 442.

(d) The Attempted Synthesis of 2-Benzoyl-2-carbamoyl-3-(2'-nitrophenyl) oxirane. (403d)

A solution of the olefin (402 d) (0.6 g, 0.002 mol) in pyridine (2.0 ml) was treated with 8% aqueous sodium hypochlorite solution (3.0 ml) and stirred for 5 min and then poured into water (20.0 ml). The aqueous solution was subjected to constant chloroform extraction. The chloroform layer was then washed with dilute aqueous hydrochloric acid (2 x 5.0 ml) and was evaporated to give an intractable yellow gum (0.54 g). T.l.c. of the gum in ethyl acetate over silica showed it to be a multicomponent mixture.

(e) The Attempted Synthesis of 2-Nitro-3-(2'-nitrophenyl)oxirane

A solution of 2,2'-dinitrostyrene[148] (406) (0.48 g, 0.0025 mol) in pyridine (3.0 ml) was treated in one portion with 8% aqueous sodium hypochlorite solution (4.0 ml) and the mixture was stirred for 2 min and then poured into water (5.0 ml). The mixture was extracted with chloroform (2 x 10.0 ml) to give a gum which was extracted with hot light petroleum to yield 2-nitrobenzaldehyde (0.2 g, 56%), m.p. 42° (from light petroleum, b.p. 40-60°), identical (m.p. and i.r. spectrum) with an authentic sample.

(f) The Attempted Epoxidation of 1-Acetyl-1-benzenesulphonyl-2-(2'-nitrophenyl)ethylene.(404)

The olefin (404) (0.66 g; 0.002 mol) in pyridine (2.0 ml) was treated with 8% aqueous sodium hypochlorite solution (4.0 ml) and the mixture was stirred for 10 min and then poured into water (10.0 ml). The gum that separated solidified on standing to give an unidentified solid (0.12 g), $\nu_{max.}$ 1530 and 1350 (NO_2) cm^{-1}.

The aqueous mother liquor was extracted with chloroform and the chloroform layer was washed with dilute aqueous sulphuric acid and then evaporated to give only a negligible amount of gum. The aqueous mother liquor was neutralised with solid sodium acetate and extracted with chloroform to give only a negligible amount of gum.

5(a) 2-Benzoyl-2-ethoxycarbonyl-3-(2'-nitrophenyl)oxirane (432) was obtained as an oil by the hypochlorite oxidation of 1-benzoyl-1-ethoxycarbonyl-2-(2'-nitrophenyl)ethylene in pyridine as described by Bayne.[119] It was used directly without further purification.

(b) 2-Benzoyl-2-cyano-3-(2'-nitrophenyl)oxirane (432) was prepared from 1-benzoyl-1-cyano-2-(2'-nitrophenyl)ethylene[119] as described by Bayne[119] (32%), m.p. 86° (lit.,[119] 91°), $\nu_{max.}$ 2220w (CN), 1690 (CO) and 1530 and 1355 (NO_2) cm^{-1}.

(c) Trans 2-carbamoyl-3-(2'-nitrophenyl)oxirane (401a)

A solution of 2-nitrobenzaldehyde (3.0 g, 0.02 mol) and chloroacetamide (1.9 g) in absolute ethanol (20.0 ml) was cooled to 0° and treated dropwise with a solution of sodium (0.46 g, 0.02 mol) in absolute ethanol (20.0 ml). The mixture was stirred at room temperature for 24 h and then acidified to pH6 with glacial acetic acid. The precipitated solid was collected, washed with water (10.0 ml) and crystallised to yield the product (1.7g, 41%), m.p. 221° (from ethanol-dimethylformamide), $\nu_{max.}$ 3360 and 3180 (NH_2), 1660 (CO) and 1525 and 1340 (NO_2) cm^{-1}

Found: C, 51.9; H, 3.9; N, 13.4%; p^+, 164 (M^+-CONH_2)

$C_9H_8N_2O_4$ requires: C, 51.9; H, 3.9; N, 13.5%; M, 208.

The filtrate was evaporated, treated with water (10.0 ml) and extracted with chloroform to give a heavy black oil (1.7 g) from which no identifiable material could be obtained.

(d) Trans 2-Benzoyl-3-(5'-bromo-2'-nitrophenyl)oxirane (401b)

A solution of 5-bromo-2-nitrobenzaldehyde (11.5g, 0.05 mol) and phenacyl bromide (0.05 mol, 10.0 g) in methanol (20 ml) was cooled to 0°, stirred and then treated dropwise with a solution of sodium (1.2 g, 0.05 mol) in methanol (20.0 ml). The mixture was then stirred at room temperature for 3 h and acidified to pH6 by the dropwise addition of glacial acetic acid. The precipitate was collected, washed with water and recyrstallised to yield the product (11.1 g, 63%) m.p. 152° (from ethanol-acetic acid), $\nu_{max.}$ 1700 (CO) and 1540 and 1350 (NO_2) cm^{-1}.

Found: N, 4.3%; p^+, 303 and 301 (M^+-NO_2)

$C_{15}H_{10}Br\ N_0O_4$ requires: N, 4.0%; M, 348.

(e) Trans 2-Benzoyl-3-(2'-nitrophenyl)oxirane (401c) was prepared by the method of Bodforss[149] (Yield, 91%) m.p. 108° (lit.,[149] 113°) $\nu_{max.}$ 1690 (CO) and 1530 and 1350 (NO_2) cm^{-1}.

(f) Trans 2-acetyl-3-(2'-nitrophenyl)oxirane (401d) was prepared by the method described by Spence and Tennant[141] (Yield 25%), m.p. 61° (from light petroleum) (lit.,[141] 61°), $\nu_{max.}$ 1690 (CO) and 1540 and 1350 (NO_2) cm^{-1}.

(g) Trans 2-ethoxycarbonyl-3-(2'-nitrophenyl)oxirane (401e) was prepared by Darzens condensation[142] of 2-nitrobenzaldehyde with ethyl chloroacetate as a colourless solid (30%), m.p. 61° (lit.,[119] 63°), $\nu_{max.}$ 1745 (CO) and 1530 and 1345 (NO_2) cm^{-1}.

6. The Attempted Reaction of 2,2-Dibenzoyl-3-(5'-bromo-2'-nitrophenyl) oxirane (403b) with Hydrogen Chloride.

(a) In Dioxan

The oxirane (403b) (0.94 g, 0.002 mol) was dissolved in dry dioxan (15.0 ml), cooled in ice and saturated with dry hydrogen chloride. The stoppered reaction vessel was kept at room temperature for 48 h. The mixture was then filtered to give the starting material a second crop of which was obtained by evaporating the dioxan filtrate and tri-truating the residue with ether (total 0.8 g), m.p. 198° (from ethanol-dimethylformamide) identical, (m.p. and i.r. spectrum) with an authentic sample.

The ether mother liquor was evaporated and the residue was triturated with methanol to give a further quantity of starting material (0.03 g) identical (i.r. spectrum) with an authentic sample. Evaporation of the methanol mother liquors gave a negligible amount of gum.

(b) In Acetic Acid

The oxirane (403b) (0.94 g, 0.002 mol) was suspended in glacial acetic acid (50.0 ml) and the mixture was saturated with hydrogen chloride and the stoppered reaction flask was kept at room temperature for 48 h. The mixture was filtered to give the starting material a second crop of

which was obtained by evaporating the acetic acid filtrate and triturating the residue with ether (total 0.83 g) identical (m.p. and i.r. spectrum) with an authentic sample.

Evaporating the mother liquors gave further starting material (0.1 g), identical (i.r. spectrum) with an authentic sample.

7. The Reaction of 2,2-Dibenzoyl-3-(5'-bromo-2'-nitrophenyl)oxirane (403b) with Hydrogen Chloride in Glacial Acetic Acid Under Reflux.

The oxirane (403b) (0.94 g, 0.002 mol) was suspended in glacial acetic acid (50.0 ml) and the mixture was saturated with dry hydrogen chloride. The flow of gas was interrupted and the suspension was heated under reflux for 2 h. The resulting orange-red solution was cooled to give the yellow 4,4'-dibromoazobenzene-2,2'-dicarboxylic acid (413) (0.1 g; 24%) which was purified by recrystallisation from dimethylformamide-water and melted at 280° with subsequent resolidification and no further melting below 340°, $\nu_{max.}$ 2650 and 2550 (OH) and 1695 (CO) cm^{-1},

Found: C, 39.3; H, 2.0; N, 6.6%; M^+, 428.

$C_{14}H_8Br_2N_2O_4$ requires: C, 39.3; H, 1.9; N, 6.5%; M, 428.

The filtrate was evaporated and the residual gum was triturated with a little methanol to give unreacted starting material (403b) (0.43 g; 45%) identical (m.p. and i.r. spectrum) with an authentic sample.

8. The Attempted Reaction of 2,2-Dibenzoyl-3-(2'-nitrophenyl)oxirane (394f) with Hydrogen Chloride in Acetic Acid Under Reflux

The oxirane (394f) (1.1 g, 0.003 mol) was dissolved in glacial acetic acid (50.0 ml) and the solution was saturated with dry hydrogen chloride. The flow of gas was interrupted and the solution was heated under reflux for 3 h and then evaporated. The resulting red gum was

dissolved in chloroform and washed with saturated aqueous sodium hydrogen carbonate solution (3 x 5.0 ml) and the aqueous sodium hydrogen carbonate washings were acidified with dilute aqueous sulphuric acid and extracted with chloroform to give a gum (0.36 g) which was triturated with benzene to afford benzoic acid (0.05 g), m.p. 120° (from water), (lit., 121°), $\nu_{max.}$ 2660 and 2550 (OH) and 1690 (CO) cm^{-1}, identical (m.p. and i.r. spectrum) with an authentic sample.

The original chloroform extract was evaporated to give a gum (0.63 g) whose t.l.c. in chloroform over alumina showed it to contain three components. Chromatography of the gum over alumina, eluting with chloroform, followed by methanol afforded only small amounts of unidentified gums.

9(a) The Reaction of 2,2-Dibenzoyl-3-(2'-nitrophenyl)oxirane (394f) with Concentrated Aqueous Hydrochloric Acid in Acetic Acid.

The oxirane (394f) (0.75 g, 0.002 mol) in glacial acetic acid (10.0 ml) was treated with concentrated aqueous hydrochloric acid (2.0 ml) and the solution was heated on a steam bath for 1 h and then cooled to afford 6-chloro-1,3-dihydroxy-2-phenylquinolin-4(1H)-one (398) (0.5 g, 91%), m.p. 265° (decomp.) (from glacial acetic acid) (lit.,[150] 264°), $\nu_{max.}$ 3400 (NH), 2350 br (OH) and 1660w (CO) cm^{-1}, identical (m.p., mixed m.p. and i.r. spectrum) with an authentic sample.

The acetic acid reaction mother liquor was concentrated to give benzoic acid (0.15 g), m.p. 120° (lit., 121°) identical (m.p. and i.r. spectrum) with an authentic sample. Complete evaporation of the acetic acid reaction mother liquor gave only an unidentified gum (0.1 g).

(b) The Attempted Reaction of 2,2-Dibenzoyl-3-(5'-chloro-2'-nitrophenyl) oxirane (403a) with Concentrated Aqueous Hydrochloric Acid in Acetic Acid

The oxirane (403a) (0.41 g, 0.001 mol) was dissolved in glacial acetic acid (8.0 ml) and treated with concentrated aqueous hydrochloric acid (1.0 ml) and the solution was heated on a steam bath for 1h.

The reaction mixture was cooled to give the starting material which was combined with a second crop obtained by concentrating the filtrate to approximately one third of its original volume and adding water (1.0 ml) (total 0.17 g; 41%), m.p. 181°, identical (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the filtrate and trituration of the residue with ethyl acetate afforded an unidentified solid (0.07 g), m.p. 158°, $\nu_{max.}$ 2700 br (OH) and 1675 (CO) cm^{-1}

The ethyl acetate mother liquor was again evaporated and the residue was dissolved in chloroform and washed with saturated aqueous sodium hydrogen carbonate solution. Acidification of the saturated aqueous sodium hydrogen carbonate washings and extraction with chloroform gave benzoic acid (0.06 g), m.p. 121° (from water) identical (m.p. and i.r. spectrum) with an authentic sample. The original chloroform layer gave only a negligible amount of gum.

10. The Reaction of Substituted 2-Nitrophenyloxiranes with Acetyl Chloride in Glacial Acetic Acid.

(a) 3-Acetoxy-6-Chloro-2-phenylquinolin-4(1H)-one (415)

Trans 2-benzoyl-3-(2'-nitrophenyl)oxirane (401c)(0.54 g; 0.002 mol) was heated under reflux for 1 h in an equimolar mixture of acetyl chloride (3.5 ml) and glacial acetic acid (2.5 ml). The solution was cooled to give 3-acetoxy-6-chloro-2-phenylquinolin-4(1H)-one (415) (0.21 g; 32%), m.p. 281° (from glacial acetic acid) (lit.,[141] 267°), $\nu_{max.}$ 2700 br (OH) and 1770 and 1640w (CO) cm^{-1}, which gave a green colour with iron(III) chloride in ethanol.

The acetic acid-acetyl chloride filtrate was evaporated and the residue was triturated with ether to give the acetylated chlorohydrin (414)(0.07 g; 10%), m.p. 143° (from ethanol), $\nu_{max.}$ 1770 and 1700 (CO)

and 1530 and 1350 (NO_2) cm^{-1}, τ [$(CO_3)_2SO$; 60MHz] 1.86-2.68 (9H, m, ArH), 3.26 (1H, d J 9Hz, CH) and 3.80 (1H, d J 9Hz, CH) and 8.12 (3H, s, CH_3).

Found: C, 58.1; H, 3.9; N, 3.7%; M, 201 (M^+-X).

$C_{17}H_{14}ClNO_5$ requires: C, 58.5; H, 4.1; N, 4.1%; M, 347.5.

(b) The Attempted Reaction of 2-Benzoyl-3-(5'-bromo-2'-nitrophenyl) oxirane with Acetyl Chloride in Acetic Acid

The oxirane (401b) (1.0 g, 0.003 mol) was treated with an equimolar mixture of acetyl chloride (5.3 ml) and glacial acetic acid (3.8 ml) and the mixture was heated under reflux for 1 h. The solution was cooled to give the strating material a second crop of which was obtained by evaporating the filtrate and triturating the residue with methanol (total 0.73 g) m.p. 155° (from ethanol-acetic acid) identical (m.p. and i.r. spectrum) with an authentic sample.

The methanol mother liquor was evaporated and the solid residue was crystallised from ethanol with hot filtration to remove a further crop of starting material (0.1 g) identical (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the ethanol recrystallisation mother liquor afforded a negligible amount of gum.

(c) The Attempted Reaction of 2-Acetyl-3-(2'-nitrophenyl)oxirane (401d) With Acetyl Chloride in Acetic Acid.

The oxirane (401d) (0.45 g, 0.002 mol) was heated under reflux in an equimolar mixture of acetyl chloride (3.5 ml) and glacial acetic acid (2.5 ml) for 1.5 h. The solution was then evaporated and the residual gum was triturated with ether to give an unidentified solid (0.11 g), m.p. 220° (from ethanol) $\nu_{max.}$ 1770 and 1740 (CO) and 1530 and 1315 (NO_2) cm^{-1}.

Found: C, 54.1; H, 4.0; N, 4.3%;

The ether mother liquors were evaporated to give a gum (0.27 g)

from which no identifiable material was obtained.

(d) The Attempted Reaction of 2-Carbamoyl-3-(2'-nitrophenyl)oxirane (401a) with Acetyl Chloride in Acetic Acid

The oxirane (401a) (0.41 g, 0.002 mol) was heated under reflux for 1 h in an equimolar mixture of acetyl chloride (3.5 ml) and acetic acid (2.5 ml). The red solution was evaporated and the residual oil was dissolved in chloroform and washed with dilute aqueous sodium hydroxide solution (2 x 5.0 ml). The alkaline phase was acidified with dilute aqueous sulphuric acid and was extracted with chloroform to give a gum (0.1 g) whose t.l.c. in ether over alumina showed it to be an unresolvable mixture.

The original chloroform extract was evaporated to give a gum (0.14 g) whose t.l.c. in ether over alumina showed it to be an unresolvable multi-component mixture.

(e) The Attempted Reaction of 2-Ethoxycarbonyl-3-(2'-nitrophenyl)oxirane (401e) with Acetyl Chloride in Acetic Acid

The oxirane (401e) (0.47 g, 0.002 mol) was heated under reflux in an equimolar mixture of acetyl chloride (3.5 ml) and acetic acid (2.5 ml) for 1 h. The solution was evaporated to leave a gum which was extracted with hot light petroleum to afford an amber oil (0.42 g), $\nu_{max.}$ 1750 and 1700 (CO) and 1530 and 1350 (NO_2) cm^{-1}. The petrol insoluble material was an intractable black tar (0.11 g).

T.l.c. of the amber oil in ether over alumina showed it to contain starting material and two other components. Dry-column chromatography of the oil in ether over silica gave only an oil (0.3 g) whose t.l.c. showed it to contain two components one of which was starting material.

(f) The Attempted Reaction of 2,2-Dibenzoyl-3-(2'-nitrophenyl)oxirane (394f) with Acetyl Chloride in Acetic Acid.

The oxirane (394f) (0.75 g, 0.002 mol) was heated under reflux with an equimolar mixture of acetyl chloride (3.5 ml) and acetic acid (2.5 ml) for 1 h. The reaction mixture was cooled to give the starting material another crop of which was obtained by evaporating the filtrate and triturating the residue with ether (total 0.53 g), identical (m.p. and i.r. spectrum) with an authentic sample.

The ether mother liquor was evaporated to leave a gum (0.24 g) whose t.l.c. in ethyl acetate over silica showed it to be a mixture containing largely starting material. The gum was not further investigated.

11. 6-Chloro-3-hydroxy-2-phenylquinoline-4(1H)-one (416)

(a) The acetoxy compound (415) (0.33 g, 0.001 mol) was dissolved in dilute aqueous sodium hydroxide (5.0 ml) at room temperature to give an orange-red solution which was filtered to remove a negligible amount of material and then acidified with dilute aqueous sulphuric acid to give the crude 6-chloro-3-hydroxyquinoline-4(1H)-one (416) (0.15, 56%), m.p. 287° (from ethanol) (lit.[141] 290°), $\nu_{max.}$ 3150 br (OH, NH) and 1660w (CO) cm^{-1} which with iron (III) chloride in ethanol gave an inky-blue colour,

Found: C, 62.5; H, 4.0; N, 4.6%; M^+, 271/273.

Calculated for $C_{15}H_{10}ClNO_2.H_2O$: C, 62.8; H, 4.1; N, 4.8%; M, 271.5.

(b) The acetoxy-quinolone (415) (0.33 g, 0.001 mol) was heated under reflux for 20 min in ethanol (15.0 ml) and cooled to give the 3-hydroxy-quinolone (416) which was combined with a second crop obtained by evaporating the filtrate and recrystallising the solid residue from ethanol to give pale yellow needles (93%) m.p. 285° (lit.,[141] 290°),

$\nu_{max.}$ 3150br (OH, NH) and 1660w (CO) cm^{-1}, identical (m.p. and i.r. spectrum) with an authentic sample.

12. The Reaction of Authentic 6-Chloro-1,3-dihydroxy-2-phenylquinolin-4(1H)-one (398a) with Acetyl Chloride in Acetic Acid

The N-hydroxyquinolone (398a) (0.35 g, 0.001 mol) was heated under reflux in an equimolar mixture of acetyl chloride (3.5 ml) and acetic acid (2.5 ml) for 1 h. The solution was evaporated and the residue was triturated with ether to give 3-acetoxy-6-chloro-2-phenylquinoline-4(1H)-one (415) which was combined with a second crop obtained by evaporating the ether mother liquor and retriturating the residue with methanol (total 0.22 g), m.p. 281° (from ethanol), $\nu_{max.}$ 2780br (OH) and 1770 and 1640 (CO) cm^{-1}, identical (m.p. and i.r. spectrum) with the sample prepared before.

13. The Reaction of 2-Benzoyl-3-(2'-nitrophenyl)oxirane (401c) with Acetyl Bromide in Glacial Acetic Acid

The oxirane (401c) (0.54 g, 0.002 mol) was treated with an equimolar mixture of acetyl bromide (4.0 ml) and glacial acetic acid (2.0 ml) and the solution was heated under reflux for 1 h. The dark solution was evaporated and the gummy residue was triturated with ethyl acetate to give 3-hydroxy-2-phenylquinolin-4(1H)-one[141] (417) (0.26 g; 52%), m.p. 260° (from ethanol) (lit.,[141] 269°), $\nu_{max.}$ 3400br and 2700br (NH, OH) and 1635w (CO) cm^{-1}.

Found: C, 75.2; H, 4.7; N, 5.7%; M^+, 237.

Calculated for $C_{15}H_{11}NO_2$: C, 75.9; H, 4.6; N, 5.9%; M, 237

which gave a blue-green colour with iron (III) chloride in ethanol

The ethyl acetate mother liquor was evaporated to give a gum (0.41 g) whose t.l.c. in chloroform over alumina showed it to contain an unresolvable mixture of ca. four components.

14. The Conversion of Substituted 2'-Nitrophenyloxiranes into N-Acylanthranilic Acids in the Presence of Polyphosphoric Acid

General Method:

(i) The oxirane (0.002 mol) was treated with polyphosphoric acid (2.5 ml) and mechanically stirred at 80° for 3 h. The mixture was then cooled in ice, treated with water (10.0 ml) and then worked-up as described for the individual reactions below.

(a) N-(Phenylglyoxyloyl)anthranilic Acid (421a)

The aqueous reaction mixture from 2-benzoyl-3-(2'-nitrophenyl) oxirane (401c) was filtered to give a brown solid (0.72 g), m.p. 115-125°, $\nu_{max.}$ 1695 and 1665 (CO) cm^{-1}, which was crystallised from ethanol-water to give the N-acylanthranilic acid (421a) (0.46 g; 43%), m.p. 199° (lit.,[144] 192°), $\nu_{max.}$ 3220 (NH), 2710 and 2650 (OH), and 1695 and 1660 (CO) cm^{-1}.

Found: C, 66.4; H, 4.0; N, 5.1%; M^+, 269.

Calculated for $C_{15}H_{11}NO_4$: C, 66.9; H, 4.1; N, 5.2%; M, 269.

The filtered aqueous mother liquor was extracted with chloroform to give benzoic acid (0.05 g), m.p. 121° (from water), identical (m.p. and i.r. spectrum with an authentic sample.

(b) N-Ethoxalylanthranilic Acid (421b)[145]

The aqueous reaction mixture from 2-ethoxycarbonyl-3-(2'-nitrophenyl) oxirane (401e) was filtered to give the crude N-ethoxalylanthranilic acid (0.47 g), m.p. 170° which was crystallised from benzene with hot filtration to give the pure N-ethoxalylanthranilic acid (421b) (0.35 g; 75%), m.p. 181° (lit.,[145] 181°), $\nu_{max.}$ 3380 (NH), 2720 and 2640 (OH) and 1735, 1720 and 1675 (CO) cm^{-1}, $\tau(CDCl_3)$-2.35 (1H, br s, OH), 1.14 (1H, dd $J_{6,5}$ 9Hz, J_{64} 1Hz, ArH), 1.83 (1H, dd $J_{3,4}$ 10Hz, $J_{3,5}$ 2Hz, ArH), 2.33 (1H, td $J_{4,3}$ 10Hz, $J_{4,5}$ 9Hz and $J_{4,6}$ 1Hz, ArH), 2.29 (1H, td $J_{5,6}$ 9Hz, $J_{5,4}$ 9Hz, $J_{5,3}$ 2Hz, ArH), 4.00 (1H, br s, NH), 5.55 (2H, q J 7Hz, CH_2) and 8.55 (3H, t J 7Hz, CH_3)

Found: C, 55.9; H, 4.7; N, 5.8%; M^+,237.

Calculated for $C_{11}H_{11}NO_5$: C, 55.7; H, 4.7; N, 5.9%; M,237.

(c) N-Oxalylanthranilic Acid (421c)

The amide (401a) was treated as described in the general method but a vigorous reaction followed the heating of the reaction mixture to 80°. The aqueous reaction mixture gave a tar (0.5 g) which was treated with dilute aqueous sodium hydroxide solution (10.0 ml) and filtered to remove a negligible amount of insoluble material. Acidification of the alklaine filtrate with dilute aqueous sulphuric acid gave a tar which was extracted with methanol to give N-oxalylanthranilic acid (0.04 g), m.p. 206° (from water) (lit.,[146] 229°), $\nu_{max.}$ 3400 br (NH,OH) and 1690 and 1655 (CO) cm^{-1}, M^+, 209, $C_9H_7NO_5$ requires M, 209, identical (i.r. spectrum) with an authentic sample.[144]

(ii) The oxiranes (401 a and c) were treated as described in the General Method (a) above with the modification that the experiments were carried out at room temperature.

(a) N-(Phenylglyoxyloyl)anthranilic Acid (421a)

The aqueous reaction mixture from the oxirane (401c) was filtered to give the N-acylanthranilic acid (421a) a second crop of which was obtained by extracting the aqueous mother liquor with chloroform and successively triturating the resulting residue with methylene chloride (total 0.19 g; 22%), m.p. 192° (from ethanol-water) identical (i.r. spectrum) with a sample prepared in (a) above.

(b) N-Oxamoylanthranilic Acid (421d)

The aqueous reaction mixture from the oxirane (401a) was filtered to give the N-acylanthranilic acid derivative (421d)(0.39 g; 93%), m.p. 265° (from ethanol-water) (lit.,[144] 266°), $\nu_{max.}$ 3400, 3230 and 3180 (NH), 261 and 2470 (OH) and 1725 and 1680 (CO) cm^{-1}.

Found: C, 51.4; H, 4.0; N, 13.1%; M^+, 208.

Calculated for $C_9H_8N_2O_4$: C, 51.9; H, 3.9; N, 13.5%; M,208.

15. The Attempted Reaction of 1-Acetyl-2-(2'-nitrophenyl)oxirane (401d) with Polyphosphoric Acid

The aqueous reaction mixture from the oxirane (401d) was extracted with chloroform (2 x 30.0 ml). Evaporation of the chloroform layer gave a black tar (0.24 g) whose t.l.c. in ether over silica showed it to contain three resolvable components. Dry-column chromatography of the tar in ether over silica yielded only small amounts of gums whose t.l.c. in ether over silica showed them to contain several ill-resolved components.

16. 2-Benzoyl-4H-3,1-benzoxazin-4-one (422)

N-(Phenylglyoxyloyl)anthranilic acid (421a)(0.53 g, 0.002 mol) was heated under reflux in acetic anhydride (2.0 ml) for 0.5 h. The solution was evaporated and the residue was triturated with ether to give the benzoxazinone (422) (0.48 g; 94%), m.p. 129°, $\nu_{max.}$ 1770 and 1680 (CO) cm^{-1}, $\tau[CDCl_3-(CD_3)SO]$; 60MHz 1.7-2.0 (2H, m, ArH) and 2.1-2.26 (7H, m, ArH), identical (i.r. spectrum) with an authentic sample.[144]

The benzoxazinone (422) (0.13 g) was heated in 60% v/v aqueous ethanol (15.0 ml) under reflux for 0.5 h. The solution was concentrated to approximately one fifth of its original volume to give the N-acylanthranilic acid (421a) (quantitative), identical (m.p. and i.r. spectrum) with an authentic sample.

17. The Hydrolysis of N-Ethoxalylanthranilic Acid (421b) to N-Oxalylanthranilic Acid (421c)

The ester (421b) (0.18 g) was heated in ethanol (4.0 ml) and 0.5 M aqueous sodium carbonate solution (2.5 ml) under reflux for 0.5 h.

The mixture was cooled in ice and acidified with dilute aqueous sulphuric acid to give initially a monocarboxylate salt which was acidified again with further dilute aqueous sulphuric acid to afford the diacid (421c) (0.1 g; 63%), m.p. 210° (decomp.) (from water) (lit.,[146] 229°), $\nu_{max.}$ 3550 and 3450 (NH), 2650 and 2450 (OH) and 1700 (CO) cm^{-1}, M^+, 209, $C_9H_7NO_5$ requires M, 209, identical (m.p. and i.r. spectrum) with an authentic sample.

18. The Conversion of Substituted 2'-Nitrophenyloxiranes into 2,1-Benzisoxazoles in the Presence of Polyphosphoric Acid.

(a) 3-(Phenylglyoxyloyl)-2,1-benzisoxazole (426a)

2,2-Dibenzoyl-3-(2'-nitrophenyl)oxirane (394f) (2.84 g, 0.008 mol) was treated with polyphosphoric acid (10.0 ml) and the mixture was stirred mechanically at 80° for 3 h after which time the dark reaction mixture was treated with water (20.0 ml). The mixture lightened to a yellow colour and was extracted with chloroform. The chloroform layer was washed with saturated aqueous sodium hydrogen carbonate solution and evaporated to give a tacky solid which was extracted with hot light petroleum. Evaporation of the petroleum extract gave the 2,1-benzisoxazole (426a) (0.9 g; 45%), m.p. 67° (from methanol-water), $\nu_{max.}$ 1665 (CO) cm^{-1}, $\lambda_{max.}$ 209,250,300,314 and 352 nm (log $\varepsilon_{max.}$ 4.29,4.15,3.77,3.77 and 3.83)

Found: C, 71.4; H, 3.5; N, 5.7%; M^+251.

$C_{15}H_9NO_3$ requires: C, 71.7; H, 3.6; N, 5.6%; M,251.

The petrol insoluble residue was a red gum (0.4 g) whose t.l.c. in ether over silica showed it to be a multicomponent mixture containing none of the 2,1-benzisoxazole (426a).

Acidification of the sodium hydrogen carbonate extract with dilute aqueous sulphuric acid afforded benzoic acid (0.8 g; 83%), m.p. 121° (from water) identical (m.p. and i.r. spectrum) with an authentic sample.

(b) 5-Bromo-3-(phenylglyoxyloyl)-2,1-benzisoxazole (436c)

2,2-Dibenzoyl-3-(5'-bromo-2'-nitrophenyl)oxirane (403b) (0.45 g, 0.001 mol) was treated with polyphosphoric acid (1.5 ml) and the mixture was stirred mechanically and heated at 80° for 6 h after which time the mixture was cooled in ice, treated with water (5.0 ml) and extracted with chloroform. The chloroform extract was washed with saturated aqueous sodium hydrogen carbonate solution (2 x 3.0 ml) and evaporated to give a tacky solid which was extracted with hot light petroleum to give the yellow bromo-2,1-benzisoxazole (426c) (0.21 g; 63%), m.p. 130° (from ethanol-water), $\nu_{max.}$ 1675 and 1665 (CO) cm^{-1}, $\lambda_{max.}$ 211, 252 and 348 nm (log $\varepsilon_{max.}$ 4.46, 4.13 and 3.85), τ($CDCl_3$; 60 MHz) 1.72 (1H, d J 2Hz, ArH), 1.95(2H, dd J 8Hz J 3Hz, ArH) and 2.22-2.62 (5H, m, ArH).

Found: C, 54.4; H, 2.5; N, 4.4%; M^+,331/329.

$C_{15}H_8BrNO_3$ requires: C,54.5; H, 2.4; N, 4.2%; M, 330.

The sodium hydrogen carbonate extract was acidified with dilute aqueous sulphuric acid to afford benzoic acid (0.12 g; quant.) m.p. 121° (from water) identical (m.p. and i.r. spectrum) with an authentic sample.

(c) 5-Chloro-3-(phenylglyoxyloyl)-2,1-benzisoxazole (426b)

The oxirane (403a) (0.82 g, 0.002 mol) was treated with phosphoric acid and the mixture was stirred mechanically at 80° for 20 h after which time the mixture was cooled, treated with water (20.0 ml) and extracted with chloroform (3 x 15.0 ml). The chloroform extract was washed with saturated sodium hydrogen carbonate solution (2 x 10.0 ml). The insoluble solid was collected and acidified with dilute aqueous sulphuric acid to give 5-chloro-N-(phenylglyoxyloyl)-anthranilic acid (431) (0.06 g; 10%), m.p. 241° (decomp.)(from ethanol-water), $\nu_{max.}$ 3190 br (NH) and 1695 and 1660 (CO) cm^{-1}

Found: C, 58.6; H, 3.2; N, 4.8%; M^+ -

$C_{15}H_{10}ClNO_4$ requires: C, 59.3; H, 3.3; N, 4.6%; M, 305.5

Evaporation of the chloroform extract gave a gum which was triturated with ether-light petroleum to give the 2,1-benzisoxazole (426b). This was combined with a second crop obtained by evaporating the ether-light petroleum mother liquor and retriturating the residue with methanol (total 0.2 g, 35%), m.p. 102° (from ethanol-water), $\nu_{max.}$ 1775 and 1765 (CO) cm^{-1}

Found: C, 62.6; H, 2.7; N, 4.9%; M^+, 287/285.

$C_{15}H_8ClNO_3$ requires: C, 63.0; H, 2.9; N, 4.9%; M, 285.5.

Evaporation of the methanol mother liquor gave a gum (0.18 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture.

Acidification of the sodium hydrogen carbonate extract with dilute aqueous sulphuric acid afforded benzoic acid (0.22 g, 91%), m.p. 121° (from water) identical (m.p. and i.r. spectrum) with an authentic sample.

19(a) The Attempted Reaction of 2,2-Dibenzoyl-3-(3',5'-dichloro-2-nitrophenyl)oxirane (403c) with Polyphosphoric Acid

The oxirane (403c) (0.44 g, 0.001 mol) was treated with polyphosphoric acid (2.5 ml) and the mixture was stirred mechanically for 6 h at 100°. The mixture was cooled in ice, treated with water (5.0 ml) and extracted with chloroform. The chloroform phase was washed with saturated aqueous sodium hydrogen carbonate solution (2 x 4.0 ml) and evaporated to leave a gum. The gum was extracted with light petroleum to afford the crude starting material (0.29 g) which was crystallised from ethanol to give the pure material (0.2 g), m.p. 170° identical (m.p. and i.r. spectrum)with an authentic sample.

The petrol insoluble material was an unidentified solid (0.02 g).

Acidification of the sodium hydrogen carbonate extract yielded only a negligible amount of gum.

(b) The Attempted Reaction of 2-Benzoyl-2-ethoxycarbonyl-3-(2'-nitrophenyl) oxirane (432) with Polyphosphoric Acid

The oxirane (432) (1.36 g, 0.004 mol) was treated with polyphosphoric acid (10.0 ml) and the mixture was stirred mechanically at 50° for 3 h. Water (15.0 ml) was added and the mixture was extracted with chloroform. The chloroform extract was washed with saturated aqueous sodium hydrogen carbonate solution (15.0 ml) and evaporated to give a gum which was triturated with methanol to yield an unidentified solid (0.05 g).

The sodium hydrogen carbonate extract was acidified with dilute aqueous sulphuric acid and extracted with chloroform to give a tar (0.24 g) from which no identifiable material could be obtained.

Neutralisation of the original aqueous phase with solid sodium acetate and extraction with chloroform afforded an intractable red gum (0.08 g).

20. 3-(2'-Phenylquinoxalin-3'-yl)-2,1-benzisoxazole (427)

A solution of the 2,1-benzisoxazole (426a) (0.25 g, 0.001 mol) and o-phenylenediamine (0.11 g) in ethanol (5.0 ml) was heated under reflux for 0.5 h. A yellow precipitate formed and was collected to give the quinoxalinyl derivative (427) (0.25 g; 82%), m.p. 196° (from ethanol), $\nu_{max.}$ 1600w (C=C),

Found: C, 78.0; H, 4.0; N, 13.1%; M^+, 323.

$C_{21}H_{13}N_3O$ requires: C, 78.0; H, 4.1; N, 13.0%; M, 323.

21. The Reductive Conversion of 3-(Phenylglyoxyl)-2,1-benzisoxazole (426a) into 3-Hydroxy-2-phenylquinolin-4(1H)-one (417)

The 2,1-benzisoxazole (426a) (0.25 g, 0.001 mol) was heated in 70% v/v aqueous ethanol (7.0 ml) under reflux in the presence of

sodium dithionite (0.5 g) for 1 h. A second portion of sodium dithionite (0.5 g) was added and heating under reflux was continued for 1 h. The solution was then evaporated and treated with water (5.0 ml) to give the quinolin-4(1H)-one (417) more of which was obtained by extracting the aqueous filtrate with chloroform (2 x 5.0 ml), evaporating the chloroform and triturating the residue with methanol (total 0.09 g; 38%), m.p. 274° (from acetic acid) (lit.,[141] 270°), $\nu_{max.}$ 3200 br (OH) and 1660 (CO) cm^{-1} identical (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the methanol mother liquor gave only a small amount of gum (<0.05 g).

22. The Oxidation of 3-(Phenylglyoxyl)-2,1-benzisoxazole (426a) to 2,1-Benzisoxazole-3-carboxylic Acid and Benzoic Acid

The 2,1-benzisoxazole derivative (426a) (0.25 g, 0.001 mol) in 70% v/v aqueous acetic acid was heated to 100° and treated in portions with potassium (VI) dichromate (0.5 g). The mixture was heated for 15 min at 100° and then evaporated and treated with water (5.0 ml). The insoluble salt was collected, washed with water (5.0 ml) and acidified with dilute aqueous sulphuric acid to give benzoic acid more of which was obtained by extracting the acidic mother liquor with chloroform (total 0.12 g; quant.), m.p. 121° (from water), identical (i.r. and m.p.) with an authentic sample.

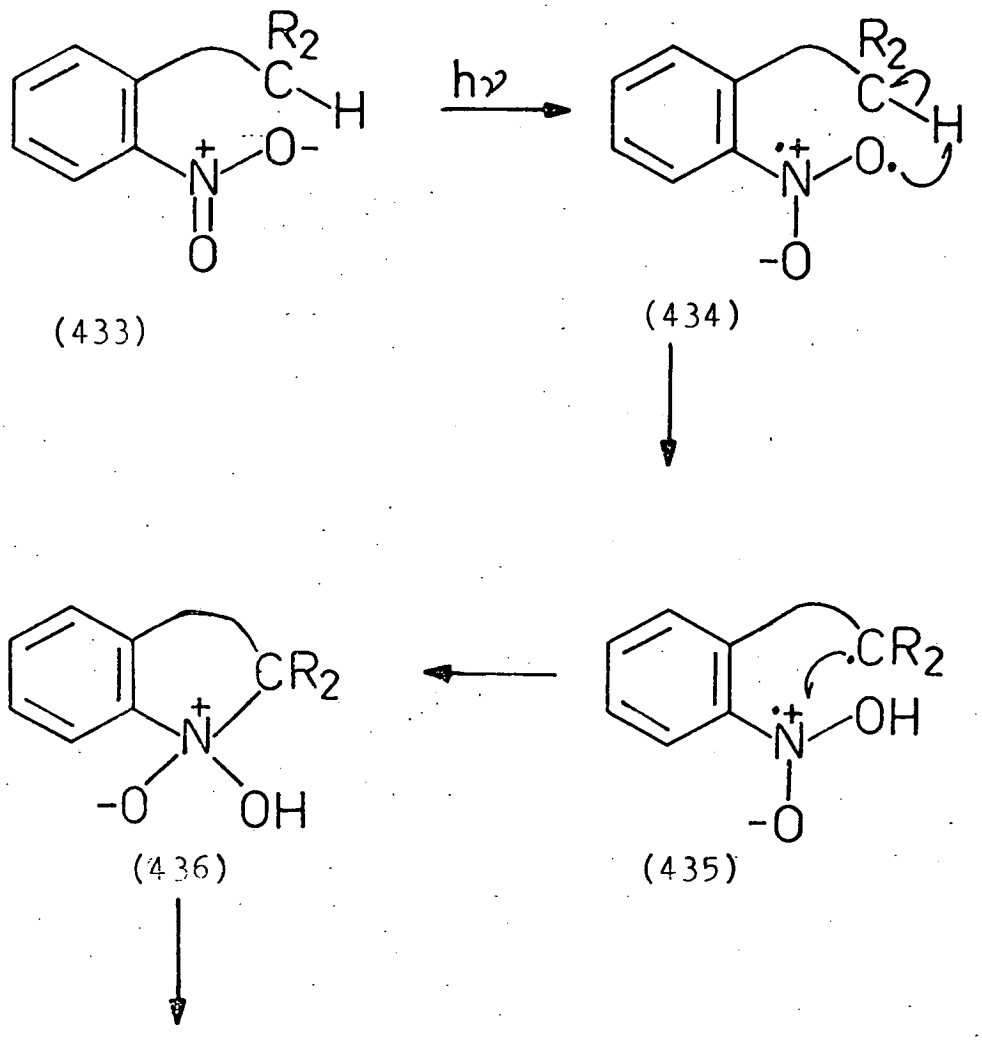
Acidification of the original aqueous phase and washings afforded 2,1-benzisoxazole-3-carboxylic acid (429) (0.06 g, 37%), m.p. 192° (lit.,[141] 192°), $\nu_{max.}$ 2660w and 2500 (OH) and 1735 (CO) cm^{-1}, identical (m.p. and i.r. spectrum) with an authentic sample.[141]

Chapter 5

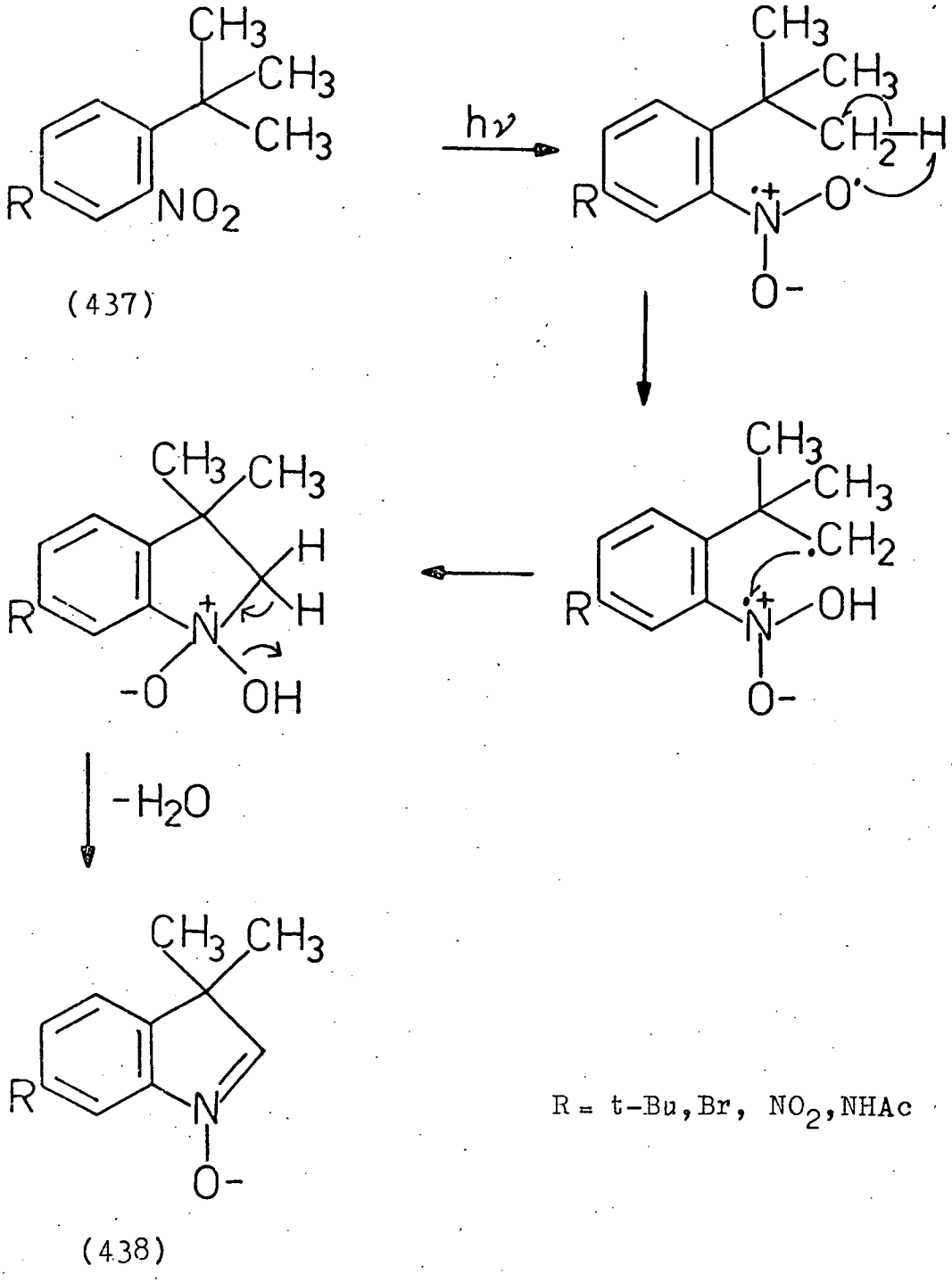
The Photochemistry of Some 2-Nitrobenzene Derivatives

Part I:- Extensions of the Photochemistry of 2-Nitrostyrylamines

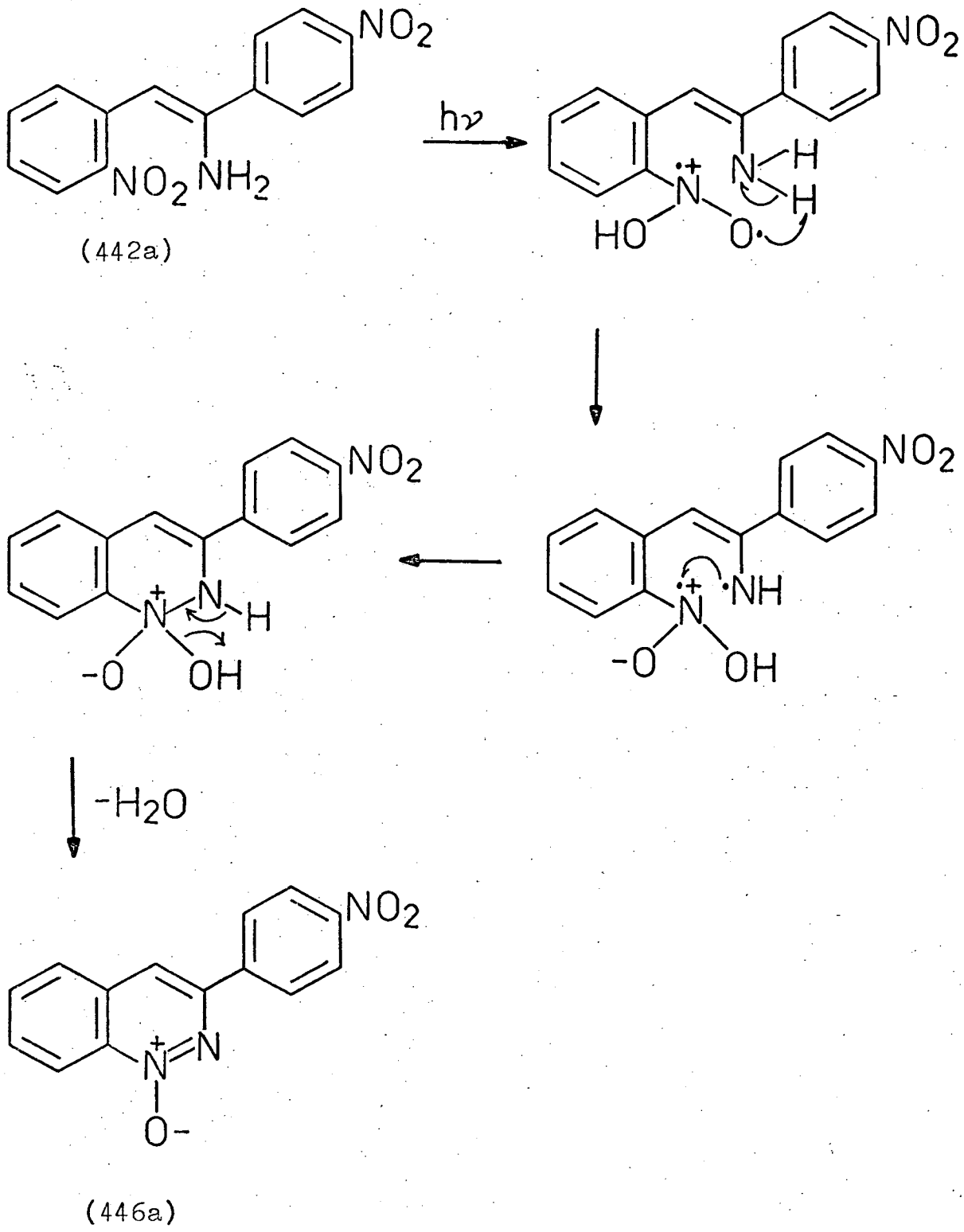
Part II:- The Photochemistry of Substituted 2-Nitrophenylacetamidines. A New Synthesis of 3-Aminocinnoline 1-N-Oxides



SCHEME 78



SCHEME 79



(442a)

(446a)

Scheme 80

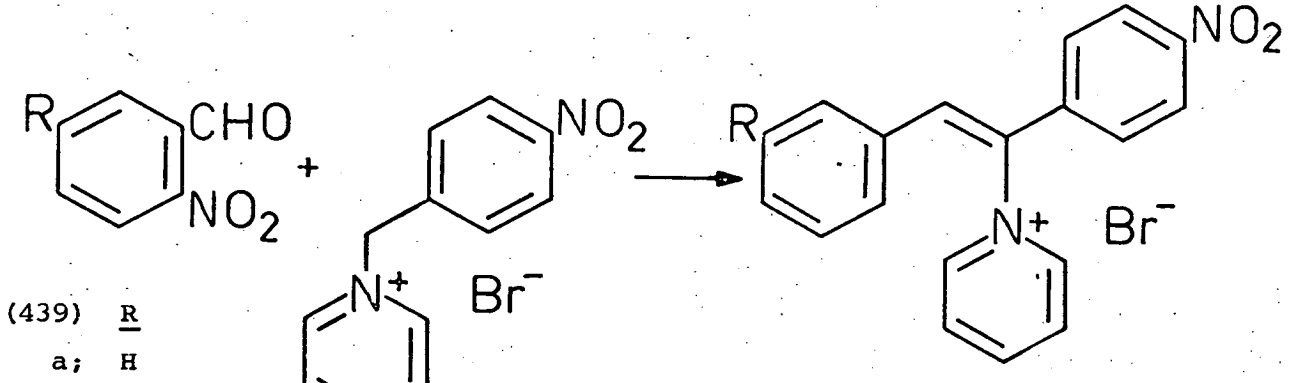
Part I

Apart from the processes of oxygen transfer, (cf. Introduction) photochemical transformations of 2-nitrobenzene derivatives may also proceed by hydrogen abstraction, not with subsequent oxygen transfer, but with the generation of radical centres which can couple to form a cyclic product. The process is depicted, in a general form, in Scheme 78. Thus, the $^{3}(n,\pi^*)$ photo-excited state of the nitro group (434) may abstract a hydrogen atom from the side-chain, generating the triplet diradical (435) which must suffer spin-inversion of one of the lone electrons before it can undergo intramolecular coupling to produce a cyclic intermediate of the type (436). This cyclic intermediate may then react further, thermally, to produce the ultimate products of the photochemical reaction. An example[151] of this type of photochemical transformation is provided by the conversion of the 2-nitro-tert-butylbenzene derivatives [(437); Scheme 79] into the nitrones (438).

Krohnke[152] has reported that the irradiation of β-amino-2-nitro-β-(4'-nitrophenyl)styrene (442a) in ethanol, by sunlight, leads to a high yield of 3-(4'-nitrophenyl)cinnoline 1-N-oxide (446a). This reaction may be rationalised again in terms of a process of hydrogen abstraction followed by radical coupling and dehydration to give the cinnoline 1-N-oxide [(446a); Scheme 80]. This reaction is interesting as it is, to the present author's knowledge, the only example of a photochemical synthesis of a cinnoline N-oxide. The high yield of cinnoline N-oxide (446a), obtained in this reaction, suggested that this area of the photochemistry of 2-nitrobenzene derivatives was worthy of further investigation as it proffers a potential synthesis of cinnoline N-oxides which are not readily available by the direct N-oxidation of the cinnoline precursor.

Since the structure of the product from irradiation of the styrylamine (442a)[152] had not been rigorously established by Krohnke[152] as 3-(4'-nitrophenyl)cinnoline 1-N-oxide (446a), it was initially decided to reinvestigate this cyclisation and to firmly establish the nature of the product. Also, the scope of the reaction with respect to the simple halogenated styrylamines (442 b and c) was investigated.

The styrylamines (442 a-c) required for investigation were prepared by first condensing the aldehydes (439 a-c) with 1-(2'-nitrophenyl)pyridinium bromide (440) and then degrading the 1-[2'-nitro-α-(4'-nitrophenyl)styryl] pyridinium bromide derivatives (441 a-c) obtained, with piperidine. The step involving degradation of the pyridinium moiety in (441 a-c)



(439) R
a; H
b; Cl
c; Br

(440)

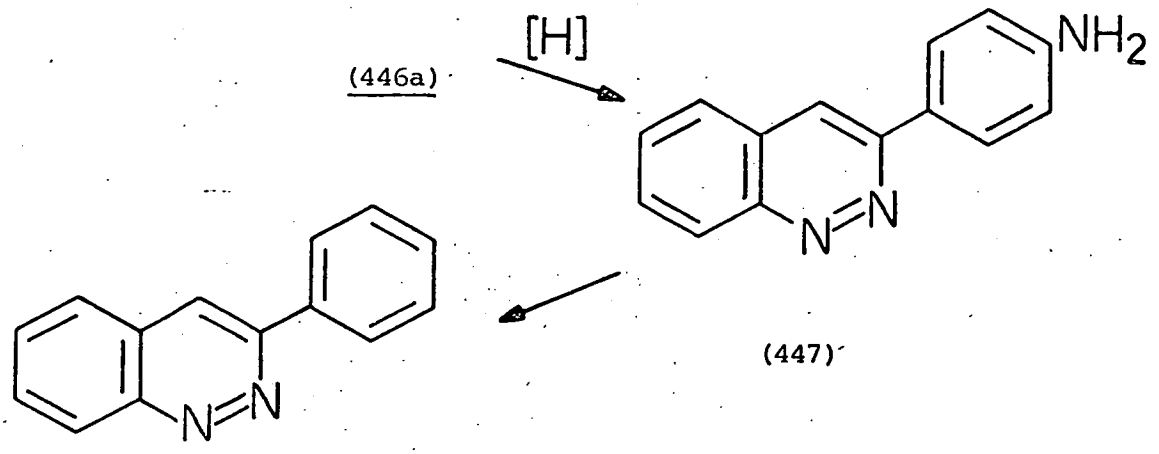
(441) R
a; H
b; Cl
c; Br

with piperidine was effected by using a method adapted from the original procedure described by Krohnke.[152] Thus, it was found that, by using methanol as a co-solvent, higher yields of the styrylamines (442 a-c) were obtained.

The photolysis of the styrylamine (442a) was carried out using a Hanovia medium-pressure photochemical reactor fitted with either a quartz or pyrex filter, in non-degassed ethanol solutions, under an atmosphere of nitrogen and after ca. 2 min, a yellow solid began to separate from the solution. After 24 h irradiation was discontinued

and a good yield (67%) of the presumed cinnoline N-oxide (446a) was obtained. This product gave elemental analysis and mass spectral data (m/e 267) in accord with a molecular formula of $C_{14}H_9N_3O_3$ and hence, with the cinnoline 1-N-oxide structure (446a). Its formulation as an N-oxide was further supported by the presence of a fragment ion at m/e 251 in its mass spectrum, indicating the loss of an oxygen atom which is characteristic of the known[112] behaviour of heterocyclic N-oxides upon electron impact. The i.r. spectrum of this product lacked bands attributable to amino group absorptions but contained bands due to the presence of the 4'-nitrophenyl substituent. Its ^1H n.m.r. spectrum yielded no useful information except to show the absence of protons other than aromatic. Irradiation of the chlorostyrylamine (442b) in ethanol, through a quartz filter for 24 h, also afforded a compound in high yield (77%), whose properties were fully consistent with its formulation a 6-chloro-3-(4'-nitrophenyl)cinnoline 1-N-oxide (446b). Similarly, the bromostyrylamine (442c) afforded the presumed 6-bromo-3-(4'-nitrophenyl)cinnoline 1-N-oxide (446c) but in lower yield (59%).

In order to rigorously prove the structure of the cinnoline 1-N-oxide (446a) and hence by analogy, the structures of both the bromocinnoline derivative (446c) and the chlorocinnoline derivative (446b), it was proposed to reduce the 3-(4'-nitrophenyl)cinnoline 1-N-oxide (446a) to the 3-(4'-aminophenyl)cinnoline (447) and then deaminate this amine (447) to give the known[153] 3-phenylcinnoline (448). However, catalytic reduction of the cinnoline 1-N-oxide (446a) proved ineffective, no reduction occurring. Sodium dithionite reduction was also attempted and initially, appeared to give encouraging results as the i.r. spectrum of the crude reaction product showed absorption bands due to a primary amino group. Furthermore, no bands attributable to a nitro group were present. However, this solid proved to be intractable and all attempts to purify it were unsuccessful.



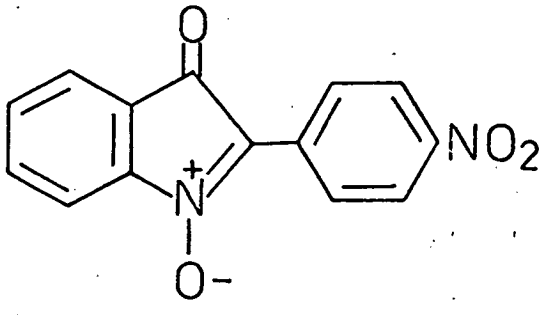
(446a) (447)

(448)

The mass spectrum of this crude reduction product showed a peak at m/e 223 which corresponds to two mass units more than the desired aminophenylcinnoline (447). This may indicate that the crude reaction mixture contains a dihydrocinnoline species. Although the attempt to convert the cinnoline N-oxide (446a) into the aminocinnoline (447) and thence by deamination to the phenylcinnoline (448) was unsuccessful, the spectroscopic properties of the compound (446a) and its halogenated derivatives (446b) and (446c) are in accord with the cinnoline 1-N-oxide structure originally proposed by Krohnke.[152]

The mechanism of the photochemical formation of the cinnoline 1-N-oxide (446a) has been formulated as shown in Scheme 80. Thus, in order to try and establish some experimental evidence for this mechanism, the styrylamine (446a) was photolysed in ethanol with added acetone to observe any triplet sensitisation of the reaction. It was realised that the high conversion of the amine (442a) to product (446a) might make it difficult to detect any increase in yield. However, with 0.5% added acetone, no significant increase in yield was observed. The photolysis of the styrylamine was then carried out in acetone alone. In this case, the product obtained was red and had a different melting-point to the yellow cinnoline 1-N-oxide (446a). Elemental analysis of this red product

indicated a molecular formula of $C_{14}H_8N_2O_4$, consistent with the loss of the elements of ammonia from the starting material (442a). The mass spectrum of the red solid was also in accord with this molecular formula showing a parent ion at m/e 268. Its i.r. spectrum showed the presence of a carbonyl band at 1710 cm^{-1} and absorption bands due to a nitro group were also present. On the basis of these data, the red compound was assigned the structure, 2-(4'-nitrophenyl)-3H-indolin-3-one 1-N-oxide (452a), a known compound.[154] In accord with this structure,

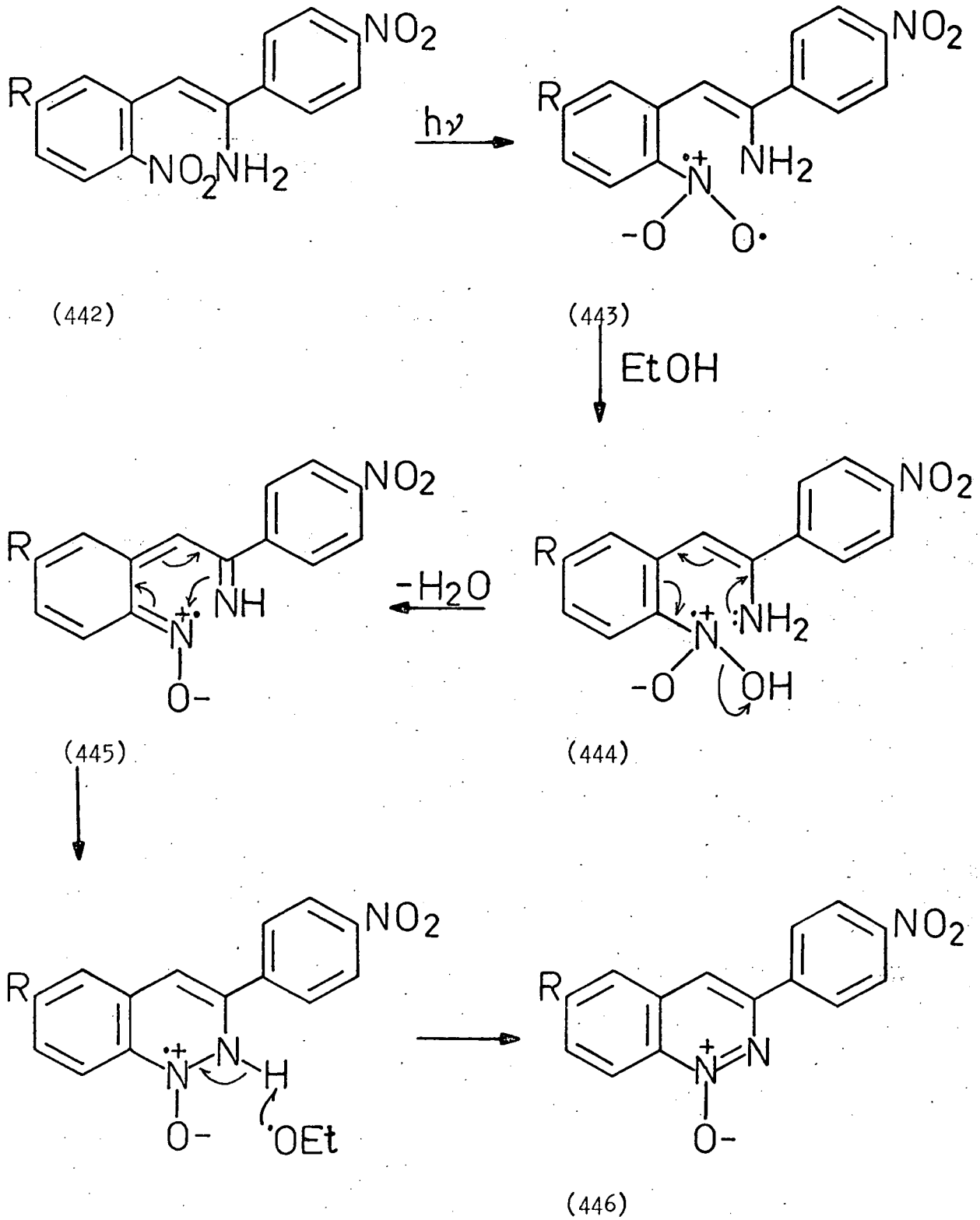


(452a)

the melting point of the red product corresponded to that quoted[154] in the literature for the isatogen (452a).

The apparent clear-cut dichotomy in the photochemical behaviour of the amine (442a) on simply changing the solvent used from ethanol to acetone is striking. In an attempt to show competition between the two modes of reaction observed, the styrylamine (442a) was irradiated through quartz in a 3:1 acetone-ethanol solution. The major product in this case was the isatogen (452a) albeit in reduced yield. However, no cinnoline 1-N-oxide (446a) could be isolated from the reaction mixture.

In order to determine whether the solvent effect upon the mode of the photochemical reaction of the styrylamine (442a) was a sensitisation effect or not, its photochemical behaviour through quartz in both dioxan and acetonitrile, was investigated. In both cases the only product isolated was a good yield (ca. 64%) of the isatogen (452a). Thus it is



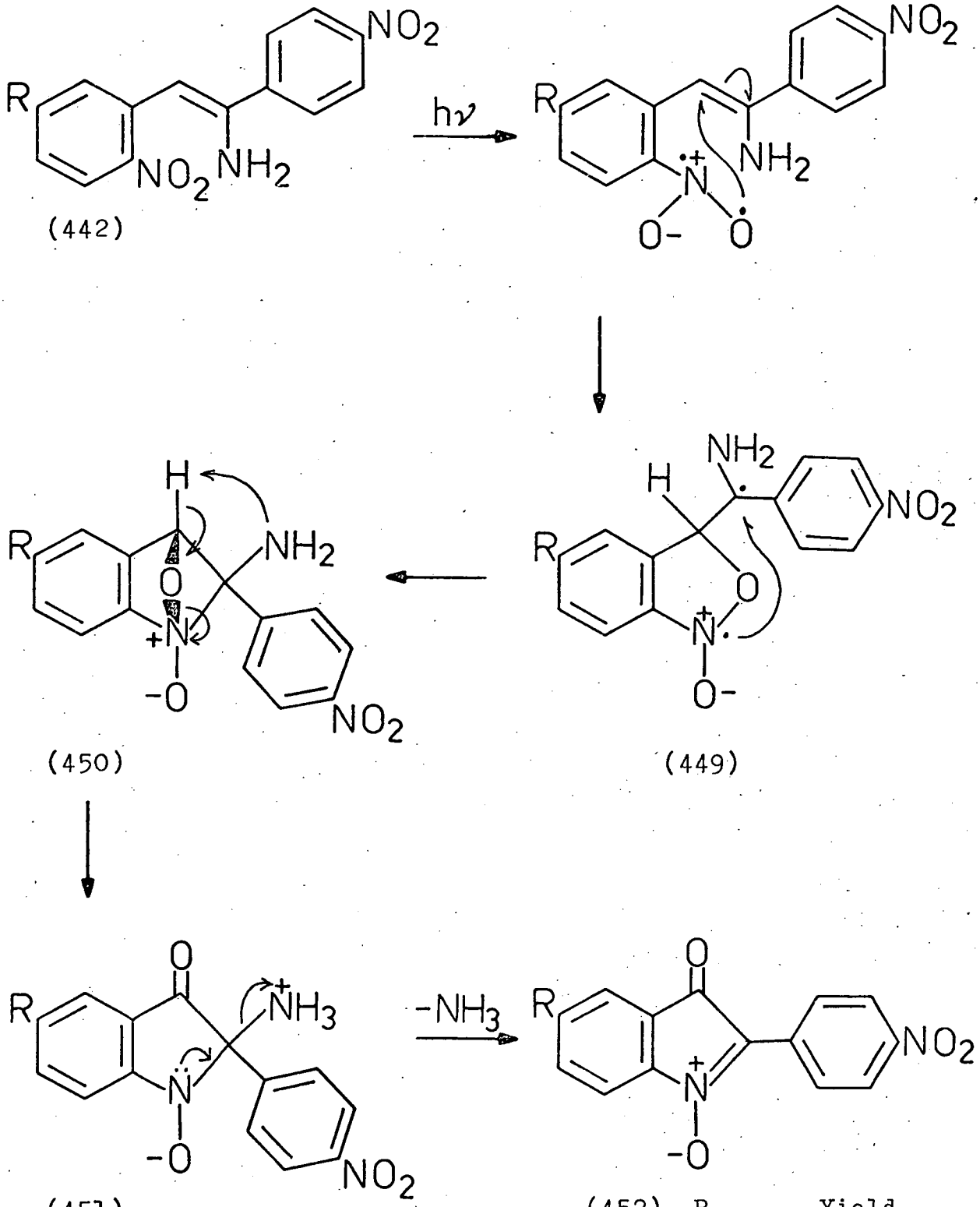
R = H, Br, Cl

Scheme 81

apparent, since dioxan and acetonitrile do not posses strong photo-sensitising properties, that isatogen formation is not due to photo-sensitisation. Further, as ethanol does not possess any strong quenching properties, it would appear that (assuming the nitro group is the chromophore which induces photochemical reaction) it is the same photo-excited state of th nitro group that reacts to give the two different products, depending upon the solvent. Consequently, the $^3(n, \pi^*)$ excited state of the nitro group is suggested to be involved, by analogy with the known photochemical behaviour of the nitro group, (cf. Introduction).

The most obvious difference between the solvent systems used in the photochemical studies being discussed, appeared to be the availability of abstractable hydrogens in the solvent molecules. Thus, when no readily abstractable proton is present as is the case with dioxan,acetone and acetonitrile, the product is the isatogen (452a). When an abstractable hydrogen is present, as is the case with the hydroxyl group in ethanol, the cinnoline 1-N-oxide (446a) is the product. The apparent requirement for cinnoline formation of a solvent with a readily abstractable hydrogen implies that the mechanism (Scheme 80) proposed earlier, in which hydrogen abstraction occurs intramolecularly from the amino group, is not correct. Consequently a revised mechanism for cinnoline 1-N-oxide formation is proposed (Scheme 81) in which the $^3(n,\pi^*)$ excited state of the nitro group (443) abstracts a hydrogen from the solvent to give the radical (444). This radical (444) then undergoes elimination of water by an enamine mechanism to give the imine (445) which cyclises by an electrocyclic process followed by loss of a hydrogen atom to afford the cinnoline 1-N-oxide (446a).

In the cases where the solvent does not have a readily abstractable proton and the product is the isatogen (452a), the observed oxidation of the side-chain implies that photochemical intramolecular oxygen-transfer from the nitro group to the side-chain, has occurred (see Introduction)

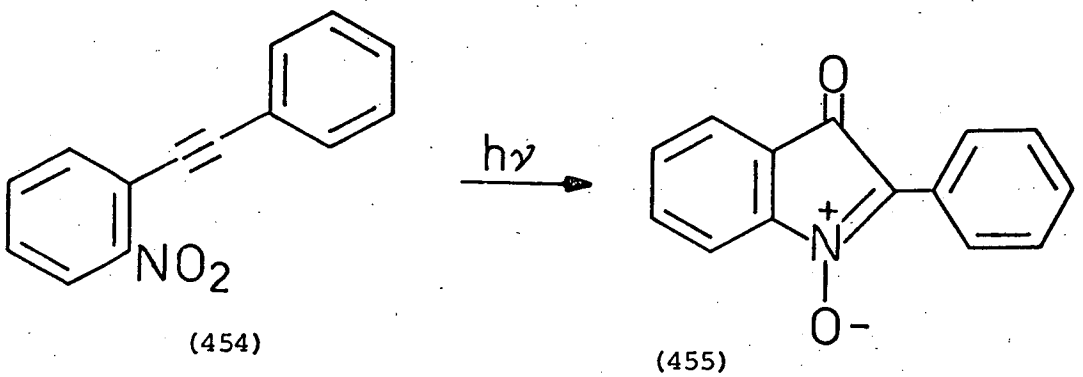


(442) (449) (450) (451)

(452)	R	Yield
a;	H	64%
b;	Cl	48%
c;	Br	33%

Scheme 82

Any mechanism for isatogen formation must also account for the loss of the amino group. It is possible that this occurs as a primary photochemical process of the enamine (442a) to give 2,4'-dinitrotolan (453) which could readily photochemically rearrange to the isatogen (452a) by analogy[154] with the known photochemical reaction of 2-nitrotolan (454) in pyridine to 2-phenylisatogen (455). Alternatively (Scheme 82), a mechanism involving attack on the double bond by the

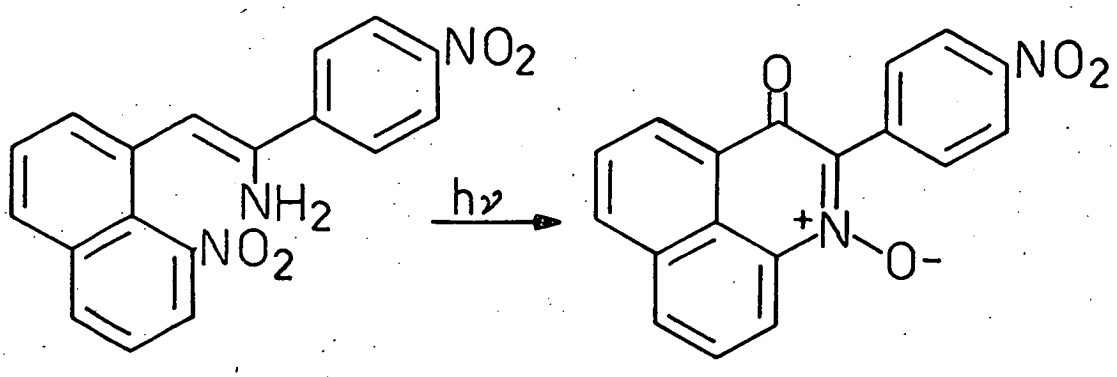


(454) (455)

$^3(n,\pi^*)$ excited state of the nitro-group to give the cyclic intermediate (449) which contains a stabilised benzyl radical, may be invoked. Thus formed, the intermediate (449) can undergo radical coupling to give the bridged cyclic intermediate (450) followed by intramolecular abstraction of the benzylic hydrogen atom by the amino group, with concomitant ring-opening, to afford the betaine intermediate (451) which then loses ammonia to give the isatogen (452a). The chlorostyrylamine (442b) similarly afforded the corresponding isatogen (452b) on irradiation in acetone. The bromostyrylamine (442c) also produced the corresponding isatogen (452c) upon irradiation in acetone but in lower yield.

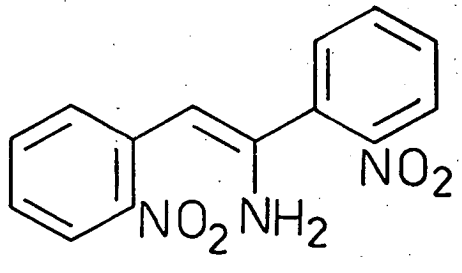
On the basis of the mechanism (Scheme 82) proposed for the photochemical formation of the isatogens (452 a-c), it was envisaged that the 8'-nitronaphthylstyrylamine derivative (456) would undergo a similar reaction to afford benzo[d,e]quinolinone N-oxide derivative (457). However, the study of the photochemical reaction of the amine

(456) was precluded by the failure of 8-nitronaphthaldehyde to condense with 1-(4'-nitrophenyl)pyridinium bromide.



(456) (457)

The interesting possibility of photolysing the 2,2'-dinitrophenylstyrylamine (458) was also thwarted by the failure of 2-nitrobenzaldehyde to condense with 1-(2'-nitrobenzyl)pyridinium chloride, in contrast with ready condensation of 2-nitrobenzaldehyde with 1-(4'-nitrobenzyl)pyridinium bromide (440). The successful synthesis of the 2,2'-dinitrostyrylamine (458) would have allowed the investigation of the competitive photochemical

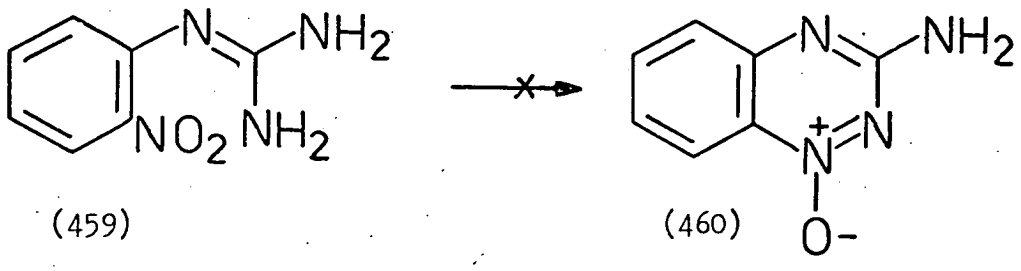


(458)

reaction between the side-chain and the two nitro groups present.

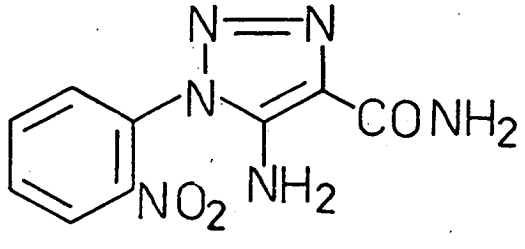
As a possible extention of the photochemical cyclisation of 2-nitrobenzene derivatives having β-aminated side-chains, the photochemical behaviour of 2-nitrophenylguanidine (459) was investigated.

However, irradiation of the guanidine (459) in ethanol gave only

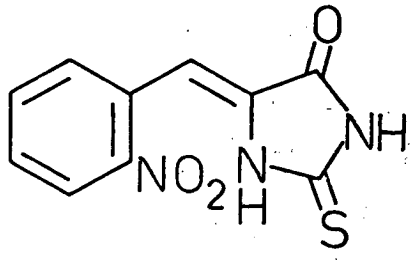


(459) (460)

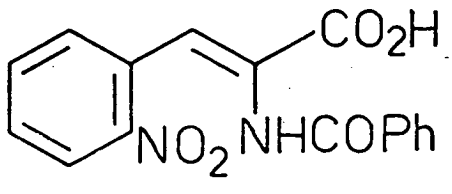
a quantitative return of starting material. On the assumption that the nitro group in the guanidine (459) can abstract a hydrogen atom from the solvent (ethanol), as appears to be the case with the styrylamines (442), then photochemical reaction of the guanidine (459) must be inhibited by the weakly nucleophilic nature of the amino groups in the guanidino moiety. The alternative mode of reaction, namely, oxygen-gransfer to the side-chain, is not feasible in this case due to



(461)



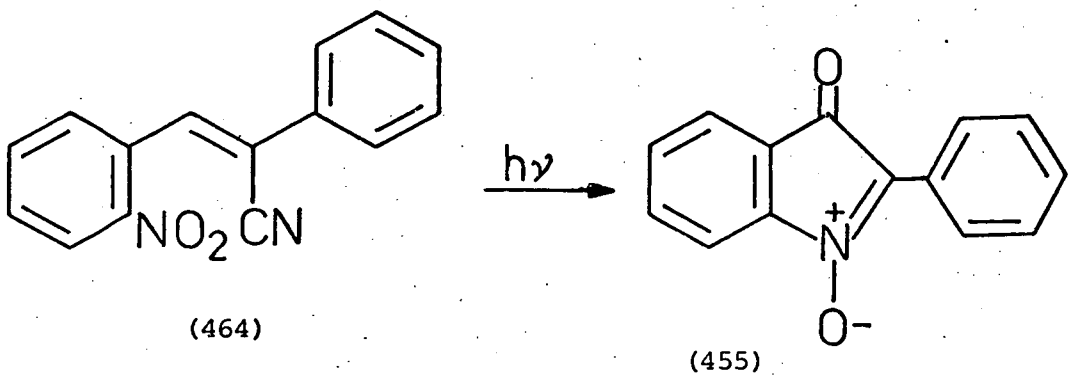
(462)



(463)

the presence of a nitrogen atom in the benzylic position. The attempted photochemical cyclisation of the 5-amino-1-(2'-nitrophenyl)triazole (461) and of 2'-nitrophenylthiohydantoin (462) were also unsuccessful. The attempted cyclisation of 2-benzamido-2'-nitrocinnamic acid (463) resulted only in the formation of intractable gums from which no identifiable material was obtained.

The mechanism (Scheme 82) proposed for the photochemical transformation of the 2-nitrostyrylamines (442 a-c) into isatogens (452 a-c) involves the ultimate elimination of the amino group as ammonia and so implies that any analogous 2-nitrostyryl derivative containing a good leaving group in the β-position of the side-chain, should undergo photochemical cyclisation to an isatogen derivative. In an attempt to substantiate this contention and also to extend the scope of the photochemical synthesis of isatogens, the photolysis of 2'-nitro-2-phenylcinnamonitrile (464) in acetone, was investigated. However, the nitrile (464) was completely inert to

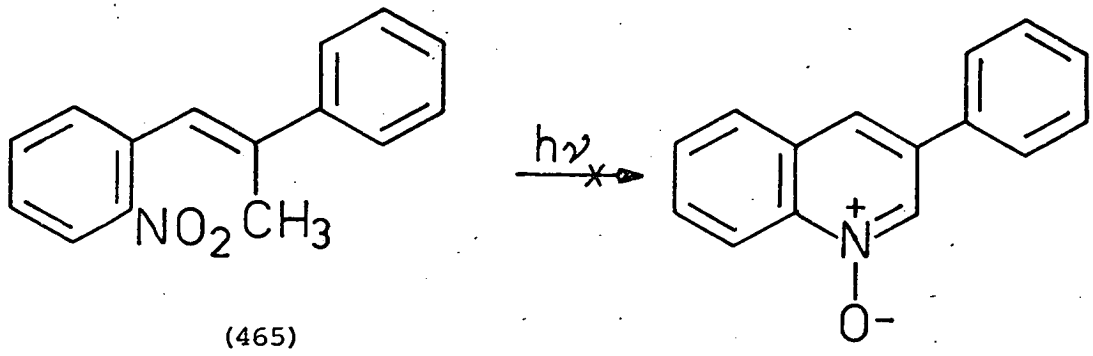


(464) (455)

prolonged irradiation in acetone. This inertness is surprising in view of the marked photochemical reactivity of 2'-nitrostilbene derivatives reported by Splitter and Calvin.[91]

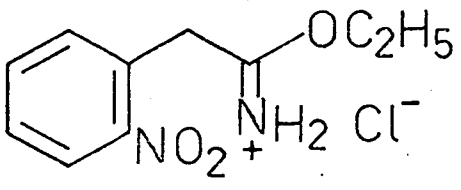
As discussed earlier, Doppe[151] has reported the photochemical cyclisation of 2-nitro-tert-butylbenzene (437) to give the nitrone (438). This reaction is postulated to proceed by hydrogen abstraction as the primary photochemical event. It seemed reasonable to expect, therefore, that 2-methyl-2'-nitrostilbene (465) which has features both of the 2'-nitrostyrylamines

(442) and 2-nitro-tert-butylbenzene (437), might undergo photochemical cyclisation leading ultimately to 3-phenylquinoline 1-N-oxide (466).

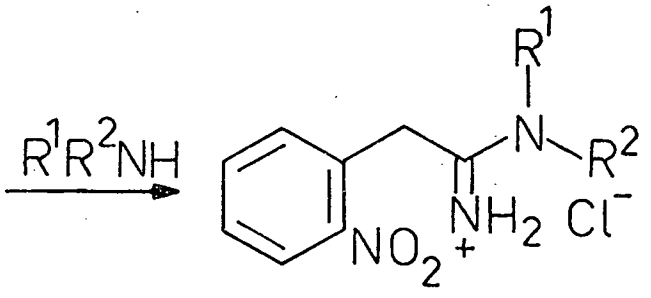


(465) (466)

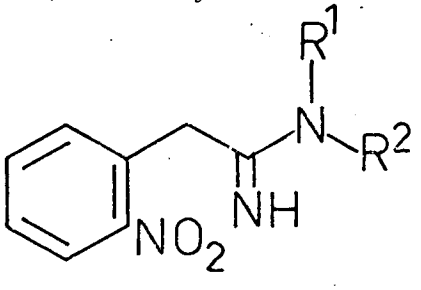
However, irradiation of the stilbene (465) in acetone or ethanol, resulted in a moderate return of starting material together with complex mixtures of starting material and unidentified products.



(467)

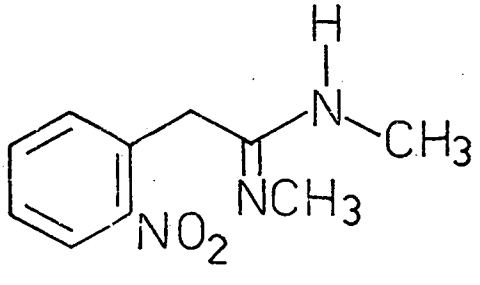


(468)



(469)

	R^1	R^2
a;	H	H
b;	CH_3	CH_3
c;	H	CH_3
d;	$-CH_2CH_2OCH_2CH_2-$	
e;	$-CH_2(CH_2)_3CH_2-$	
f;	$-CH_2(CH_2)_4CH_2-$	
g;	C_2H_5	C_2H_5



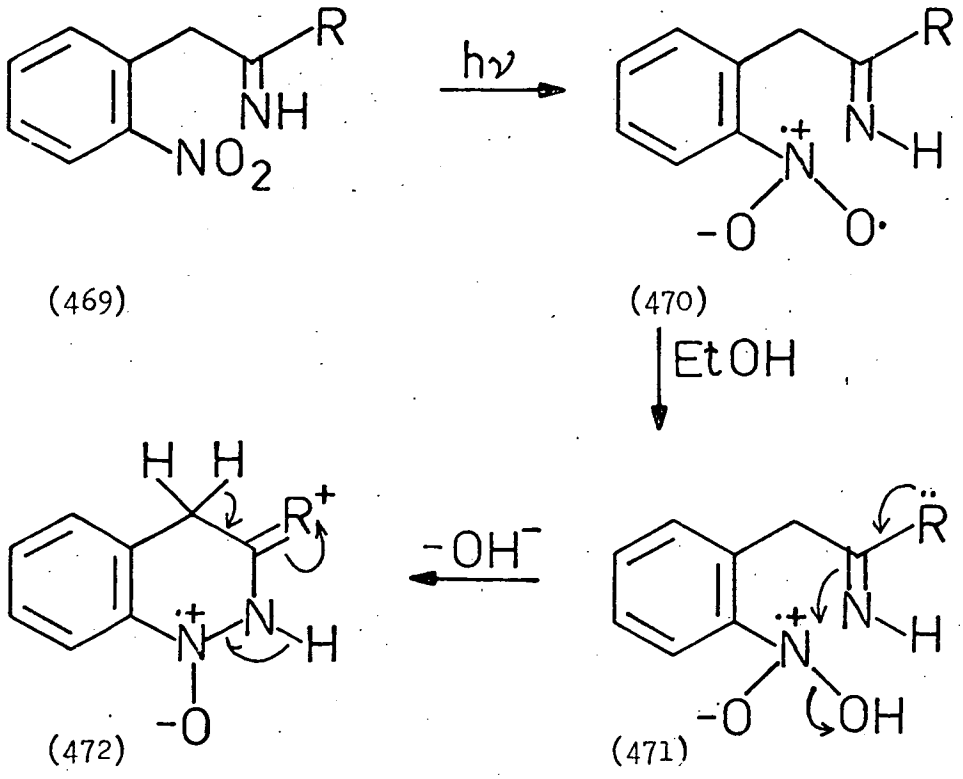
(476)

SCHEME 83

Part II

Despite the failure of 2-nitrophenylguanidine (459) to undergo photochemical cyclisation as discussed before, it was decided to investigate the photochemical cyclisations of the structurally similar 2-nitrophenylacetamidines (469 a-g). If successful, these cyclisations would provide a new synthesis of 3-aminocinnoline 1-N-oxides which are not readily available by more orthodox methods (e.g. peracid oxidation of the corresponding 3-aminocinnolines). The amidines (469 a-g) required for study were readily prepared by reaction of ethyl 2-nitrophenylacetimidate hydrochloride (467) with the corresponding amines (Scheme 83) to give the amidine hydrochlorides (468 a-g), followed by treatment with dilute alkali. The majority of the hydrochloride derivatives failed to give analytical data consistent with their formulation and the mass spectra showed parent ions corresponding to the free amidine bases. The majority of the hitherto unknown amidines were however, characterised by their elemental analysis, mass spectra, and i.r. spectra. However, the amidine (469e) and 469f), derived from piperidine and pyrrolidine respectively, were oils which were shown to be pure by t.l.c. and by their ^{1}H n.m.r. spectra. The ^{1}H n.m.r. spectra of the amidines (469 e and f) showed a sharp singlet due to two protons at ca. τ 5.9 indicating the presence of a methylene group and a broad singlet at τ 5.73, due to one proton is assigned to a single NH group. These features indicate that the amidines (469 a-g) exist in the imine form rather than in the enamine form of the type (474). The diethyl-substituted amidine (469g) was also an oil and could not be characterised due to lack of material.

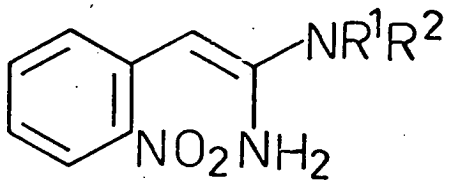
Irradiation of 2-nitrophenylacetamidine (469a) in ethanol for 48 h resulted in the initially colourless solution becoming a strong yellow colour and on work-up, a yellow solid was isolated in low yield.



(469) (470) (471) (472) (473)

	R	Yield %
a;	NH_2	26
b;	$NHCH_3$	31
c;	$(CH_2)_4N$	49
d;	$(CH_2)_5N$	57
e;	$O(CH_2)_4N$	65
f;	$N(C_2H_5)_2$	62
g;	$N(CH_3)_2$	87

Scheme 84



(474)

This solid gave an elemental analysis and mass spectrum (m/e 161) consistent with a molecular formula of $C_8H_7N_3O$, and with the loss of the elements of water from the amidine (469a). The i.r. spectrum of the yellow solid showed bands at 3390 and 3300 cm^{-1}, attributable to a primary amino group. Bands attributable to a nitro group were absent. The band at 1615 cm^{-1} is assigned to the NH deformation. These properties are fully consistent with the yellow product being the cinnoline 1-N-oxide [(473a); Scheme 84]. This structure was also supported by the ^1H n.m.r. spectrum of the yellow product. Thus, a low field resonance at τ 1.66 showed ortho-coupling and is assigned to H-(8) of the cinnoline nucleus which is deshielded due to the anisotropic effect of the N-oxide function. The multiplet in the range τ 2.45-2.82 is assigned to the remaining three benzo-hydrogens. The singlet at τ 3.35 is assigned to H-(4) which is shielded by the +M effect of the amino group. The latter appears in the ^1H n.m.r. spectrum as a broadened singlet at τ 4.86.

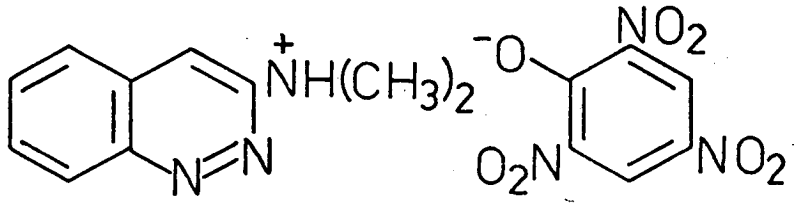
In contrast to the low yield of the cinnoline 1-N-oxide (473a) obtained from the photolysis of 2-nitrophenylacetamidine (469a), the amidines (469 b-g) derived from primary or secondary amines, afforded moderate to good yields of the corresponding cinnoline 1-N-oxides [(473 b-g); Scheme 84] on irradiation in ethanol. Satisfactory elemental analyses and mass spectral data were obtained for all of the

hitherto unknown cinnoline 1-N-oxides (473 a-g). The ^{1}H n.m.r. spectra of these cinnoline 1-N-oxides (473 b-e and g), like that of 3-amino-cinnoline 1-N-oxide (473a) showed a low field doublet at ca. τ 1.65 attributed to the H-(8) nucleus in each case. This value is in accord with the chemical shifts[155] of H-(8) in other cinnoline 1-N-oxides. The ^{1}H n.m.r. spectra of the cinnoline 1-N-oxides (473 a-e and g) also showed, in general, a singlet at ca.τ 3.5 attributable to the H-(4) of the cinnoline nucleus. These values are higher than typical values quoted[155] for H-(4) in other cinnoline 1-N-oxides. However, the values for H-(4) resonances in the 3-aminocinnoline 1-N-oxides (473) are in keeping with the value (τ 3.08)[155] for the H-(4) nucleus in 3-methoxycinnoline 1-N-oxide. The upfield shift observed in the H-(4) resonance in the cinnoline 1-N-oxides (473) is therefore, attributable to the +M effect of the C-(3) amino substituents which will shield the H-(4) nucleus in each case. Typically, the H-(4) resonance is higher in the cinnoline 1-N-oxides (473 c-e and g) which have a tertiary amino substituent than in the cinnoline 1-N-oxides (473 a and b) having secondary or primary amino substituents.

The u.v. spectra of the 3-aminocinnolines (473 a-g) were obtained in ethanol and were qualitatively identical in the shape of the absorption envelope. All showed a weak absorption in the visible region (ca. 450 nm). The remaining u.v. data however, could not be usefully compared to the u.v. spectra of other cinnoline 1-N-oxides,[155] probably due to the perturbation of the "typical" cinnoline 1-N-oxide absorption spectra by the amino substituents in the cinnoline 1-N-oxides (473 a-g).

An unambiguous proof of the structure of 3-aminocinnoline 1-N-oxide (473a) and hence by analogy of the cinnoline 1-N-oxides (473 b-g) would have been achieved by the reduction of the cinnoline 1-N-oxide (473a)

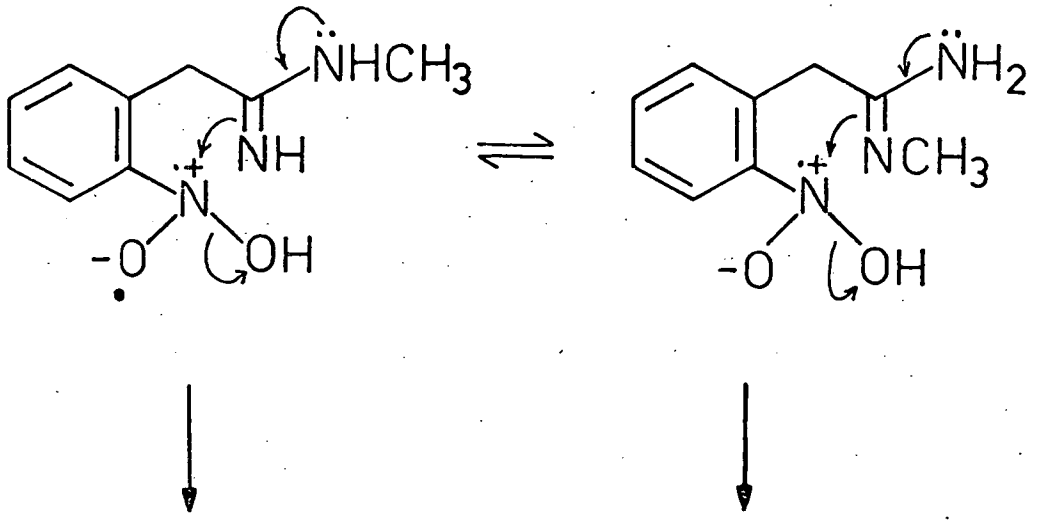
to the known[156] 3-aminocinnoline. However, lack of material thwarted this approach. In order to establish the presence of an N-oxide function in the cinnolines (473 a-g), an attempt was made to reduce 3-(N,N-dimethylamino)cinnoline 1-N-oxide (473g). However, although reduction did occur, the product was a multicomponent gum. Treatment of an ethanolic solution of this gum with a hot saturated solution of sodium picrate afforded a red solid, however, whose elemental analysis was consistent with that expected for 3-(N,N-dimethylamino)cinnoline picrate (475). Also its mass spectrum showed a parent ion (m/e 173) due to



(475)

3-(N,N-dimethylamino)cinnoline. No peak was present at m/e 189 which eliminates the presence of 3-(N,N-dimethylamino)cinnoline 1-N-oxide (473g) which could also form a picrate.

The irradiation of 2-nitrophenylacetamidine (469a) and N,N-dimethyl-2-nitrophenylacetamidine (469b) in acetone did not result in the isolation of any cinnoline 1-N-oxide derivatives. Therefore, by analogy with the photolysis of the 2-nitrostyrylamines (442) in ethanol, it is proposed that the mechanism of the formation of the 3-aminocinnolines (473 a-g) proceeds by initial hydrogen abstraction (Scheme 84) from the ethanol solvent by the $^3(n,\pi^*)$ excited state of the nitro group to give the radical [(471) ; Scheme 84]. Nucleophilic attack by the imine nitrogen then gives the cyclised intermediate (472) containing an oxonium ion centre. This mode of attack will be favoured when R is a secondary or



Products

Products

from

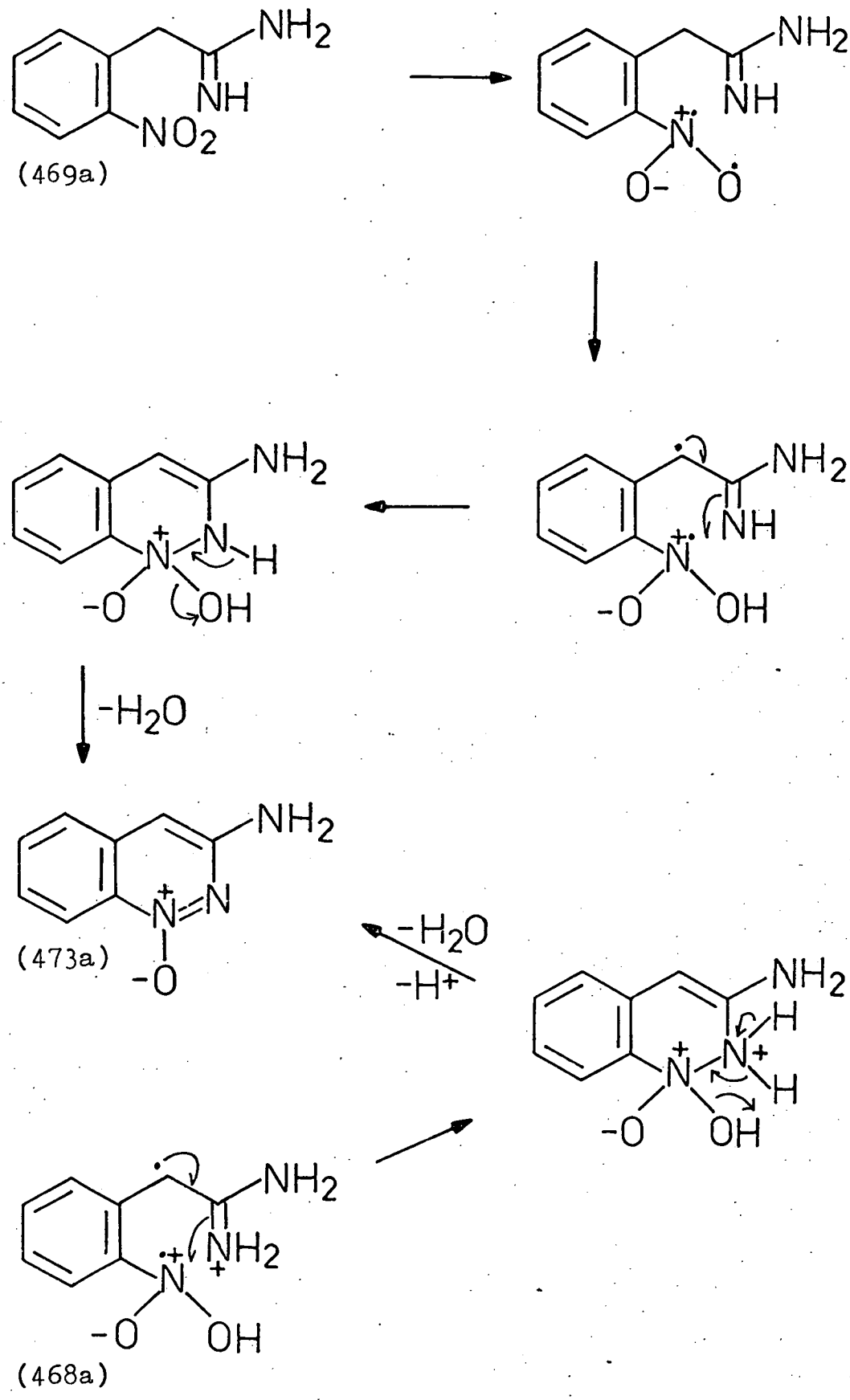
(469c)

Scheme 85

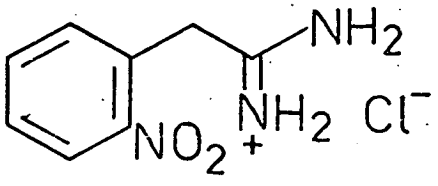
tertiary amine since these will stabilise the positive charge produced. Further, there is no possibility of tautomerism between the amidine nitrogen atoms when one of the amine groups is tertiary. This will fix the imine group and hence remove the possibility of competitive nucleophilic attack by both nitrogen atoms in the amidine moiety. When a secondary amine is present in the amidine, the existence of tautomeric forms (469c) will allow two modes of attack resulting in cyclisation (Scheme 85). These effects of ion stabilisation and of the number of possible modes of nucleophilic attack in the cyclisation step are fairly reflected in the observed yields of products (cf. Scheme 84).

The mechanism postulated for the photochemical formation of the cinnoline N-oxides (473 a-g) involves a step (472) → (473) which might be susceptible to base-catalysis. To examine the possibility of base-catalysis augmenting the efficiency of this dark reaction (472 → (473) in the photochemically induced transformation of 2-nitrophenylacetamidine (469a) into 3-aminocinnoline 1-N-oxide (473a), the reaction was carried out in ethanol with added triethylamine. However, no increase in yield was observed.

The possibility that photochemical cyclisation might be inhibited by acid was also investigated by irradiating 2-nitrophenylacetamidine hydrochloride (468a) in ethanol. After 24 h, almost 70% of the starting material was recovered and no cinnoline N-oxide was isolated from the accompanying gum. This result indicates that inhibition of the reaction occurs if the amidine group is protonated. It can therefore, be inferred that the mechanism for the formation of the cinnoline 1-N-oxides (473 a-g) cannot involve hydrogen abstraction from the benzylic position (Scheme 86) since it is not envisaged that any inhibition should occur as this purely radical cyclisation should be insensitive to charge effects. However,


NH2
NH
NO2
(469a)
NH2
NH
O-
O
NH2
NH
-O
OH
NH2
N
H
-O
OH
-H2O
NH2
N
(473a)
-O
-H2O
-H+
NH2
H
H
-O
OH
NH2
NH2
-O
OH
(468a)

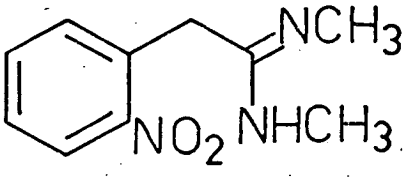
Scheme 86



(468a)

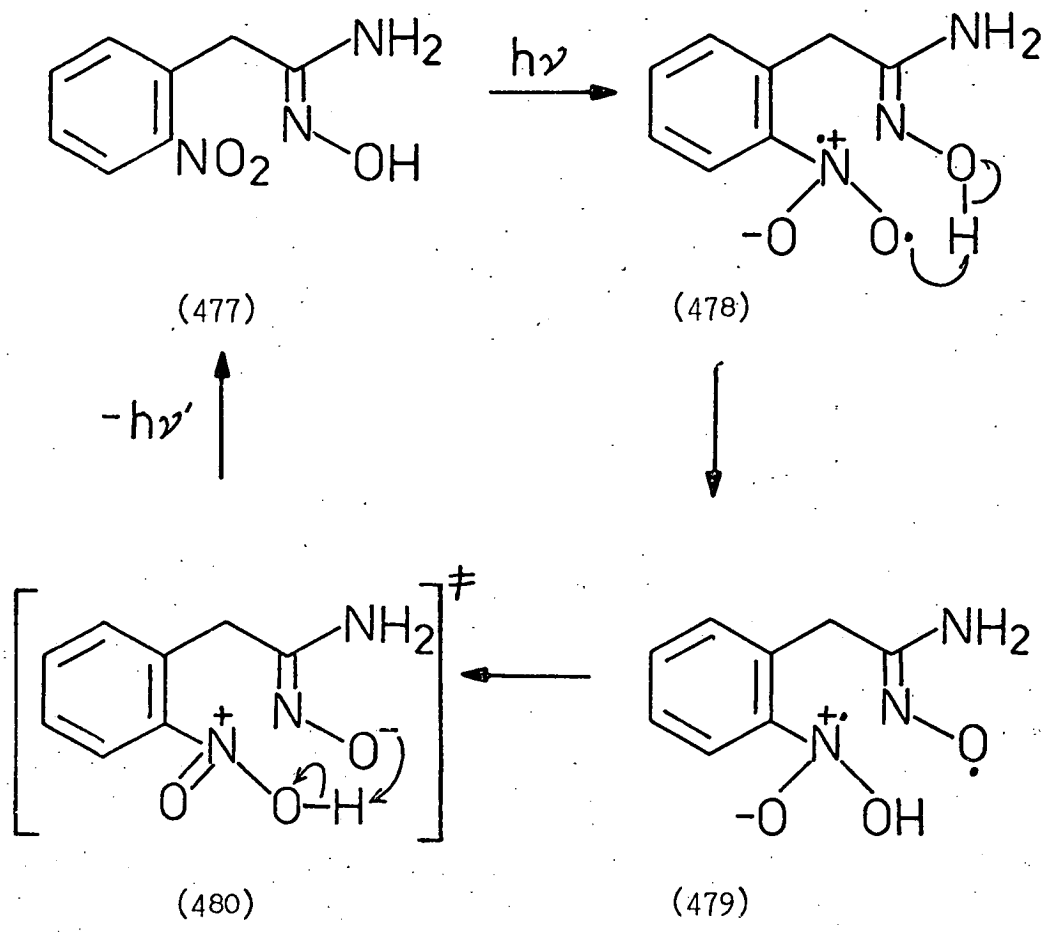
in the proposed mechanism (Scheme 84) the presence of a positive charge on the amidine group would inhibit the reaction as the nucleophilic capacity of the amidine will have been lost due to protonation and consequently, the cyclisation step (471) → (472) will be inhibited.

The attempted photochemical cyclisation of N,N'-dimethylamino-2-nitrophenylacetimidate (476) resulted only in the formation of intractable gums.

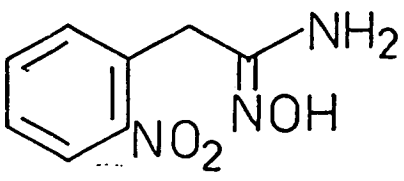


(476)

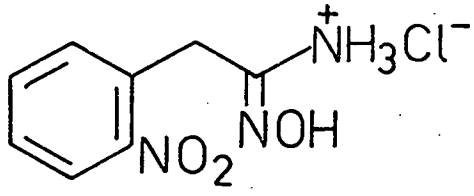
As an extention to the photochemical synthesis of substituted cinnoline 1-N-oxides, the photochemical reaction of the amidoxime (477) was investigated. The hitherto unknown amidoxime (477) was readily prepared by the reaction of hydroxylamine with 2-nitrobenzyl-cyanide and was characterised by its elemental analysis, mass spectrum and i.r. spectrum and by the formation of a hydrochloride derivative (478).



Scheme 87

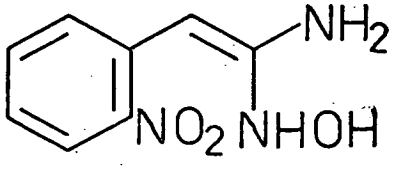


(477)



(478)

The ^{1}H n.m.r. spectrum of the free amidoxime (477) contained a sharp singlet due to two protons at τ 6.27 which is attributed to the methylene group. A broad signal at τ 4.78 due to two protons, is attributed to the amino group. It also contained a broadened singlet at τ 0.98, due to one proton which is assigned to the proton of the hydroxyl group. These features demonstrate that the amidoxime (477) exists (in chloroform solution at least) in the oxime form (477) and not in the enamine form (482). However, in contrast to the ready cyclisation of the 2-nitrophenyl-acetamidines (469 a-g) in ethanol, irradiation of the amidoxime (477) in

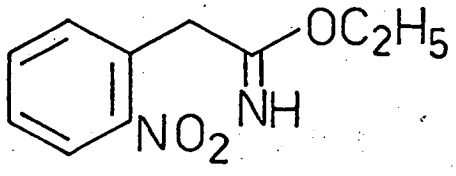


(482)

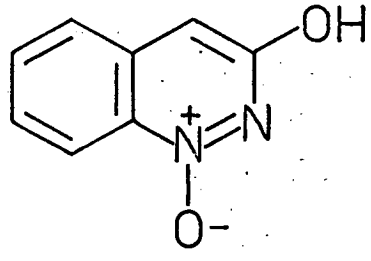
ethanol for 24 h resulted in its being recovered, largely unchanged. Also, its irradiation in acetone for 65 h resulted in the majority of the amidoxime (477) being recovered unchanged and no identifiable product was isolated. The inertness of the amidoxime to irradiation with u.v. light may be due to the formation of an excimer [(48I); Scheme 87]. This may

arise by hydrogen-abstraction from the oxime hydroxyl group by the $^3(n,\pi^*)$ excited-state of the nitro group, followed by electron-transfer from the negatively charged oxygen atom to nitroxide radical of the oxime group. This excimer (481), unstable in the ground state, can then revert to the starting material (477). Such one-electron transfers are postulated[157] to occur in the photoreduction of carbonyl compounds facilitated by the presence of amines.

As the imidate (482) is structurally analogous to the amidines (469) its behaviour on irradiation was also investigated in an attempt to synthesise 3-methoxycinnoline 1-N-oxide. The imidate (482) was prepared as an oil, by neutralisation of its hydrochloride derivative (467a) with diethylamine. On its irradiation in ethanol, a colourless solid was isolated whose elemental analysis was consistent with the empirical formula, $C_8H_6N_2O_2$ which corresponds to the structure, 3-hydroxycinnoline 1-N-oxide (483). However, the i.r. spectrum of the product suggested the



(482)



(483)

presence of a nitro group. No other functional groups were indicated (e.g. OH) by the i.r. spectrum of the colourless solid. The precise nature of this product remains to be established since its mass spectrum did not give a m/e value which was consistent with its empirical formula, obtained from its elemental analysis.

3-Hydroxycinnoline 1-N-oxide (483) might be expected to be the product of the photochemical cyclisation of 2-nitrophenylacetamide. However, irradiation of this amide in ethanol, resulted only in a quantitative

return of the starting material. This result is not surprising as the amide nitrogen in 2-nitrophenylacetamide is only weakly nucleophilic and hence, might not be expected to be able to effect a cyclisation step of the type [(471) → (472); Scheme 84].

In conclusion, it has been shown that otherwise inaccessible 3-aminocinnoline 1-N-oxides are readily available, in good yields, by the photochemical cyclisation of 2-nitrophenylacetamidine substrates in ethanol.

Experimental (Part I)

1. The Synthesis of 1-[2'-Nitro-α-(4'-nitrophenyl)styryl]pyridinium Bromide Derivatives

a) 1-α-[2'-Nitro-α-(4'-nitrophenyl)styryl]pyridinium Bromide[152] (441)

The pyridinium salt (441) was prepared by the method of Krohnke[152] (84%), m.p. 311° (decomp.)(lit.,[152] 312°)

b) 1-α-[5'-Chloro-2'-nitro-α-(4'-nitrophenyl)styryl]pyridinium Bromide (441b)

A solution of 1-(4'-nitrobenzyl)pyridinium bromide (440)(4.0 g; 0.016 mol) and 5-chloro-2-nitrobenzaldehyde (439b)(3.85 g, 0.021 mol) in acetic anhydride (40.0 ml) was treated with glacial acetic acid (2.0 ml) and anhydrous potassium acetate (0.8 g) and the mixture was stirred at 75° for 48 h. The mixture was then evaporated and the residue was treated with water (50.0 ml) and washed with chloroform. The aqueous phase was treated with 50% w/v aqueous hydrobromic acid (20.0 ml) and then concentrated to give a green oil which was triturated with a little water to afford the pyridinium salt (441b)(3.2 g; 50%), m.p. 283° (from ethanol), $\nu_{max.}$ 1650 (C=C) and 1515 and 1340 (NO_2) cm^{-1}

Found: C, 48.6; H, 2.8; N, 8.7%; p^+304/302(M^+-pyridine)

$C_{19}H_{13}BrClN_3O_4$ requires: C, 49.3; H, 2.8; N, 9.1%; M, 382.5 (cation).

c) 1-α-[5'-Bromo-2'-nitro-α-(4'-nitrophenyl)styryl]pyridinium Bromide (441c)

A solution of 1-(4'-nitrobenzyl)pyridinium bromide (440) (2.0 g, 0.008 mol) and 5-bromo-2-nitrobenzaldehyde (439c)(2.3 g, 0.01 mol) was treated with glacial acetic acid (1.0 ml) and anhydrous potassium acetate (0.4 g) and the mixture was stirred at 75° for 48 h. The cooled mixture was filtered to remove inorganic material and the filtrate was treated with ether (40.0 ml) and washed with water (40.0 ml). The aqueous phase was separated, treated with 50% w/v aqueous hydrobromic acid (10.0 ml), and

then concentrated. The resulting oil was triturated with water to give the pyridinium salt (441c) which was combined with a second crop obtained by evaporating the ether layer and treating the residue with water (100 ml) and chloroform and then treating the aqueous phase with 50% w/v aqueous hydrobromic acid (10.0 ml) as before (total 2.8 g, 81%), m.p. 295° (decomp.) (from acetic acid), $\nu_{max.}$ 1630 (C=C) and 1515 and 1350 (NO_2) cm^{-1}.

Found: C, 44.6; H, 2.6; N, 8.0%; p^+, 348/346 (M^+-pyridine)

$C_{19}H_{13}Br_2N_2O_4$ requires: C, 44.9; H, 2.6; N, 8.3%; M, 427 (cation).

d) The Attempted Preparation of 1-β-[4'-Nitro-α-(8'-nitronaphth-1-yl)styryl]-pyridinium Bromide

The attempted reaction of 8-nitro-1-naphthaldehyde with 1-(4'-nitrobenzyl) pyridinium bromide (440) was carried out as described in (b) and (c) above. The cooled reaction mixture precipitated unreacted 1-(4'-nitrobenzyl) pyridinium bromide (25%)[152] identical (m.p. and i.r. spectrum) with an authentic sample. The filtrate was concentrated, treated with water (30.0 ml) and washed with chloroform. The aqueous phase was separated, clarified with animal charcoal, and then treated with 50% w/v aqueous hydrobromic acid (10.0 ml). Evaporation of the aqueous solution gave a gummy residue from which no identifiable material could be obtained.

Evaporation of the chloroform layer gave a dark gummy residue which was triturated with methanol to afford unreacted 8-nitro-1-naphthaldehyde (85%), m.p. 120° (lit.,[158] 124°), identical (i.r. spectrum) with an authentic sample.

e) The Attempted Preparation of 1-α-[2'-Nitro-α-(2"-nitrophenyl)styryl]-pyridinium Bromide

The attempted reaction of 2-nitrobenzaldehyde (439a) with 1-(2'-nitrobenzyl)pyridinium chloride was carried out as described in (b) and (c) above. The reaction mixture was cooled and concentrated to approximately

one-third of its original volume then treated with water (30.0 ml) and washed with ether (2 x 25.0 ml). The aqueous phase was separated and treated with 50% w/v aqueous hydrobromic acid (10.0 ml) and then concentrated to give a gum which was triturated with water to give 1-(2'-nitrobenzyl)pyridinium bromide (0.6g) m.p. 200°.

Evaporation of the ether layer afforded unreacted 2-nitrobenzaldehyde (80%), m.p. 43° (lit.,[159] 44°).

2. The Formation of the 2-Nitrostyrylamines (442 a-c)

a) β-Amino-2-nitro-β-(4'-nitrophenyl)styrene[152] (442a)

(i) The pyridinium salt (441a) (0.005 mol) was suspended in methanol (15.0 ml) and treated with piperidine (10.0 ml) to give a solution that was heated under reflux for 1 h. The solution was then concentrated to approximately one half of its original volume, warmed and treated with water (10.0 ml) to give the enamine[152] (442 a) (quantitative) on cooling as a red powder, m.p. 136° (lit.,[152] 133°).

(ii) The enamine (442a) was prepared by the method of Krohnke[152] (76%) m.p. 132° (from benzene) (lit.,[152] 133°) τ($CDCl_3$; 60MHz) 1.72-2.72 (8H, m, ArH), 4.00 (1H, s, CH) and 6.00 (2H, br s, NH_2).

b) β-Amino-5-bromo-2-nitro-β-(4'-nitrophenyl)styrene (442c)

The enamine (442c) was prepared as described for the enamine (442a) in (i) above, as a red powder (80%), m.p. 148° (from benzene), $\nu_{max.}$ 3480 and 3380 (NH_2), 1620 (C=C), and 1525 and 1340 (NO_2) cm^{-1}.

Found: C, 46.3; H, 2.7; N, 11.2%; M^+, 365/363.

$C_{14}H_{10}BrN_3O_4$ requires: C, 46.2; H, 2.8; N, 11.5%; M, 364.

(c) β-Amino-5-chloro-2-nitro-β-(4'-nitrophenyl)styrene (442b)

The enamine (441b) was prepared as described for the enamine (442b) in (i) above, as a red powder (85%), m.p. 131° (from benzene), $\nu_{max.}$ 3500 and 3400 (NH_2) and 1530 and 1350 (NO_2) cm^{-1}.

Found: C, 52.8; H, 3.1; N, 13.0%; M^+, 321/319.

$C_{14}H_{10}ClN_3O_4$ requires: C, 52.8; H, 3.1; N, 13.2%; M, 319.5.

3. The Photochemical Formation of 3-Arylcinnoline 1-Oxides

Note: All photochemical experiments were carried out using a medium pressure Hanovia photochemical reactor. All solutions were irradiated under nitrogen.

a) 3-(4'-Nitrophenyl)cinnoline 1-N-Oxide (446a)[152]

(i) The enamine (442a) (2.0g) was dissolved in ethanol (1000 ml) and irradiated through either a quartz or pyrex filter for 24 h. The solid which separated was collected and combined with a second crop obtained by evaporating the filtrate and triturating the residue with methanol to give the cinnoline 1-N-oxide (446a) (1.25 g; 67%) as yellow needles, m.p. 273° (from ethanol dimethylformamide) (lit.,[152] 268°), $\nu_{max.}$ 1515 and 1350 (NO_2) cm^{-1}, $\lambda_{max.}$ 207 sh, 237, 271, 285, and 344 nm, (log $\varepsilon_{max.}$ 4.17, 4.43, 4.25, 4.28 and 4.19).

Found: C, 62.9; H, 3.4; N, 15.6%; M^+, 267

Calculated for $C_{14}H_9N_3O_3$: C, 62.9; H, 3.4; N, 15.7%; M, 267.

Evaporation of the methanol mother liquors gave a gum (0.7 g) whose t.l.c. in ethyl acetate over silica showed it to be a mixture containing starting material and from which no identifiable material could be isolated.

ii) A solution of the enamine (442a) (0.4 g) in ethanol (200 ml) with the addition of acetone (0.1 ml) was irradiated through a quartz filter for 24 h. The reaction mixture was filtered and the solid that was collected was combined with another crop obtained by evaporating the filtrate and triturating the residue with methanol to give the cinnoline-N-oxide (446a) (total 0.27 g; 73%), m.p. 272° (lit.,[152] 268°) identical (m.p. and i.r. spectrum) with a sample prepared before.

The methanol mother liquors were evaporated to give a gum (0.16 g) whose t.l.c. in methanol over silica showed it to be a multicomponent mixture.

b) 6-Chloro-3-(4'-nitrophenyl)cinnoline 1-N-Oxide (446b)

A solution of the enamine (442b) (0.62 g, 0.002 mol) in ethanol (200 ml) was irradiated through a quartz filter for 42 h to give the insoluble cinnoline 1-N-oxide (446b) which was combined with a second crop obtained by evaporating the ethanol filtrate and triturating the residue with methanol (total 0.46 g; 77%), m.p. 280° (from glacial acetic acid), $\nu_{max.}$ 1520 and 1350 (NO_2) cm^{-1}.

Found: C, 55.4; H, 2.6; N, 13.5%; M^+, 303/301.

$C_{14}H_8ClN_3O_3$ requires: C, 55.7; N, 2.7; N, 13.9%; M, 301.5.

The methanol mother liquors were evaporated to leave a gum (0.12 g) whose t.l.c. in methanol over alumina showed it to be a mixture from which no identifiable material could be obtained.

c) 6-Bromo-3-(4'-nitrophenyl)cinnoline 1-N-Oxide (446c)

A solution of the enamine (442 c) (0.58 g, 0.0016 mol) in ethanol (200 ml) was irradiated through quartz for 24 h to give the insoluble cinnoline 1-N-oxide (446c) (0.28 g) which was combined with a second crop obtained by irradiating the filtrate (whose t.l.c. in ethyl acetate over alumina showed it to contain starting material) for a further 42 h (total 0.32 g; 59%). The cinnoline 1-N-oxide formed yellow plates m.p. 295° (from dimethylformamide), $\nu_{max.}$ 1515 and 1348 (NO_2) cm^{-1}.

Found: C, 48.3; H, 2.3; N, 11.8%; M^+, 347/345.

$C_{14}H_8BrN_3O_3$ requires: C, 48.6; H, 2.3; N, 12.1%; M, 346.

The ethanolic filtrate was evaporated to give a gum (0.24 g) whose t.l.c. in ethyl acetate over alumina showed it to contain four ill-resolved components which were not further investigated.

4. The Attempted Reduction of 3-(4'-Nitrophenyl)cinnoline 1-N-Oxide

a) Using Hydrogen over Palladium Charcoal

A solution of the cinnoline 1-N-oxide[152] (446a) (0.23 g) in glacial acetic acid (100 ml) containing concentrated aqueous hydrochloric acid (10.0 ml) was hydrogenated over 10% palladium-charcoal at atmospheric pressure until the uptake of hydrogen had ceased. The filtered mixture was evaporated to give the unreacted N-oxide (446a) (0.2 g) m.p. 269° (lit.,[152] 273°) identical (i.r. spectrum) with an authentic sample.

b) Using Sodium Dithionite

The cinnoline 1-N-oxide[152] (446a) (1.07 g, 0.004 mol) in glacial acetic acid (60.0 ml) was heated under reflux in the presence of sodium dithionite (2.0 g). A second aliquot of sodium dithionite was added and heating under reflux for a further 1 h. The solution was hot filtered to remove inorganic material and the filtrate was evaporated to give a crude solid which was washed with water (10.0 ml) and collected (1.36 g). The crude solid was recrystallised twice from ethanol with charcoaling to give an unidentified product, m.p. 196°,

Found: C, 57.8; N, 4.8; N, 11.7%; M^+ 223.

5. The Photochemical Formation of 2-(4'-Nitrophenyl)-3H-indolin-3-one 1-N-oxides (452 a-c)

a) 2-(4'-Nitrophenyl)-3H-indolin-3-one 1-N-oxide[154] (452a)

(i) A solution of the enamine (442a) (0.57 g, 0.002 mol) in acetonitrile (200 ml) was irradiated through a quartz filter for 24 h. Evaporation of the photolysate gave a red solid (0.54 g) which recrystallised from ethanol-dimethylformamide to give the isatogen (452a) (0.27 g; 51%) as an orange amorphous solid, m.p. 256°, (lit.,[154] 254°), $\nu_{max.}$ 1710 (CO) and 1510 and 1350 (NO_2) cm^{-1}.

Found: C, 63.1; H, 2.9; N, 10.5%; M^+, 268.

Calculated for $C_{14}H_8N_2O_4$: C, 62.8; H, 3.0; N, 10.5%; M, 268.

The ethanol-dimethylformamide mother liquors were evaporated to give a gum (0.17 g) whose t.l.c. in methanol over silica showed mainly one component corresponding to the starting material from which however, no identifiable material could be isolated.

(ii) A solution of the enamine (442a) (0.57 g, 0.002 mol) in acetone was irradiated either through a quartz or a pyrex filter for 24 h and then the solution was evaporated. The red semi-solid residue was triturated with methanol to afford the isatogen[154] (452a) (0.34 g; 64%), m.p. 256° (from ethanol-dimethylformamide) identical (m.p. and i.r. spectrum) with a sample prepared before.

The methanol mother liquors were evaporated to leave a gum (0.3 g) whose t.l.c. in methanol over silica showed it to contain two or three close running components. The mixture was not further investigated.

(iii) A solution of the enamine (442a) (0.57 g, 0.002 mol) in redistilled dioxan (200 ml) was irradiated for 24 h through a quartz filter and then evaporated. The residue was triturated with methanol to afford the isatogen[154] (452a) another crop of which was obtained by evaporating the methanol mother liquors and crystallising the tacky solid residue from ethanol-dimethylformamide (total 0.33 g; 64%), m.p. 256°, identical (m.p. and i.r. spectrum) with a sample prepared before.

(iv) A solution of the enamine (442a) (0.57 g, 0.002 mol) in a mixture of acetone (150 ml) and ethanol (50.0 ml) was irradiated through quartz for 24 h. The solution was evaporated and the residue was triturated with methanol to afford the isatogen[154] (452a) (0.28 g; 58%), m.p. 256° (from ethanol-dimethylformamide) identical (m.p. and i.r. spectrum) with a sample prepared before.

The methanol mother liquor was evaporated to yield a gum which was triturated with ether to afford a tacky solid (0.16 g). This was recrystallised from ethanol-dimethylformamide to afford more of the isatogen[154] (452a) (0.07 g; 14%), m.p. 256° identical (m.p. and i.r. spectrum) with a sample prepared before.

Evaporation of the ether mother liquor gave a gum (0.34 g) whose t.l.c. in methanol over silica showed it to be a multicomponent mixture from which no identifiable material could be obtained.

(b) 5-Chloro-2-(4-nitrophenyl)-3H-indolin-3-one 1-N-Oxide (452b)

A solution of the enamine (442b) (0.22 g; 0.0007 mol) in acetone (200 ml) was irradiated for 24 h through a quartz filter. The solution was evaporated and the residue was triturated with methanol to give the chloro-isatogen (452b) (0.1 g, 48%), as an orange solid m.p. 269° (from ethanol-dimethylformamide), $\nu_{max.}$ 1710 (CO) and 1515 and 1350 (NO_2) cm^{-1}.

Found: C, 55.9; H, 2.3; N, 9.2%; M^+, 304/302.

$C_{14}H_7ClN_2O_4$ requires: C, 55.6; H, 2.3; N, 9.3%; M, 302.5.

The methanol mother liquor was evaporated to leave a gum (0.08 g) whose t.l.c. in ether over silica showed it to be a multicomponent mixture from which no identifiable material could be obtained.

(c) 5-Bromo-2-(4-nitrophenyl)-3H-indolin-3-one 1-N-Oxide (452c)

A solution of the enamine (442c) (0.54 g, 0.0015 mol) in acetone (200 ml) was irradiated through a quartz filter for 32 h. The solution was evaporated to yield a gum (0.61 g) whose t.l.c. in ether or ethyl acetate over alumina showed it to contain two, ill-resolved components. The gum was triturated with ether benzene to afford the isatogen (452c) (0.16 g; 33%) m.p. 266° (from ethanol-dimethylformamide), $\nu_{max.}$ 1710 (CO) and 1510 and 1350 (NO_2) cm^{-1}.

Found: C, 47.9; H, 2.0; N, 7.8%; M^+ 348/346.

$C_{14}H_7BrN_2O_4$ requires: C, 48.4; H, 2.0; N, 8.3%; M, 347.

The ether-benzene mother liquor was evaporated to leave a tacky solid (0.31 g) whose t.l.c. in ether over silica showed it to contain two ill-resolved components one of which corresponded to starting material Attempts to purify this solid for further investigation were unsuccessful.

6. 2-Nitrophenylguanidine[160] (459)

2-Nitroaniline (5.0 g) and cyanamide (6.0 g) were melted together on a steam bath and then immersed in a water bath at room temperature. Concentrated aqueous hydrochloric acid (15.0 ml) was added to the melt and the mixture was left at room temperature for 15 min by which time a sample gave no precipitate with water. The mixture was then cooled in ice and neutralised by the dropwise addition of dilute aqueous sodium hydroxide solution to give unreacted 2-nitroaniline, a second crop of which was obtained by extracting the aqueous mother liquor with chloroform (total 1.39 g) m.p. 67° (lit.,[161] 71°), identical (i.r. spectrum) with an authentic sample.

The aqueous phase was then made alkaline (pH 12) by the further dropwise addition of dilute aqueous sodium hydroxide to give 2-nitrophenylguanidine (459) (2.7 g 49 %), m.p. 139° (from ethanol-light petroleum) (lit.,[161] —), $\nu_{max.}$ 3490, 3410 and 3370 (NH_2) and 1650-1550 br (NH def., NO_2) and 1350 (NO_2) cm^{-1}. τ $CDCl_3$-$(CD_3)_2SO$ 2.32 (1H, dd $J_{3,4}$ 7Hz, $J_{3,5}$ 2Hz, ArH), 2.64 (1H, dt $J_{5,6}$ 7Hz $J_{5,4}$ 7Hz $J_{5,3}$ 2Hz, ArH), 2.83-2.96 (2H, m, ArH) and 5.18 (4H, br s, NH_2).

Found: C, 46.7; H, 4.5; N, 31.2%; M^+, 180.

Calculated for $C_7H_8N_4O_2$: C, 46.7; H, 4.5; N, 31.1%; M, 180.

2-Nitrophenylguanidine (459) (0.18 g; 0.001 mol) as prepared above, was dissolved in hot water (2.0 ml) and treated with dilute aqueous sodium hydroxide (1.0 ml). The mixture was heated under reflux for 1 min and then cooled to give 3-aminobenzo-1,2,4-triazine 1-N-oxide[162]

(460) as a yellow solid (quantitative), m.p. 275° (lit.,[162] 275°), $\nu_{max.}$ 3240 and 3140 (NH_2) and 1650 (NH def.).

7. The Attempted Photochemical Cyclisation of 2-Nitrophenylguanidine (459)

2-Nitrophenylguanidine (459) (0.72 g, 0.004 mol) in ethanol (200 ml) was irradiated through quartz for 48 h. Evaporation of the solution gave the unreacted starting material (0.71 g), m.p. 135° identical (i.r. spectrum) with an authentic sample.

8. The Attempted Photocyclisation of 5-Amino-1-(2'-nitrophenyl)-1,2,3-triazole 4-carboxamide[163] (461)

A solution of the triazole[163] (461) (0.49 g, 0.002 mol) in ethanol (200 ml) was irradiated through quartz for 24 h. The solution was evaporated to give the starting material (461) (0.49 g, quantitative), m.p. 270°, identical (m.p. and i.r. spectrum) with an authentic sample.[163]

9. The Attempted Photochemical Cyclisation of 5-(2'-Nitrobenzylidene) thiohydantoin[164] (462)

The thiohydantoin[164] (462) (0.5 g; 0.002 mol) in acetone (200 ml) was irradiated through quartz for 6.5 h. The solution was evaporated to give the starting material (462) (0.48 g), m.p. 245°, identical (i.r. spectrum) with an authentic sample.

10. 2'-Nitrobenzylidene azlactone (483)

The azlactone (483) was prepared by the method of Burton[165] (Yield 63%), m.p. 122° (lit.,[165] 124°).

Ethyl 2-Benzamido-2'-nitrocinnamate (484)

A solution of the azlactone (483) (0.88 g, 0.003 mol) in ethanol (5.0 ml) was treated with 5% w/v aqueous potassium cyanide solution (1.2 ml)

and the mixture was heated on a steam bath for 1 h. The solution was cooled and treated with water (3.0 ml) to afford a gum which solidified on scratching to give a yellow solid (0.67 g). This solid was recrystallised from ethanol to yield the amide-ester (484) as a colourless solid (0.6 g), m.p. 170°, $\nu_{max.}$ 3210 (NH), 1730 and 1720 (CO), 1630 (NH def.) and 1520 and 1350 (NO_2) cm^{-1}.

Found: C, 62.9; H, 4.8; N, 8.1%; p^+ 267 (M^+-CO_2Et)

Calculated for $C_{18}H_{16}N_2O_5$: C, 63.5; H, 4.7; N, 8.2%; M, 340.

2-Benzamido-2'-nitrocinnamic Acid (463)

The amide-ester (484) (0.68 g, 0.002 mol) was heated under reflux in dilute aqueous sodium hydroxide (2.5 ml) for 5 min by which time a red solution had formed. The solution was cooled in ice and acidified by the dropwise addition of dilute aqueous sulphuric acid giving a gummy solid which completely solidified on scratching to give the acid (463) (0.6 g, 92%), m.p. 192° (lit.,[166] 195°), $\nu_{max.}$ 3380 (NH), 2600 br (OH), 1695 and 1640 (CO), 1630 (NH def.) and 1520 and 1350 (NO_2) cm^{-1}, p^+ 294 (M^+-H_2O), $C_{16}H_{12}N_2O_5$ requires M, 312.

11. The Attempted Photochemical Cyclisation of 2-Benzamido-2'-nitrocinnamic Acid[166] (463)

The acid (463) (0.6 g; 0.002 mol) in ethanol (200 ml) was irradiated through quartz for 48 h. The solution was evaporated and the gummy residue was dissolved in chloroform and washed with saturated aqueous sodium hydrogan carbonate solution. Evaporation of the chloroform layer gave a gum (0.31 g) whose t.l.c. in ether or ethyl acetate over silica showed it to be a multicomponent mixture from which no identifiable material could be obtained.

The aqueous phase was acidified with dilute aqueous hydrochloric acid and extracted with chloroform to give an unidentified gum (0.1 g).

12. The Attempted Photochemical Cyclisation of 2'-Nitro-2-phenylcinnamonitrile (464)

A solution of the nitrile[167] (0.5 g, 0.002 mol) in acetone (200 ml) was irradiated through quartz for 24 h. The solution was evaporated to give the starting material (0.49 g, quantitative), m.p. 100°, identical (m.p. and i.r. spectrum) with an authentic sample.

13. 2-Methyl-2'-nitrostilbene (465)[168]

The stilbene (465) was prepared by the method of Dombrovski et al. (Yield 51%), m.p. 71° (from ethanol (lit.,[168] 71°).

14. The Attempted Photochemical Cyclisation of 2-Methyl-2'-nitrostilbene[168] (465).

A solution of the stilbene (465) (0.5 g, 0.002 mol) in ethanol (200 ml) was irradiated through quartz for 20 h. The solution was evaporated to give a dark gum which was triturated with methanol to afford the starting material (0.19 g, 38%), m.p. 69° (lit.,[168] 71°) identical (m.p. and i.r. spectrum) with an authentic sample.

The methanol mother liquor was evaporated to give a gum (0.23 g) whose t.l.c. in chloroform over alumina or silica showed it to be a multicomponent mixture containing starting material. The gum was not further investigated.

(b) A solution of the stilbene[168] (465) (0.5 g, 0.002 mol) in acetone (200 ml) was irradiated through quartz for 15 h. The solution was evaporated and the residue was triturated with methanol to give the starting material (0.22 g; 44%) identical (m.p. and i.r. spectrum) with an authentic sample.

The methanol mother liquor was evaporated to give a gum (0.3 g) whose t.l.c. in chloroform over alumina showed it to contain four close-running components, one of which was starting material. No identifiable material could be isolated from the mixture.

Experimental:Part II

1. The Photochemical Formation of 3-Aminocinnoline 1-N-Oxides

(a) 2-Nitrophenylacetimidate Hydrochloride (467)

A solution of 2-nitrobenzyl cyanide (32.0 g, 0.2 mol) in absolute ethanol (20.0 ml) and anhydrous ether (60.0 ml) was cooled to 0°C and saturated with hydrogen chloride. The reaction flask was stoppered and shaken at room temperature for 2 h and kept at 0° for 16 h. The solvent was evaporated and the residue was washed with acetone to give the imidate hydrochloride (467) (16.0 g, 25%), m.p. 124° (lit.,[169] 124°).

The acetone filtrate was evaporated to give unreacted 2-nitrobenzyl cyanide (20.3 g), m.p. 84° (lit.,[170] 84°) identical, (m.p. and i.r. spectrum) with an authentic sample.

2(a) 2-Nitrophenylacetamidine Hydrochloride (468a)

The imidate hydrochloride (467) (8.0 g, 0.035 mol) was added to freshly prepared 5 M ethanolic ammonia (7.0 ml). The reaction flask was stoppered and shaken at ambient temperatures for 2 h and then kept at 0° for 16 h. The solution was then evaporated and the residue was washed with ether to give the amidine hydrochloride (468a) (6.5 g; 86%), m.p. 211° (lit.,[169] 213°).

The ethereal washings were evaporated to give unreacted 2-nitrobenzyl cyanide (0.8 g), m.p. 84° (lit.,[170] 84°) identical (m.p. and i.r. spectrum) with an authentic sample.

(b) N,N-Dimethyl-2-nitrophenylacetamidine Hydrochloride (468b)

The imidate hydrochloride (467) (9.9 g, 0.04 mol) was added to 33% w/w ethanolic dimethylamine (5.1 g, 5.0 ml) and the stoppered solution was shaken at room temperature for 2 h and kept at 0° for 16 h. The solvent was evaporated and the residue was triturated with acetone to

give the amidine hydrochloride (468b) (3.3 g, 37%), m.p. 220° (from ethanol), $\nu_{max.}$ 3200 br (NH), 1675 (NH def.) 1615 (C=C) and 1515 and 1345 (NO_2) cm^{-1}.

Found: C, 46.7; H, 5.8; N, 16.2%; M^+, 208.

$C_{10}H_{14}ClN_3O_2$ requires: C, 49.3; H, 5.8; N, 17.3%; M, 208 (cation).

The acetone filtrate was evaporated to give 2-nitrobenzyl cyanide (6.0 g), m.p. 80° (lit., 84°) identical (i.r. spectrum) with an authentic sample.

(c) N-Methyl-2-nitrophenylacetamidine Hydrochloride (468c)

The imidate hydrochloride (467) (4.8 g, 0.02 mol) was reacted with a 5 M ethanolic solution of methylamine (4.5 ml) as described for dimethylamino compound (468a) before. The solvent was then evaporated and the residue was triturated with ether to give the amidine hydrochloride (468c) (4.1 g; 91 %), m.p. 200° (from ethanol-light petroleum), $\nu_{max.}$ 3210 br and 3170 (NH), 1675 (NH def.) and 1520 and 1345 (NO_2) cm^{-1}.

Found: C, 44.4; H, 5.4; N, 18.7%; p^+, 193 (M^+-H)

$C_9H_{12}ClN_3O_2$ requires: C, 47.1; H, 5.2; N, 18.3%; M, 194 (cation).

The ether mother liquor was evaporated to give 2-nitrobenzyl cyanide (0.3 g) identical (m.p. and i.r. spectrum) with an authentic sample.

(d) 4-[2-(2'-nitrophenyl)acetimidoyl]morpholine Hydrochloride (468d)

The imidate hydrochloride (467) (2.4 g, 0.01 mol) was added to a solution of morpholine (1.0 g, 0.011 mol) in absolute ethanol (2.0 ml) at 0°. The stoppered reaction flask was shaken at room temperature and kept at 0° for 16 h. The solvent was evaporated and the residue was triturated with ether to give the amidine hydrochloride (468d) (2.4 g, 84%), m.p. 238° (from ethanol), $\nu_{max.}$ 3200 br (NH), 1670 (NH def.) and 1520 and 1360 (NO_2) cm^{-1}.

Found: C, 50.3; H, 5.5; N, 14.6%; p^+, 249 (M^+-H)

$C_{12}H_6ClN_3O_3$ requires: C, 50.4; H, 5.6; N, 14.7%; M, 250 (cation).

(e) 1-[2-(2'-nitrophenyl)acetimidoyl]piperidine Hydrochloride (468e)

The imidate hydrochloride (467) (2.4 g; 0.01 mol) was reacted with piperidine (0.93 g; 0.011 mol) in ethanol (2.0 ml)as described for dimethylamine before. The solvent was evaporated and the residue was triturated with acetone to give the amidine hydrochloride (468e) (2.5 g; 88%), m.p. 254° (from absolute ethanol), $\nu_{max.}$ 3200 br (NH), 1670 (NH def.) and 1515 and 1340 (NO_2) cm^{-1}.

Found: C, 55.3; H, 6.3; N, 14.6%; p^+, 247 (M^+-H).

$C_{13}H_{18}ClN_3O_2$ requires: C, 55.0; H, 6.4; N, 14.8%; M, 248 (cation).

(f) 1-[2-(2'-nitrophenyl)acetimidoyl]pyrrolidine Hydrochloride (468f)

The imidate hydrochloride (467) (2.4 g, 0.01 mol) added to a solution of pyrrolidine (0.78 g, 0.011 mol) in ethanol (2.0 ml) and was shaken at room temperature for 2 h and then kept at 0° for 3 h. The solvent was evaporated and the residue was triturated with acetone to give the amidine hydrochloride (468f) (2.2 g; 82%), m.p. 231° (from ethanol-light petroleum), $\nu_{max.}$ 3360 w and 3180 br (NH), 1680 (NH def.) and 1510 and 1345 (NO_2) cm^{-1}.

Found: C, 54.0; H, 5.9; N, 15.5%; p^+, 233 (M^+-H)

$C_{12}H_{16}ClN_3O_2$ requires: C, 53.5; H, 5.9; N, 15.6%; M, 234.

(g) N,N-Diethyl-2-nitrophenylacetamidine Hydrochloride (468g)

The imidate hydrochloride (467) (2.4 g, 0.01 mol) was reacted with diethylamine (0.8 g, 0.011 mol) in ethanol (2.0 ml) as described for morpholine before. The solvent was evaporated and the gummy solid residue was triturated with acetone to give the amidine hydrochloride (468g) contaminated with diethylamine hydrochloride, m.p. 125°, $\nu_{max.}$ 3180 br (NH), 2480 and 2380 (NH), 1673 (NH def.) and 1520 and 1340 (NO_2) cm^{-1}. All attempts to further purify the product failed.

The acetone mother liquor was evaporated and the residue was triturated with ether to give 2-nitrobenzyl cyanide (0.42 g), m.p. 83° (lit.,[170] 84°) identical (i.r. spectrum) with an authentic sample.

N,N'-Dimethyl-2-nitrophenylacetamidine Hydrochloride

The imidate hydrochloride (467) (2.4 g, 0.01 mol) was added to a three-fold excess of methylamine (0.93 g) in ethanol (5.0 ml). The stoppered reaction flask was shaken at room temperature for 2 h and kept at 0° for 5 days. Evaporation of the solvent and trituration of the residue with ether afforded the amidine hydrochloride (2.1 g; 86%), m.p. 272° (decomp.) (from absolute ethanol), $\nu_{max.}$ 3200 br (NH), 1675 (NH def.) and 1535 and 1360 (NO_2) cm^{-1}.

Found: C, 48.9; H, 5.6; N, 17.2; p^+, 207 ($M-H^+$).

$C_{10}H_{14}ClN_3O_2$ requires: C, 49.4; H, 6.0; N, 18.0; M, 208 (cation).

3. The Conversion of the Amidine Hydrochlorides (468 a-g) into the Free Amidines (469 a-g)

The amidine hydrochloride (468) was dissolved in a minimum volume of water and an equal volume of chloroform was added. The two phase mixture was treated dropwise with dilute aqueous sodium hydroxide solution with occasional agitation until no more turbidity resulted (aqueous phase pH 8-10). The chloroform layer was separated and evaporated to yield an inky blue oil which solidified on trituration with ether to give the amidines (469) as colourless solids.

(a) 2-Nitrophenylacetamidine (469a) was obtained from its hydrochloride (468a) as colourless needles (63%) m.p. 132° (from benzene), $\nu_{max.}$ 3430, 3210 w and 3070 br (NH), 1650 (NH def.) and 1530 and 1335 (NO_2) cm^{-1}.

Found: C, 53.4; H, 5.0; N, 23.3%; M^+, 179.

$C_8H_9N_3O_2$ requires: C, 53.6; H, 5.1; N, 23.5%; M, 179.

(b) N,N-Dimethyl-2-nitrophenylacetamidine (469b) was obtained from its hydrochloride (468b) as colourless needles (62%) m.p. 60° (from benzene) $\nu_{max.}$ 3280 br (NH), 1600 (NH def.) and 1520 and 1340 (NO_2) cm^{-1}, τ($CDCl_3$:60MHz) 1.90(1H, d $J_{3,4}$ 8Hz, ArH), 2.30-2.70 (3H, m, ArH), 5.73 (1H, br s NH), 5.90 (2H, s, CH_2) and 6.98 (6H, s, CH_3).

Found: C, 54.7; H, 6.4; N, 19.5%; M^+, 207.

$C_{10}H_{13}N_3O_2$ requires: C, 58.0; H, 6.3; N, 20.3%; M, 207.

(c) N-Methyl-2-nitrophenylacetamidine (469c)was obtained from its hydrochloride (468c) as a colourless needle (64%), m.p. 86° (from benzene), $\nu_{max.}$ 3320 w, 3200 and 3170 (NH), 1610 (NH def.) and 1520 and 1345 (NO_2) cm^{-1}.

Found: C, 55.4; H, 5.7; N, 21.4%; M^+, 194.

$C_9H_{11}N_3O_2$ requires: C, 55.9; H, 5.7; N, 21.8%; M, 194.

(d) 4-[2-(2'-Nitrophenyl)acetimidoyl]morpholine (469d) was obtained from its hydrochloride (468d) as colourless needles (80%) m.p. 86° (from benzene-light petroleum), $\nu_{max.}$ 1600 (NH def.) and 1510 and 1350 (NO_2) cm^{-1}.

Found: C, 57.6; H, 5.9; N, 16.7%; M^+, 249.

$C_{12}H_{15}N_3O_3$ requires: C, 57.8; H, 6.1; N, 16.9%; M, 249.

(e) 1-[2-(2'-Nitrophenyl)acetimidoyl]piperidine (469e) was obtained from its hydrochloride (468e) as a blue oil (94%) which was shown to be pure by t.l.c. in ether over alumina, $\nu_{max.}$ 3310 br (NH), 1590 (NH def.) 1520 and 1350 (NO_2) cm^{-1}, τ($CDCl_3$; 60MHz) 1.90(1H, d $J_{3,4}$ 8Hz, ArH), 2.28-2.65 (3H, m, ArH), 4.53 (1H, s br, NH), 5.93 (2H, s, CH_2), 6.50 (4H, m, CH_2) and 8.36 (6H, m, CH_2).

(f) 1-[2-(2'-Nitrophenyl)acetimidoyl]pyrrolidine (469f) was obtained from its hydrochloride (468f) as a blue oil (94%) which was shown to be pure by t.l.c. in ether over alumina, $\nu_{max.}$ 3300 br (NH), 1595 (NH def.) and 1520 and 1350 (NO_2), τ($CDCl_3$, 60 MHz) 1.90 (1H, d J 7Hz, ArH), 2.30-2.65 (3H, m,ArH), 4.40 (1H, s, NH), 6.00 (2h, s, CH_2), 6.54 (4H, m, CH_2) and 8.04 (4H, m, CH_2).

(g) N,N-Diethyl-2-nitrophenylacetamidine (469g) was obtained from its hydrochloride as a blue oil (28%) which was shown to be pure by t.l.c. in ether over silica. Spectral data was not obtained due to lack of material.

4. N,N'-Dimethyl-2-nitrophenylacetamidine (476) was obtained from its hydrochloride as colourless needles (80%), m.p. 113° (From ethyl acetate-light petroleum), $\nu_{max.}$ 3240 and 3180 (NH), 1640 (NH def.) and 1520 and 1365 (NO_2) cm^{-1},

Found: C, 57.5; H, 6.0; N, 20.2%; M^+, 207

$C_{10}H_{13}N_3O_2$ requires: C, 58.0; H, 6.3; N, 20.3%; M, 207.

5. 2-Nitrophenylacetamidoxime (477)

(a) A solution of 2-nitrobenzyl cyanide (6.5 g, 0.04 mol) in ethanol (250 ml) was treated with a solution of hydroxylamine hydrochloride (2.8 g) in a solution of hydroxylamine hydrochloride (2.8 g) in water (6.0 ml), followed by sodium carbonate (2.2 g, 0.02 mol) and the mixture was left at room temperature for 48 h. The mixture was then filtered to remove inorganic material, evaporated, and treated with ether (250 ml). The ether layer phase was separated and saturated with hydrogen chloride to afford the amidoxime hydrochloride (478) (3.7 g; 40%), m.p. 166° (from ethanol-light petroleum), $\nu_{max.}$ 3450 and 3420 (NH), 3180 br (NH, OH), 1685 (NH def.) and 1520 and 1340 (NO_2) cm^{-1},

Found: C, 41.5; H, 4.3; N, 18.0%; M^+, 195 (M^+-H)

$C_8H_{10}ClN_3O_3$ requires: C, 41.4; H, 4.3; N, 18.1%; M, 196 (cation).

The amidine hydrochloride (478) (2.8 g) was dissolved in water (10.0 ml) and neutralised with solid sodium acetate to give the free amidoxime (477) (1.0 g), m.p. 135° (from benzene), $\nu_{max.}$ 3440, 3300 and 3150 br (NH, OH) and 1680 (NH def.) and 1530 and 1350 (NO_2) cm^{-1}, τ $(CD_3)_2CO$ 0.98 (1H, br s, OH), 2.11 (1H, dd $J_{3,4}$ 8Hz, $J_{3,5}$ 1Hz, ArH), 2.52 (3H, m, ArH), 4.78 (2H, br s, NH_2) and 6.27 (2H, s, CH_2).

Found: C, 49.4; H, 4.8; N, 21.5%; M^+, 195.

$C_8H_9N_3O_3$ requires: C, 49.2; H, 4.7; N, 21.5%; M, 195.

The ether mother liquor was evaporated and the residue was triturated with ether to give 2-nitrobenzyl cyanide (2.8 g), m.p. 83° (lit.,[170] 84°) identical (i.r. spectrum) with an authentic sample.

b) 2-Nitrobenzyl cyanide (5.5 g, 0.035 mol) was treated with a solution of hydroxylamine (0.042 mol) in butanol (25.0 ml) and the mixture was stirred at 40° for 48 h. The cooled mixture deposited the crude product which was recrystallised from ethyl acetate to afford the amidoxime (476) (2.8 g, 42%) m.p. 135°, $\nu_{max.}$ 3340, 3300 and 3150 br (NH,OH), 1680 (NH def.) and 1530 and 1345 (NO_2) cm^{-1}, identical (m.p. and i.r. spectrum) with a sample prepared before. The initial butanol filtrate and the ethyl acetate mother liquor were combined and evaporated to afford unreacted 2-nitrobenzyl cyanide (2.7 g, 49%), m.p. 84° (lit.,[170] 84°) identical (m.p. and i.r. spectrum with an authentic sample.

6.. The Photochemical Cyclisation of the Amidines (469 a-g) to the Cinnoline 1-N-Oxides (473 a-g).

Solutions of the amidines (469 a-g) (0.002-0.004 mol) in ethanol were irradiated through a quartz filter in a Hanovia medium pressure photochemical reactor for 24 h except in the case (i)a of the amidine (469a) where the duration of irradiation was 48 h. The resulting yellow photolysates were then worked-up as described for the individual reactions below.

(i) 3-Aminocinnoline 1-N-Oxide (473a)

a) The photolysate from 2-nitrophenylacetamidine (469a) was evaporated and the resulting gum was extracted with warm ether (2 x 40.0 ml). Trituration of the residue with methanol gave 3-aminocinnoline 1-N-oxide (473a) (0.08 g, 26%), which formed yellow needles, m.p. 220° (from ethanol), $\nu_{max.}$ 3390 and 3300 (NH_2) and 1615 (NH def.), $\lambda_{max.}$ 219, 248, 297, and 440 nm (log $\varepsilon_{max.}$ 4.16, 4.51, 3.78, and 3.69), τ($CDCl_3$; 60 MHz) 1.67 (1H, d J 8Hz, ArH), 2.44-2.65 (3H, m, ArH), 3.37 (1H, s, ArH) and 4.86 (2H, br s, NH_2).

Found: C, 59.6; H, 4.4; N, 25.8%, M^+, 161.

$C_8H_7N_3O$ requires: C, 59.6; H, 4.4; N, 26.0%, M, 161.

The ether washings and methanol mother liquor were combined, evaporated and the residue was dissolved in chloroform and washed with dilute aqueous hydrochloric acid (2 x 2.0 ml). Basification with dilute aqueous sodium hydroxide solution gave the unreacted amidine (469a) (0.06 g), m.p. 115° identical (i.r. spectrum) with a sample prepared before.

Extraction of the aqueous alkaline mother liquor with chloroform gave 2-nitrobenzyl cyanide (0.01 g) identical (i.r. spectrum) with an authentic sample.

(b) The irradiation of 2-nitrophenylacetamidine (469a) described in (a) was repeated in the presence of triethylamine (1 mol equivalent). The photolysate was evaporated and gummy residue was triturated with methanol to give the cinnoline 1-N-oxide (473a) (0.08 g; 25%), m.p. 219° identical (i.r. spectrum) with a sample prepared before.

Evaporation of the methanol mother liquor left a gum (0.41 g) from which no identifiable material could be obtained.

ii) 3-(N,N-Dimethylamino)cinnoline 1-N-Oxide (473 g)

The photolysate from N,N-dimethyl-2-nitrophenylacetamidine (469b) was evaporated and the orange-brown tacky solid residue was triturated with ether to give the cinnoline 1-N-oxide (473 g) a second crop of which was obtained by applying the ether mother liquors to a preparative silica t.l.c. plate and developing with ether, collecting the major orange band and extracting it with chloroform. (total 0.32 g, 87%), m.p. 121° (from water), $\lambda_{max.}$ 219, 256, 279 sh, 306, and 450 nm (log $\varepsilon_{max.}$ 4.15, 4.55, 4.09, 4.06 and 3.63), $\tau(CDCl_3)$ 1.64 (1H, d $J_{8,7}$ 8 Hz, ArH), 2.54 (2H, m, ArH), 2.67-2.86 (1H, m, ArH), 3.54 (1H, s, ArH) and 6.90 (6H, s, CH_3).

Found: C, 63.1; H, 5.8; N, 22.4; M^+, 189

$C_{10}H_{11}N_3O$ requires: C, 63.5; H, 5.8; N, 22.2; M, 189.

iii) 3-(N-Methylamino)cinnoline 1-N-Oxide (473b)

The photolysate from N-methyl-2-nitrophenylacetamidine (469c) was evaporated and the yellow solid obtained was triturated with methanol to give the cinnoline 1-N-oxide (473b) (0.11 g, 31%), m.p. 175° (from water) $\nu_{max.}$ 3280 (NH), $\lambda_{max.}$ 219, 251, 275 sh, 303 and 440 nm (log $\varepsilon_{max.}$ 4.11, 4.51, 4.09, 3.90 and 3.63), τ $CDCl_3$-$(CD_3)_2SO$ 1.70 (1H, d $J_{8,7}$ 9Hz, ArH), 2.48-2.83 (3H, m, ArH), 3.52 (1H, s, ArH), 3.88 (1H, br q, NH) and 7.08 (3H, d J 5Hz, CH_3).

Found: C, 61.3; H, 5.1; N, 24.2%; M^+ 175.

$C_9H_9N_3O$ requires: C, 61.7; H, 5.2; N, 24.0%; M, 175.

The methanol mother liquor was evaporated to afford a dark gum (0.14 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture from which no identifiable material could be obtained.

iv) 3-Morpholinocinnoline 1-N-oxide (473e)

The photolysate from the amidine (469d) was evaporated and the residue was triturated with methanol to give the cinnoline 1-N-oxide (473e) (0.29 g, 65%), m.p. 185° (from water), $\lambda_{max.}$ 219, 256, 276 sh, 306 and 432 nm (log $\varepsilon_{max.}$ 4.19, 4.51, 4.12, 4.03 and 3.57), τ($CDCl_3$) 1.63 (1H, d $J_{8,7}$ 9Hz, ArH), 8.46-8.76 (3H, m, ArH), 3.40 (1H, s, ArH), 4.10-4.22 (4H, m, CH_2) and 4.40-4.52 (4H, m, CH_2).

Found: C, 51.5; H, 5.6; N, 18.2%; M^+, 231.

$C_{12}H_{13}N_3O_2$ requires: C, 62.3; H, 5.7; N, 18.2%; M, 231.

The methanol mother liquor was evaporated to yield a gum (0.13 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable mixture of three components from which no further identifiable material could be obtained.

(v) 3-Piperidinocinnoline 1-N-oxide (473d)

The photolysate from the amidine (469e) was evaporated and the residue was subjected to dry column chromatography in ether over silica. The major orange band was extracted with chloroform to give the cinnoline 1-N-oxide (473d) (0.26 g, 57%), m.p. 105° (from ethanol-water), $\lambda_{max.}$ 219, 258, 280, 310 and 444 (log $\varepsilon_{max.}$ 4.17, 4.52, 4.12, 4.10 and 3.53), $\tau(CDCl_3)$ 1.64 (1H, d $J_{8,7}$ 9Hz, ArH), 2.52-2.93 (3H, m, ArH), 3.44 (1H, s, ArH), 6.46 (4H, m, CH_2) and 8.34 (6H, m, CH_2)

Found: C, 67.9; H, 6.5; N, 18.4%; M^+, 229.

$C_{13}H_{15}N_3O$ requires: C, 68.1; H, 6.6; N, 18.3%; M, 229.

No further material was isolated from the dry column.

(vi) 3-Pyrrolidinocinnoline 1-N-Oxide (473c)

The photolysate from the amidine (469f) was evaporated and the residue was triturated with ether to give the cinnoline 1-N-oxide (473c) (0.26 g, 49%), m.p. 203° (from ethanol-water), $\lambda_{max.}$ 219, 258, 283 sh, 310, 325 sh 455 nm (log $\varepsilon_{max.}$ 4.12, 4.55, 4.08, 4.08, 3.80 and 3.60), $\tau(CDCl_3)$ 1.65 (1H, d $J_{8,7}$ 8Hz, ArH), 2.57-2.90 (3H, m, ArH), 3.74 (1H, s, ArH), 6.56 (4H, m, CH_2) and 8.0 (4H, m, CH_2).

Found: C, 66.5; H, 6.0; N, 19.7%; M^+, 215.

$C_{12}H_{13}N_3O$ requires: C, 66.9; H, 6.1; N, 19.5%; M, 215.

The ether mother liquor was evaporated to give a gum (0.16 g) whose t.l.c. in ether over alumina showed it to be a multicomponent mixture.

(vii) 3-(N,N-Diethylamino)cinnoline 1-N-oxide (473f)

The photolysate from N,N-diethyl-2-nitrophenylacetamidine (469g) was evaporated and the residue was triturated with ether-ethanol to give the cinnoline 1-N-oxide (473f), a second crop of which was isolated by preparative t.l.c. in ether over silica of the ether-ethanol mother liquor and extracting the major orange band with chloroform. (total 0.27 g, 62%), m.p. 87° (from ethyl acetate-light petroleum, b.p. 40-60°),

$\lambda_{max.}$ 219, 258, 283 sh, 309, 326 and 458 nm (log $\varepsilon_{max.}$ 4.22, 4.55, 4.15, 4.12, 3.84 and 3.70),

Found: C, 66.3; H, 6.9; N, 19.5%; M^+, 217.

$C_{12}H_{15}N_3O$ requires: C, 66.3; H, 7.0; N, 19.3%; M, 217.

7. 3-(N,N-Dimethylamino)cinnoline Picrate (475)

A solution of the cinnoline 1-N-oxide (473 g) (0.19 g, 0.001 mol) in ethanol (40.0 ml) was hydrogenated over 10% palladium-charcoal (0.02 g). Evaporation of the filtered mixture gave a dark gum (0.18 g) whose t.l.c. in ethyl acetate over silica showed it to contain four close-running components. The gum was dissolved in ethanol and treated with a hot saturated ethanolic solution of picric acid to afford 3-(N,N-dimethylamino)-cinnoline picrate (475) as an insoluble red solid, m.p. 180° (decomp.) (from ethanol).

Found: C, 47.9; H, 3.6; N, 20.5%; M^+, 173

$C_{16}H_{14}N_6O_7$ requires: C, 47.8; H, 3.5; N, 20.9%; M, 174 (cation).

8. The Attempted Photochemical Cyclisation of 2-Nitrophenylacetamidoxime (477)

a) A solution of the amidoxime (477) (1.17 g, 0.006 g) in ethanol (200 ml) was irradiated for 24 h through a quartz filter as described before. The mixture was evaporated and the residue was triturated with methanol to give unreacted amidoxime (0.8 g) m.p. 165°, identical (m.p. and i.r. spectrum) with an authentic sample. The methanol mother liquor was evaporated and triturated with methanol to give an unidentified solid (0.01 g), m.p. 232°, M^+ 268.

b) The amidoxime (477) was irridiated in ethanol as in (a) but for a period of 65 h. The ethanolic solution was evaporated and the residue

was triturated with methanol to yield the unchanged amidoxime (477) (0.64 g), m.p. 166°, identical (m.p. and i.r. spectrum) with an authentic sample. The methanol mother liquor was evaporated to give a gum (0.51 g) whose t.l.c. in ether over silica showed it to be a multicomponent mixture from which no identifiable material could be obtained.

9. The Attempted Photochemical Cyclisation of 2-Nitrophenylacetamidine (469a) in Acetone Solution

The amidine (469a) (0.54 g, 0.003 mol) was irradiated in acetone (200 ml) for 48 h and then the solution was evaporated to leave a gum (0.51 g) whose t.l.c. in ether over silica showed to be a multicomponent mixture containing at least 7 components. The gum was dissolved in chloroform and washed with dilute aqueous hydrochloric acid (3.0 ml). The acidic aqueous phase was separated and basified with dilute aqueous sodium hydroxide solution and was then extracted with chloroform to give only an intractable gum (0.08 g).

The original chloroform layer was evaporated to leave a gum (0.37 g) which was triturated with methanol to give only an unidentified brown solid (0.02g), m.p. 202°.

No further identifiable material was isolated.

10. The Attempted Photochemical Cyclisation of N,N-Dimethyl-2-nitrophenylacetamidine (469b) in Acetone Solution

A solution of the dimethylamidine (469b) (0.4 g, 0.002 mol) in acetone (200 ml) was irradiated for 24 h through a quartz filter as described before. The solution was evaporated and the gum (0.39 g) obtained was subjected to wet column chromatography over silica. Elution with ether, ethyl acetate and then ethyl acetate-methanol afforded only small amounts of multicomponent gums (total 0.31g).

11. The Attempted Photochemical Cyclisation of N,N'-Dimethyl-2-nitrophenylacetamidine (476)

The amidine (476) (0.88 g, 0.004 mol) was irradiated in ethanol (200 ml) for 24 h through a quartz filter as described before. The solution was evaporated to give a gum (0.85 g) whose t.l.c. in ether over alumina showed it to be a mixture containing several components. The gum was subjected to wet column chromatography over alumina. Elution with benzene gave an oil (0.23 g) whose t.l.c. in ether over alumina showed it to contain three components. Further elution with ethyl acetate afforded a black tar (0.56 g) whose t.l.c. likewise showed it to consist of three components. No identifiable material was obtained from these two chromatographic fractions.

12. The Attempted Photochemical Cyclisation of 2-Nitrophenylacetamidine Hydrochloride (468a)

The amidine hydrochloride (468a) (0.65 g, 0.003 mol) was dissolved in absolute ethanol (200.0 ml) and irradiated for 48 h, through quartz. The solution was evaporated and the residue was triturated with acetone to give a solid (0.45 g), m.p. 211° identical, (m.p. and i.r. spectrum) with the starting material.

Evaporation of the acetone mother liquor afforded a gum (0.08 g) from which no identifiable material could be obtained.

13. 2-Nitrophenylacetimidate (482)

a) The imidate hydrochloride (467) (4.7 g; 0.02 mol) in water (10.0 ml) was treated with 40% w/v aqueous sodium hydroxide solution (2.1 ml) and then with solid potassium carbonate until the solution was saturated. The mixture was filtered to remove undissolved potassium carbonate and was then washed with ether. Evaporation of the ethereal washings gave

a colourless solid (3.6 g) whose t.l.c. in ether over silica showed it to be a mixture of three components. The solid was extracted with hot light petroleum (2.50 ml) to give the free imidate (482) (3.2 g), m.p. 43° (from light petroleum), $\nu_{max.}$ 3320 w (NH), 1650 (NH def.) and 1530 and 1350 (NO_2) cm^{-1}, τ($CDCl_3$; 60 MHz) 2.1 (1H, d J 8Hz, ArH), 2.40-2.75 (3H, m, ArH), 5.28 (2H, q J 8H, CH_2), 6.11 (2H, s, CH_2) and 8.73 (3H, t J 8Hz, CH_3).

Found: C, 57.6; H, 5.7; N, 12.4%; p^+, 162 (M^+-NO_2)

$C_{10}H_{12}N_2O_3$ requires: C, 57.6; H, 5.8; N, 13.5%; M, 208.

b) The imidate hydrochloride (467) (1.2 g, 0.005 mol) was added to a solution of diethylamine (0.4 g, 0.0052 mol) in ethanol (1.0 ml) and reaction flask was stoppered and shaken at room temperature for 2 h. After being kept at 0° for 16 h the mixture was evaporated and the residue was triturated with ether to give diethylamine hydrochloride, m.p. 221° (from absolute ethanol) (lit., 223°), $\nu_{max.}$ 2470 and 2380 (NH) cm^{-1}.

The ether mother liquor was evaporated to give the imidate (482) as a colourless oil (0.84 g), $\nu_{max.}$ 3320 (NH), 1650 (NH def.) and 1520 and 1350 (NO_2) cm^{-1}, identical (i.r. spectrum and 60 MHz ^1H n.m.r. spectrum) with a sample prepared before.

14. <u>The Attempted Photocyclisation of 2-Nitrophenylacetimidate</u> (482)

The imidate (482) (0.64 g, 0.003 mol) in absolute ethanol was irradiated for 36 h through a quartz filter. The mixture was evaporated to give an oil (0.6 g), whose t.l.c. in ether over silica showed it to contain three ill-resolved components. The oil was triturated with ether-ethanol to afford an unidentified solid a second crop of which was obtained by evaporating the ether-ethanol mother liquor and retriturating the residue with methanol (total 0.15 g), m.p. 136° (from ethanol-

dimethylformamide), $\nu_{max.}$ 1520 and 1350 (NO_2) cm^{-1},

Found: C, 58.8; H, 3.7; N, 17.3%; M^+, 440.

$C_8H_6N_2O_2$ requires: C, 59.3; H, 3.7; N, 17.3%; M, 162.

The methanol mother liquor was evaporated to give a dark gum (0.4 g) from which no identifiable material could be obtained.

15. 2-Nitrophenylacetamide[171]

2-Nitrobenzyl cyanide (3.2 g, 0.02 mol) was treated with polyphosphoric acid (25.0 g) and the mixture was stirred at 80° for 3 h. Ice (80 g) was then added to the dark mixture to give the crude product (2.5 g) (m.p. 136°) which was recyrstallised from ethanol (with hot filtration to remove a small amount of tar) to afford the pure amide (1.5 g, 42%), m.p. 159° (lit.,[171] 161°), $\nu_{max.}$ 3390 and 3180 (NH_2), 1660 (CO) 1640 (NH def.) and 1520 and 1340 (NO_2) cm^{-1}.

Evaporation of the ethanol mother liquors gave a gum (0.4 g) from which no further identifiable material could be obtained.

16. The Attempted Photochemical Cyclisation of 2-Nitrophenylacetamide[171]

A solution of 2-nitrophenylacetamide[171] (0.20 g) in ethanol (200 ml) was irradiated for 24 h through quartz. The solution was evaporated to give the starting material (0.20 g), m.p. 159°, identical (m.p. and i.r. spectrum) with an authentic sample.

Appendix

Experimental Details

Infra-red Spectra of compounds were obtained either as nujol mulls of solids or thin films of liquids between sodium chloride discs using a Unicam S.P. 200 or a Perkin Elmer G157 Spectrometer.

Proton Magnetic Resonance Spectra (^{1}H n.m.r.) were obtained at 100 MHz on a Varian HA100 Spectrometer or at 60 MHz on a Varian EM360 Spectrometer, using tetramethylsilane as internal standard.

Ultra-Violet Spectra (u.v.) were obtained on a Unicam S.P. 800A Spectrophotometer.

Mass Spectra were obtained on a MS902 High Resolution Mass Spectrometer.

Melting Points were obtained using a Kofler hot-stage microscope and are uncorrected.

Solvents: Absolute ethanol was 'super-dried' using the magnesium-iodine method. Light petroleum had a boiling range of 60-80°, unless otherwise stated. All organic solvent extracts were dried over anhydrous magnesium sulphate, prior to evaporation.

Chromatography: Dry-column chromatography was carried out using activity III silica or alumina containing a fluorescent marker and prepared from the Commercial adsorbants. Thin layer chromatography was carried out using Silica Gel GF_{254} (Merck) or Aluminium Oxide GF_{254} (Merck).

BIBLIOGRAPHY

1. Georges H.Wagnier, 'The Chemistry of the Nitro and Nitroso Groups', Part 1, Ed., H.Feuer, Interscience Publishers (1969).
2. P. Buck, Angew. Chem., 1969, 8 , 120.
3. A. Reissert, Ber., 1896, 29 , 639.
4. J. D. Loudon & I. Wellings, J.Chem.Soc., 1960, 3462.
5. I. P. Sword, J.Chem.Soc., 1970, 1916.
6. S. Gabriel, W. Gerhard, R. Walter, Ber., 1923, 56 , 1024.
7. F. M. Dean, C. Patampongse, V. Podimuang, J.Chem.Soc., 1974, 583.
8. K. Wagner , H. Heitzer & L. Oelham, Chem.Ber., 1973, 106 , 640.
9. K. J. Morgan, J.Chem.Soc., 1959, 3502.
10. J. D. Loudon & G. Tennant, J.Chem.Soc., 1963, 4286.
11. G. W. Stacey, T. E. Wollner & T. R. Oakes, J.Het.Chem., 1966, 3 , 51.
12. A. E. Luetzow & J. P. Vercelletti, J.Chem.Soc., 1967, 1750.
13. L. A. Ljublinskaya & V. M. Stepanov, Tetrahedron Lett., 1971, 4511.
14. D. M. Smith , J. Machin, R. K. Mackie, J.Chem.Soc.,1976 , 394.
15. R. Marshall & D. M. Smith, J.Chem.Soc., 1971, 3510.
16. A. Zaki & Y. Iskander, J.Chem.Soc., 1943, 68.
17. J. P. Cairns, J. D. Loudon & D. Wylie, (Glasgow) , Unpublished work.
18. C. W. Muth, J. C. Ellers & O. F. Folmer, J.Amer.Chem.Soc., 1957, 79 , 6500.
19. C. W. Muth,N. Abraham & M. L. Linfield, J.Org.Chem., 1960, 25 , 736.
20. T. W. N. Spence & G. Tennant, J.Chem.Soc.(Chem.Comm.), 1972, 97.
21. G. Tennant & K. Vaughan, J.Chem.Soc.(C), 1966, 2287.
22. G. Tennant, J.Chem.Soc., 1964, 2666.
23. G. Tennant, J.Chem.Soc., 1966, 2285.
24. R. Fusco & S. Rossi, Gazz.Chim.Ital., 1964, 94 ,3.
25. Y. Amhad, M. S. Habib, Z. & N. Bashir, Tetrahedron, 1965, 21 ,861.
26. G. Tennant, J.Chem.Soc., 1963, 2428.
27. G. Heller & G. Spielmeyer, Chem.Ber., 1925, 58 ,834.
28. K. Akashi, Bull.Inst.Chem.Phys.Rev.(Tokyo),1941, 20 ,798.

29. A. Reissert & F. Lemmer, Chem.Ber., 1926, 59 ,351.

30. S. Secareanu & I. Lupas, Bull.Soc.Chim.Fra., 1933, 53 ,1436.

31. S. Secareanu & I. Lupas, Bull.Scc.Chim.Fra., 1934, 373.

32. S. Secareanu & I. Lupas, Bull.Soc.Chim.Fra., 1935, 69.

33. A. R. Katrizky & J. M. Lagowski, 'Chemistry of Heterocyclic N-Oxides' Academic Press N.Y.(1970) ,p.30.

34. R. Nietzki & R. Braunschweig, Ber., 1894, 27 ,3381.

35. F. R. Benson & W. L. Savell, Chem.Ber., 1950, 46 ,44.

36. A. Angeletti, Gazetta, 1923, 53 ,672.

37. B. Vis, Rec.Trav.Chim., 1939, 58 ,387.

38. J. P. Cairns, Ph.D. Thesis (Glasgow) 1964.

39. C. W. Muth, N. Abraham, M. L. Linfield, R. B. Wobing & E. A. Pacofsky, J.Org.Chem., 1960, 25 ,736

40. J. F. Corbett & P. F. Holt, J.Chem.Soc., 1961, 5029.

41. J. W. Barton & M. A. Cockett, J.Chem.Soc., 1962, 2454.

42. J. W. Barton & J. F. Thomas, J.Chem.Soc., 1964, 1265.

43. H. S. Backer & J. Groot, Recl.Trav.Chim.Pays-Bas, 1950, 69 ,1323.

44. F. Ardnt & B. Rosenau, Chem.Ber., 1917, 50 ,1248.

45. J. D. Loudon & G. Tennant, J.Chem.Soc., 1962, 3092.

46. T. Zincke & W. Prentzell, Chem.Ber., 1905, 38 ,4116.

47. A. Kliegel, Chem.Ber., 1908, 41 ,1845.

48. K. Lehmstedt, Chem.Ber., 1935, 68 ,1455.

49. I. Tanesescu & Z. Frenkel, Bull.Soc.Chim.Fr., 1960, 693.

50. W. B. Dickinson, J.Amer.Chem.Soc., 1964, 86 ,3580.

51. A. Silberg & Z. Frenkel., Rev.Roum.Chim., 1965, 10 ,1035.

52. S. Kim, S. S. Friedlich & L. J. Andrews & R. M. Keefer, J.Amer.Chem.Soc., 1970, 92 ,2452.

53. S. Kim, S. S. Friedlich, L. J. Andrews, J.Amer.Chem.Soc.,1974, 96 , 1850.

54.J. D. Loudon & I. Wellings, J.Chem.Soc.,1960, 3470.

55. A. Baeyer, Chem.Ber., 1881, 14 ,1714.

56. J. Bakke, Acta.Chem.Scand., 1975, 29, 1063.

57. J. L. Pinkis, T. Cohen, M. Sundaralingam & G. A. Jeffery, Proc.Chem.Soc., 1960, 70.

58. J. L. Pinkis, G. G. Woodyard & T. Cohen, J.Org.Chem., 1965, 30 ,1104.

59. F. D. Chattaway & A. J. Walker, J.Chem.Soc., 1925, 2407.

60. M. S. Gibson , Tetrahedron, 1962, 18 ,1377; Nature(London) 1962, 193 , 474.

61. R. C. Kerber, J.Org.Chem., 1972, 37 ,1587.

62. A. McKillop & R. J. Kobylecki, J.Org.Chem., 1974, 39 ,2710.

63. M. D. Abdul Hamid, Ph.D. Thesis(Manchester),1974.

64. F. Ardnt , B. Eistert & W. Bartule, Chem.Ber., 1927, 60 ,1364.

65. E. Giovanni & P. Portmann, Helv.Chim.Acta, 1948, 31 ,1381.

66. J. A. Moore & D. H. Ahlstrom, J.Org.Chem., 1961, 26 ,5254

67. W. Seibert, Ber., 1947, 86 ,494; 1948, 87 ,266.

68. P. A. S. Smith & J. H. Boyer, Org.Synth., 1951, 31 ,14.

69. R. A. Abramovitch & B. A. Davis, Chem.Ber., 1964, 64 ,149.

70. A. G. Green & F. M. Rowe, J.Chem.Soc., 1912, 101 ,2443.

71. F. M. Rowe & J. S. H. Davies, J.Chem.Soc., 1920, 117 ,1344.

72. L. K. Dyall & J. E. Kemp, Austral.J.Chem., 1968, 21 ,409.

73. L. K. Dyall, J. O. M. Evans, J. E. Kemp, Austral.J.Chem., 1968, 21 ,409.

74. D. R. Hogg & J. Stewart, J.Chem.Soc., 1974, 436.

75. N. Kharasch, W. King & T. C. Bruice, J.Amer.Chem.Soc., 1955, 77 ,931.

76. T. Zincke & F. Farr, Annalen, 1912, 57 ,391.

77. F. Kaluza & G. W. Perold, Chem.Abs., 1961, 55 ,11346

78. N. Karasch, C. M. Buess & W. King, J.Amer.Chem.Soc., 1953, 75 ,6035.

79. H. A. Morrison in 'The Chemistry of the Nitro and Nitroso Groups' Part 1, Ed., H. Feuer, Interscience Publishers(1969).

80. R. Chapman, Pure and Applied Chem., 1964, 9 ,584.

81. G. Ciamicin & P. Silber, Ber., 1900, 34 ,2040.

82. P. de Mayo & S. T. Ried, Quart. Rev., 1961, 15 ,414.

83. J. A. Berson & E. Brown, J.Amer.Chem.Soc., 1955, 77 ,447.

84. I. Tanesescu, Bull.Soc.Chim.Fr., 1926, 1718.

85. C. P. Joshua & P. K. Ramdas., Tetrahedron Lett., 1974, 4359.

86. J. A. Van Allen, S. Farid, G. A. Reynolds & S. Chie Chang, J.Org.Chem., 1973, 2834.

87. Y. Maki & T. Furuta, Synthesis, 1976, 263.

88. B. C. Gunn & M. F. G. Stevens, J.Chem.Soc.,1973, 1682.

89. G. Buchi & D. E. Ayer, J.Amer.Chem.Soc., 1956, 78 ,689.

90. J. L. Charlton & P. de Mayo, Can.J.Chem., 1968, 46 ,1041.

91. J. S. Splitter & M. Calvin, J.Org.Chem., 1955, 20 ,1086.

92. R. Jacquier, P. Bouchet, C. Coquelet, J. Elguero, Bull.Soc.Chim.Fr., 1976, 184.

93. R. Jacquier, P. Bouchet, C. Coquelet & J. Elguero, Bull.Soc.Chim.Fr., 1976, 192.

94. Y. Maki, M. Suzuki, T. Hosokami & T. Furuta, J.Chem.Soc., 1974, 1354.

95. Y. Amhad & S. A. Shamsi, Bull.Chem.Soc.Japan, 1966, 39 ,195 (Chem.Abs., 1966, 64 ,9680.).

96. H. Stobbe, Annalen, 1899, 308 ,89.

97. W. S. Johnson & W. P. Schnieder, Org.Syn., 30 ,18.

98. G. Wittig & U. Schollkopf, Ber.duet.chem.Ges.,1954, 87 ,1318.

99. R. Ketchum, D. Jambotkar, & L. Martinelli, J.Org.Chem., 1962, 27 ,466.

100. F. Ramirez, O. P. Madan & C. P. Smith, Tetrahedron, 1966, 22 ,567.

101. R. Eyjolfsson, Acta Chem.Scand., 1970, 24(8) ,3075.

102. T. A. Bryce & J. R. Maxwell, J.Chem.Soc.(Chem.Comm.), 1965, 206.

103. Dictionary of Organic Compounds, 5 ,2844, Ed., Heilbron,

104. 'Dictionary of Organic Compounds' Ed., Heilbron, 5 ,2843.

105. H. O. House & G. H. Rassmusson, J.Org.Chem., 1961, 26 , 4278.

106. L. D. Bergenson & M. M. Shemyakin, Tetrahedron, 1963, 19 ,149.

107. A. J. Speziale & D. E. Bissing, J.Amer.Chem.Soc.,1963, 85 , 3878.

108. C. K. Ingold, 'Structure and Mechanism in Organic Chemistry' p.546 , G. Bell & Sons Ltd., London 1973.

109. A. P.Gara, R. A. Massy-Westropp & J. H. Bowie, Austral.J.Chem., 1970, 23 , 307.

110. J. N. Murrell, 'The Theory of the Electronic Spectra of Organic Molecules' p.75, Methuen Publishing Co. Ltd.,1963.

111. E. Hedaya & S. Theodoropolous, Tetrahedron, 1968, 24 ,2241.

112. J. H. Beynon ,'Mass Spectroscopy and its Application to Organic Chemistry', pp.406-409; Elsvier Publishing Co. Ltd.,1960.

113. F. Hudson & P. A. Chopwood, Helv.Chim.Acta, 1963 , 46 , 2178.

114. M. A. A. Beg & M. S. Siddiqui, Tetrahedron, 1966 , 22(2) , 2203.

115. F. Krohnke, Ber., 1950 , 83 , 291.

116. M. Butcher, R. J. Matthews & S. Middleton, Austral.J.Chem., 1973, 26 ,2067.

117. M. Van den Ikker & F. Jellinck, Rec.Trav.Chim.,1967, 86 ,275.

118. G. Tennant & J. D. Loudon, J.Chem.Soc.(Quart.Revs.), 1963 , 4298.

119. D. W. Bayne, Ph.D. Thesis(Edinburgh),1975.

120. T. Naito, R. Dohmori & O. Nagase, J.Pharm.Soc.,(Japan) ,1954, 74 ,593; R. J. Sundberg & D. E. Blackburn, J.Org.Chem., 1969, 34 ,2799.

121. J. Reihsig & H. W. Krause, J.prakt.Chem., 1966, 31 ,167; C. Kaneko & S. Yamada, Chem.Pharm.Bull.,(Japan) , 1967, 15 ,663; E. D. Hannah, G. R. Proctor & M. A. Rehman, J.Chem.Soc., 1967, 256.

122. J. D. Loudon & I. Wellings, J.Chem.Soc., 1963, 4268.

123. G. A. Reynolds & C. A. Hauser, Org.Syn.,1950, 30 ,70.

124. S. Forsen & M. Nilsson in 'The Chemistry of the Carbonyl Group', 2 , 216; Ed., J. Zabicky, Interscience Publishers, 1970.

125. Belstein's 'Handbuch der organischen Chemie' II ,23,161.

126. H. C. Van der Plas, 'Ring Transformations in Heterocycles', 2 ,164, Academic Press, London 1973.

127. K. Brand & E. Wild, Chem.Ber., 1923, 56 ,105.

128. W. R. Mitchell & G. Tennant, Unpublished work.

129. K. G. Hampton, T. M. Harris & C. R. Hauser, Org.Syn., 1967, 47 ,92.

130. D. C. Nonhebel, J.Chem.Soc., 1962,4628.

131. R. Adams & R. L. Jenkins, Org.Syn., 3 ,75.

132. P. J. Montagne, Rec.Trav.Chim., 1901, 20 ,213.

133. J. B. Cohen & H. D. Arme, J.Chem.Soc., 89, 1479.

134. A. Giacolone & F. Russo, Gazz., 1935, 65 ,1127.

135. 'Dictionary of Organic Compounds' 5 ,2515.Ed., Heilbron.

136. 'Dictionary of Organic Compounds' 4 ,2436,Ed., Heilbron.

137. H. Gevekoft, Ann., 1883, 221 ,323.

138. A. Schillinger & S. Wleügel, Chem.Ber., 1883, 16 , 2222.

139. E. Bamberger, Ber.,1909, 42 ,1665.

140. F. Ardnt, B. Eistert & W. Partale, Ber.,1928, 61 ,1107.

141. T. W. M. Spence & G. Tennant, J.Chem.Soc., 1971,3712.

142. N. H. Cromwell & R. A. Setterquist, J.Amer.Chem.Soc., 1954, 76 ,5752.

143. I. P. Sword, J.Chem.Soc., 1970,1916.

144. T. W. M. Spence & G. Tennant, Unpublished work.

145. A. Baeyer, Ber., 1882, 15 ,775.

146. E. Spath & H. Bretschmeider, Ber., 1930, 63 ,2997.

147. A. Dornow, I. Kuhlcke & F. Baxmann, Ber., 1949, 82 ,254.

148. L. F. Fieser & W. H. Daudt, J.Amer.Chem.Soc.,1946, 68 , 2248.

149. S. Bodfross, Ber., 1918, 15 ,192.

150. I. P. Sword, J.Chem.Soc., 1971,820.

151. D. Doppe, Chem.Ber., 1971, 104 ; 1035, 1043, 1058.

152. F. Krohnke & I. Vogt., Ann., 1954, 589 ,26.

153. H. S. Lowrie, J.Med.Chem.,1966, 9 ,664.

154. F. Krohnke & M. Meyer-Delius, Chem.Ber., 1951, 84 ,941.

155. G. A. Singerman in 'Heterocyclic Compounds' 27,291, Ed., R. N. Castle, Interscience Publishers 1973.

156. H. E. Baumgarten & M. B. De Brunner, J.Amer.Chem.Soc., 1951, 3318.

157. R. S. Davidson & R. J. Wilson, J.Chem.Soc., 1970,71.

158. P. Ruggli & E. Burckhardt, Helv.Chim.Acta, 1940, 23 ,441.

159. 'Dictionary of Organic Compounds' 4 ,2430, Ed., Heilbron.

160. F. J. Wolf, K. Pfister, R. M. Wilson & C. A. Robinson, J.Amer.Chem.Soc., 1954, 76 ,3551

161. 'Dictionary of Organic Compounds', 4 , 2426., Ed., Heilbron.

162. F. Ardnt, Chem.Ber.,1913, 46 ,3522.

163. D. R. Sutherland & G. Tennant, Unpublished work.

164. C. Henze & F. Allen, J.Amer.Chem.Soc.,1955, 77 ,461.

165. H. Burton, J.Chem.Soc., 1935, 1265.

166. M. Vanghelovici & A. Stefanescu, Chem.Abs., 1944, 38 ,5501.

167. K. Brand & O. Loehr, J.prakt.Chem.,1925, 109 ,359.

168. A. V. Dombrovski, Chem.Abs., 1963, 58 ,1383.

169. T. Naito, Chem.Abs., 1956, 50 ,1647.

170. A. Reissert, Ber., 1908, 41 ,3814.

171. R. Pschorr & G. Hoppe, Ber., 1910, 43(11), 2543.

Synthesis of 2-Acyl-3-hydroxyquinolines Embodying a Novel Variant of the Smiles Rearrangement

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Synthesis of 2-Acyl-3-hydroxyquinolines Embodying a Novel Variant of the Smiles Rearrangement

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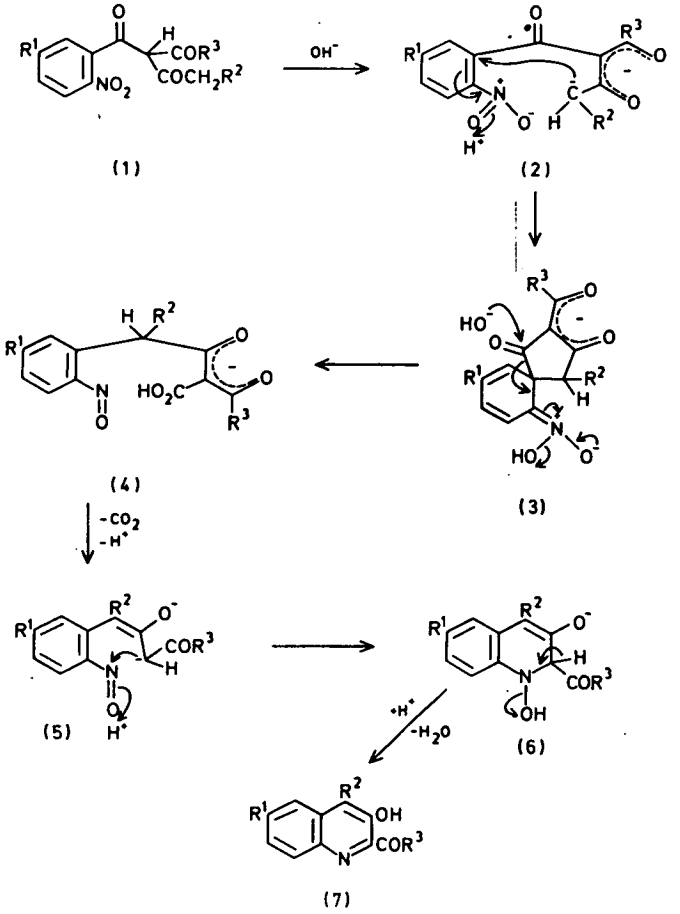
Summary. 2-(2′-Nitrobenzoyl) derivatives of certain 1,3-diketones undergo base-catalysed cyclisation to hitherto inaccessible 2-acyl-3-hydroxyquinolines by a process explicable in terms of a new version of the Smiles rearrangement.

Two modes of base-catalysed nitro-group side-chain interaction[1] in 2′-nitrobenzoyl derivatives have been reported previously. These involve direct aldol-type condensation[2] between the nitro-group and the side chain and the side-chain displacement[3,4] of the nitro-group respectively. We now report a third mode of interaction which involves a novel variant of the Smiles rearrangement, and provides a potentially general route to otherwise inaccessible[5] 2-acyl-3-hydroxyquinolines.

3-(2′-Nitrobenzoyl)pentane-2,4-dione (1; $R^1 = R^2 = H$, $R^3 = Me$) heated under reflux (0·5 h) with 20% w/v aq. KOH afforded as the major product a yellow acidic solid, $C_{11}H_9NO_2$, ν_{max} 1660 (CO) cm^{-1}; τ ($CDCl_3$) — 1·16 (1H, s OH), 1·90—2·56 (5H, m, ArH), and 7·09 (3H, s, Me), which

formed an acetate and a hydrazone and is identified as the hitherto unknown 2-acetyl-3-hydroxyquinoline (**7a**) on the basis of the following evidence. Catalytic (H_2, 10% Pd–C) or dithionite reduction of the yellow acidic product afforded

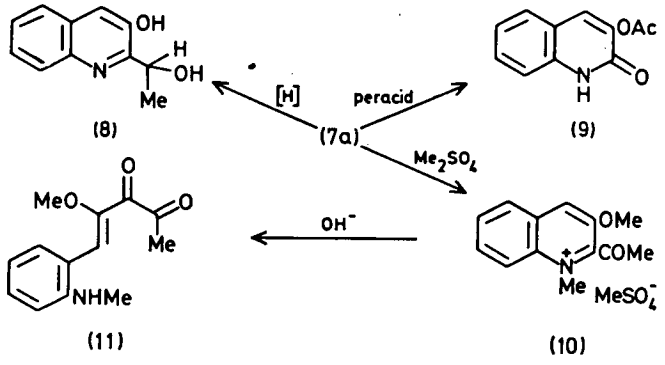


(7)	R^1	R^2	R^3	Yield/%	M.p./°C
a;	H	H	Me	83	118
b;	Me	H	Me	71	126
c;	Cl	H	Me	55	149
d;	H	H	Ph	15	86
e;	H	Me	Et	82	82

SCHEME

a secondary alcohol (**8**) (70–80%), which gave a diacetate. The presence of the quinoline nucleus was established by oxidation with peracid (30% aq. H_2O_2–glacial AcOH; *m*-chloroperbenzoic acid) to give the acetoxyquinolin-2(1*H*)-one (**9**) of established structure.[6] Since the yellow acidic product is not identical with the known[7] 3-acetylquinolin-2(1*H*)-one [the rational precursor of (**9**)], it can only have the structure (**7a**) and is converted into (**9**) by Baeyer–Villiger rearrangement (with preferential migration of the heterocyclic nucleus[4]) followed by acetyl migration. In further support of the structure (**7a**), exhaustive methylation gave the methoxy *N*-methylquinolinium methosulphate (**10**) (86%), which underwent ring-opening in cold dilute aq. NaOH to yield the methylaminodiketone (**11**) as a gum (quantitative yield), characterised as the quinoxaline derivative.

Cyclisations of the type [(**1**; $R^1 = R^2 = H$, $R^3 = Me$) → (**7a**)] are readily applicable to the synthesis of other 2-acyl-3-hydroxyquinolines (**7b**—**e**) (Scheme).†



The unprecedented cyclisations [(**1**) → (**7**)] are readily explained in terms of a mechanism (Scheme) which involves a new variant of the Smiles rearrangement. Thus, intramolecular nucleophilic attack at C-1′ in the dicarbanion (**2**) affords the spiro-intermediate (**3**) which, unlike the corresponding species [*e.g.* (**3**), SO_2 replaces CO] in the Smiles rearrangement of analogous sulphonyl derivatives,[8] cannot achieve stabilisation in the usual way (*i.e.* by ejection of the C-1′ sulphonyl leaving group). Consequently an alternative pathway [(**3**) → (**4**) → (**5**)], involving nucleophilic attack by hydroxide ion at the carbonyl group with ring scission and concomitant reduction of the nitro-group to nitroso, is followed. Subsequent cyclisation of the nitroso-intermediate [(**5**) → (**6**) → (**7**)] then affords the 2-acyl-3-hydroxyquinoline product.

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† Satisfactory analyses and spectral data were obtained for all new compounds.

[1] J. D. Loudon and G. Tennant, *Quart. Rev.*, 1964, **18**, 389; P. N. Preston and G. Tennant, *Chem. Rev.*, 1972, **72**, 627.
[2] T. W. M. Spence and G. Tennant, *J.C.S. Perkin I*, 1972, 97.
[3] T. W. M. Spence and G. Tennant, *J.C.S. Perkin I*, 1972, 835.
[4] A. A. Sandison and G. Tennant, *J.C.S. Chem. Comm.*, 1974, 752.
[5] J. Reihsig and H. W. Krause, *J. prakt. Chem.*, 1966, **31**, 167; C. Kaneko and S. Yamada, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 663; E. D. Hannah, G. R. Proctor, and M. A. Rehman, *J. Chem. Soc. (C)*, 1967, 256.
[6] G. Heller, *Ber.*, 1919, **52**, 741; F. Arndt, B. Eistert, and W. Ender, *ibid.*, 1929, **62**, 44.
[7] P. Friedlander and C. F. Gohring, *Ber.*, 1883, **16**, 1833.
[8] T. Naito, R. Dohmori, and O. Nagase, *J. Pharm. Soc. Japan*, 1954, **74**, 593 (*Chem. Abs.*, 1954, **48**, 10647); R. J. Sundberg and D. E. Blackburn, *J. Org. Chem.*, 1969, **34**, 2799.