SUBSTITUENT INTERACTIONS IN *ortho*-SUBSTITUTED NITROBENZENES

By J. D. LOUDON
(UNIVERSITY OF GLASGOW)
and G. TENNANT
(QUEEN'S COLLEGE, DUNDEE)

THE interactions to be discussed in this Review extend beyond the influence exerted by two substituents on each other's reactivity to mutually accommodating changes in their chemical structures. The purpose of the Review is to assemble the scattered information on one of the less familiar aspects of nitro-group behaviour. The subject embraces redox reactions, intramolecular condensations involving the nitro-group, and photochemical transformations. The last topic has recently been reviewed by De Mayo and Reid[1] and, except for incidental mention, it is omitted here. The other topics together comprise a wide range of reactions of varying complexity and whilst no attempt is made to exhaust individual examples, the Reviewers have tried to include representatives of all known and relevant types of interaction.

It is common experience in aromatic chemistry that the reactions of a nitro-compound unexpectedly differ from those of its parent. The difference, frequently disclosed by an abnormal display of colour and an uninviting product, is often dismissed as merely regrettable evidence of the nitro-group's ease of reduction. Yet such departures can lead to products which are otherwise inaccessible. The nitro-group's demand for electrons may be supplied from outside the molecule or from within, and for *ortho*-nitro-compounds the internal supply lines may run either through the molecular framework or across space. The last route is barred to *para*-substituted nitrobenzenes wherein, significantly, interactions are neither so numerous nor so varied: some of them are mentioned in the sequel.

There has been no systematic study of interactions between *ortho*-situated nitro-groups and side-chains. Information on the reactions which occur has to be gathered almost entirely from the nature of the products isolated and this limitation creates some major difficulties. Two broad paths of interaction may be differentiated according as oxygen or nitrogen of the original nitro-group becomes attached to an appropriate (not necessarily carbon) centre of the side-chain. Thereby the formation of, among others, oxaza- or aza-heterocycles is implied and subsequent scission of these heterocycles can account for the observed transfer of an oxygen atom from nitrogen to the side-chain (cf. p. 408) or that of a carbon-centred group from the side-chain to nitrogen (cf. p. 409). Such postulates however do not specify the exact oxidation level of the nitrogen atom when the ring-forming step occurs and analogy with *para*-substituted nitrobenzenes shows that acinitro- and nitroso-intermediates, resulting from

[1] P. de Mayo and S. T. Reid, *Quart. Rev.*, 1961, **15**, 393.

adjustments within the conjugated system, must be taken into general account. Moreover reduction by an *external* reagent is admissible as a step in a reaction where it does not preclude or reverse some interaction of the nitro-group and side-chain.

The questions to which these general considerations give rise can seldom be given definite answers. It follows that even the choice and arrangement of material for review must be somewhat arbitrary whilst discussion of reaction mechanisms can only be speculative and is here based on the assumption that polar mechanisms operate throughout.

Base-catalysed Cyclisations

One proposition to be considered is that a nitro-group can provide the electrophilic centre for additive reactions of the type exemplified by the aldol condensation.

$$
\begin{array}{lll}
:C{=}O + H_2CXY & \rightleftharpoons :C(OH).CHXY & \rightarrow :C{=}CXY \\
:C{=}O + H_2NR & \rightleftharpoons :C(OH).NHR & \rightarrow :C{=}NR \\
\cdot N{=}O + H_2CXY & \rightleftharpoons \cdot N(OH).CHXY & \rightarrow \cdot N{=}CXY \\
\cdot N{=}O + H_2NR & \rightleftharpoons \cdot N(OH).NHR & \rightarrow \cdot N{=}NR \\
O{\leftarrow}N{=}O + H_2NR & \rightleftharpoons O{-}N(OH).NHR & \rightarrow O{-}N{=}NR \\
O{\leftarrow}N{=}O + H_2CXY & \rightleftharpoons O{-}N(OH).CHXY & \rightarrow O{-}N{=}CXY
\end{array}
$$

This proposition is neither new nor commonplace: it has been advanced by various authors sometimes in less specific terms, but it has never achieved prominence or wide acceptance. There are several reasons for this. Nitroso-compounds, by their intermolecular reactions with primary amines to form azo-compounds or with reactive methylene compounds to form azomethines, provide cogent evidence that the nitroso-group can attract and add nucleophils. But in the nitro-group it must be expected that resonance will restrict the reactivity of the nitrosyl component. The restriction is apparently severe for among intermolecular reactions it is difficult to find an example which unequivocally shows an aldol-type of interaction between nitro-group and nucleophil.

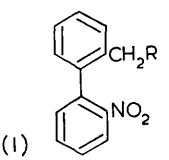
The best evidence comes from intramolecular reactions where the steric factor is most favourably enlisted and a heterocyclic product is formed. Yet even here the mechanism of cyclisation is seldom clear and the recurrent difficulty in interpreting the course of such interactions makes it expedient to consider first the more compelling evidence for the nitro-group's direct participation in aldol-type reactions.

Diphenyl Derivatives.—Muth and his colleagues,[2] surprised by the outcome of an attempt to saponify the ester (1*a*), established that this ester in common with some other 2′-substituted 2-nitrodiphenyls (1*b*—*e*)

[2] C. W. Muth, J. C. Ellers, and O. F. Folmer, *J. Amer. Chem. Soc.*, 1957, **79**, 6500; C. W. Muth, N. Abraham, M. L. Linfield, R. B. Wotring, and E. A. Pacofsky, *J. Org. Chem.*, 1960, **25**, 736.

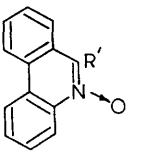
undergoes cyclodehydration when briefly heated with sodium hydroxide in methanol. It will be observed that among the phenanthridine derivatives so obtained (*2a—e*) a few are not simple dehydration products but, in interesting variety (2; R′ = CO_2H), (*2d*), (*2e*), are exactly the products to be expected of dehydration followed by hydrolysis.

(*1a*) R=CO_2Me
(*1b*) R=$CONH_2$
(*1c*) R=CN
(*1d*) R=COPh
(*1e*) R=SO_2Ph

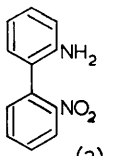


(1)

NaOH
MeOH



(*2a*) R′=CO_2Me, CO_2H
(*2b*) R′=$CONH_2$
(*2c*) R′=CN
(*2d*) R′=H (+Ph·CO_2H)
(2) (*2e*) R′=OH (+Ph·SO_2H)



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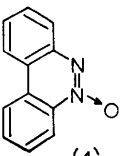

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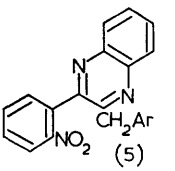

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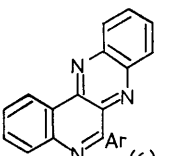


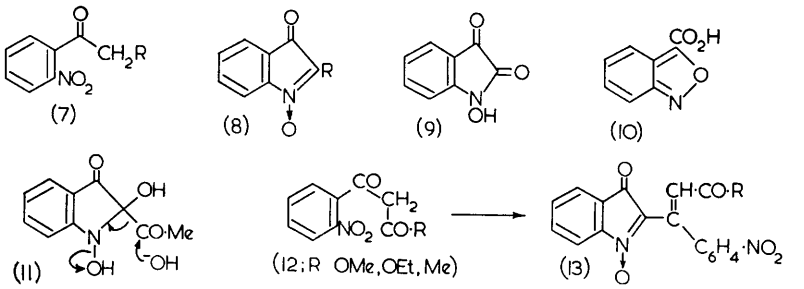
(6)

The stability of the diphenyl system, the mild conditions of the reaction, and the stark simplicity of the result provide in these examples the best available evidence for the aldol type of interaction. A conditioning feature appears to be the provision of a nucleophilic centre (*e.g.*, a carbanion) immediately attached to the un-nitrated nucleus. Thus with diphenyls (1) having the substituents R = H, OH, Br, Ph, or CO_2H, or having $CO{\cdot}CH_2CN$ instead of CH_2R, comparable cyclisation fails whereas 2′-amino-2-nitrodiphenyl (3) yields the benzocinnoline (4) although it cyclises more slowly. Furthermore, methylene reactivity in a quinoxaline derivative allows the similar cyclisation (5) → (6).[3]

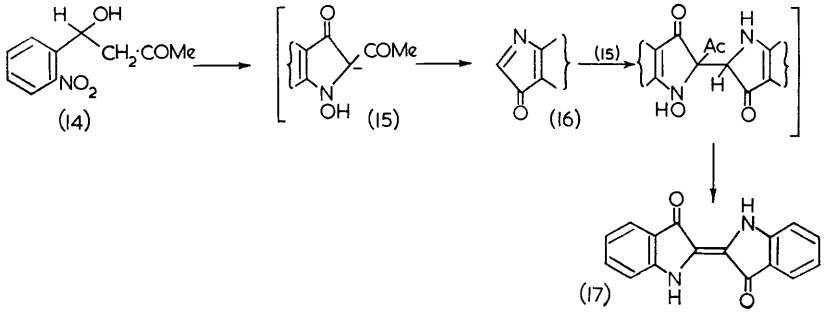
o-**Nitrobenzoyl Derivatives, etc.**—*o*-Nitroacetophenone, and especially those of its derivatives wherein methylene reactivity is enhanced by an ω-substituent, should be capable of this type of cyclisation. Examples however are few and complicated, perhaps because the reagents and the isatogens (8) to be expected as products are both highly sensitive. *o*-Nitrophenacyl chloride (7; R=Cl) when heated with aqueous ethanolic potassium hydroxide yields anthranil-3-carboxylic acid (10),[4] and a rational course would be the formation and known rearrangement of 1-hydroxyisatin (9) (= 2-hydroxyisatogen). Under similar conditions *o*-nitrobenzoylacetone (7; R = COMe) yields isatin[4] which may well be formed by hydroxide attack on the hydrated form (11) of 2-acetylisatogen. *o*-Nitrophenylpropiolic acid when heated with dilute alkali also yields isatin[5] whereas its ethyl ester when heated with pyridine yields ethyl

[3] R. P. Barnes, J. H. Graham, and M. A. Salim Qureshi, *J. Org. Chem.*, 1963, **28**, 2890.
[4] J. D. Loudon and G. Tennant, *J.*, 1963, 4268.
[5] A. Baeyer, *Ber.*, 1880, **13**, 2254; 1881, **14**, 1741.

isatogenate (8; R = CO_2Et).[6] In these two reactions *o*-nitrobenzoylacetic acid and ester respectively are plausible intermediates but direct proof is lacking. However compounds of this class (12) are converted by cold aqueous sodium hydrogen carbonate into isatogen derivatives:[7] these are formulated as (13) although their relationship to certain co-products, and the observed formation of the latter by condensation of ethyl isatogenate with the reagents (12), await elucidation.



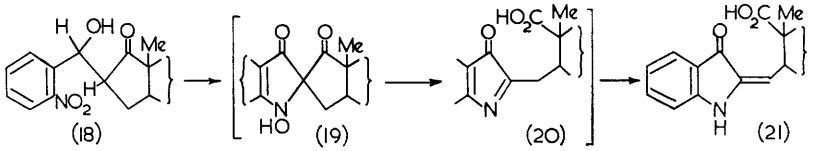
Indigo is formed when *o*-nitrobenzoylacetic acid is treated with alkali in presence of glucose as reducing agent.[5] *o*-Nitro-α-hydroxybenzyl compounds are already at the required level of reduction and such compounds are intermediates in the Baeyer–Drewsen synthesis of indigo.[8] Thus with aqueous sodium hydroxide the pre-formed aldol (14), or its

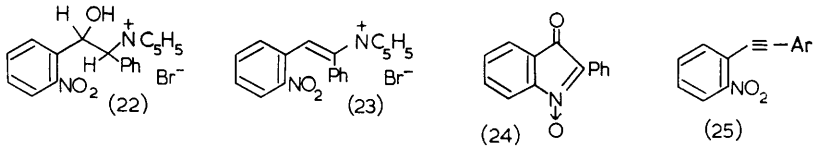


formative mixture of *o*-nitrobenzaldehyde and acetone, rapidly yields indigo (17); moreover the aldehyde reacts in similar fashion with 17-oxo-steroids forming, *via* the aldols (18), products of type (21).[9] For the two reactions parallel courses are conceivable leading, through 1-hydroxy-indoxyls (15) and (19), to deoxyisatogens (16) and (20) respectively, but whereas the latter of these can achieve the stable isatinoid structure (21)

[6] P. Pfeiffer, *Annalen*, 1916, **411**, 72.
[7] R. T. Coutts, M. Hooper, and D. G. Wibberley, *J.*, 1961, 5205.
[8] A. Baeyer and V. Drewsen, *Ber.*, 1882, **15**, 2856; L. E. Hinkel, E. E. Ayling, and W. H. Morgan, *J.*, 1932, 985.
[9] A. Hassner and M. J. Haddadin, *Tetrahedron Letters*, 1962, No. 21, 975.

by a simple proton shift, the former must combine with a precursor for the ultimate formation of indigo. *o*-Nitrostyryl ketones do not yield indigo under the conditions of the Baeyer–Drewsen reaction but they are convertible by alkali into salt-like products from which the dyestuff can be obtained.[8,10]





For another type of cyclisation the relative importance of aldols and their dehydration products appears to be reversed. Kröhnke *et al.* have shown[11] that aldols of type (22) undergo retroaldol scission when treated with bases. On the other hand their acetates, or the derived styrylpyridinium salts (23), yield isatogens, *e.g.* (24), in reaction with sodium carbonate or pyridine–diethylamine. The ease of such cyclisations is incompatible with a course which is otherwise practicable running from the styryl compounds (23) to tolanes (25) and hence, in presence of pyridine, to isatogens (24).[6] The latter stage normally requires irradiation (although this is not necessary for all derivatives of *o*-nitrophenylacetylene) and Huisgen suggests[12] that these routes to isatogens may converge upon an intermediate pyridiniumbetaine, reaction (i), formed by elimination of hydrogen halide from the salt (23) or by photochemical addition of pyridine to the tolane (25). On this basis the precursor of the isatogen is a nitrosophenyl ketone (or its equivalent) whose formation involves transfer of an oxygen atom from the nitro-group to the side-chain, a process which, detailed mechanism apart, is commonly postulated for photochemical interactions.[1,13] Nitrosophenyl ketones* are also possible intermediates in the Baeyer–Drewsen type of reaction but here, even if real, their formation from the aldols could be the result of internal transfer either of oxygen from, or of hydrogen to, the nitro-group. Equally uncertain is the mechan-

* It has recently been shown that 2-nitrodiphenylmethanol reacts with (*a*) formic acid or toluene-*p*-sulphonyl chloride in pyridine yielding 2-nitrosobenzophenone; (*b*) thionyl chloride in hot chloroform yielding 5-chloro-3phenylanthranil (W. B. Dickinson, *J. Amer. Chem. Soc.*, 1964, **86**, 3580).

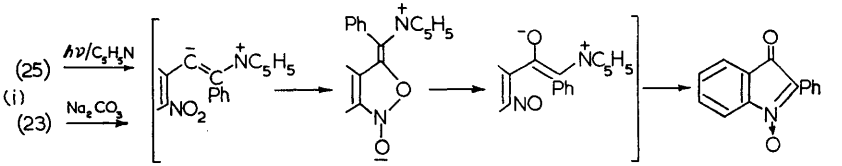
[10] Cf. I. Tanasescu and E. Tanasescu, *Bull. Soc. chim. France*, 1936, **3**, 865; A. Georgescu, *J. prakt. Chem.*, 1934, **139**, 189.

[11] F. Kröhnke and M. Meyer-Delius, *Chem. Ber.*, 1951, **84**, 932, 941; F. Kröhnke, and I. Vogt, *Ber.*, 1952, **85**, 376.

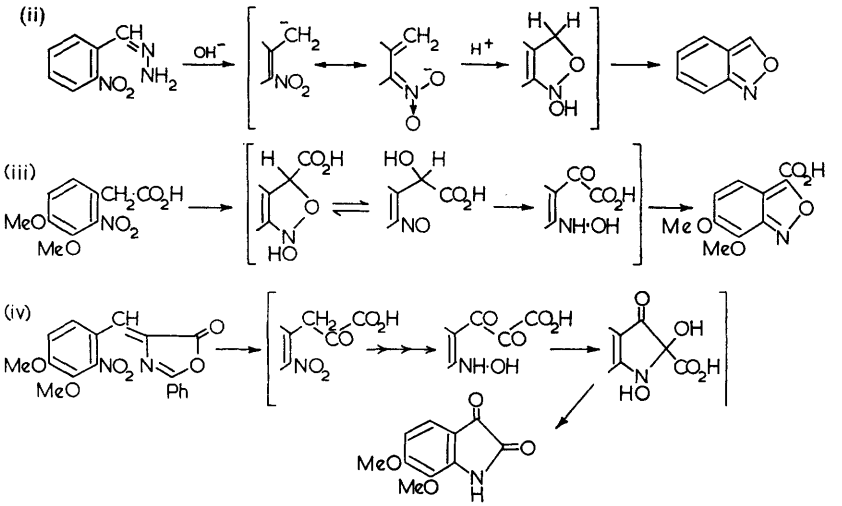
[12] R. Huisgen, *Angew. Chem.. Internat. Edn.*, 1962, **2**, 565.

[13] J. S. Splitter and M. Calvin, *J. Org. Chem.*, 1955, **20**, 1086.

ism by which phenylisatogen is formed as a by-product when *o*-nitrobenzaldehyde, sodium phenylacetate, and sodium acetate are heated in acetic anhydride.[14]

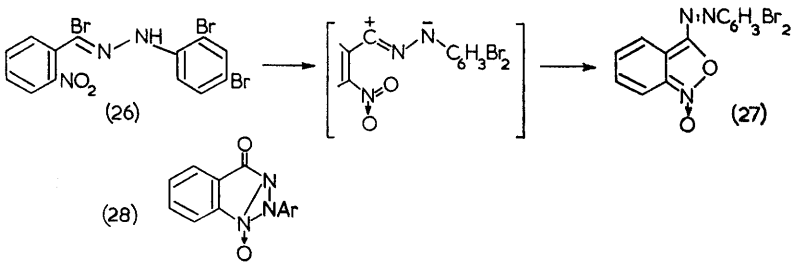


Anthranil derivatives, more commonly found under acidic conditions (p. 402), have been isolated from a few base-catalysed interactions (cf. p. 391 and formation of thioanthranil, p. 412) and may well be intermediates in others (p. 408). During a study of the Kishner–Wolff reaction Seibert[15] noted the formation of anthranil (as well as *o*-nitrotoluene) by the action of dilute alkali on the hydrazone of *o*-nitrobenzaldehyde [reaction (ii)]. A similar course initiated by extraction of an α-proton can explain the conversion of 3,4-dimethoxy-2-nitrophenylacetic acid by alkali into the corresponding anthranil-3-carboxylic acid (iii).[16] Here the heterocyclic intermediate (the equivalent of an *o*-nitrosomandelic acid) may undergo direct dehydration or, conceivably, can yield the anthranil after isomerisation to an hydroxyaminophenyl ketone [cf. (iii)]. A simple variant of the latter process then accounts for the formation of isatins[17] from certain azlactones as in reaction (iv). While the presence of methoxyl adjacent to the nitro-group appears to assist formation of isatins in this



[14] Cf. P. Ruggli, E. Caspar, and B. Hegedüs, *Helv. Chim. Acta*, 1937, **20**, 250.
[15] W. Seibert, *Ber.*, 1947, **80**, 494; 1948, **81**, 266.
[16] J. M. Gulland, *J.*, 1931, 2872.
[17] H. Burton and J. L. Stoves, *J.*, 1937, 402.

way it is noteworthy that isatin itself is formed by the action of aqueous alkali on *o*-nitrophenylpyruvic acid.[18]



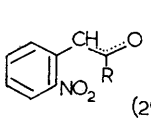
The formation of anthranil derivatives by a different type of mechanism is inherent in a re-interpretation of the base-catalysed transformations of compounds of type (26). These compounds, prepared by halogenating arylhydrazones of *o*-nitrobenzaldehyde, eliminate hydrogen halide yielding products which were formulated by Chattaway and Walker[19] as triazine oxides (28), but are regarded by Gibson[20] as anthranil 1-oxides (27) formed through cyclisation of transient nitrilimines. Anthranil 1-oxides are very elusive compounds but according to Szmant and Harmuth[21] 3-phenylanthranil 1-oxide may be the product isolated from the reaction of *o*-nitrobenzoic acid with trifluoroacetic anhydride and boron trifluoride.

o-**Nitrobenzyl Derivatives.**—[See reactions (iii) and (iv) above.] Proton removal from *o*-nitrophenylacetone is more likely to occur at the doubly activated methylene than at the terminal methyl group, and a condition such as shown in (29; R = Me) may help to explain why there is no record of cyclisation to a quinoline derivative here, or with 2,4-dinitrophenylacetone or 2,4-dinitrophenylacetoacetic esters (30; R = H). Yet a closely similar compound (30; R = Ph) undergoes cyclodehydration. Zaki and Iskander who noted[22] this reaction regarded the product as the naphthalene derivative (32), but the quinoline structure (31) is in accord with the ester behaviour and is supported by the infrared spectra which show that the ester and the derived acid are of the salicylic type.[23]

o-Nitrophenylacetamide likewise does not undergo cyclodehydration, but here the nucleophilic potentialities of the amino-group should be released in the anion (29; R = NH_2) and indeed *o*-nitrophenylcyanoacetamide (33) which is better equipped to provide an anion is cyclised to the cinnoline (34) by warm aqueous sodium hydroxide.[24] The amide (33)

[18] A. Reissert, *Ber.*, 1897, **30**, 1030.
[19] F. D. Chattaway and A. J. Walker, *J.*, 1927, 323; cf. J. G. Ericson in "The Chemistry of Heterocyclic Compounds," Interscience, New York, 1956, Vol. 10, p. 27.
[20] M. S. Gibson, *Tetrahedron*, 1962, **18**, 1377.
[21] H. H. Szmant and C. M. Harmuth, *J. Amer. Chem. Soc.*, 1959, **81**, 962.
[22] A. Zaki and Y. Iskander, *J.*, 1943, 68.
[23] J. P. Cairns, J. D. Loudon, and A. S. Wylie, unpublished work.
[24] J. P. Cairns, Ph.D. Thesis, Glasgow, 1964.

can be prepared by base-catalysed Smiles rearrangement, followed by hydrolysis, from the sulphonamide (35; R = CN).[25] The same procedure applied to the sulphonamide (35; R = Ph) leads to 3-phenylindazole (36a), possibly through ring-contraction of the cinnoline (36) (for analogous contraction of triazines, see p. 400).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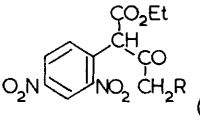
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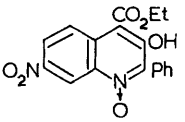
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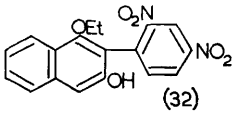
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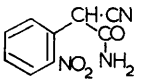
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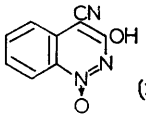
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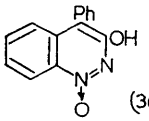
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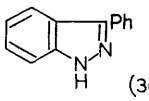
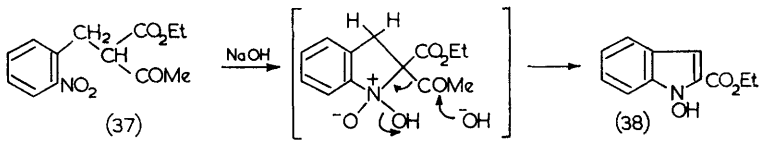

(36a)

In the next set of nitro-compounds each of the α- and β-carbon atoms of the side chain carries a hydrogen atom which is acidic, but although the degree of acidity at the respective centres varies widely the compounds are remarkably consistent in their ability to yield derivatives of 1-hydroxyindole. Nevertheless, in certain cases and in a strongly alkaline environment, this type of product is accompanied by another derived from 1-hydroxyquinoline.

(v)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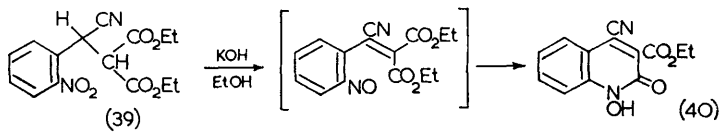
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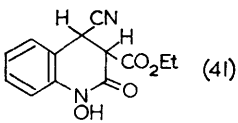
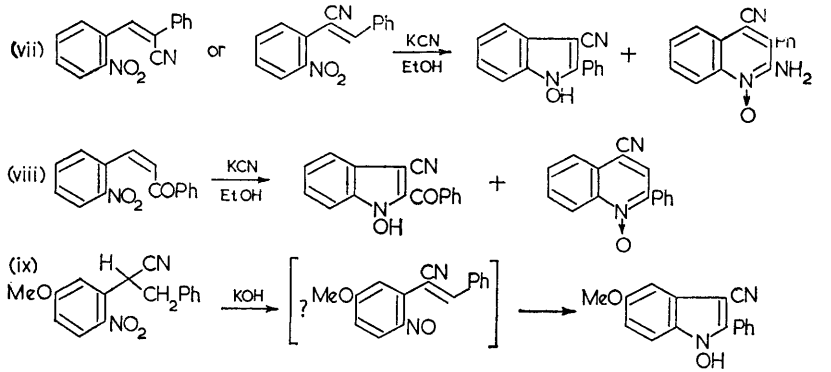

(41)

[25] T. Naito and R. Dohmori, cf. *Chem. Abs.*, 1954, **48**, 10647.

o-Nitrobenzylmalonic acid[26] and ethyl *o*-nitrobenzylacetoacetate (37)[27] each reacts with aqueous alkali to form 1-hydroxyindole-2-carboxylic acid, the latter reaction occurring so readily that the ester (38) is also isolated. The allied nitrile (39) and the derived amide (39; $CONH_2$ for CN) respectively yield the 3-cyano- and 3-carbamoyl-derivatives of the indole (38) in smooth reactions effected by sodium carbonate.[28] But the nitrile (39) reacts with hot ethanolic potassium hydroxide to form the 1-hydroxyquinoline (40) and this product may be obtained directly by the action of potassium cyanide on diethyl *o*-nitrobenzylidenemalonate in ethanol. Moreover, as exemplified in reactions (vii)[29] and (viii)[30] where the first-formed adducts (as 39) have not been isolated, other *o*-nitrobenzylidene compounds react with potassium cyanide affording mixed products of the indole and quinoline types. Two derivatives of α-benzyl-*o*-nitrobenzyl cyanide have been examined:[29] both are methoxylated in the nitrobenzene ring, and both yield indoles in reaction [cf. (ix)] with potassium hydroxide despite the feeble activation of the β-methylene centre of the side-chain.

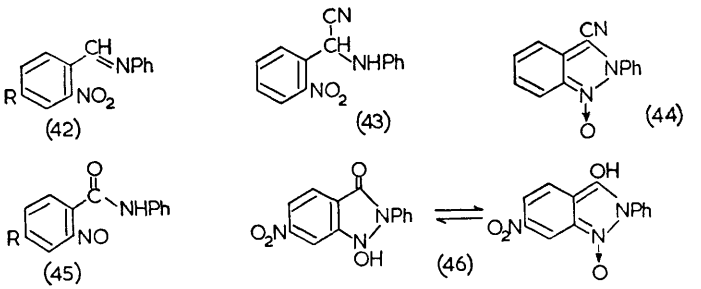


There are too many uncontrolled variables to warrant extensive discussion of these reactions. Broadly, a highly reactive α-hydrogen atom in the side-chain of the nitro-compound appears to be a facilitating factor even for indole formation, but whether it operates before or after the ring-forming step is uncertain. Reduction, presumably by the reaction medium, is involved in the formation of the quinolines. Thus the product of reaction (vi) requires a hydroxylamine precursor whereas the nitro-compound (39) can only provide a nitroso-intermediate, for instance by base-catalysed transfer of protons from its side-chain. On the other hand direct external reduction of the nitro-compound (39), by zinc and ammonium chloride, designed[28] to yield the corresponding hydroxylamine and

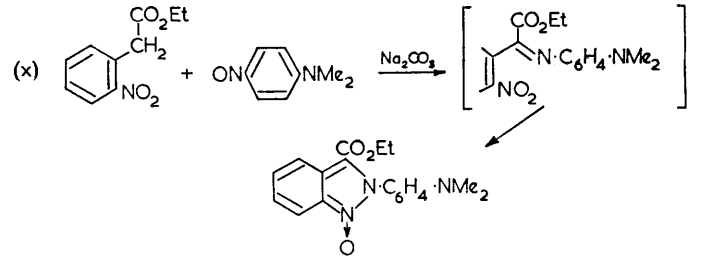
[26] A. Reissert, *Ber.*, 1896, **29**, 639.
[27] S. Gabriel, W. Gerhard, and R. Wolter, *Ber.*, 1923, **56**, 1024.
[28] J. D. Loudon and I. Wellings, *J.*, 1960, 3462.
[29] J. D. Loudon and G. Tennant, *J.*, 1960, 3466.
[30] J. D. Loudon and A. C. Mackay, unpublished work.

hence the 3,4-dihydroquinolone (41), yields instead the de-cyanoquinoline (40; H for CN). If on this evidence the dihydride can be rejected as an intermediate in reaction (vi), then the course depicted for this particular reaction becomes a likely one.

Among the reactions so far described there are several examples of ring-closure through formation of a nitrogen–nitrogen bond (pp. 391, 395). Although 2-nitrobenzylamine is well known it shows no tendency to undergo cyclodehydration. The simple amino-nitrile (43; H for Ph) is not known but reactions likely to yield it yield 2-nitrosobenzoic acid instead (p. 408). However the related anilino-nitrile (43) is known and is readily cyclised by sodium carbonate to the indazole 1-oxide (44)[31] and shares this behaviour with a number of its derivatives.[32] A similar course, *via* the anilino-nitrile, in all probability accounts for the formation[33] of the indazole oxide (44) from *o*-nitromandelonitrile and aniline in acetic acid. Effectively therefore 2-nitrobenzylidene-anilines (42; R = H) are convertible into indazoles, as (44), *via* adducts of type (45)[34] wherein again the α-cyano-substituent seems to facilitate cyclisation. 2-Nitrobenzylidene-anilines are themselves isomerised to 2-nitrosobenzanilides (45) by light,[35] but not by purely chemical means. On the other hand more highly nitrated analogues, *e.g.* (42; R = NO_2), are isomerised by sodium carbonate in ethanol, and although the products have been given heterocyclic structures such as (46)[36] there is an implied close relation to 2-nitrosobenzanilides, *e.g.* (45; R = NO_2), through ring-chain tautomerism. Confirmation is desirable for these structures and also for the course depicted for the reaction (x)[37] wherein the alleged product is indicative of an α-anilino-ester as precursor [cf. (43) → (44)], whereas the reagents suggest an anil as intermediate.



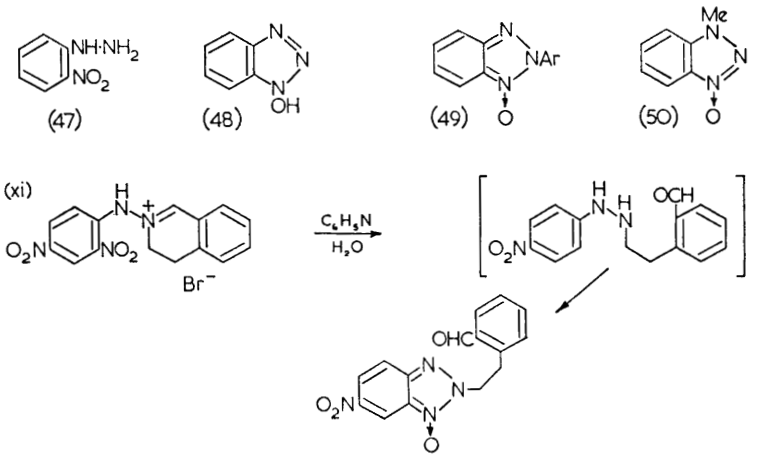
[31] A. Reissert and F. Lemmer, *Ber.*, 1926, **59**, 351.
[32] L. C. Behr, *J. Amer. Chem. Soc.*, 1954, **76**, 3672; *J. Org. Chem.*, 1962, **27**, 65.
[33] G. Heller and G. Spielmeyer, *Ber.*, 1925, **58**, 834.
[34] Cf. K. Akashi, *Chem. Abs.*, 1949, **43**, 7934.
[35] F. Sachs and R. Kempf, *Ber.*, 1902, **35**, 2704.
[36] S. Secareanu and I. Lupas, *Bull. Soc. chim. France*, 1933, [4], **53**, 1436; 1934, [5], **1**, 373; 1935, [5], **2**, 69. Cf. L. Jacobs in "Heterocyclic Compounds", Wiley, New York, 1957, Vol. 5, p. 169.
[37] I. Tanasescu and E. Tanasescu, *Bull. Soc. chim. France*, 1935, **2**, 1016.



Derivatives of *o*-Nitroaniline.—The prototype of this class of reaction was discovered by Nietzki and Braunschweig, who showed[38] that treatment of *o*-nitrophenylhydrazine (47) with aqueous alkali did not liberate hydrazine as expected, but gave the salt of 1-hydroxybenzotriazole (48). The reaction has been extended in various ways. 2,4-Dinitrophenylhydrazine is conveniently cyclised to 1-hydroxy-6-nitrobenzotriazole by hydrazine hydrate[39] which may thus be used to prepare hydroxybenzotriazoles in one operation from *o*-halogenonitrobenzenes[40] or from *o*-dinitrobenzenes.[41] The comparable use of phenylhydrazine, or cyclisation of pre-formed 2-nitrohydrazobenzenes, yields *N*-oxides of type (49),[42] but in this series reduction to 2-substituted benzotriazoles is often incurred; moreover cyclisation is variously effected, *e.g.*, by alkali or by hot acetic acid, and reductive cyclisation occurs in acetic acid in presence of potassium iodide. A particular example of this type of cyclisation is given in reaction (xi) although other interpretation of its course has been suggested.[43] By contrast, methylhydrazine, which with reactive chloronitro- or dinitro-benzenes affords 1,1-disubstituted hydrazines,[44,45] leads to triazoles of type (50).[41]

The internal-aldol mechanism offers an attractively simple interpretation of how these *N*-oxygenated benzotriazoles are formed, but the powerful reducing properties of hydrazines are also much in evidence. Thus 2,4-dinitrophenylhydrazine yields [46] 3,3′-dinitroazoxybenzene, *m*-dinitrobenzene, and 1-hydroxy-6-nitrobenzotriazole in proportions which vary with the pH of the medium and are minimal for the heterocycle at low concentrations of basic condensing agent. While for each of these products an oxidised hydrazine of the type, ArN=NH (Ar variously substituted), is a conceivable precursor, it cannot in so far as it leads to *m*-dinitrobenzene

[38] R. Nietzki and E. Braunschweig, *Ber.*, 1894, **27**, 3381.
[39] T. Curtius and M. Mayer, *J. prakt. Chem.*, 1907, **76**, 369.
[40] E. Müller, and G. Zimmermann, *J. prakt. Chem.*, 1925, **111**, 277.
[41] B. Vis, *Rec. Trav. chim.*, 1939, **58**, 847.
[42] Cf. F. R. Benson and W. L. Savell, *Chem. Rev.*, 1950, **46**, 1; cf. A. Angeletti, *Gazzetta*, 1923, **53**, 672.
[43] R. Grashey, *Angew, Chem., Internat. Edn.*, 1962, **1**, 158.
[44] K. Fries, W. Franke, and W. Bruns, *Annalen*, 1934, **511**, 264; J. J. Blanksma and M. L. Wackers, *Rec. Trav. chim.*, 1936, **55**, 655.
[45] B. Vis, *Rec. Trav. chim.*, 1939, **58**, 387.
[46] A. K. Macbeth and J. R. Price, *J.*, 1934, 1637; cf. O. M. Shemyakina, B. M. Bogoslovskii, and M. M. Shemyakin, *Chem. Abs.*, 1957, **51**, 5057.

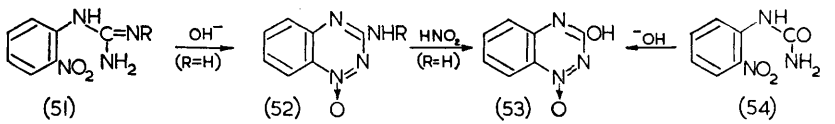


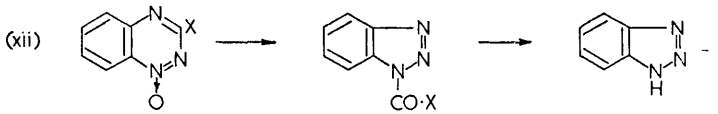
be derived by *internal* oxidation–reduction of the hydrazine: yet a competing internal process, by supplying an *o*-nitroso-substituent in the oxidised hydrazine, could still be a route to the triazole.

3-Aminobenzotriazole 1-oxide (52; R = H) is formed rapidly and almost quantitatively when *o*-nitrophenylguanidine (51; R = H) is warmed with dilute alkali. Neither ammonia nor aqueous sodium carbonate is effective as condensing agent, and cyclisation of the analogous urea derivative, (54) → (53), requires stronger alkali, *e.g.*, 10% potassium hydroxide. These reactions were discovered by Arndt[47] and were later extended[48] to include cyclisation of the guanidine (51; R = Ph), of *o*-nitrophenylthiourea (51; S for NR), and various aryl-substituted guanidines (as 51; R = H).[49] Since the process often occurs with deepening followed by fading of colour Arndt suggested that a salt of the pseudo-nitro-compound might be an intermediate: here again removal of the α-proton may assist cyclisation as in the nitrophenylacetamide (33). On the practical side it should be noted that while these 1-oxides are formed in presence of alkali they are themselves affected by prolonged exposure to hot alkali.[50] In this respect the 3-amino- are more susceptible than the 3-hydroxy-compounds, but both undergo ring-contraction to benzotriazole derivatives [reaction (xii)].

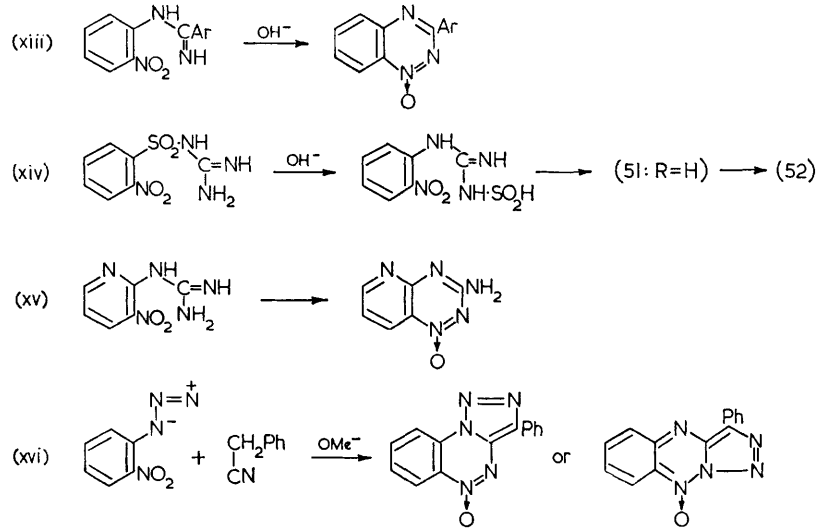
o-Nitrophenylbenzamidines are also cyclised by alkali, yielding 3-arylbenzotriazine 1-oxides [reaction (xiii)].[51] Other variants include the use

[47] F. Arndt, *Ber.*, 1913, **46**, 3522.
[48] F. Arndt and B. Rosenau, *Ber.*, 1917, **50**, 1248.
[49] F. J. Wolf, K. Pfister, R. M. Wilson, and C. A. Robinson, *J. Amer. Chem. Soc.*, 1954, **76**, 3551; F. J. Wolf, R. M. Wilson, K. Pfister, and M. Tishler, *ibid.*, 1954, **76**, 4611; J. Jiu and G. P. Mueller, *J. Org. Chem.*, 1959, **24**, 813.
[50] J. A. Carbon, *J. Org. Chem.*, 1962, **27**, 185.
[51] R. F. Robbins and K. Schofield, *J.*, 1957, 3186; R. Fusco and G. Bianchetti, *Chem. Abs.*, 1959, **53**, 9243.





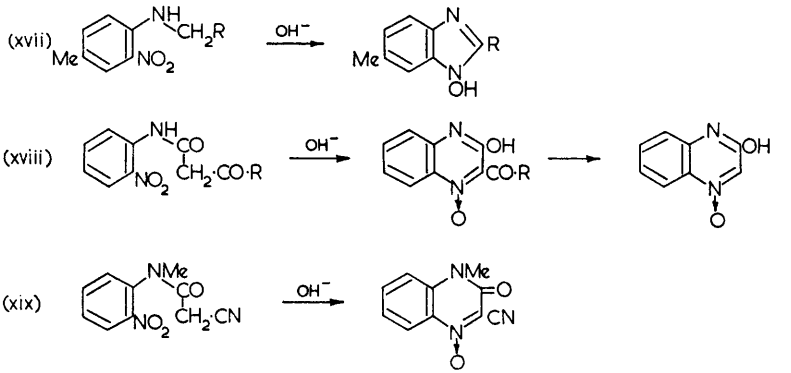
of *o*-nitrobenzenesulphonyl derivatives of guanidine[52] and urea[53] respectively to provide in a combined operation [cf. (xiv)] the reagents and conditions for cyclisation. Applications to the synthesis of fused heterocyclic systems are exemplified by reactions (xv)[54] and (xvi),[55] and further examples may be implicit in reactions, still obscure, which occur when 5-chloro-3-methyl-1-(2,4-dinitrophenyl) pyrazole is heated with ammonia or primary amines.[56]



Two reactions, (xvii; R = COPh)[4] and (xviii; R = Me or Ph),[57] respectively illustrate extension of the Nietzki and Arndt cyclisations to cases wherein the side-chain provides the nucleophil in the form of a carbanion. The potentialities in such extensions are virtually unexplored,

[52] H. J. Backer and H. D. Moed, *Rec. Trav. chim.*, 1947, **66**, 689.
[53] H. J. Backer and J. Groot, *Rec. Trav. chim.*, 1950, **69**, 1323.
[54] J. A. Carbon and S. H. Tabata, *J. Org. Chem.*, 1962, **27**, 2504.
[55] E. Lieber, T. S. Chao, and C. N. R. Rao, *J. Org. Chem.*, 1957, **22**, 654.
[56] C. A. Rojahn and H. Fegeler, *Ber.*, 1930, **63**, 2510.
[57] G. Tennant, *J.*, 1963, 2428; R. Fusco and S. Rossi, *Chimica e Industria*, 1963, **45**, 834; cf. Y. Ahmad, M. S. Habib, and Ziauddin, *Tetrahedron*, 1964, **20**, 1107.

but it is particularly noteworthy that, as in reaction (xix), *N*-methylation of the reagent is found[58] to enhance both the yield and the apparent rate of cyclisation. However the recently reported[59] cyclisation of *N*-benzyl-*o*-nitroaniline to 1-hydroxy-2-phenylbenziminazole, reaction (xvii; R = Ph, H for Me) invites comparison with cyclisations of type (ix; p. 397) wherein a mobile α-hydrogen atom appears to compensate for feeble activation at the β-methylene centre of the side-chain.

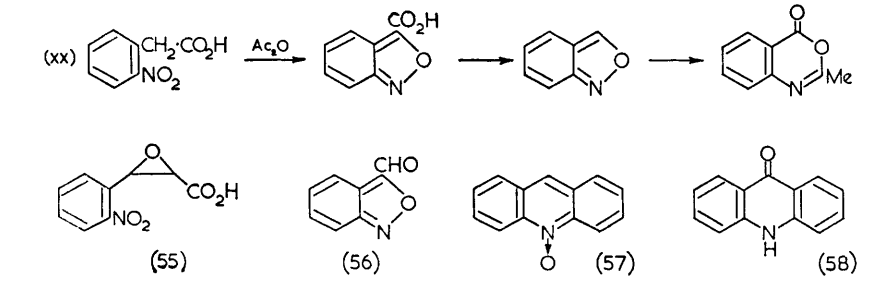


Acid-catalysed Cyclisations

Anthranil derivatives are often products or intermediates in acid-catalysed transformations of *o*-nitrobenzyl compounds. The parent anthranil is formed by the action of hydrochloric acid on *o*-nitrobenzylidene dimercurichloride;[60] it is almost certainly an intermediate in the conversion[61] (reaction xx) of *o*-nitrophenylacetic acid by hot acetic anhydride into the internal anhydride of *N*-acetylanthranilic acid; moreover 6-nitroanthranil is obtained when 2,4-dinitrophenyl-acetone[62] or -acetic acid[63] is heated with concentrated sulphuric acid, and amides of the appropriate anthranil-3-carboxylic acids result[64] from heating certain derivatives of *o*-nitrophenylacetamide with phosphorus pentachloride in benzene. *o*-Nitrophenylglycidic acid (55), possibly reacting *via* *o*-nitrophenylacetaldehyde, yields a mixture of anthranil and its aldehyde (56) when distilled in steam or heated in acetic acid.[65] Heating alone sometimes leads to anthranils as in the cyclisation[66] of ethyl *o*-nitrophenyl-malonate

[58] G. Tennant, *J.*, 1964, 2666; cf. R. Fusco and S. Rossi, *Gazetta*, 1964, **94**, 3.
[59] G. W. Stacey, B. V. Ettling, and A. J. Papa, *J. Org. Chem.*, 1964, **29**, 1537.
[60] Kalle and Co., *Chem. Zentr.*, 1908, **11**, 210; A. Reissert, *Ber.*, 1907, **40**, 4209.
[61] G. N. Walker, *J. Amer. Chem. Soc.*, 1955, **77**, 6698.
[62] S. S. Joshi and I. R. Gambhir, *J. Amer. Chem. Soc.*, 1956, **78**, 2222; *J. Org. Chem.*, 1961, **26**, 3714.
[63] H. G. Garg, *J. Org. Chem.*, 1962, **27**, 3683.
[64] D. H. Hey and A. L. Palluel, *J.*, 1956, 4123.
[65] A. Schillinger and S. Wleugel, *Ber.*, 1883, **16**, 2222.
[66] C. A. Grob and O. Weissbach, *Helv. Chim. Acta*, 1961, **44**, 1748.

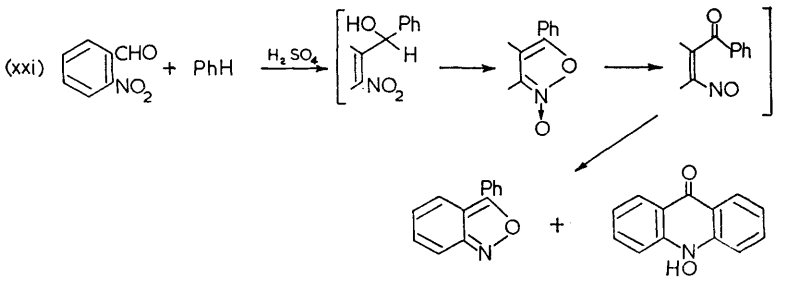
and -cyanoacetate to 3-ethoxycarbonyl- and 3-cyano-anthranil respectively. Moreover anthranils are probably intermediates of thermal or acid-catalysed reactions which lead to acridones (see below). Thus aluminium chloride catalyses cyclisation of *o*-nitrodiphenylmethane to a product which is formulated[67] as acridine 10-oxide (57), whereas thermal cyclisation[68] affords acridone (58) possibly *via* 3-phenylanthranil (see below). Nevertheless the ease of anthranil formation is disconcertingly varied: for instance neither *o*-nitrobenzyl cyanide nor esters of *o*-nitrophenylacetic acid are cyclised under the conditions of reaction (xx).[61]



o-Nitrobenzaldehyde reacts with aromatic compounds affording triarylmethanes,[69] 3-arylanthranils,[70] or acridones,[71,72] depending on the acidic environment and on the reactivity of the aromatic compound. Although 2-nitrodiarylmethanols are undoubtedly intermediates, there is no convincing evidence that they have isolated from such reactions:[73] on the other hand 2-nitrobenzophenones are not uncommon by-products[70,74] and are presumably formed by oxidation of the methanols. For the reaction which occurs at ordinary temperature between *o*-nitrobenzaldehyde and benzene in presence of concentrated sulphuric acid, a plausible course[71] is given by the sequence (xxi). In this it will be noted that the step from 2-nitrosobenzophenone to 3-phenylanthranil requires a reducing agent which may well be the methanol since *o*-nitrobenzophenone is also isolated.

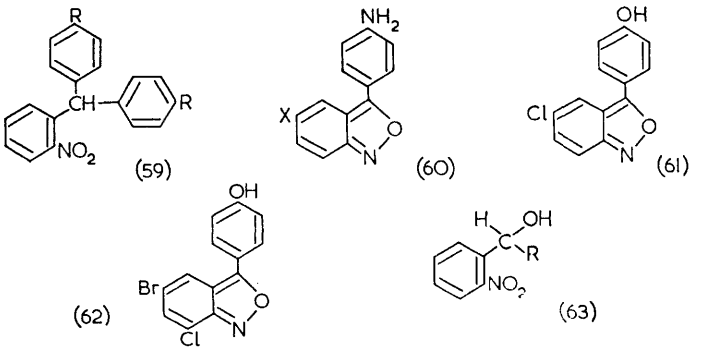
In general *N*-unsubstituted acridones must also be reckoned among the products of such reactions: thus *N*-hydroxyacridone[67] is formed as a by-product in reaction (xxi), whilst acridone is the principal product when the condensation (xxi) is effected by hot polyphosphoric acid.[72] Moreover it is known that the 3-arylanthranils are converted into acridones by traces

[67] M. Freund, *Sitzungsber. Akad. Wiss., Wien.* 1896, **105,** 381; A. Kliegl and A. Brösamle, *Ber.*, 1936, **69,** 197.
[68] A. Kliegl, *Ber.*, 1909, **42,** 591.
[69] J. E. Driver and S. F. Mok, *J.*, 1955, 3914.
[70] A. Kliegl, *Ber.*, 1908, **41,** 1845; cf. J. C. E. Simpson and O. Stephenson, *J.*, 1942, 353.
[71] A. Albert, "The Acridines", Arnold and Co., London, 1951.
[72] I. Tanasescu, M. Ionescu, I. Goia, and H. Mantsch, *Bull. Soc. chim., France,* 1960, **4,** 698.
[73] J. D. Loudon and G. Tennant, *J.*, 1962, 3092.
[74] K. Lehmstedt, *Ber.*, 1932, **65,** 999.



of nitrous acid[75] whose presence therefore, whether incidental[74] or contrived,[76] greatly affects the proportions of products.

Anthranils are almost exclusively the heterocyclic products when *o*-nitrobenzaldehyde condenses with the more reactive types of aromatic reagent. Thus with aniline the reaction effected by zinc chloride is reported[77] to give a mixture of the triarylmethane (59; R = R = NH_2) and the 3-arylanthranil (60; X = H), whereas in hydrochloric acid–acetic acid it affords the same anthranil together with the 5-chloro-derivative (60; X = Cl).[78] Dimethylaniline likewise reacts to give the chlorinated anthranil (60; X = Cl, NMe_2 for NH_2).[79] The allied reactions of phenols are discussed below and are especially interesting because of features held in common with some reactions of reactive methylene compounds.

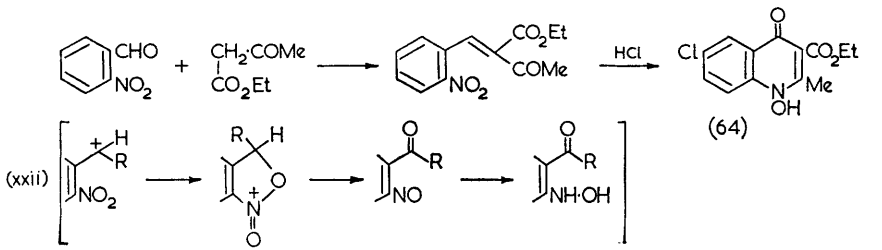


The following reactions all occur at low temperatures (0—20°) and in acetic acid or ether as solvent. Therein phenol and *o*-nitrobenzaldehyde are converted by sulphuric acid into the triarylmethane (59; R = R = OH),[69] by hydrogen chloride into 5-chloro-3-*p*-hydroxyphenylanthranil

[75] E. Bamberger, *Ber.*, 1909, **42**, 1716.
[76] F. R. Bradbury and W. H. Linnell, *J.*, 1942, 377.
[77] I. Tanasescu and A. Silberg, *Bull. Soc. chim. France*, 1932, **51**, 1357; cf. I. Tanasescu and M. Suciu, *ibid.*, 1937, **4**, 245.
[78] S. Seczreanu and A. Silberg, *Bull. Soc. chim. France*, 1936, **3**, 1777.
[79] T. Zincke and W. Prenntzell, *Ber.*, 1905, **38**, 4116.

(61),[80] and by hydrogen bromide into a mixture of 3-*p*-hydroxyphenylanthranil and its 5-bromo-derivatives.[73] A more complete contrast in the behaviour of the two hydrogen halides as condensing agents is found[73] in the reactions of phenol with 4-bromo- or 4-chloro-2-nitrobenzaldehyde: these reagents with hydrogen chloride yield 5,7-dihalogentated anthranils, *e.g.* (62), through entry of chlorine, whereas with hydrogen bromide they react forming 5-halogenated anthranils without entry of bromine. It is noteworthy also that when the aromatic component is a reducing phenol, namely quinol, even hydrogen chloride effects the reaction without entry of chlorine, the product from *o*-nitrobenzaldehyde being 3-(2,5-dihydroxyphenyl)anthranil.[73] Of three pre-formed carbinols, (63; R = Me) is not appreciably affected by hydrogen chloride under the reaction conditions, (63; R = Ph) reacts slowly and incompletely giving 5-chloro-3-phenylanthranil, whereas (63; R = *p*-C_6H_4·OH) readily yields the anthranil (61).[81] (See also footnote, p. 393.)

Hydrogen chloride reacts with *o*-nitrobenzaldehyde and ethyl acetoacetate to form the 6-chloro-1-hydroxy-4-quinolone (64).[82] Analogous products are formed when the last reagent is replaced by acetylacetone, benzoylacetone, or diethyl acetonedicarboxylate, and 6,8-dichloro-1-hydroxyquinolones result from the use of 5-chloro-2-nitrobenzaldehyde.[73] Nitrobenzylidene derivatives of the methylene reagents behave as intermediates, but those derived from acetone, deoxybenzoin, and notably ethyl benzoylacetate fail to cyclise. Hydrogen bromide again provides a contrast by effecting the reaction without inserting a halogen substituent; and again through the presence of quinol, ethyl *o*-nitrobenzylideneacetoacetate may be cyclised even by hydrogen chloride to the halogen-free 1-hydroxyquinolone (64; H for Cl).[73]



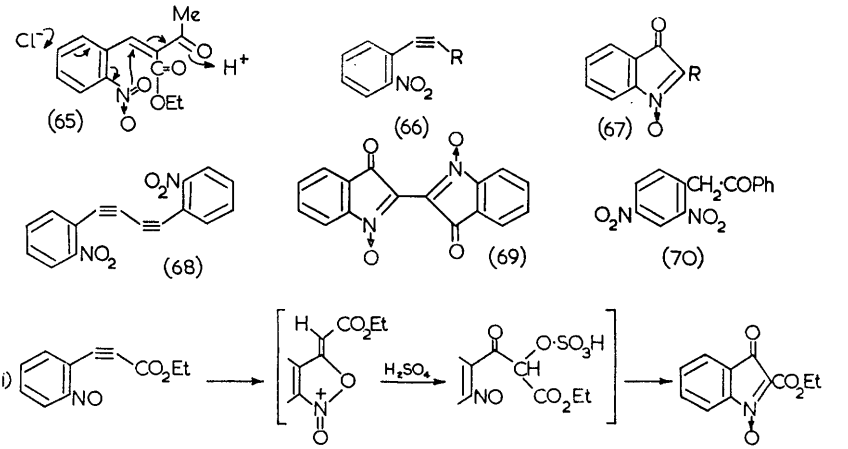
The 3-*p*-hydroxyphenylanthranils and 1-hydroxy-4-quinolones may both be regarded as cyclodehydration products of appropriate *o*-hydroxylaminophenyl ketones. Their formation seems to require at an early stage a carbonium type of intermediate [cf. sequence (xxii)], whereby an oxygen atom of the nitro-group can be linked to the benzylic carbon atom. Then,

[80] T. Zincke and K. Siebert, *Ber.*, 1906, **39**, 1930.
[81] J. P. Cairns, unpublished work.
[82] J. D. Loudon and I. Wellings, *J.*, 1960, 3470.

or after transformation to a nitrosophenyl ketone, reduction to the hydroxylamino-level must occur. The evidence suggests that hydrogen bromide or quinol can effect this reduction whereas hydrogen chloride cannot readily do so but supplies the necessary electrons through entry of chloride ion into the nucleus. For this stepwise process a part-analogy is available in the conversion[83] of nitrosobenzene into *p*-chlorophenylhydroxylamine by hydrogen chloride, but a more concerted mechanism, *e.g.*, (65) is not excluded.

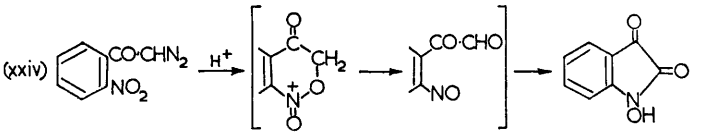
By the action of concentrated sulphuric acid the acetylenes (66; R = CO_2Et) and (68) are converted respectively into the isotogens (67; R = CO_2Et) and (69), and although *o*-nitrophenylpropiolic acid (66; R = CO_2H) thereby yields isatin the unstable isatogenic acid (67; R = CO_2H) is the probable intermediate.[84] Under similar conditions *p*-nitrophenylpropiolic acid yields *p*-nitrobenzoylacetic acid[85] and, governed by the powerful orienting influence of two nitro-groups, 2,4-dinitrotolane [as (66; R = Ph)] affords the deoxybenzoin (70).[86] However, hydration of the acetylene (66; R = CO_2Et) does not appear to be a significant step in forming the isatogenic ester since the hydration product, ethyl *o*-nitrobenzoylacetate, is hydrolysed rather than cyclised by concentrated sulphuric acid.[87] Presumably therefore cyclisation involves some direct interaction between the nitro-group and the acetylenic side-chain [cf. sequence (xxiii)].

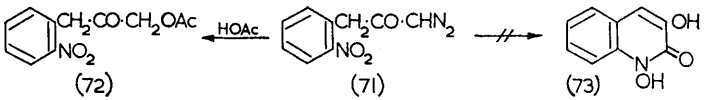
Interaction as shown in sequence (xxiv) is the mechanism proposed[88]

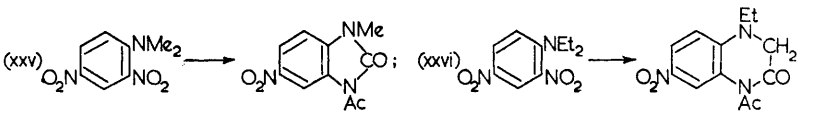


[88] E. Bamberger, H. Busdorf, and B. Szolayski, *Ber.*, 1899, **32**, 210.
[84] A. Baeyer, *Ber.*, 1881, **14**, 1741; 1882, **15**, 50.
[85] C. Engler and O. Zielke, *Ber.*, 1889, **22**, 203.
[86] P. Pfeiffer, *Annalen*, 1916, **411**, 72.
[87] E. R. Needham and W. H. Perkin, *J.*, 1904, **85**, 148.
[88] J. A. Moore and D. H. Ahlström, *J. Org. Chem.*, 1961, **26**, 5254; but cf. E. C. Taylor and D. R. Eckroth, *Tetrahedron*, 1964, **20**, 2057.

for the conversion[89] of *o*-nitrobenzoyldiazomethane into 1-hydroxyisatin by mixed formic and acetic acids. Thus the homologous diazoketone (71) is found to yield the normal ester (72) instead of the analogous 1,3-dihydroxycarbostyryl (73), and the difference is plausibly explained by the greater difficulty of forming a 7-membered in place of a 6-membered cyclic intermediate: it would be less easily explained if the initial step in the mechanism were direct nucleophilic attack on the nitro-group by the ω-carbon atom of the side-chain.







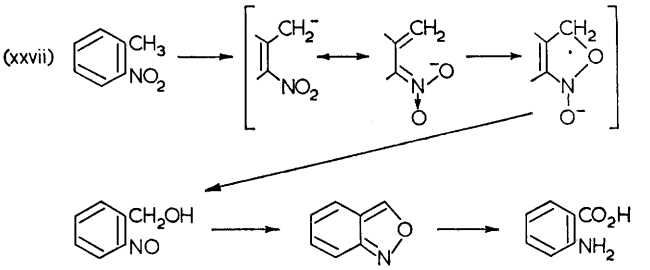
Among derivatives of *o*-nitroaniline a remarkable type of interaction[90] is represented by the reactions (xxv) and (xxvi) which are effected by zinc chloride in hot acetic anhydride. Acid-catalysed cyclisation of 2-nitrohydrazobenzenes has already been mentioned (p. 399; ref. 42) and operates in the formation[91] of benzotriazole derivatives from 4-alkyloxybutan-2-ones and 2,4-dinitrophenylhydrazine in presence of hydrochloric acid.

Uncyclised Products

When heated with aqueous alkali, *o*-nitrotoluene yields anthranilic acid (and *o*-toluidine),[92] 2,4-dinitrotoluene yields 4-nitroanthranilic acid,[93] and 2-nitrotoluene-4-sulphonic acid, aided by its solubility, smoothly yields 4-sulphoanthranilic acid.[92] However all nuclear substituted *o*-

[89] F. Arndt, B. Eistert, and W. Partale, *Ber.*, 1927, **60**, 1364.
[90] P. van Romburgh and H. W. Huyser, *Rec. Trav. chim.*, 1930, **49**, 165; cf. "Heterocyclic Compounds," ed. R. C. Elderfield, Wiley and Sons Inc., New York, 1957, Vol. 6, p. 493.
[91] H. J. Shine, L. Fang, H. E. Mallory, N. F. Chamberlain, and F. Stehling, *J. Org. Chem.*, 1963, **28**, 2326.
[92] Kalle and Co., *Chem. Zentr.*, 1908, **1**, 1345; L. Preuss and A. Binz, *Z. angew, Chem.*, 1900, **13**, 385.
[93] K. G. Rosdahl, *Chem. Abs.*, 1950, **44**, 9480.

nitrotoluenes do not behave in this way for some, *e.g.*, the 5-6- and 7,6-methylnitroquinolines[94] more closely resemble the *p*-nitrotoluenes which commonly undergo reduction to azoxy-compounds or oxidative coupling to dinitrodiaryl-ethanes or -stilbenes.[95]



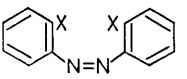
Although claims[92] to have isolated anthranil and its precursor, *o*-nitrosobenzyl alcohol, from the reaction with *o*-nitrotoluene have been questioned[96] and other courses proposed,[97] experiments using ^{18}O labels indicate[98] that only one of anthranilic acid's two oxygen atoms comes from the reaction medium. The assumption that the second oxygen atom is internally transferred from the nitro-group then allows a mechanism, proposed by Scholl,[96] to be elaborated as in (xxvii).

Although fairly stable, *o*-nitrobenzyl alcohol is variously converted[99] by alkali into products which include anthranil, *o*-aminobenzaldehyde, anthranilic acid, the azo-compounds (74; X = Y = CO_2H) and (74; X = CHO,Y = CO_2H) and the presumably derived indazoles of type (75). Some of these products are also obtained from *o*-nitrobenzaldehyde which can furnish *o*-nitrobenzyl alcohol as part-product of a normal Cannizzaro reaction with aqueous alkali.[100] As mentioned later (p. 412) *o*-nitrophenylmethanethiol reacts in aqueous alkali to form thioanthranil.

It is possible that some of these changes begin with a step similar in its effect to the light-catalysed transformation of *o*-nitrobenzyl alcohol into *o*-nitrosobenzaldehyde,[101] but this has never been demonstrated as a purely chemical process. On the other hand the comparable conversion of *o*-nitrobenzaldehyde into *o*-nitrosobenzoic acid is known both as a photochemical[102] and chemical[103] reaction. The latter is best effected by the joint action of ammonium cyanide and hydroxide on the aldehyde in aqueous

[94] R. Huisgen, *Annalen*, 1948, **559**, 101.
[95] O. Fischer and E. Hepp, *Ber.*, 1893, **26**, 2231.
[96] R. Scholl, *Monatsh.*, 1913, **34**, 1011.
[97] G. Lock, *Ber.*, 1940, **73**, 1377; G. A. Russell and E. G. Janzen, *J. Amer. Chem. Soc.*, 1962, **84**, 4153.
[98] I. I. Kukhtenko, *Chem. Abs.*, 1960, **54**, 24619.
[99] G. Lock, *Ber.*, 1930, **63**, 855; P. Carré, *Compt. Rend.*, 1905, **140**, 663.
[100] T. A. Geissman, *Org. Reactions*, 1944, **11**, 112.
[101] E. Bamberger, *Ber.*, 1918, **51**, 606.
[102] G. Ciamician and P. Silber, *Ber.*, 1901, **34**, 2040.
[103] G. Heller, *J. prakt. Chem.*, 1923, **106**, 1.

ethanol. *o*-Nitromandelonitrile is a potential intermediate and yields *o*-nitrosobenzoic acid by reaction with ammonium hydroxide:[104] moreover by irradiation in liquid hydrogen cyanide it yields the same acid and not the conceivable alternative, *o*-nitrosobenzoyl cyanide.[105] It is claimed[103] that 2,4-dinitrobenzaldehyde reacts with ammonium cyanide to form 4-nitro-2-nitrosobenzoic acid, but with potassium cyanide in acetic acid yields the isomeric 2-nitro-4-nitrosobenzoic acid. *o*-Nitromandelic acids are also susceptible to oxidation–reduction: for instance the acid (76) forms the appropriate azobenzoic acid, as (74; X = Y = CO_2H) when heated in nitrobenzene, and yields a mixture of this product with the corresponding azoxybenzaldehyde when warmed in aqueous alkali.[106]



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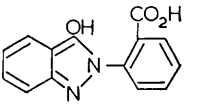

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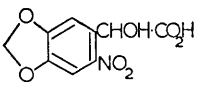


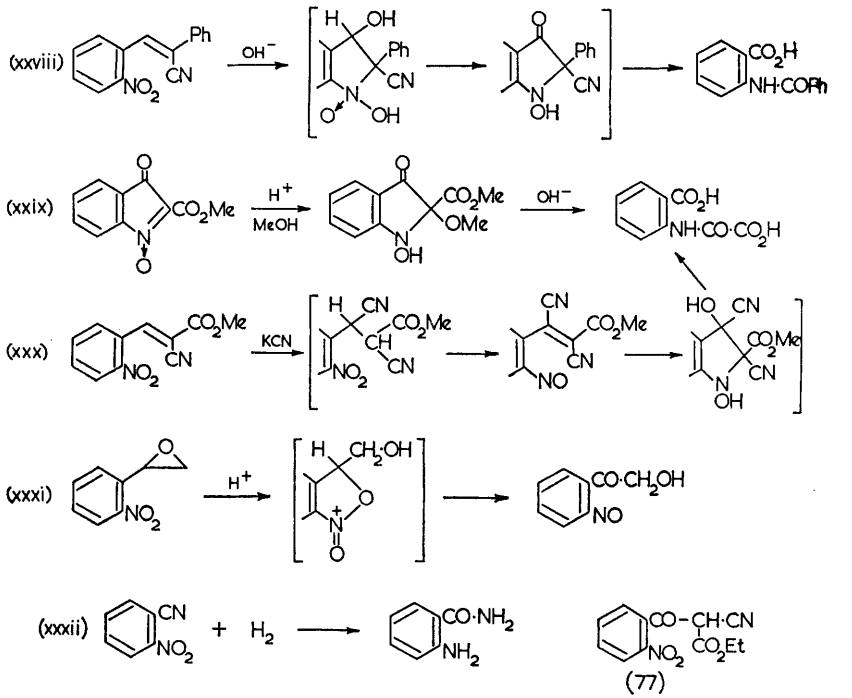
(76)

α-Phenyl-*o*-nitrocinnamonitrile reacts exothermally with potassium hydroxide in warm aqueous ethanol forming *N*-benzoylanthranilic acid.[107] A plausible course (xxviii)[29] involving formation and hydrolytic scission of an indolinone derivative has some analogy in the hydrolysis[108] of the adduct which is obtainable from methyl isatogenate and methanol [cf. (xxix)]. However, methyl α-cyano-*o*-nitrocinnamate is merely hydrolysed to the corresponding cyano-acid by potassium hydroxide: here for a comparable redox reaction cyanide ion appears to be necessary[109] and leads to the formation of *N*-oxalylanthranilic acid [cf. (xxx)].

Reactions which occur under acidic conditions include the formation of 3,5-dibromoanthranilic acid by the action of bromine on *o*-nitrotoluene,[110] and that of *N*-*o*-nitrobenzoylanthranilic acid by heating *o*-nitrobenzaldehyde with polyphosphoric acid in the presence of anthracene (which furnishes some anthraquinone).[111] *o*-Nitrophenylethylene oxide yields the very sensitive *o*-nitrosobenzoylmethanol, reaction (xxxi), on careful treatment with acid, or the acetate of this methanol in reaction with acetic anhydride.[112]

An intriguing example of an *ortho*-interaction is provided by hydrogenation of *o*-nitrobenzonitrile over a platinum or palladium catalyst in methanol [reaction (xxxii)]. The product, isolated in high yield, is *o*-aminobenzamide which, however, cannot arise by reduction with incidental

[104] G. Heller, *Ber.*, 1906, **39**, 2334.
[105] F. Sachs and S. Hilpert, *Ber.*, 1904, **37**, 3425.
[106] G. M. Robinson, *J.*, 1917, **111**, 109.
[107] R. Pschorr and O. Wolfes, *Ber.*, 1899, **32**, 3399.
[108] G. Heller and W. Boessneck, *Ber.*, 1922, **55**, 474.
[109] J. D. Loudon and G. Tennant, unpublished work.
[110] P. Greiff, *Ber.*, 1880, **13**, 288; W. Gluud, *Ber*, 1915, **48**, 432.
[111] M. Ionescu, H. Mantsch, and I. Goia, *Chem. Ber.*, 1960, **93**, 2063.
[112] F. Arndt, B. Eistert, and W. Partale, *Ber.*, 1928, **61**, 1107.



hydrolysis since there is no incorporation of ^{18}O when the reaction is conducted in presence of [^{18}O] water.[113] The oxygen of the amide function must therefore come from the nitro-group ultimately, but not necessarily directly. It may also be relevant that the same reaction (xxxii) can be effected by hydrazine in presence of Raney nickel,[114] and that hydrogenation of the ester (77) is said[115] to produce anthranilic acid.

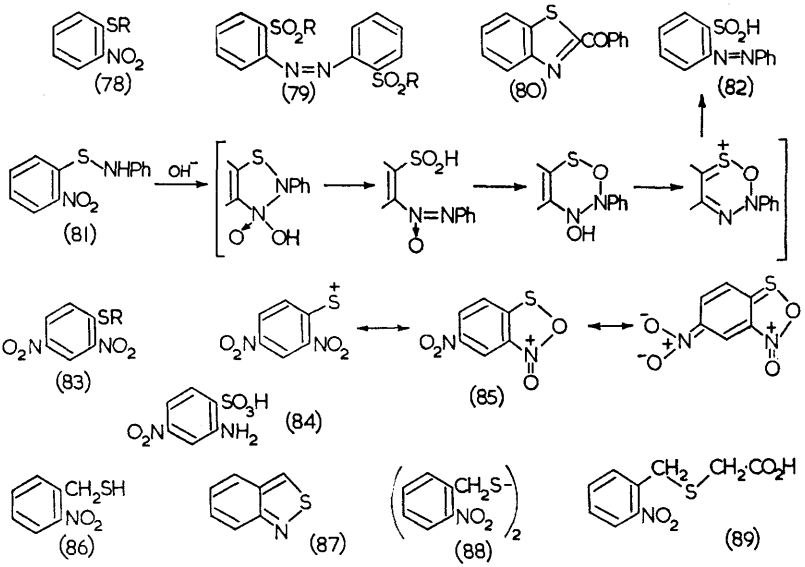
Sulphur-containing Compounds

Whilst examples of substituent interaction are fairly common among derivatives of *o*-nitroaniline, they are lacking among derivatives of *o*-nitrophenol, and scarce among those of *o*-nitrothiophenol. There are indeed a number of reactions which give rise to products wherein a thio-substituent has been oxidised and a nitro-group reduced, but the two changes are not always in balance and the reactions are usually complex.

o-Nitrothiophenol (78; R = H) when heated with sodium pentyloxide in pentyl alcohol affords the sodium salt of the sulphinic acid (79; R = R = H), but under the same conditions the thio-ether (78; R = Me) is

[113] H. Moll, H. Musso, and H. Schröder, *Angew. Chem., Internat. Edn.*, 1963, **2**, 212; C. W. Jefford, *Diss. Abs.*, 1963, 834.
[114] K. Butler and M. W. Partridge, *J.*, 1959, 2396.
[115] R. T. Coutts, M. Hooper, and D. G. Wibberley, *J.*, 1961, 5058.

simply reduced to the corresponding azo- or azoxy-compound without oxidation of the sulphur atom.[116] In alkaline media (*o*-nitrophenylthio)-acetic acid is relatively stable, whereas the acetophenone (78; R = CH_2.COPh) yields substantial amounts of 2-benzoylbenzothiazole (80),[117] but the reduction here involved could either precede or follow the cyclisation step and is probably effected by *o*-nitrothiophenol which is always formed in a competing reaction. The isomerisation of *o*-nitrobenzenesulphenanilide (81) to phenyl azobenzenesulphinic acid (82) is an example of a balanced oxidation–reduction and the suggested course of the reaction is outlined.[118] However in the 2,4-dinitrobenzenesulphenyl series (83; R = NHPh or OMe) the aminosulphonic acid (84) is one of the observed products and in a strongly acidic medium can be obtained in 70% yield from the methyl sulphenate (83; R = OMe).[119]



o-Nitrobenzenesulphenyl chloride (78; R = Cl) also reacts in hot aqueous methanol to form orthanilic acid (84; H for NO_2),[120] and in a vigorous reaction with hydrogen fluoride yields the azobenzenesulphonyl fluoride (79; R = R = F) among other products.[121] According to Kaluza and Perold[122] the reaction (83; R = Cl) → (84) in boiling acetic acid requires activation by light and proceeds through the hydroxylamine (84;

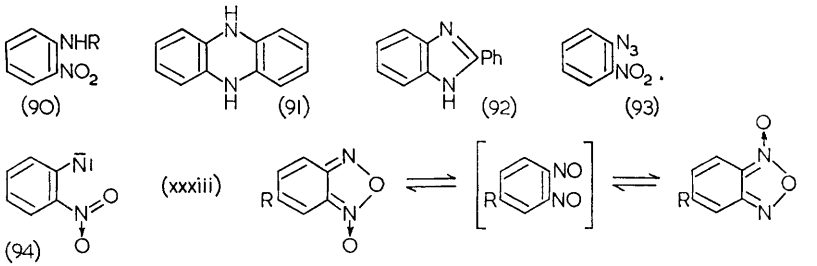
[116] C. Simons and L. G. Ratner, *J.*, 1944, 421.
[117] K. J. Morgan, *J.*, 1959, 3502.
[118] M. P. Cava and C. E. Blake, *J. Amer. Chem. Soc.*, 1956, **78**, 5444.
[119] N. Kharasch, W. King, and T. C. Bruice, *J. Amer. Chem. Soc.*, 1955, **77**, 931.
[120] T. Zincke and F. Farr, *Annalen*, 1912, **391**, 57.
[121] D. L. Chamberlain, D. Peters, and N. Kharasch, *J. Org. Chem.*, 1958, **23**, 381.
[122] F. Kaluza and G. W. Perold, *Chem. Abs.*, 1961, **55**, 11346.

NHOH for NH_2) which can be isolated as its *O*-acetyl derivative. Such compounds as the sulphenyl chloride (83; R = Cl, but not NHPh) dissolve in concentrated sulphuric acid to give bright red solutions containing the dinitrophenylsulphenium ion to which a resonance-stabilised structure (85) is ascribed.[123]

In interesting contrast with the slow reaction of *o*-nitrobenzyl alcohol (p. 408), *o*-nitrophenylmethanethiol (86) reacts vigorously with strong aqueous alkali forming thioanthranil (87) together with the disulphide (88).[124] The retention of sulphur in the heterocyclic product is noteworthy, but in the strongly reducing environment provided by the thiol the stage at which the sulphur–nitrogen bond is formed is again not clear. Thioanthranil is also formed in base-catalysed decomposition of the sulphide (89).[125]

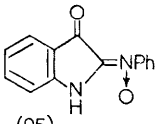
Reactions in Neutral Media

Some interactions occur under seemingly neutral conditions (pp. 402 and 403). For instance, when heated with sand at 220°, *o*-nitrodiphenylamine (90; R = Ph) yields phenazine (91) and *N*-benzyl-*o*-nitroaniline (90; R = CH_2Ph) yields 2-phenylbenziminazole (92).[126] Benzofuroxans, which are capable of the isomerisation shown in (xxxiii),[127] can be prepared by thermolysis of *o*-nitrophenyl azides, *e.g.* (93),[128] and intermediate formation of a nitrene (94)[129] is one of several possible pathways.[12] Alternatively benzofuroxans are formed through oxidation of *o*-nitroanilines by alkaline hypochlorite[130] or, in benzene but not in acetic acid, by phenyliodoso diacetate.[131]



Nitroso-compounds, already mentioned in this Review as products or as possible intermediates of various reactions, may also rank as initial

[123] N. Kharasch, C. M. Buess, and W. King, *J. Amer. Chem. Soc.*, 1953, **75**, 6035.
[124] S. Gabriel and R. Stelzner, *Ber.*, 1896, **29**, 160.
[125] Y. Iskander and Y. Riad, *J.*, 1951, 2054.
[126] R. H. Smith and H. Suschitzky, *Tetrahedron*, 1961, **16**, 80.
[127] Cf. F. B. Mallory and C. S. Wood, *J. Org. Chem.*, 1962, **27**, 4109.
[128] Cf. J. H. Boyer and F. C. Canter, *Chem. Rev.*, 1954, **54**, 35.
[129] Cf. R. A. Abramovitch and K. A. H. Adams, *Canad. J. Chem.*, 1961, **39**, 2516.
[130] A. G. Green and F. M. Rowe, *J.*, 1912, **101**, 2443; cf. F. M. Rowe and J. S. H. Davies, *J.*, 1920, **117**, 1344.
[131] L. K. Dyall and K. H. Pausacker, *Austral. J. Chem.*, 1958, **11**, 491.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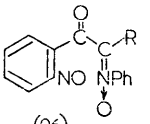
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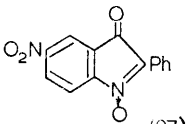
(97)

reagents. Thus, when reacting in ether, nitrosobenzene and *o*-nitrophenylacetylene provide a mixture of products from which the di-isatogen (69), azobenzene, and a compound formulated as (95) have been isolated.[132] The reaction occurs in absence of light and, when conducted in acetic acid, affords some 1-hydroxyisatin (9). Similarly from *o*-nitrophenylpropiolic acid the products identified are azoxybenzene, isatin, 1-hydroxyisatin, the nitrone (95), and (from the ethyl ester) ethyl isatogenate. The process despite its complexity is recommended[133] for preparing 2-phenylisatogen (8; R = Ph) from *o*-nitrotolane and here, as in allied reactions, nitrones of type (96) are the suggested intermediates from which, upon cyclisation, *o*-nitrosobenzene is regenerated. In connection with isatogen-formation it is of interest to note that the isatogen (97) is part-product of the reaction at 0° between dinitrogen tetroxide and tolane.[134]

[132] L. Alessandri, *Gazzetta*, 1927, **57**, 195; 1928, **58**, 551; (*Chem. Abs.*, 1929, **23**, 3690.)
[133] P. Ruggli, E. Caspar, and B. Hegedüs, *Helv. Chim. Acta*, 1937, **20**, 250.
[134] K. N. Campbell, J. Shavel, and B. K. Campbell, *J. Amer. Chem. Soc.*, 1953, **75**, 2400.