SYNTHETIC METHODS INVOLVING NEIGHBORING GROUP INTERACTION IN ORTHO-SUBSTITUTED NITROBENZENE DERIVATIVES

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Contents

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I. Introduction

The purpose of this review is to focus attention on the synthetic value of processes involving chemical interaction between aromatic nitro groups and ortho side chains. Certain aspects of such interactions have been reviewed previously. The textbooks by Ochiai[2a] and by Katritzky and Lagowski[3] contain brief surveys of the cyclization reactions of ortho-substituted nitrobenzenes which lead to heteroaromatic N-oxides. Photochemical processes were covered briefly by de Mayo and Reid[4] in 1961 and more extensively by Morrison[5] in 1969. Since a previous review[6] by one of us in 1964, a considerable number of papers (*ca.* 120) have been published in this field. We have attempted to accumulate much of this new material and, together with some of the material covered by the previous review,[6] to assess the synthetic value of the processes involved.

The types of reaction to be discussed include redox processes, cyclizations involving both intramolecular condensations of the aldol type for which the nitro group provides the electrophilic center, intramolecular nucleophilic displacements of nitro groups, and photochemical and thermal transformations. Such reactions lead often, but not always, to (benzaza) heterocycles and in many cases afford otherwise inaccessible products (*e.g.*, heteroaromatic N-oxides of unequivocal structure and nitroso arenes). Reactions in which the nitro group is modified prior to interaction (*e.g.*, cyclizations involving reduction of the nitro group by an external reagent[7]) are excluded from the scope of the review. The Wohl–Aue phenazine synthesis[8a,9] and the anthranil synthesis described by Davis[10] also come into this category.

The subject material is broadly divided into (a) reactions which lead to cyclized (*i.e.*, heterocyclic) products (section II), (b) reactions in which the end products at least are not cyclic (section III), and (c) miscellaneous processes which do not fit into either of the categories a or b (section IV). Section II is subdivided according to the ring size and the number and type of heteroatom(s) present in the heterocyclic product. Section III accommodates a variety of reactions, some of which are

(2) E. Ochiai, Ed., "Aromatic Amine Oxides," Elsevier, New York, N. Y., 1967: (a) pp 59–62; (b) p 49.
(3) A. R. Katritzky and J. M. Lagowski, "Chemistry of Heterocyclic N-Oxides," Academic Press, New York, N. Y., 1971, pp 120–141.
(4) P. de Mayo and S. T. Reid, *Quart. Rev., Chem. Soc.*, **15**, 393 (1961).
(5) H. A. Morrison in "The Chemistry of Nitro and Nitroso Groups," Part I, H. Feuer, Ed., Interscience, New York, N. Y., 1969, pp 165–213.
(6) J. D. Loudon and G. Tennant, *Quart. Rev., Chem. Soc.*, **18**, 389 (1964).
(7) J. I. G. Cadogan, *ibid.*, **22**, 222 (1968); *Synthesis*, 11 (1969).
(8) G. A. Swan and D. G. I. Felton in "Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., New York, N. Y., 1957: (a) pp 7–10; (b) pp 3–4; (c) pp 44–45.
(9) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 377 (1951).
(10) R. B. Davis and L. C. Pizzini, *J. Org. Chem.*, **25**, 1884 (1960).

connected with reactions in section II. The synthetic value of a number of the reactions discussed is difficult to assess principally because product yields are either unreported or difficult to ascertain from the available data. No attempt has been made to provide exhaustive coverage of the wide areas of aromatic and heteroaromatic chemistry which come within the scope of the review. Rather, by demonstrating the synthetic value of neighboring-group interaction in ortho-substituted nitrobenzene derivatives, we hope to stimulate the use of such processes to syntheses where conventional procedures cannot be applied.

II. Formation of Cyclized Products

A. FIVE-MEMBERED HETEROCYCLES CONTAINING ONE HETEROATOM

1. Indoles

1-Hydroxyindoles (**2**) are synthesized in moderate to excellent yields by the base-catalyzed cyclization of a variety of *o*-nitrobenzyl derivatives (**1**) (Table I).[11-15] Reactions of this type

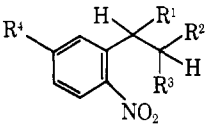
Table I

The Base-Catalyzed Formation of 1-Hydroxyindoles (2) from *o*-Nitrobenzyl Derivatives (1) and *o*-Nitrobenzylidene Derivatives (3)

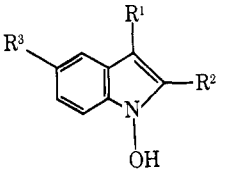
Starting material	*Reaction conditions*	*Product (2)*	*Yield, %*	*Ref*
1a	33% aq NaOH/reflux/0.5 hr	**a**	80	11
1b	3% aq KOH/room temp/15 min	**a** / **b**	*a* / 30	12
1c	Na_2CO_3–H_2O–EtOH/reflux/2 hr	**c**	*a*	13
1d	1% aq Na_2CO_3/warm/10 min	**d**	*a*	13
1d	1% aq Na_2CO_3/warm/10 min	**e**	*a*	13
1i	20% aq KOH–EtOH/reflux/1 hr	**i**	*a*	14
3a	*d*	**c**	*a*	13
3b	KCN–H_2O–DMF/100°/0.5 hr	**f**[b]	*a*	15
3c	KCN–H_2O–EtOH/reflux/1.75 hr	**g**	67	15
3d	KCN–EtOH–H_2O/reflux/2 hr	**g**	80[c]	15
3e	KCN–EtOH–H_2O/warm	**h**	23	14
3f	KCN–EtOH–H_2O/warm	**h**	60	14
3g	KCN–EtOH–H_2O/reflux/0.5 hr	**j**	97	15
1j	NaOEt–EtOH/room temp/15 hr	**k**	18	15
1j	Na_2CO_3–EtOH–H_2O/reflux/1.25 hr	**k**	42	15
1k	K_2CO_3–H_2O–EtOH/reflux/1.5 hr	**l**	*a*	15

[a] Yield not quoted. [b] Not obtained pure. [c] Based on starting material consumed. [d] No data quoted.

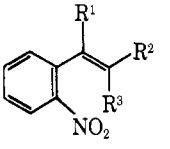
probably provide the best general route to 1-hydroxyindoles. Cyclization occurs readily where the benzyl side chain contains at least one moderately acidic center. Where two such centers are present, competing cyclization to quinoline *N*-oxides intervenes (*cf.* section II.D.1). Suitable substrates are available either by the base-catalyzed condensation of *o*-nitrobenzyl chloride with active methylene compounds (*e.g.*, **1a,b**)[11,12] or by the addition of hydrogen cyanide to suitable



	R^1	R^2	R^3	R^4
1a	H	CO_2Me	CO_2Me	H
b	H	COMe	CO_2Et	H
c	CN	CO_2Et	CO_2Et	H
d	$CONH_2$	CO_2Et	CO_2Et	H
e	CN	COPh	H	H
f	CN	COPh	Me	H
g	CN	COMe	Me	H
h	CN	CN	Ph	H
i	CN	Ph	H	MeO
j	CN	COPh	CH_2COPh	H
k	CN	*p*-$NO_2C_6H_4$	H	H



	R^1	R^2	R^3
2a	H	CO_2H	H
b	H	CO_2Et	H
c	CN	CO_2H	H
d	$CONH_2$	CO_2Et	H
e	$CONH_2$	CO_2H	H
f	CN	COPh	H
g	CN	Me	H
h	CN	Ph	H
i	CN	Ph	OMe
j	CN	$(CH_2)_4CO_2H$	H
k	CN	CH_2COPh	H
l	CN	*p*-$NO_2C_6H_4$	H



	R^1	R^2	R^3
3a,	H	CO_2Et	CO_2Et
b	H	H	COPh
c	H	Me	COPh
d	H	Me	COMe
e	H	CN	Ph
f	CN	H	Ph
g	H	$(CH_2)_3$—CO	

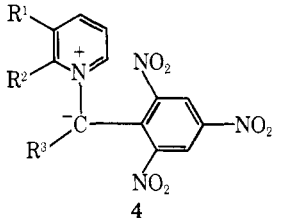
o-nitrobenzylidene derivatives[15a] (*e.g.*, **3a** → **1c**[13]). Alternatively, the 1-hydroxyindole can be prepared directly from the requisite *o*-nitrobenzylidene derivative by warming with aqueous ethanolic potassium cyanide, in reactions which presumably involve the intermediate formation and cyclization of the corresponding hydrogen cyanide adducts [*cf.* **3a–d** → **1c** and **1e–g** → **2c** and **2f,g**].[13-15] The common adduct **1h**

(11) A. Reissert, *Chem. Ber.*, **29**, 639 (1896).
(12) S. Gabriel, W. Gerhard, and R. Wolter, *ibid.*, **56**, 1024 (1923).
(13) J. D. Loudon and I. Wellings, *J. Chem. Soc.*, 3462 (1960).
(14) J. D. Loudon and G. Tennant, *ibid.*, 3466 (1960).
(15) I. P. Sword, *J. Chem. Soc. C*, 1916 (1970).

(15a) Stereochemistry about the double bond not determined.

must likewise be involved in the parallel conversions of the benzylidene compounds **3e** and **3f** into the 1-hydroxyindole (**2h**). This procedure suffers from the disadvantage that quinoline *N*-oxides are formed simultaneously (*cf.* section II.D.1),[13-15] though not when the benzylidene side chain bears an alkyl group.[15] Also, 1-hydroxyindole formation is favored by the use of weakly basic cyclizing agents. Conversely, the stronger the basic catalyst used, the greater is the tendency for cyclization to afford the quinoline *N*-oxide.[15] Enhanced reactivity at both methine centers in the *o*-nitrobenzyl precursor is not a prerequisite for successful cyclization as demonstrated by the conversion of the nitriles **1i** and **1k** into the 1-hydroxyindoles **2i** and **2l** on warming with aqueous ethanolic potassium hydroxide (Table I).[14,15] The use of *o*-nitrobenzylidenecycloalkanones provides a synthetic route to fatty acid derivatives of 1-hydroxyindoles (*cf.* **3g** → **2j**).[15] The compound **1j** could in theory undergo base-catalyzed cyclization to a five- or six-membered ring. In practice,[15] only the 1-hydroxyindole **2k** is obtained, demonstrating a preference for the former mode of cyclization.

The base-catalyzed cyclization of *N*-picrylmethylcyclimmonium enol betaines affords benzo[*a*]indolizines (*e.g.*, **5**) in moderate to high yield,[16,17] These interesting reactions involve the novel intramolecular nucleophilic displacement of aromatic nitro groups by nucleophilic carbon in the enol betaine intermediate (*cf.* **4**) and are closely related to similar processes leading to condensed isoquinoline derivatives (*cf.* section II.D.2). The following reactions are typical of such cyclizations.[16,17]



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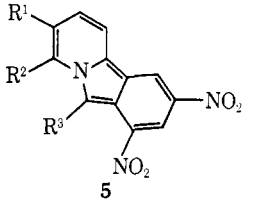
piperidine–DMSO, 24°, 3 hr



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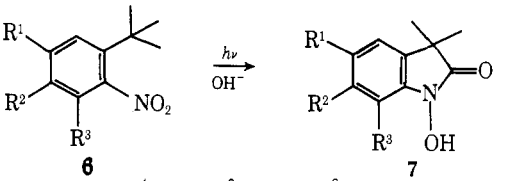
R^1	R^2	R^3	Yield, %
H	H	COPh	96
H	Me	COPh	61
Me	H	COPh	93–96
H	H	CN	39–42

2. Oxindoles

1-Hydroxyoxindoles (**7**) are the major products of the photochemical transformations of *o*-nitro-*tert*-butylbenzenes (**6**) in aqueous alkaline media.[18-20] Smaller amounts of oxindoles **8** and azobenzene derivatives (*cf.* section III.B) are also formed

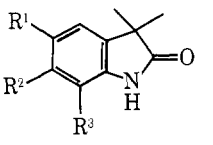


6 → **7**

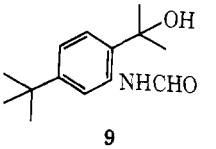
	R^1	R^2	R^3
a	H	H	H
b	H	*t*-Bu	H
c	H	Br	H
d	H	NO_2	H
e	H	NHAc	H
f	*t*-Bu	H	*t*-Bu

in these intriguing reactions together with a variety of other minor by-products.[18-20]

In general the efficiency of these photochemical reactions is low (overall conversion *ca.* 12–16%), but the yields of 1-hydroxyoxindoles (**7**) (based on consumed nitro compound **6**) are moderate to high (Table II). Irradiation is carried out



	R^1	R^2	R^3
8a	H	*t*-Bu	H
b	*t*-Bu	H	*t*-Bu



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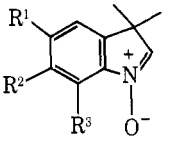
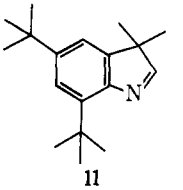


	R^1	R^2	R^3
10a	H	*t*-Bu	H
b	*t*-Bu	H	*t*-Bu



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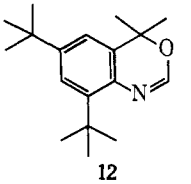

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either in alkaline solution or in the solid state followed by work-up with aqueous alkali in the presence of oxygen.[18,19] Yields are lower when the photolysis is carried out in diethylamine.[20] The reaction fails when the nitro compound **6** contains electron-donating groups such as amino (*cf.* **6e**, NH_2 for NHAc).[19] No reaction occurs in the dark and the yields fall drastically in the absence of base.[19] It appears therefore that these reactions involve both a photochemical process and a base-catalyzed "dark reaction." Recent studies[21,22] bear this out: irradiation of 2,5-di-*tert*-butylnitrobenzene (**6b**) or of 2,4,6-tri-*tert*-butylnitrobenzene (**6f**) in neutral solution gives separable mixtures of the oxindole derivatives **7b,f** and **8a,b**, and the nitrones **10a,b** which are the major products

(16) W. Augstein and F. Kröhnke, *Justus Liebigs Ann. Chem.*, **697**, 158 (1966).
(17) F. Kröhnke and D. B. Reuschling, *Chem. Ber.*, **104**, 2103 (1971).
(18) D. Döpp, *ibid.*, **104**, 1035 (1971).
(19) D. Döpp, *ibid.*, **104**, 1043 (1971).
(20) D. Döpp, *ibid.*, **104**, 1058 (1971).
(21) D. Döpp, *Tetrahedron Lett.*, 2757 (1971).
(22) D. Döpp and K. H. Sailer, *ibid.*, 2761 (1971).

Table II

Photochemical Conversion of *o-tert*-Butylnitrobenzenes (6) into Oxindoles 7 and 8 and Related Products.

Starting material (6)	*Reaction conditions*	*Product*	*Yield,*[a] *%*	*Ref*
a	*hν*/NaOH–H_2O–MeOH/5 hr	**7a**	66	18
b	(1) *hν*/NaOH–H_2O–MeOH–dioxane/5 hr; (2) O_2/1 hr	**7b**	52	18
b	*hν*/1% NaOH–MeOH/4 hr	**7b**	60	18
b	(1) *hν*/dioxane/MeOH; (2) 8% NaOH/O_2/2 hr	**7b**	62	19
b	(1) *hν*/solid/8 hr; (2) 8% NaOH/O_2/2 hr	**7b**	48	19
b	*hν*/Et_2NH/1.5 hr	**7b**	3	20
c	*hν*/NaOMe–MeOH/4.5 hr	**7c**	29	19
d	*hν*/1% NaOH–*t*-BuOH–MeOH/3 hr	**7d**	28	19
e	*hν*/1% NaOH–MeOH/4 hr	**7e**	30	19
b	*hν*/solid	**10a**	42	21
		7b	10	
		8a	5	
		9	3	
b	(1) *hν*/solid; (2) NaOH–H_2O–MeOH/O_2	**7b**	48	21
		8a	13	
f	*hν*/solid	**10b**	18	22
		7f	25	
		8b	4	
		11	3	
		12	2	
f	(1) *hν*/solid; (2) NaOH–H_2O–MeOH/O_2	**7f**	41	22
		8b	4	
f	*hν*/cyclohexane/room temp/1 hr	**8b**	20	23
f	*hν*/benzene/room temp/67 hr	**8b**	36	23

[a] With the exception of the reactions described in ref 23, yields are based on starting material consumed.

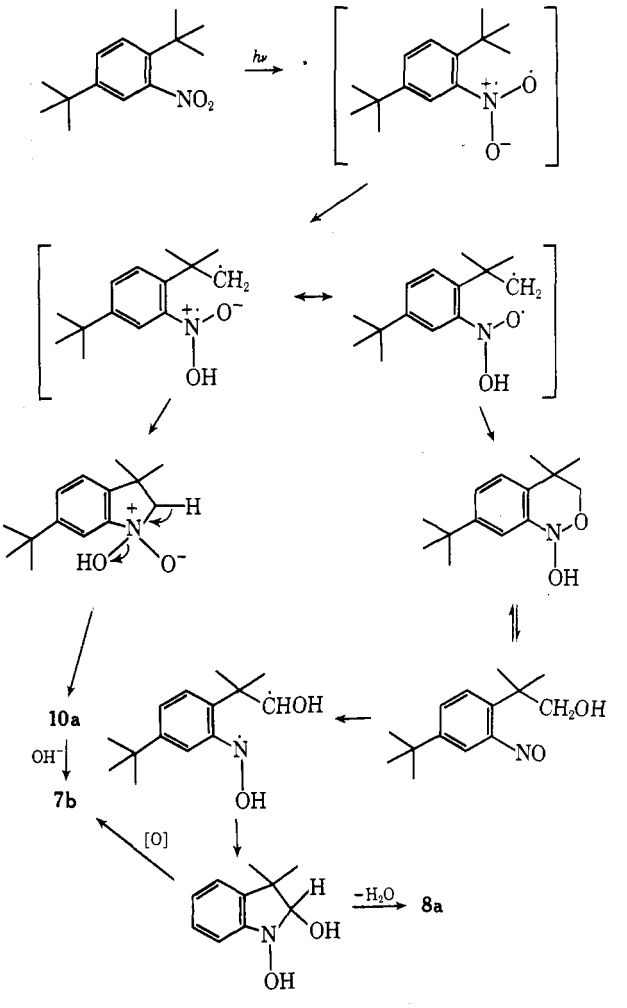
(Table II). In the case of compound **6b**, some of the formylamino derivative **9** was also isolated, while small amounts of the by-products **11** and **12** were found in the photolysate from the nitro compound **6f**. On the other hand, working-up the photolysates from these reactions with alkali in the presence of oxygen gives the 1-hydroxyoxindoles **7b,f** as the main products together with smaller amounts of the oxindoles **8a,b** (Table II).[21,22]

These results indicate that the nitrones **10** are the primary photoproducts and are converted into the oxindoles **7** and **8** in alkaline solution in the presence of oxygen. This is further supported by the conversion of the nitrone **10a** in alkaline solution in high yield into the oxindole **7b** (Scheme I).[21] Irradiation of 2,4,6-tri-*tert*-butylnitrobenzene **6f** in neutral solution is reported[23] to afford the oxindole **8b** in moderate yield (Table II). The interesting feature of all of these photocyclizations is the apparent interaction between the nitro group and a relatively inert hydrocarbon side chain. Mechanisms[19,23] involving intramolecular hydrogen abstraction by the *o*-nitro group have been proposed. However, further experimental support for these proposals would be desirable.

2-(2′-Nitrophenyl)ethanol is converted in moderate yield photochemically into 1-hydroxyoxindole possibly by the intermediate formation and cyclization of *o*-hydroxylaminophenylacetic acid.[24]

(23) L. R. Barclay and I. T. McMaster, *Can. J. Chem.*, **49**, 676 (1971).
(24) J. Bakke, *Acta Chem. Scand.*, **24**, 2650 (1970).

Scheme I



3. *Indoxyls*

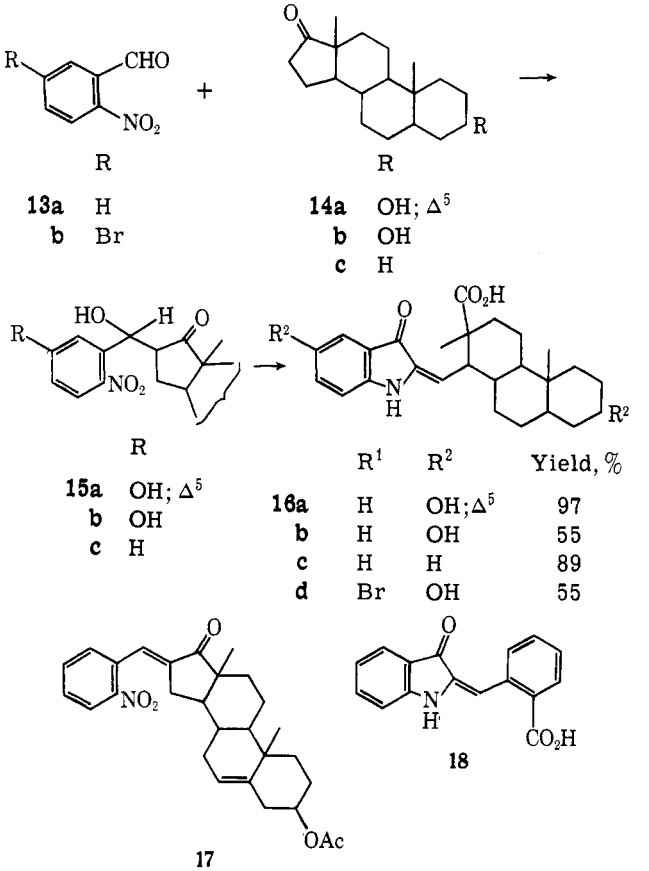
Indigo is the end product of a number of base-catalyzed reactions of *o*-nitrobenzene derivatives,[25-28] the available data indicating that yields are moderate to excellent. Indigo formation in alkaline acetone solutions (the Baeyer–Drewsen reaction) has been widely used as a test for *o*-nitrobenzaldehydes, though it fails if a *m*- or *p*-hydroxyl group is present.[29] However, the inhibiting effect of a hydroxyl group is overcome if a second nitro group is present as evidenced[29] by indigo formation from 2,6-dinitroisovanillin.

Reactions of the Baeyer–Drewsen type have also been observed with steroidal ketones though in these cases the products are indoxyl derivatives.[30] The androstan-17-ones **14a–c** undergo base-catalyzed condensation with *o*-nitrobenzaldehyde (**13a**) and 5-bromo-2-nitrobenzaldehyde (**13b**) to afford the indoxyls **16a–d** in good yield.[30] The intermediate aldols

(25) A. Baeyer, *Chem. Ber.*, **13**, 2254 (1880).
(26) A. Baeyer and V. Drewsen, *ibid.*, **15**, 2856 (1882); **16**, 2205 (1883).
(27) I. Tanasescu and A. Georgescu, *J. Prakt. Chem.*, **139**, 189 (1934).
(28) I. Tanasescu and E. Tanasescu, *Bull. Soc. Chim. Fr.*, **3**, 865 (1936).
(29) L. E. Hinkel, E. E. Ayling, and W. H. Morgan, *J. Chem. Soc.*, 985 (1932).
(30) A. Hassner and M. J. Haddadin, *Tetrahedron Lett.*, 975 (1962); A. Hassner, M. J. Haddadin, and P. Catsoulacos, *J. Org. Chem.*, **31**, 1363 (1966).

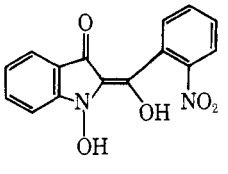
15a–c are similarly cyclized to the same products, whereas the benzylidene compound **17** failed to undergo cyclization.[30]

Similarly, the base-catalyzed condensation of *o*-nitrobenzaldehyde with indan-1-one is reported[31] to afford the indoxyl **18** (*cf.* also section II.D.1).

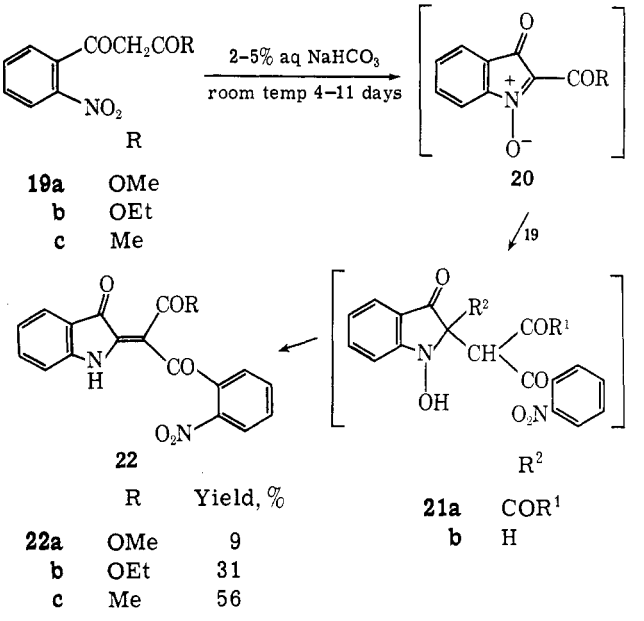


Indoxyl derivatives **22** are also obtained together with isatogens (*cf.* section II.A.5) when certain *o*-nitrobenzyl derivatives (**19a–c**) are stirred at room temperature for several days with aqueous sodium hydrogen carbonate.[32] These reactions are rationalized by initial base-catalyzed cyclization to isatogen derivatives **20** which then undergo nucleophilic addition by unreacted nitro compound **19**. Deacylation of the resulting adducts (**21a** → **21b**) followed by dehydration then affords the indoxyls **22**.[32]

It is of interest that the reaction of *o*-nitrobenzaldehyde with diazomethane affords[33] among other products the 1-hydroxyindoxyl

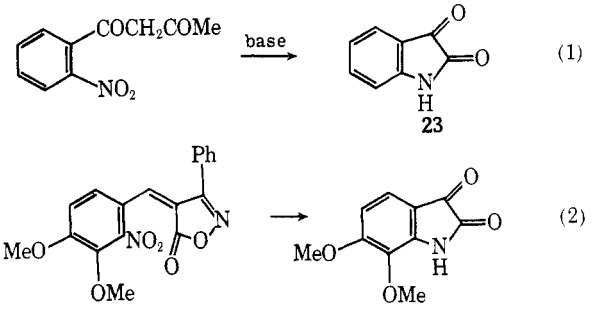


In general terms, however, the above syntheses of indoxyl derivatives are more interesting from a mechanistic rather than a synthetic viewpoint.



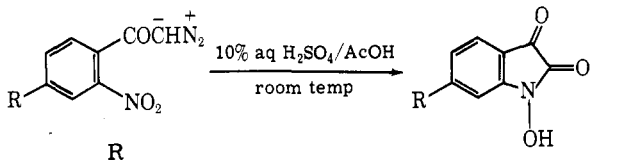
4. *Isatins*

Isatin (**23**) and its derivatives are formed in variable yield by the base- or acid-catalyzed transformations of a variety of *o*-nitrobenzene derivatives;[25,34–38] processes of this type are exemplified by reactions 1[35] and 2.[37,38] The detailed courses of none of these reactions have been elucidated though in reaction 1 a plausible intermediate is 2-acetylisatogen, subsequent hydration and deacylation of which in the alkaline medium would afford isatin (**23**).[6]



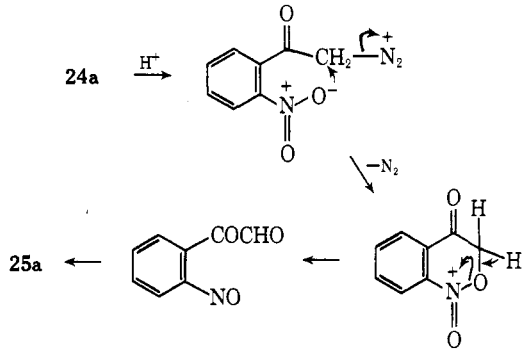
1-Hydroxyisatins (**25**) are formed in high yield by the acid-catalyzed cyclization of *o*-nitrobenzoyldiazomethane and its derivatives **24a–c**.[39,40] The mechanism of these cyclizations is controversial.[41,42] Moore and Ahlstrom[41] have proposed the course shown in Scheme II. An alternative course[42] involving a Wolf rearrangement has been excluded by labeling experiments.

(31) A. Hassner and D. R. Fitchmun, *Tetrahedron Lett.*, 1991 (1966).
(32) R. T. Coutts, M. Hooper, and D. G. Wibberley, *J. Chem. Soc.*, 5205 (1961); M. Hooper and D. G. Wibberley, *J. Chem. Soc. C*, 1596 (1966).
(33) L. Capuano, *Chem. Ber.*, **98**, 3187 (1965).
(34) A. Baeyer, *ibid.*, **14**, 1741 (1881).
(35) J. D. Loudon and G. Tennant, *J. Chem. Soc.*, 4268 (1963).
(36) A. Reissert, *Chem. Ber.*, **30**, 1030 (1897).
(37) J. M. Gulland, R. Robinson, J. Scott, and S. Thornley, *J. Chem. Soc.*, 2924 (1929).
(38) H. Burton and J. L. Stoves, *ibid.*, 402 (1937).
(39) F. Arndt, B. Eistert, and W. Partale, *Chem. Ber.*, **60**, 1364 (1927).
(40) E. Giovannini and P. Portmann, *Helv. Chim. Acta*, **31**, 1381 (1948).
(41) J. A. Moore and D. H. Ahlstrom, *J. Org. Chem.*, **26**, 5254 (1961).
(42) E. C. Taylor and D. R. Eckroth, *Tetrahedron*, **20**, 2059 (1964).



R		R	Yield, %
24a	H	**25a**	H 82
b	NHAc	**b**	NHAc 60–70
c	MeO	**c**	MeO 56

Scheme II



Since isatins, and their 1-hydroxy derivatives, are relatively inaccessible, further studies of the scope and mechanism of these cyclizations are warranted.

5. 3H-Indol-3-one 1-N-Oxides (Isatogens)

o-Nitrophenylacetylene derivatives **26** and **33** are cyclized under acidic, basic, or neutral conditions, or photochemically to afford isatogens **34, 35,** and **36** in moderate to high yield (Table III).[43–50] Cyclization is variously effected by stirring in concentrated sulfuric acid at room temperature,[43,44] by irradiating[45–49] or heating[46,47] in pyridine, or by treatment with nitrosobenzene in an inert solvent such as chloroform.[47–50] The latter method is recommended[48] for the preparation of 2-phenylisatogen (**35c**) and also succeeds[49] for 2-(2-pyridyl)-isatogen (**35f**) where the sulfuric acid method fails. However, in other cases[51] reaction of *o*-nitrophenylacetylenes with nitrosobenzene leads to complex mixtures. The preparation of diisatogen (**34**) by the photochemical method from the dinitrophenyldiacetylene (**33**) is reported[50] to give a better yield than the corresponding sulfuric acid method.[44] The photochemical formation of diisatogen (**34**) from the diacetylene **33** in pyridine is unsuccessful.[50] 2-Arylisatogens have recently been prepared by heating copper *o*-nitrophenylacetylides (*e.g.*, **29**) with iodoarenes (*e.g.*, **30**) in pyridine (Table III).[47] These reactions probably involve the intermediate formation and cyclization of *o*-nitrotolans (*cf.* ref 46). 2-Arylisatogens are also obtained in good yield by irradiating 2-nitrostilbene dichlorides (**27**) or *o*-nitromonochlorostilbenes (**28**) in pyridine[46,48,52–54] (Table III).

Table III

Formation of Isatogens 34–36 from *o*-Nitrophenylacetylene Derivatives 26 and 29, *o*-Nitrostilbene Dichlorides (27), and *o*-Nitromonochlorostilbenes (28)

Starting material	*Reaction conditions*	*Product*	*Yield, %*	*Ref*
26a	Concd H_2SO_4/room temp/few min	**35a**	*a*	43
26a	Concd H_2SO_4/room temp/10–15 min	**35a**	44	46
26b	Pyridine/100°/3 min	**35b**	50	46
26c	$h\nu^b$/pyridine/31 hr	**35c**	8	48
26c	PhNO–$CHCl_3$/room temp/19 days	**35c**	75	48
26d	Pyridine/heat/few min	**36a**	*a*	46
26e	Pyridine/reflux/48 hr	**35d**	75	47
26f	[c]	**36b**	*a*	46
26g	$h\nu^b$/pyridine/21 days	**35f**	30	49
26g	PhNO–$CHCl_3$/room temp/7 days	**35f**	90–95	49
26h	PhNO–$CHCl_3$/reflux/72 hr	**35g**	70	47
33	Concd H_2SO_4/room temp	**34**	*a*	44
33	Sunlight–chloroform/room temp/4 days	**34**	70	50
29 + 30	Pyridine/reflux/8 hr	**35e**	37	47
27a	Sunlight–pyridine/room temp/15 months	**35c**	61	52
27a	$h\nu^b$–pyridine/room temp/31 hr	**35c**	40	48
27b	Sunlight–pyridine/room temp/several weeks	**36d**	*a*	46
28	Sunlight–pyridine–H_2O/ room temp/0.5 hr	**36c**	78	46

[a] Yield not quoted. [b] Mercury vapor lamp. [c] Data not available.

The application[53,54] of this type of photocyclization to the synthesis of bisisatogens is illustrated by reaction 3;[53] it is interesting that none of the expected bisisatogen **37** was obtained.[54] 2-Arylisatogens are also formed together with other products when *o*-nitrostilbenes are irradiated in sunlight.[55]

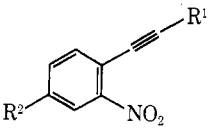
Isatogen syntheses which may be[6,56] mechanistically related to the *o*-nitrophenylacetylene cyclizations (see before) involve the base-catalyzed conversions[45] of *o*-nitrostyrylpyridinium salts (**38**) into the 2-arylisatogens (**39**) (Table IV). Either sodium carbonate or pyridine in combination with diethylamine can be used as the base, the former giving the best yields though the use of the latter is more convenient in practice.[45] The isatogen **39b** is also obtained in low yield together with the tolan **40** by pyrolysis of the salt **38b**.[57] Heating the acetoxy compound **41** with aqueous pyridine–diethylamine also affords 2-phenylisatogen (**39a**), albeit in low yield.[45] In contrast, the corresponding alcohol **42a** is stable under these con-

(43) A. Baeyer, *Chem. Ber.*, **14**, 1741 (1881).
(44) A. Baeyer, *ibid.*, **15**, 50 (1882).
(45) F. Kröhnke and M. Meyer-Delius, *ibid.*, **84**, 932 (1951).
(46) P. Pfeiffer, *Justus Liebigs Ann. Chem.*, **411**, 72 (1916).
(47) C. C. Bond and M. Hooper, *J. Chem. Soc. C*, 2453 (1969).
(48) P. Ruggli, E. Casper, and B. Hegedüs, *Helv. Chim. Acta*, **20**, 250 (1937).
(49) P. Ruggli and H. Cuenin, *ibid.*, **27**, 649 (1944).
(50) P. Ruggli and A. Bolliger, *ibid.*, **4**, 626 (1921).
(51) L. Alessandri, *Gazz. Chim. Ital.*, **57**, 195 (1927); *Chem. Abstr.*, **21**, 2127 (1927); *Gazz. Chim. Ital.*, **58**, 551 (1928); *Chem. Abstr.*, **23**, 1635 (1929); *Gazz. Chim. Ital.*, **58**, 738 (1928); *Chem. Abstr.*, **23**, 3690 (1929).
(52) P. Ruggli, H. Zaeslin, and R. Grand, *Helv. Chim. Acta*, **21**, 33 (1938).
(53) P. Ruggli and A. Zimmermann, *ibid.*, **16**, 69 (1933).
(54) P. Ruggli and E. Wolff, *ibid.*, **19**, 5 (1936).
(55) J. S. Splitter and M. Calvin, *J. Org. Chem.*, **20**, 1086 (1955).
(56) R. Huisgen, *Angew. Chem. Int. Ed. Engl.*, **2**, 565 (1963).
(57) F. Kröhnke and M. Meyer-Delius, *Chem. Ber.*, **84**, 941 (1951).

Table IV

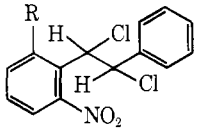
Base-Catalyzed Formation of Isatogens 39 from *o*-Nitrostyrylpyridinium Bromides (38)[46]

Starting material (38)	*Reaction conditions*	*Product* (39)	*Yield*, %
a	Pyridine–Et_2NH–H_2O/reflux/3 hr	a	39
b	Pyridine–Et_2NH–H_2O/reflux/2 hr	b	77
b	Aq Na_2CO_3–EtOH {24 hr/room temp; 3 hr/50–60°	b	91
c	Pyridine–Et_2NH–H_2O/reflux/0.5 hr	c	41

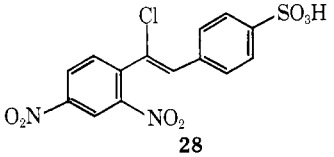


26

	R^1	R^2
26a	CO_2Et	H
b	CO_2Me	H
c	Ph	H
d	Ph	NO_2
e	2-MeC_6H_4	H
f	4-$O_2NC_6H_4$	NO_2
g	2-pyridyl	H
h	1-naphthyl	H



27a, R = H
b, R = NO_2



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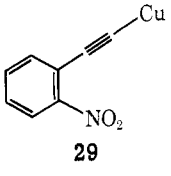

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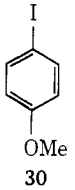
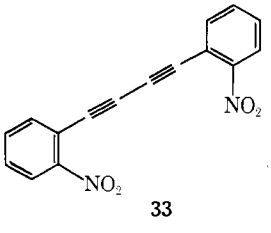


30 → 35e



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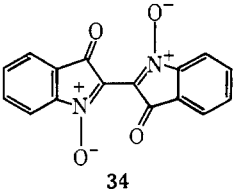


34

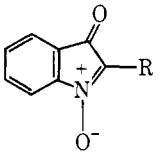
ditions. However *o*-nitrophenylpyridinium ethanols (**42**) in general afford high yields of the corresponding 2-arylisatogens (**43**) on exposure to sunlight;[58] some examples are shown

Table V

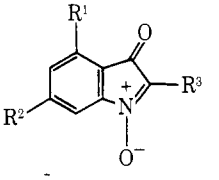
Photochemical Conversion of 2-Nitrophenylpyridinium Ethanols (42) to 2-Arylisatogens (43)[58]

Starting material (42)	*Reaction conditions*	*Reaction time, hr*	*Product* (43)	*Yield*, %
a	*a*	2.5	a	69
	a	18		82
	b	2.5		75
b	*a*	2.5	b	76
	a	18		75
	b	6		57
c	*a*	2.5	c	84
	a	18		93
	b	6		92
d	*a*	2.5	d	81
	a	18		94
	b	6		93

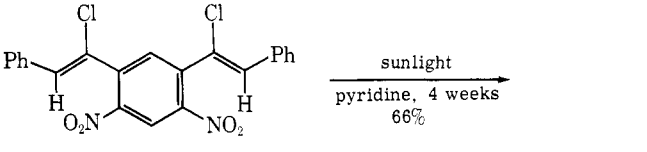
[a] Irradiation in 50% aq AcOH using sunlight. [b] Irradiation in 50% aq AcOH using a 300-W Osram lamp.



	R
35a	CO_2Et
b	CO_2Me
c	Ph
d	2-MeC_6H_4
e	4-$MeOC_6H_4$
f	2-pyridyl
g	1-naphthyl



	R^1	R^2	R^3
36a	H	NO_2	Ph
b	H	NO_2	4-$O_2NC_6H_4$
c	H	NO_2	4-$HSO_3C_6H_4$
d	NO_2	H	Ph



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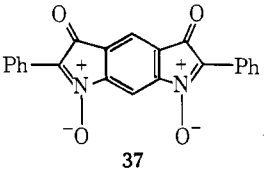


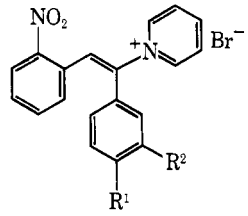
37

in Table V. The pyridyl derivative **44** is also converted in high yield photochemically into 2-pyridylisatogen (**45**).[59]

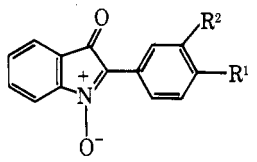
The isatogen derivatives **46** accompany indoxyl products **22** produced in the reactions of the β-dicarbonyl compounds **19**

(58) F. Kröhnke and I. Vogt, *Chem. Ber.*, **85**, 376 (1952).

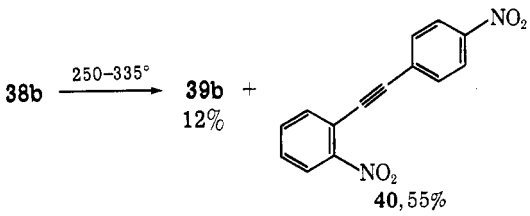
(59) D. A. Patterson and D. G. Wibberley, *J. Chem. Soc.*, 1706 (1965).

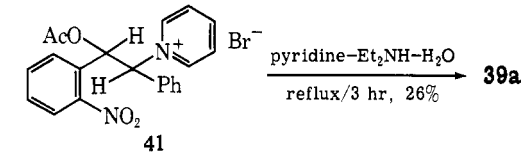


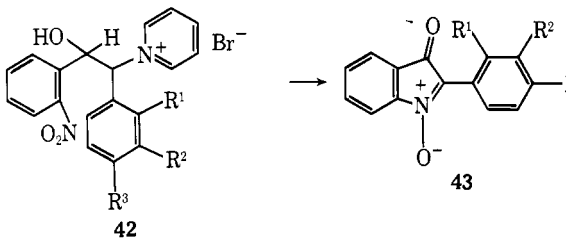
	R^1	R^2
38a	H	H
b	NO_2	H
c	H	NO_2



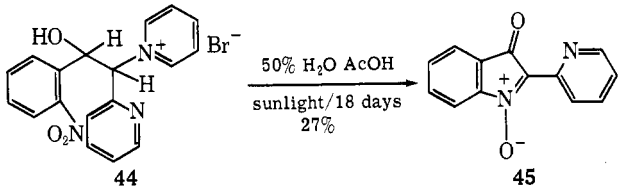
	R^1	R^2
39a	H	H
b	NO_2	H
c	H	NO_2







	R^1	R^2	R^3
a	H	H	H
b	Cl	H	H
c	H	Cl	H
d	H	H	Cl



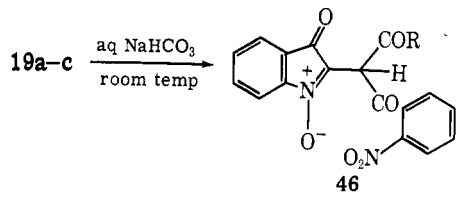
with cold aqueous sodium hydrogen carbonate[60] (*cf.* section II.A.3).

B. FIVE-MEMBERED HETEROCYCLES CONTAINING TWO HETEROATOMS

1. Indazoles

Reaction of *o*-nitrobenzylidene anils (*e.g.*, **50**) with aqueous potassium cyanide followed by acetic acid provides a general route to 2-aryl-3-cyanoindazole 1-*N*-oxides (**52**) (Table VI).[61,62] These reactions probably involve the intermediate formation and base-catalyzed cyclization of the corresponding HCN adducts (*e.g.*, **51**) as evidenced by the conversion of the cyano compound **51** in warm aqueous sodium hydroxide or sodium carbonate, or in cold concentrated sulfuric acid, into 3-cyano-2-phenylindazole 1-*N*-oxide (**52a**).[63] The corresponding hydrogen cyanide adduct (*e.g.*, **51**) is also presumably the active intermediate in the formation[61] of 2-aryl-3-cyanoindazole 1-*N*-oxides (**52**) when *o*-nitromandelonitriles (*e.g.*, **53**) are treated at room temperature with arylamines in ethanol containing sodium acetate. In modified procedures[61,64,65] moderate to excellent yields of 2-aryl-3-cyanoindazole 1-*N*-oxides (**52**) are obtained (Table VI) by preparing the requisite anils (*e.g.*, **50**[61,65]) or their bisulfite adducts[64] *in situ* from *o*-nitrobenzaldehydes (*e.g.*, **47**) and arylamines (**48**) or arylamine hydrochlorides (*e.g.*, **49**) followed by cyclization in the presence of sodium or potassium cyanide (Table VI).

In reactions closely related to the 3-cyanoindazole *N*-oxide syntheses discussed above, 1-hydroxyindazol-3-ones (**56**) (which are tautomeric with 3-hydroxyindazole 1-*N*-oxides (**55**)) are formed in moderate yield (Table VII) by heating *o*-nitrobenzylidene anils (**54**) under reflux with ethanolic sodium carbonate.[66-68] The concomitant formation[67] of the indazolone



	R	Yield, %
46a	OMe	7
b	OEt	9
c	Me	16

Table VI

2-Aryl-3-cyanoindazole 1-*N*-Oxides (52)

Starting material	*Reaction conditions*	*Product (52)*	*Yield, %*	*Ref*
47 + 49	NaOAc–KCN–H_2O–EtOH/room temp/few min	**a**	*a*	61
47 + 48c	1. Heat 2. 40% aq $NaHSO_3$/room temp/24 hr 3. NaCN–H_2O/room temp/3 days	**b**	30	64
47 + 48b	AcOH–KCN/room temp/12 hr	**c**	54	65
50	1. KCN–H_2O/room temp 2. AcOH/room temp	**b**	*a*	61
51	5% aq Na_2CO_3/100°/1 hr	**a**	95	63

[a] Yield not quoted.

(60) R. T. Coutts, M. Hooper, and D. G. Wibberley, *J. Chem. Soc.*, 5205 (1961); M. Hooper and D. G. Wibberley, *J. Chem. Soc. C*, 1596 (1966).

(61) G. Heller and G. Spielmeyer, *Chem. Ber.*, **58**, 834 (1925).
(62) K. Akashi, *Bull. Inst. Phys. Chem. Res. (Tokyo)*, **20**, 798 (1941); *Chem. Abstr.*, **43**, 7934 (1949).
(63) A. Reissert and F. Lemmer, *Chem. Ber.*, **59**, 351 (1926).
(64) L. C. Behr, *J. Amer. Chem. Soc.*, **76**, 3672 (1954).
(65) L. C. Behr, E. G. Alley, and O. Levand, *J. Org. Chem.*, **27**, 65 (1962).
(66) S. Secareanu and I. Lupas, *Bull. Soc. Chim. Fr.*, **53**, 1436 (1933).
(67) S. Secareanu and I. Lupas, *ibid.*, 373 (1934).
(68) S. Secareanu and I. Lupas, *ibid.*, 69 (1935).

Table VII

Base-Catalyzed Formation of *N*-Hydroxyindazol-3-ones (56) from *o*-Nitrobenzylidene Anils (54)

Starting material (54)	*Reaction conditions*	*Product*	*Yield, %*	*Ref*
b	Solid Na_2CO_3–EtOH/reflux/7 hr	**56b**	17	67
		57a	16	
c	Solid Na_2CO_3–EtOH/reflux/8 hr	**57b**	*a*	68
d	Solid Na_2CO_3–EtOH/reflux/2 hr	**56d**[b]	50	66
e	Solid Na_2CO_3–EtOH/reflux/2 hr	**56e**[b]	83	68
f	Solid Na_2CO_3–EtOH/reflux/2 hr	**56f**	50	68

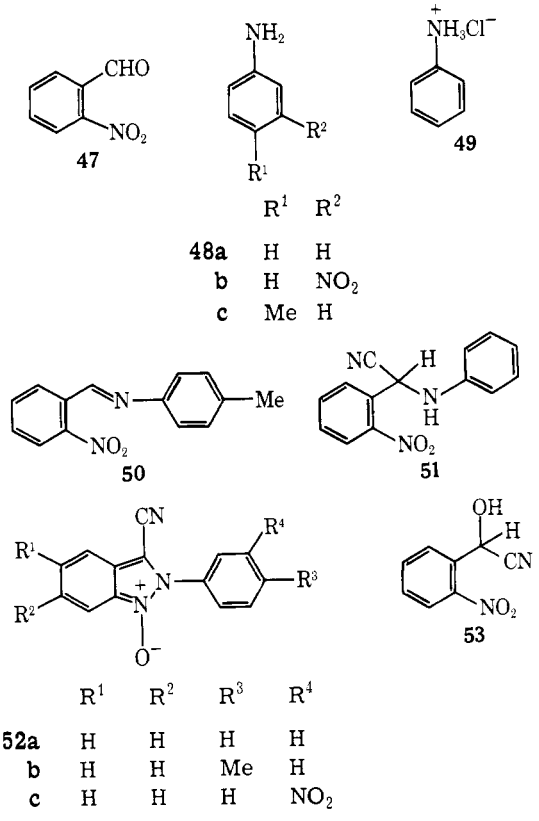
[a] Yield not quoted. [b] Sodium salt.

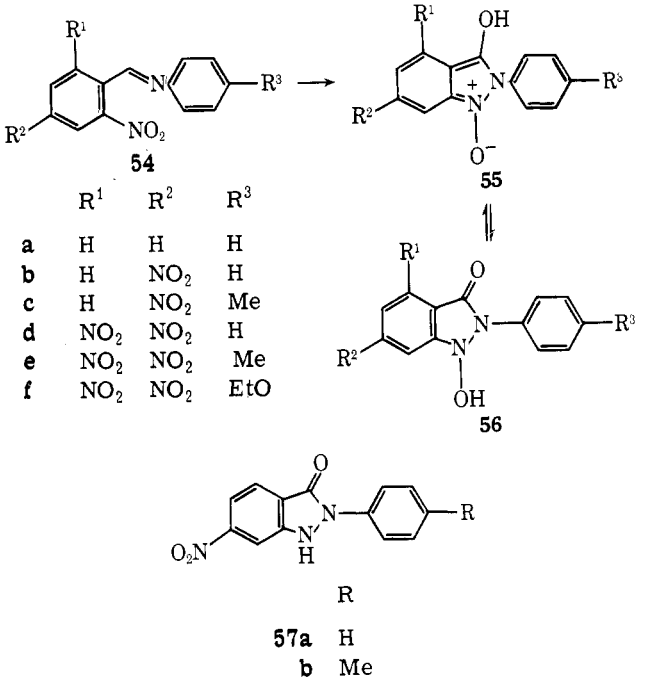
Table VIII

Base-Catalyzed[a] Formation of Indazolones 62 from N,N-Disubstituted *o*-Nitrobenzamides 61 and 63[70,71]

Starting material	*Product* (62)	*Yield, %*	*Ref*
61a	**a**	50	70
61b	**a**	50	70
63a	**a**	76	70
63b	**b**	66	70
61c	**b**	36	71

[a] NaOEt–EtOH/reflux/1 hr.





57a from the dinitroanil **54b** and the sole formation[68] of the indazolone **57b** in the case of the methyl compound **54c** can be attributed to reduction of the corresponding *N*-hydroxyindazolones **56a,b** in the alkaline medium. The parent anil **54a** is reported[67] to be stable to heating with aqueous ethanolic sodium carbonate. The formation[69] of 2-(4-*N*,*N*′-dimethylaminophenyl)-3-ethoxycarbonylindazole 1-*N*-oxide (**60**) from the condensation of ethyl *o*-nitrophenylacetate (**58**) and *p*-nitroso-*N*,*N*′-dimethylaniline (**59**) may likewise involve an *o*-nitrobenzylidene anil intermediate, but the precise course of this reaction requires clarification.

Moderate yields of indazolone derivatives (**62**) are obtained from the base-catalyzed transformation of N,N-disubstituted *o*-nitrobenzamides **61** and **63**[70] (Table VIII). These reactions are explicable[70] by the intermediate formation and subsequent transformation of quinazolin-4(3*H*)-one 1-*N*-oxides (*cf.* section II.E.2). On the other hand, the base-catalyzed conversion[71] of *N*-benzyl-*o*-nitrobenzamide (**61c**) into 2-benzylindazolone (**62b**) (Table VIII) must involve reduction by the alkaline medium at some stage. It has been reported[72] recently that *N*,*N*-dimethyl-*o*-nitrobenzylamine (**64**) is unstable and cyclizes readily to 2-methylindazole (**65**) which is also formed directly by treating *o*-nitrobenzyl chloride with dimethylamine.[72]

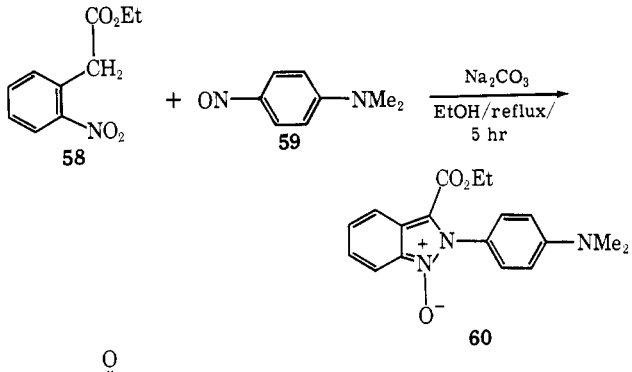
The mechanism of these intriguing reactions remains to be elucidated. In related processes 2-bromomethyl-3-nitropyridine (**66**) reacts with arylamines (**67**) in refluxing ethanol to afford high yields (Table IX) of pyrazolo[4,3-*b*-]pyridines (**68**).[73] The same products are also obtained[73] but in lower yield (Table IX) by heating 2-arylaminomethyl-3-nitropyridines (**69**) with arylamines (**67**) under acidic conditions. 4-Bromomethyl-3-nitropyridine hydrobromide (**70**) reacts similarly with arylamines (**67**) in refluxing ethanol to afford the corresponding pyrazolo[3,4-*c*]pyridines (**71**)[73] (Table IX). These syntheses constitute valuable routes to pyrazolopyridines (*cf.* ref 73).

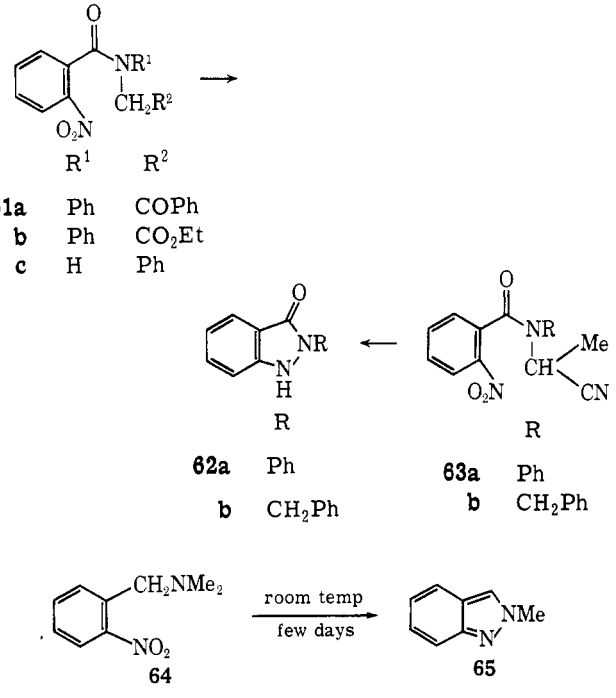
(69) I. Tanasescu and E. Tanasescu, *Bull. Soc. Chim. Fr.*, 1016 (1935).
(70) T. W. M. Spence and G. Tennant, *J. Chem. Soc. C*, in press; *Chem. Commun.*, 194 (1969); *J. Chem. Soc., Perkin Trans. 1*, 98 (1972).
(71) G. Tennant and K. Vaughan, unpublished results.
(72) A. L. Patey and N. M. Waldron, *Tetrahedron Lett.*, 3375 (1970).
(73) J. Hurst and D. G. Wibberley, *J. Chem. Soc. C*, 1487 (1968).

Table IX

Pyrazolo[4,3-*b*]pyridines (68) and Pyrazolo[3,4-*c*]pyridines (71) from Nitropyridine Derivatives[73]

Starting materials	*Reaction conditions*	*Product*	*Yield, %*
66 + **67a**	EtOH/reflux/2 hr	**68a**	74
66 + **67b**	EtOH/reflux/2 hr	**68b**	80
66 + **67c**	EtOH/reflux/2 hr	**68c**	75
69a + **67a**, HBr	EtOH/reflux/1 hr	**68a**	24
69a + **67a**	AcOH/100°/3 hr	**68a**	27
69b + **67b**	60% HBr–EtOH/reflux/1 hr	**68b**	26
69c + **67c**	AcOH/100°/3 hr	**68c**	18
70 + **67a**	EtOH/reflux/2–3.5 hr	**71a**	66
70 + **67b**	EtOH/reflux/2–3.5 hr	**71b**	91
70 + **67c**	EtOH/reflux/2–3.5 hr	**71c**	55





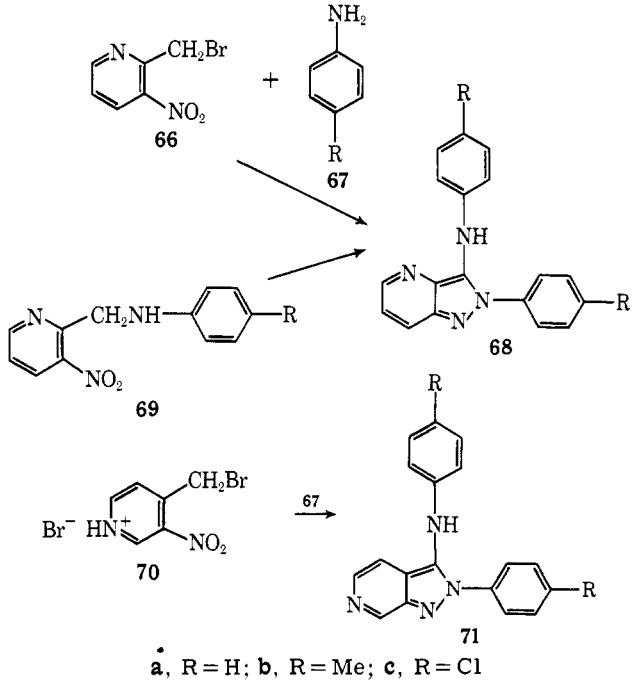
The base-catalyzed cyclization of dinitrobenzylidene arylhydrazones (**72**) affords moderate to high yields of the corresponding 1-arylindazoles (**73**) (Table X).[74-81] These cyclizations involve the intramolecular nucleophilic displacement of aromatic nitro groups. Cyclization fails in the cases of the amide **72o**[76] and the *o*-nitro derivative **72n**.[78] The

Table X

Base-Catalyzed Cyclization of Dinitrobenzylidene Arylhydrazones (72) to *N*-Arylindazoles (73)

Starting material (72)	*Reaction conditions*	*Product* (73)	*Yield, %*	*Ref*
a	KOH–EtOH/warm	**a**	*a*	76
b	KOH–EtOH/warm	**b**	*a*	76
c	Alkali–pyridine/heat/5 min	**c**	*a*	77
d	Alkali–pyridine/heat/5 min	**d**	*a*	77
e	Aq NaOH/room temp	**e**	*a*	74
f	10% NaOH–MeOH/reflux/0.25 hr	**f**	Quant	79
g	4% aq NaOH–MeOH/room temp or heat/0.5 hr	**g**	97	78
h	10% aq NaOH–MeOH/reflux/0.25 hr	**h**	*a*	79
i	4% aq NaOH–MeOH/room temp or heat/0.4 hr	**i**	69	78
j	40% aq KOH–MeOH–DMSO/70°/15 min	**j**	96	80
k	10% aq NaOH–MeOH/reflux/0.25 hr	**k**	Quant	79
l	20% NaOH–EtOH/room temp/few min	**l**	*a*	75
m	5% NaOH/reflux/5 min	**m**	50	81

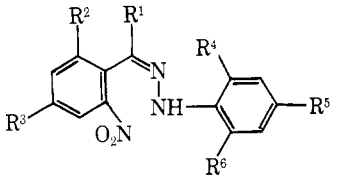
[a] No yield quoted.



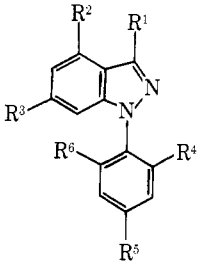
a, R = H; **b**, R = Me; **c**, R = Cl

failure of the latter to undergo cyclization is surprising in view of the successful cyclization[80] of the corresponding carboxylic acid **72j** which had been earlier reported[78] not to undergo cyclization. Cyclization also fails in the case of hydrazones in which the group attached to nitrogen is electron withdrawing (*e.g.*, carbonyl, 2,4-dinitrophenyl, picryl, etc.).[77] The intramolecular displacement of nitro groups is also involved in the reactions of the uracil derivative **74** with aldehyde and ketone

(74) V. Meyer, *Chem. Ber.*, **22**, 319 (1889).
(75) W. Borsche, *ibid.*, **42**, 601 (1909).
(76) S. Reich and G. Gaigailian, *ibid.*, **46**, 2380 (1913).
(77) K. V. Auwers and E. Frese, *ibid.*, **58**, 1369 (1925).
(78) W. Borsche and K. Diacont, *Justus Liebigs Ann. Chem.*, **510**, 287 (1934).
(79) W. Borsche and L. Bütschli, *ibid.*, **522**, 285 (1936).
(80) K. Schimmelschmidt and H. Hoffmann, *ibid.*, **677**, 157 (1964).
(81) A. Prakash and I. R. Ghambhir, *J. Indian Chem. Soc.*, **43**, 529 (1966).



	R^1	R^2	R^3	R^4	R^5	R^6
72a	H	NO_2	H	H	H	H
b	H	NO_2	H	H	Me	H
c	H	NO_2	H	Me	H	H
d	H	NO_2	H	Me	H	Me
e	CO_2Me	H	NO_2	H	H	H
f	CO_2Me	H	NO_2	H	Me	H
g	CO_2Me	H	NO_2	H	MeO	H
h	CO_2Me	H	NO_2	H	COMe	H
i	CO_2Me	H	NO_2	Me	H	H
j	CO_2Me	H	NO_2	CO_2H	H	H
k	CO_2Me	H	NO_2	Cl	Cl	H
l	COMe	H	NO_2	H	H	H
m	COMe	H	NO_2	H	F	H
n	CO_2Me	H	NO_2	NO_2	H	H
o	H	NO_2	H	H	$CONH_2$	H

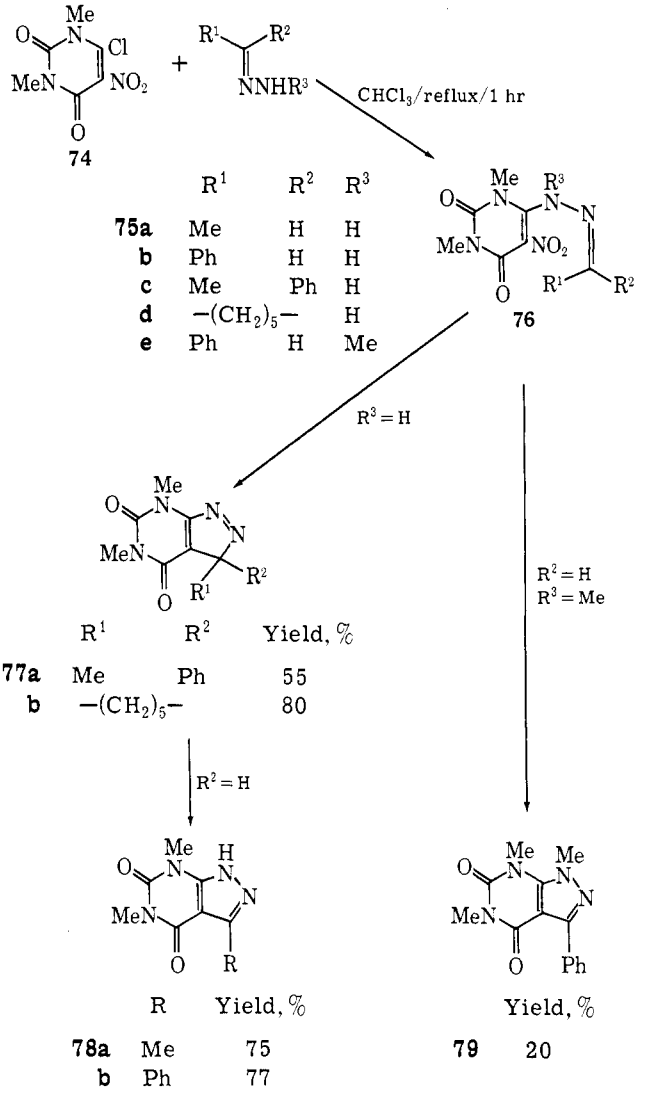


	R^1	R^2	R^3	R^4	R^5	R^6
73a	H	NO_2	H	H	H	H
b	H	NO_2	H	H	Me	H
c	H	NO_2	H	Me	H	H
d	H	NO_2	H	Me	H	Me
e	CO_2H	H	NO_2	H	H	H
f	CO_2H	H	NO_2	H	Me	H
g	CO_2H	H	NO_2	H	MeO	H
h	CO_2H	H	NO_2	H	COMe	H
i	CO_2H	H	NO_2	Me	H	H
j	CO_2Me	H	NO_2	CO_2H	H	H
k	CO_2H	H	NO_2	Cl	Cl	H
l	COMe	H	NO_2	H	H	H
m	COMe	H	NO_2	H	F	H

hydrazones **75**.[82] These reactions appear to be quite general and provide a valuable synthetic route to pyrazolo[3,4-*d*]-pyrimidines (**77–79**). The intermediate condensates **76** can be isolated and merely on warming in a suitable solvent (methanol, dimethylformamide, dimethyl sulfoxide) are converted into the pyrazolopyrimidines (**77–79**) in high yield.[82]

2. *Benzimidazoles*

The standard route[83] to benzimidazoles involves the condensation of an *o*-arylenediamine with a carbonyl-containing compound. This method is simple in practice and yields are



	R^1	R^2	R^3
75a	Me	H	H
b	Ph	H	H
c	Me	Ph	H
d	$-(CH_2)_5-$		H
e	Ph	H	Me

	R^1	R^2	Yield, %
77a	Me	Ph	55
b	$-(CH_2)_5-$		80

	R	Yield, %
78a	Me	75
b	Ph	77

	Yield, %
79	20

often high. An alternative method is reductive cyclization of ortho-substituted nitrobenzene derivatives. Recent variants of the latter method include the trialkyl phosphite induced reactions of *N*-benzylidene-*o*-nitroanilines[84] and N-substituted *o*-nitroanilines.[85] In the course of a general investigation of the reductive cyclization of the latter, Smith and Suschitzky[86] found that *N*-benzyl-*o*-nitroaniline underwent thermal uncatalyzed cyclization, albeit in low yield (20%), to afford 2-phenylbenzimidazole; subsequently,[87] the scope of the thermal reactions [*e.g.*, 4 and 5] (Table XI) has been demonstrated. In general yields are high and cyclization occurs smoothly especially when the nitrated ring contains electron-withdrawing substituents (*e.g.*, **80a,b**). The absence of a substituent (*e.g.*, **80f**) or the presence of electron-donating substituents (*e.g.*, **80c,g**) results in lower yields and necessitates longer reaction times.

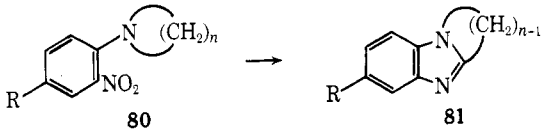
A recent variant[88] is the use of the solvent system benzylamine–benzyl alcohol for the thermolytic conversion of *N*-benzyl-*o*-nitroanilines (**84a–d**) into 2-phenylbenzimidazoles

(82) Y. Maki, K. Izuta, and M. Suzuki, *Chem. Commun.*, 1442 (1971); 298 (1972).
(83) J. B. Wright, *Chem. Rev.*, **48**, 397 (1951).
(84) J. I. G. Cadogan, R. Marshall, D. M. Smith and M. J. Todd, *J. Chem. Soc. C*, 2441 (1970).
(85) R. Garner, G. V. Garner, and H. Suschitzky, *ibid.*, 825 (1970).
(86) R. H. Smith and H. Suschitzky, *Tetrahedron*, **16**, 80 (1961).
(87) H. Suschitzky and M. E. Sutton, *Tetrahedron Lett.*, 3933 (1967).
(88) V. M. Maryanovskii, A. M. Simonov, and V. V. Firsov, *Zh. Org. Khim.*, **5**, 2196 (1969); *Chem. Abstr.*, **72**, 66524 (1970).

Table XI

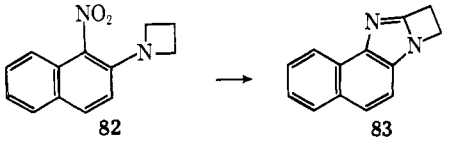
Thermal Cyclization of *o*-Nitroarylamines to Benzimidazoles at ~ 240°

Starting material	*Reaction time, hr*	*Product*	*Yield, %*
80a	0.5	**81a**	88
80b	0.5	**81b**	82
80c	0.75	**81c**	70
80d	0.5	**81d**	65
80e	1	**81e**	40
82	0.25	**83**	70

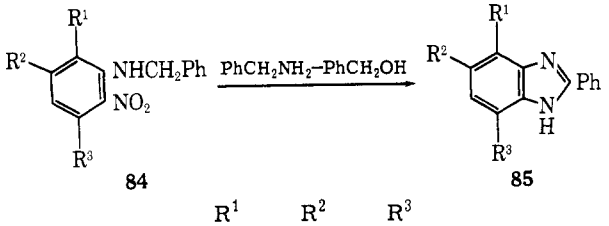


(4)

	n	R
a	4	CO_2H
b	4	NO_2
c	4	Cl
d	3	CF_3
e	4	NHAc
f	4	H
g	4	Me



(5)

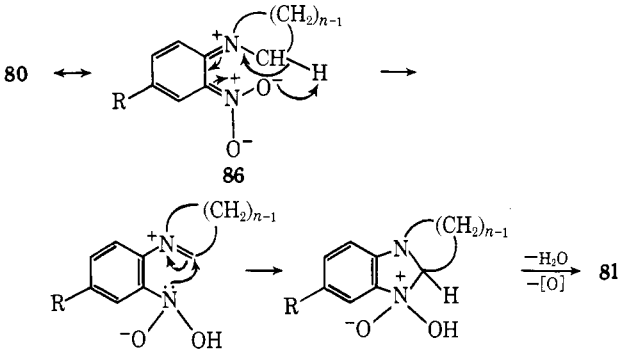


	R^1	R^2	R^3
a	H	H	H
b	MeO	H	H
c	MeO	H	MeO
d	MeO	MeO	NO_2

(**85a–d**). Cyclization reactions of this type are presumed[86,87] to involve the *aci*-nitro form (**86**) of the nitro compound (Scheme III). The *aci*-nitro mechanism was initially questioned[89] but later acceded to[90] by Abramovitch and Davies. Recently, further evidence has been presented[91] in favor of the *aci*-nitro process as opposed to the alternative[89] nitrene route. A similar *aci*-nitro mechanism has been proposed[92] to explain the thermal cyclizations of 2-methyl-2′-nitrobiphenyls to phenanthridines in diphenyl ether.

Thermolysis of *o*-nitro- and 2,4-dinitrophenyl derivatives of α-amino acids (**87**) also affords benzimidazole derivatives.[93]

Scheme III



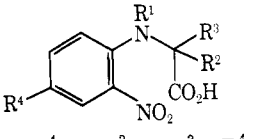
With the exception of *o*-nitrophenylalanine (**87e**), however, these cyclizations do not provide viable synthetic routes to benzimidazoles (*cf.* Table XII) although working tempera-

Table XII

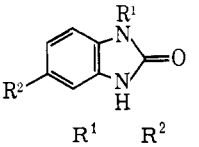
Formation of Benzimidazoles and Related Products from the Pyrolysis of *o*-Nitroaryl Derivatives of α-Amino Acids at 200°

Starting material (**87**)	*Products*	*Yield, %*
a	**88a**	60
b	**88b**	60
	89b	15
c	**88c**	60
	89a	10
d	**88d**	42
	89a	4
	89c	8
e	**89d**	65
	90	10
f	**89e**	40
	91	30

tures (200°)[93] are lower than those employed[87] (240°) for the thermal cyclization of N,N-disubstituted *o*-nitroanilines. The greater ease of cyclization in the case of the amino acids may be due to facilitation of the initial proton abstraction (*cf.* **86**) as a result of electron withdrawal by the carboxyl group. The



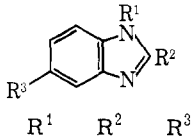
	R^1	R^2	R^3	R^4
87a	H	H	H	NO_2
b	Ph	H	H	NO_2
c	H	H	H	H
d	Me	H	H	H
e	H	Me	H	H
f	H	Ph	H	H



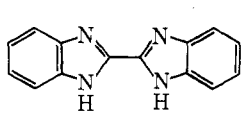
	R^1	R^2
88a	H	NO_2
b	Ph	NO_2
c	H	H
d	Me	H

isolation[93] of 2-phenylbenzimidazole *N*-oxide (**91**) from one of the reactions is significant in terms of the proposed[86,87,91] *aci*-nitro mechanism. Furthermore, the formation (Table XII) of benzimidazolones **88** and bibenzimidazolyls **90** is also

(89) R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 149 (1964).
(90) R. A. Abramovitch and B. A. Davis, *J. Chem. Soc. C*, 119 (1968).
(91) G. V. Garner and H. Suschitzky, *Tetrahedron Lett.*, 169 (1971).
(92) G. Smolinsky and B. I. Feuer, *J. Org. Chem.*, **31**, 3882 (1966).
(93) R. S. Goudie and P. N. Preston, *J. Chem. Soc. C*, 1139 (1971).



	R^1	R^2	R^3
89a	H	H	H
b	Ph	H	NO_2
c	Me	H	H
d	H	Me	H
e	H	Ph	H



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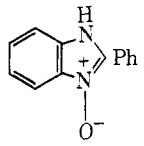
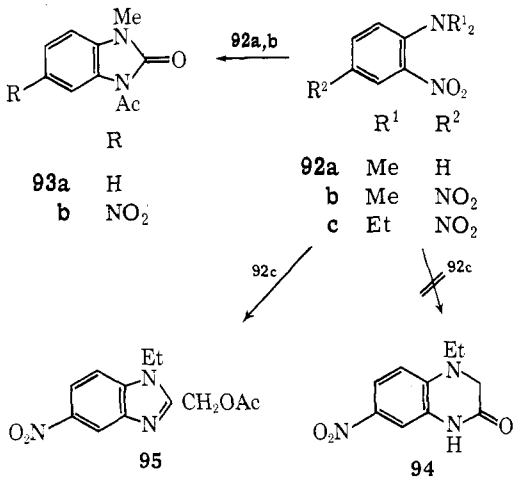


91

consistent[94,95] with the intermediacy of benzimidazole *N*-oxides.

N,N-Disubstituted *o*-nitroanilines have also been converted into benzimidazoles photochemically in the presence of acid (*cf.* section II.B.3)[96] and also by heating with zinc chloride in acetic anhydride. The latter type of cyclization was originally reported by van Romburgh, *et al.*,[97] who showed that treatment of *N,N*-dimethyl-*o*-nitroaniline (**92a**) and *N,N*-dimethyl-2,4-dinitroaniline (**92b**) with zinc chloride in boiling acetic anhydride affords the *N*-acetylbenzimidazolones **93a** and **93b**, respectively. They also formulated the product from



	R
93a	H
b	NO_2

	R^1	R^2
92a	Me	H
b	Me	NO_2
c	Et	NO_2

95 **94**

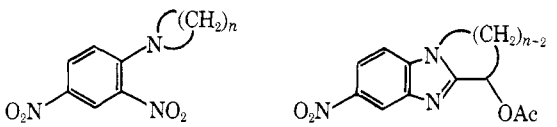
N,N-diethyl-2,4-dinitroaniline (**92c**) as the quinoxaline **94**. A reinvestigation[98] of these reactions revealed that though the products derived from the amines **92a** and **92b** were correctly formulated, the *N,N*-diethylaniline **92c** is in fact converted into the benzimidazole derivative **95**. The synthetic value of the reaction has been evaluated[98] (*cf.* **96** → **97**), and yields of benzimidazole derivatives are often high (Table XIII).

The mechanism of these zinc chloride catalyzed cyclizations is unclear, but both reagents appear to play a vital role. One possibility[98] is that an organometallic complex is involved; such a process may have precedent in the work of Price[99] who obtained benzimidazoles in *ca.* 60% yields [isolated as the (dichlorobisbenzimidazole)cobalt(II) complexes] by allowing 2,2′-bis(dialkylaminobenzenes) to react with hydrated cobalt chloride.

Table XIII

Benzimidazolones and Benzimidazoles from the Reaction of N,N-Disubstituted *o*-Nitroanilines with Zinc Chloride in Acetic Anhydride

Starting material	*Reaction time, hr*	*Product*	*Yield, %*
92a	4	**93a**	48
92b	4	**93b**	Not quoted
92c	4	**95**	65
96a	4	**97a**	68
96b	4	**97b**	85
96c	2.5	**97c**	87



96 **97**

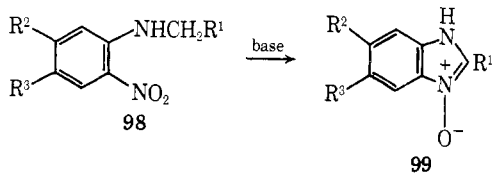
a, $n=4$; **b**, $n=5$; **c**, $n=6$

3. *Benzimidazole N-Oxides*[99a]

In general, simple benzimidazole *N*-oxides are accessible by reductive cyclization[100] of N-substituted *N*-acyl-*o*-nitroanilines (*e.g.*, *o*-nitroformanilide, *o*-nitroacetanilide) in moderate (40%) to good (80%) yield. 2-Aryl derivatives are accessible[101] (*ca.* 60% yields) by the acid-catalyzed condensation of substituted *o*-nitrosoanilines (prepared[102] by the irradiation of *N*-*o*-nitrophenyl derivatives of α-amino acids; see section III.A) with aromatic aldehydes. However none of these methods is suitable for the synthesis of benzimidazole *N*-oxides containing functional groups in the 2 position. Also, conventional[103] oxidative methods have been unsuccessful in the case of benzimidazoles,[104-106] and alternative routes to the N-oxides are therefore important.

Base-catalyzed aldol-type cyclizations of N-substituted *o*-nitroanilines (**98**) containing an active methylene group in the side chain have been successfully applied to the synthesis of a number of benzimidazole *N*-oxide derivatives; some examples are as follows (**98** → **99**).

(94) R. Kuhn and W. Blau, *Justus Liebigs Ann. Chem.*, **615**, 99 (1958).
(95) S. Takahashi and H. Kano, *Chem. Pharm. Bull.*, **12**, 783 (1964).
(96) R. Fielden, O. Meth-Cohn, and H. Suschitzky, *Tetrahedron Lett.*, 1229 (1970).
(97) (a) R. van Romburgh and H. W. Huyser, *Versl. Gewone Vergad. Afd. Natuurk. Kon. Ned. Akad. Wetensch.*, **35**, 665 (1926); *Chem. Abstr.*, **21**, 382 (1927); (b) *Recl. Trav. Chim. Pays-Bas*, **49**, 165 (1930); (c) P. van Romburgh and W. B. Deys, *Proc. Acad. Sci. Amsterdam*, **34**, 1004 (1931); *Chem. Abstr.*, **26**, 989 (1932).
(98) R. K. Grantham and O. Meth-Cohn, *J. Chem. Soc. C*, 70 (1969).
(99) R. Price, *J. Chem. Soc. A*, 521 (1967).
(99a) The tautomeric nature of benzimidazole *N*-oxides of the type **99** is well established (see ref 183b) but for the sake of clarity they are represented throughout this section as aromatic amine *N*-oxides rather than *N*-hydroxy compounds.
(100) S. Takahashi and H. Kano, *Chem. Pharm. Bull.*, **11**, 1375 (1963).
(101) D. W. Russell, *J. Med. Chem.*, **10**, 984 (1967).
(102) P. H. MacFarlane and D. W. Russell, *Tetrahedron Lett.*, 725 (1971), and references cited therein.
(103) E. Ochiai, Ed., "Aromatic Amine Oxides," Elsevier, N. Y., 1967, pp 19–51.
(104) E. Hayashi, E. Ishiguro and N. Enomoto, paper presented at the 13th Annual Meeting of the Pharmaceutical Society of Japan, 1960.
(105) D. J. Kew and P. F. Nelson, *Aust. J. Chem.*, **15**, 792 (1962).
(106) G. W. Stacey, B. V. Ettling, and A. J. Papa, *J. Org. Chem.*, **29**, 1537 (1964).

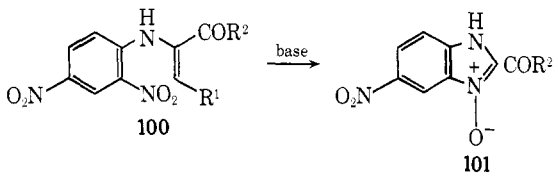


98 99

	R^1	R^2	R^3	Yield, %	Ref
a	PhCO	H	Me	Not quoted	107
b	Ph	H	H	71	106, 108, 109
c	CO_2Me	H	NO_2	63	110

The scope of the benzylamine-type cyclization (**98b** → **99b**) has been investigated,[108,111] and a wide range of N-oxides containing a 2-(2′-thiazolyl) nucleus and a variety of substituents (halogen, alkyl, aryl, thienyl, alkoxy, phenoxy, alkylthio, and phenylthio) on the benzene ring have been prepared[108] for biological evaluation. More recently[112] the cyclization of a number of peptides containing a terminal 2,4-dinitrophenylglycine moiety (*e.g.*, **98**, R^1 = $CONHCH_2CO_2H$; R^2 = H; R^3 = NO_2) has been effected under mildly basic conditions [trimethylammonium carbonate buffer (pH 8.3)] to give the appropriate N-oxide (*e.g.*, **99**, R^1 = $CONHCH_2CO_2H$; R^2 = H; R^3 = NO_2; 59% yield). In contrast to this behavior, however, 2,4-dinitrophenylglycine (**98c**, CO_2H for CO_2Me) undergoes[112,113] cyclization with concomitant decarboxylation to give 6-nitrobenzimidazole 1-*N*-oxide (**99c**, H for CO_2Me). Formation of the latter product is not unexpected in view of the observed[114] behavior of 1-methylbenzimidazole-2-carboxylic acid 3-*N*-oxide.

A cyclization procedure that closely resembles the ester type (*cf.* **98c** → **99c**) is the base-catalyzed conversion[110] of 2,4-dinitrophenylaminoalkenes **100** into the benzimidazole

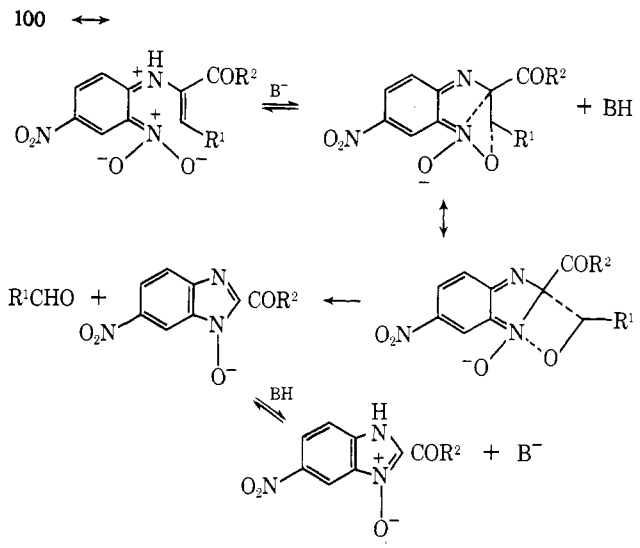


100 101

R^1 = H, Me, or Ph
R^2 = OMe or $NHPr^n$

N-oxides **101**. Very good yields (70–80%) are obtained when the reactions are carried out in polar solvents (*e.g.*, dimethyl sulfoxide, dimethylformamide, or methanol). The mechanism of these reactions is unclear although the route in Scheme IV incorporating an intramolecular 2 + 2 cycloaddition has been invoked.[110] It should be noted, however, that such a mechanism is unsupported by experimental evidence so that in some of the reactions investigated[110] an alternative route involving hydration of the double bond, retroaldol cleavage, and cyclization of an ensuing 2,4-dinitrophenylglycine ester

Scheme IV



(or amide) derivative is conceivable. It would be of interest to follow the course of such reactions in the absence of the *o*-nitro group; the use of labeled (ortho $N^{18}O_2$) starting materials would also be instructive.

The recently reported[115] conversion of *o*-nitrobenzylideneaniline into 2-phenylbenzimidazole *N*-oxide (79% yield) by treatment with potassium cyanide in methanol is encouraging since the conditions are less drastic than the base-catalyzed procedures[106–111] used on *o*-nitroaniline derivatives. The mechanism of the reaction is probably related to analogous procedures for the synthesis[14,15] of indole derivatives from α-*o*-nitrophenylcinnamonitrile derivatives (see section II.A.1).

Intramolecular acid-catalyzed cyclizations of N,N-disubstituted *o*-nitroanilines provide[116] an excellent synthetic route to benzimidazole *N*-oxides. Thus the amines **102** are converted by treatment with hot hydrochloric acid in high yield into the N-oxides **103** (Table XIV).

Table XIV

Acid-Catalyzed Cyclization of N,N-Disubstituted *o*-Nitroanilines to Benzimidazole *N*-Oxides

Starting material (**102**)	*Reaction conditions* *Temp, °C*	*Time, hr*	*Product* (**103**)	*Yield,*[a] %
a	110	20	a	63
b	110	20	b	100
c	110	20	c	99
d	110	20	d	72
e	150	12	e	52

[a] Yields are based on consumed starting material.

A closely related type of cyclization occurs[96] when N,N-disubstituted *o*-nitroanilines **102** are irradiated in aqueous methanolic hydrogen chloride. For this case, however, the type of product [either benzimidazole *N*-oxide (**103**) or benzimidazole (**104**)] is determined by the nature of the amino and ring substituents (Table XV).

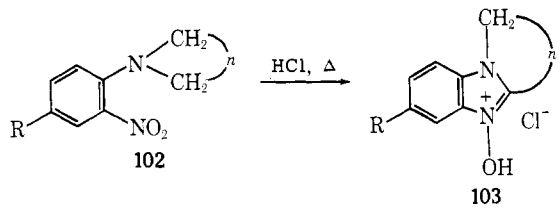
(107) J. D. Loudon and G. Tennant, *J. Chem. Soc.*, 4268 (1963).
(108) Merck and Co., Inc., British Patent 1,133,853; U. S. Patent, 3,265,706; *Chem. Abstr.*, **65**, 13724 (1966).
(109) G. W. Stacey, T. E. Wollner, and T. R. Oakes, *J. Heterocycl. Chem.*, **3**, 51 (1966).
(110) A. E. Luetzow and J. R. Vercellotti, *J. Chem. Soc. C*, 1750 (1967).
(111) Netherlands Patent 6,515,833; *Chem. Abstr.*, **65**, 15388 (1966).
(112) L. A. Ljublinskaya and V. M. Stepanov, *Tetrahedron Lett.*, 4511 (1971).
(113) R. S. Goudie, Ph.D. Thesis, Heriot-Watt University, Edinburgh, Scotland, 1971.
(114) S. Takahashi and H. Kano, *Chem. Pharm. Bull. Tokyo*, **16**, 527 (1968)
(115) R. Marshall and D. M. Smith, *J. Chem. Soc. C*, 3510 (1971).
(116) R. Fielden, O. Meth-Cohn, D. Price, and H. Suschitzky, *Chem. Commun.*, 772 (1969).

Table XV

Acid-Catalyzed Photochemical Cyclization of N,N-Disubstituted *o*-Nitroanilines to Benzimidazoles or Benzimidazole *N*-Oxides[a]

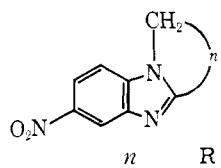
Starting material (**102**)	*Reaction time, hr*	*Product*	*Yield, %*
a	48	**103a**	78
g	66	**104a**	83
d	24	**104b**	81
f	65	**103f**	79

[a] Carried out with a 200-W medium-pressure lamp on 0.002 *M* solutions of the nitro compounds in 1 *M* HCl in 10% aqueous methanol.



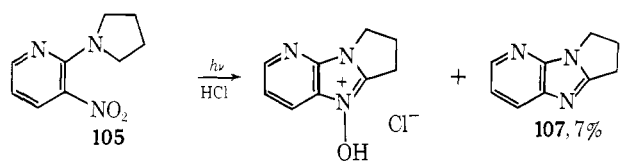
102 **103**

	n	R
a	$(CH_2)_2$	H
b	$(CH_2)_3$	NO_2
c	CH_2OCH_2	NO_2
d	$(CH_2)_4$	H
e	Me	H
f	$(CH_2)_4$	Cl
g	$(CH_2)_3$	H



	n	R
104a	$(CH_2)_3$	H
b	$(CH_2)_4$	H

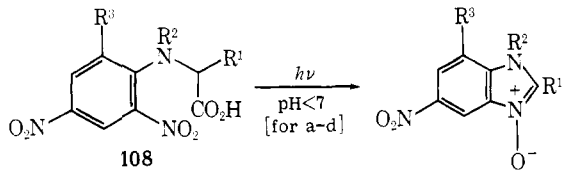
The photochemical cyclization has also been applied to the pyridine derivative **105** which affords the imidazopyridines **106** and **107**; however, the scope of this variant has not been investigated.



105 **106**, 78% **107**, 7%

Since the N-oxides (**103**) are photostable under the reaction conditions, they cannot be the precursors of the benzimidazoles **104**; an *aci*-nitro mechanism[86,87] (see section II.B.2) has been proposed[96] to account for the formation of the N-oxides while a route involving a reduced benzofuroxan intermediate has been invoked[96] to account for benzimidazole formation. However the possibility of free-radical or radical-ion intermediates cannot be excluded.

The photochemical decomposition of *N*-2,4-dinitrophenyl derivatives of α-amino acids **108** in the solid state has been known for some time[117] and has been shown[118] to result in decarboxylation to afford the corresponding *N*-alkyl-2,4-dinitroaniline. In aqueous solution, however, the products are



108 **109**

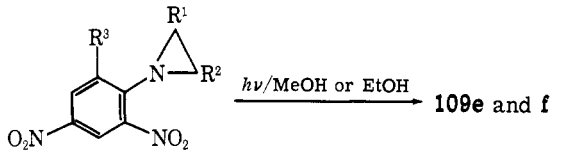
	R^1	R^2	R^3	Yield, %
a	H	H	H	70
b	CH_2OH	H	H	33
c	*i*-Bu	H	H	76
d	*sec*-Bu	H	H	78
e	Ph	H	NO_2	
f	Ph	H	H	

either 4-nitro-2-nitrosoaniline (at pH ≥7) (*cf.* section III.A) or 2-substituted 5-nitrobenzimidazole *N*-oxides at low pH.[119] Yields are often high (*cf.* (**109a–d**)), and the method is an attractive one in view of the ready availability[120] of the starting materials. The effect of structure and pH on the yield of amino acid has been evaluated.[121] Optimum yields are obtained at low pH and also at pH *ca.* 3; successful cyclization at pH 3 requires a hydrogen atom on the amino group, whereas at low pH it does not. The mechanism of this type of cyclization is in doubt; Russell's original contention[122] that the primary chemical event is decarboxylation was modified by Neadle and Pollitt[121] to include a step involving concerted oxygen transfer. More recently[102] it has been shown that *p*-nitrophenylvaline undergoes rapid photodecarboxylation at pH 6 making a recently proposed[123] mechanism unlikely. Verification that this type of reaction may proceed by an intermolecular mechanism is provided by the report[124] that irradiation of acetonitrile solutions of aromatic nitro compounds (*e.g.*, 1-nitronaphthalene, 4-nitrobiphenyl) containing *N*-(2-chlorophenyl)glycine or phenylthioacetic acid causes decarboxylation of the latter.

Further details of the photocyclization[125] of the aziridines **110a,b** to the N-oxides (**109e** and **109f**) have not yet appeared; reactions of this type probably have considerable potential since the yields are high (95–96%) and the starting materials are readily available.

In general, thermal reactions of *o*-nitroaniline derivatives and *o*-nitroaryl derivatives of α-amino acids afford benzimidazoles (see section II.B.2). However, 2-phenylbenzimidazole *N*-oxide is formed[93] (yield 30%) by heating the appropriate amino acid (**108**, R^1 = Ph; R^2 = H; H for 4-NO_2) in sand at 200°.

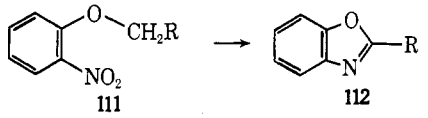
(117) S. Blackburn, *Biochem. J.*, **45**, 579 (1949); G. L. Mills, *ibid.*, **50**, 707 (1952); S. Akabori, T. Ikenaka, Y. Okada, and K. Ohno, *Proc. Japan Acad.*, **29**, 509 (1953).
(118) B. Pollara and R. W. von Korff, *Biochim. Biophys. Acta*, **39**, 364 (1960).
(119) D. J. Neadle and R. J. Pollitt, *J. Chem. Soc. C*, 1764 (1967).
(120) F. Sanger, *Biochem. J.*, **39**, 507 (1946).
(121) D. J. Neadle and R. J. Pollitt, *J. Chem. Soc. C*, 2127 (1969).
(122) D. W. Russell, *J. Chem. Soc.*, 894 (1963).
(123) O. Meth-Cohn, *Tetrahedron Lett.*, 1235 (1970).
(124) R. S. Davidson, S. Korkut, and P. R. Steiner, *Chem. Commun.*, 1052 (1971).
(125) H. W. Heine, G. J. Blosick, and G. B. Lowrie, *Tetrahedron Lett.*, 4801 (1968).



	R^1	R^2	R^3
110a	Ph	Ph	NO_2
b	Ph	PhCO	H

4. Benzoxazoles

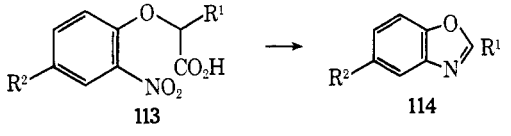
Procedures incorporating *o*-nitro substituent interactions provide benzoxazoles in only poor yields compared with conventional[126] approaches. Thermolysis[127] of the *o*-nitrophenyl ethers **111a,b** in the absence of an external reductant affords 2-phenylbenzoxazole (**112a**) and 2-benzylbenzoxazole (**112b**) in 15 and 8% yield, respectively.



111 **112**

a, R = Ph; **b**, R = CH_2Ph

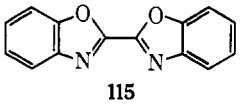
In contrast to the photolysis[128] of *o*-nitroaryloxyacetic acids **113** (see section III.A), thermolysis[129] of such compounds affords the benzoxazoles **114** among other products



113 **114**

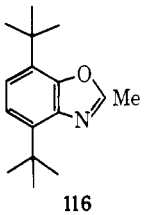
	R^1	R^2	Reaction temp, °C	Yield, %
a	Me	H	240	3
b	Me	NO_2	220–230	12
c	Ph	NO_2	230	42

(see section II.E.5). By analogy with the pyrolysis[93] of *o*-nitrophenylalanine which affords 2,2′-bibenzimidazolyl as one of the products (see section II.B.2), pyrolysis[129] of both *o*-nitrophenoxyacetic acid and α-(*o*-nitrophenoxy)propionic acid (**113a**) affords 2,2′-bibenzoxazolyl (**115**) in low yield (5–9%). Although no attempt was made[129] to optimize the yield of the product **115**, its formation by this route is unlikely to supersede the alternative synthetic procedure involving oxidation of 2,2′-bibenzoxazolines.[130]



115

A benzoxazole derivative (**116**) has also been characterized[20] as a minor product (*cf.* section II.A.2) from the photolysis of 1,4-di-*tert*-butyl-2-nitrobenzene in diethylamine or triethylamine. However, the very low yield observed (<5%) suggests that little synthetic value can be anticipated from this type of reaction.



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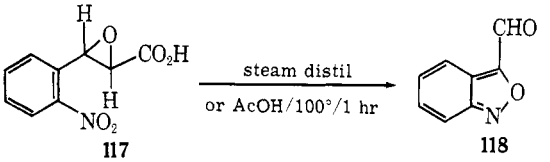
5. 2,1-Benzisoxazoles (*Anthranils*)

Reactions leading to anthranils include some of the earliest recorded examples of nitro-group side-chain interaction in ortho-substituted nitrobenzene derivatives. Anthranil itself plays a key role in many such reactions,[6] notably those leading to anthranilic acids (*cf.* section III.C), and is obtained in moderate to low yield when *o*-nitrobenzaldehyde hydrazone is heated with alkali[131] or when *o*-nitrobenzaldimercuric chloride is treated with aqueous hydrochloric acid.[132] It is also formed in low yield together with anthranil-3-carboxaldehyde (**118**) when *o*-nitrophenylglycidic acid (**117**) is heated with



117 **118**

glacial acetic acid or water.[133] The formation of anthranils in general from *o*-nitrobenzene derivatives is catalyzed both by acids and by bases and can also be initiated thermally or photochemically. Apparently the nitro group can behave as both an electrophile and nucleophile in anthranil formation, but mechanistic investigations in this area would be of interest.

The acid-catalyzed condensation of *o*-nitrobenzaldehyde derivatives (**119**) with arenes, phenols, or arylamines (**120**) provides a general method for the synthesis of 3-arylanthranils (**121**) (Table XVI). Catalysts include concentrated sulfuric acid,[134–139] hydrogen halides,[140,141] aqueous hydrochloric acid,[142,143] or zinc chloride.[144,145] Anthranil formation in sulfuric acid can be rationalized on the basis of a benzhydrol intermediate (**122**) which is subsequently converted into 2-nitrosobenzophenone. The reduction step required to convert the latter into the anthranil can be effected by unreacted benzhydrol **122** which suffers concomitant oxidation to 2-nitrobenzophenone which is isolated usually as a by-product.[134] In the hydrogen chloride catalyzed reactions,[141,142] the products are chlorinated anthranils, the reduction step in

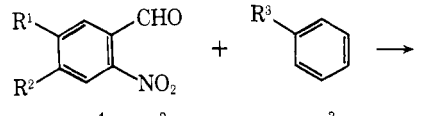
(126) J. W. Cornforth in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, pp 418–451.
(127) R. Higginbottom and H. Suschitzky, *J. Chem. Soc.*, 2367 (1962).
(128) P. H. McFarlane and D. W. Russell, *Chem. Commun.*, 475 (1969).
(129) R. S. Goudie and P. N. Preston, *J. Chem. Soc. C*, 1718 (1971).
(130) I. Murase, *Bull. Chem. Soc. Jap.*, **32**, 827 (1959).
(131) W. Seibert, *Chem. Ber.*, **81**, 266 (1948).
(132) A. Reissert, *ibid.*, **40**, 4209 (1907).
(133) A. Schillinger and S. Wleügel, *ibid.*, **16**, 2222 (1883).
(134) A. Kliegl, *ibid.*, **41**, 1845 (1908).
(135) I. Tanasescu and E. Ramontianu, *Bull. Soc. Chim. Fr.*, **53**, 918 (1933).
(136) K. Lehmstedt, *Chem. Ber.*, **68**, 1455 (1935).
(137) I. Tanasescu and Z. Frenkel, *Stud. Univ. Babes-Bolyai, Ser. 1*, No. 2, 145 (1959); *Chem. Abstr.*, **55**, 5496 (1961).
(138) I. Tanasescu and Z. Frenkel, *Bull. Soc. Chim. Fr.*, 693 (1960).
(139) I. Tanasescu, L. Almasi, and A. Hantz, *Acad. Repub. Pop. Rom., Filiala Cluj, Stud. Cercet. Chim.*, **11**, 105 (1960); *Chem. Abstr.*, **55**, 11415 (1961).
(140) T. Zincke and K. Siebert, *Chem. Ber.*, **39**, 1930 (1906).
(141) J. D. Loudon and G. Tennant, *J. Chem. Soc.*, 3092 (1962).
(142) T. Zincke and W. Prenntzell, *Chem. Ber.*, **38**, 4116 (1905).
(143) S. Secareanu and A. Silberg, *Bull. Soc. Chim. Fr.*, **3**, 1777 (1936).
(144) I. Tanasescu and A. Silberg, *ibid.*, **51**, 1357 (1932).
(145) I. Tanasescu and M. Suciu, *ibid.*, **3**, 1753 (1936).

Table XVI

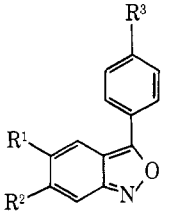
Acid-Catalyzed Conversion of *o*-Nitrobenzene Derivatives into Anthranils

Starting material	*Reaction conditions*	*Product*	*Yield, %*	*Ref*
119a + 120a	Concd H_2SO_4/room temp/4 days	**121a**	20	134
122	$SOCl_2$–$CHCl_3$/reflux	**121m**	*a*	146
122	Concd H_2SO_4/room temp/few min	**121a**	45	147
119a + 120b	Concd H_2SO_4/room temp/24 hr	**121b**	*a*	134
122 (Br for OH)	AcOH/45°/few min	**121c**	*a*	150
119c + 120a	Concd H_2SO_4/room temp/24 hr	**121d**	26	135
119c + 120b	*b*	**121e**	*a*	139
119c + 120c	Concd H_2SO_4/room temp/48 hr	**121f**	72	138
119c + 120d	Concd H_2SO_4–$NaNO_2$/room temp/48 hr	**121g**	54	137
119a + 120e	HBr–ether/room temp/24 hr	**121h** **121j**	*a* *a*	141
119a + 120e	HCl–AcOH/room temp/1 hr	**121i**	80	140
119a + 120e	HCl–ether/room temp/24 hr	**121i**	Quant	141
119b + 120f	$ZnCl_2$/100°/10 hr	**121k**	*a*	145[c]
119a + 120g	Concd HCl/110–115°/10 hr	**121l**	33	142

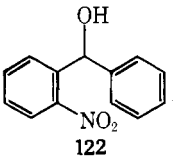
[a] No yield quoted. [b] No conditions given. [c] *Cf.* ref 144.



	R^1	R^2		R^3
119a	H	H	**120a**	H
b	Cl	H	**b**	Me
c	H	NO_2	**c**	Br
			d	I
			e	OH
			f	NH_2
			g	NMe_2

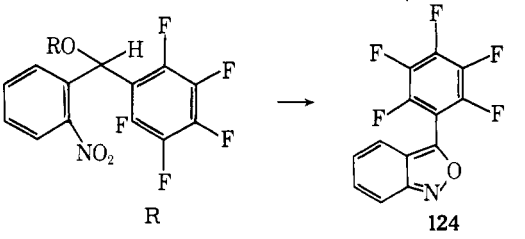


	R^1	R^2	R^3
121a	H	H	H
b	H	H	Me
c	Br	H	H
d	H	NO_2	H
e	H	NO_2	Me
f	H	NO_2	Br
g	H	NO_2	I
h	H	H	OH
i	Cl	H	OH
j	Br	H	OH
k	Cl	H	NH_2
l	Cl	H	NMe_2
m	Cl	H	H



122

this case being achieved by entry of chloride ion (Table XVI).[141] In the reactions catalyzed by hydrogen bromide[141] or hydrogen chloride in the presence of quinol,[141] halogen-free products are obtained (Table XVI). The initial formation of benzhydrol intermediates (*cf.* **122**) in these reactions is supported by the conversion of *o*-nitrobenzhydrol (**122**) either by treatment with thionyl chloride[146] or concentrated sulfuric acid[147] into 3-phenylanthranil (**121a**) (Table XVI) and by the related process (**123** → **124**)[148] (*cf.* also ref 149).



123a H
b Ts

Starting material **123**	Reaction conditions	Yield, % **124**
a	50 aq H_2SO_4/15°/1.5 hr	61
a	Liq paraffin/165°/45 min	14
a	Liq paraffin/210°/15 min	25
b	Toluene/reflux/2 hr	28

Significantly, the benzhydrol **122** is also converted under acidic conditions[147] to *o*-nitrosobenzophenone (*cf.* section III.A). In related reactions[150,151] 2-nitrobenzhydryl bromide (**122**, Br for OH) is rapidly transformed in acetic acid into *o*-nitrosobenzophenone (*cf.* section III.A) or into 5-bromo-3-phenylanthranil (**121c**), the proportion of the latter product increasing with increasing concentration of hydrobromic acid in the medium.[150]

Szmant and Harmuth[152] report that *o*-nitrobenzoic acid condenses with benzene in trifluoroacetic anhydride in the presence of boron trifluoride to give a product which they formulate[152] as 3-phenylanthranil *N*-oxide (**124**: H for F; $\gtrless N^+-O^-$ for $=N-$). The pentafluoro analog (**124**, $\gtrless N^+-O^-$ for $=N-$) is also obtained when the *o*-nitrobenzhydrol derivative **123a** is treated with cold concentrated sulfuric acid.[148]

(146) W. B. Dickinson, *J. Amer. Chem. Soc.*, **86**, 3580 (1964).
(147) A. Silberg and Z. Frenkel, *Rev. Roum. Chim.*, **10**, 1035 (1965); *Chem. Abstr.*, **64**, 12641 (1966).
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(152) H. H. Szmant and C. M. Harmuth, *ibid.*, **81**, 962 (1959).

Table XVII

3-Arylazoanthranil *N*-Oxides (128)

Starting material	*Reaction conditions*	*Product (128)*	*Yield, %*	*Ref*
125a	$Pb(OAc)_4$–CH_2Cl_2/70°	**a**	76	161
125b	Br_2–NaOAc–AcOH/room temp	**b**	*a*	153
125c	Br_2–NaOAc–AcOH/room temp	**c**	*a*	154
125d	$Pb(OAc)_4$–CH_2Cl_2/0°	**d**	54	161
126a	Concd NH_4OH–benzene	**e**	*a*	153
126b	EtOH/reflux/few min	**c**	*a*	154
126c	NH_4OH–benzene/25°/5 min	**d**	77	160
126d	Concd NH_4OH–benzene/room temp/few min	**f**	*a*	153
126e	Concd NH_4OH/warm	**g**	*a*	156
126f	NH_4OH–benzene/25°/5 min	**h**	91	160
126g	Concd NH_4OH–benzene/room temp/few min	**i**	*a*	153
126h	EtOH/reflux	**j**	*a*	158
126i	Concd NH_4OH/warm/few min	**k**	*a*	155
126j	Concd NH_4OH/warm/few min	**l**	*a*	155
126k	NH_3(gas)–benzene/room temp/few min	**m**	*a*	157

[a] No yield quoted.

The products formed[153–158] in unspecified yield when arylhydrazones (**125**) of *o*-nitrobenzaldehydes are treated with bromine in the presence of sodium acetate, or when the derived hydrazidic halides (**126**) react with ammonia in benzene, are formulated[159] as 3-arylazoanthranil *N*-oxides (**128**) (Table XVII). A recent study[160] of the hydrazidic halide transformation indicates that the yields of N-oxides **128** are of the order of 90%. The formation of nitrile–imine intermediates[159] (**127**) in these reactions is substantiated by a recent kinetic study.[160] 3-Phenylazoanthranil *N*-oxide (**128a**) and the nitro derivative **128d** are also obtained in moderate yield by oxidizing the corresponding hydrazones (**125a** and **125d**) with lead tetraacetate[161] (Table XVII) at low temperature.

A variety of *o*-nitrobenzylcarbonyl derivatives (**129**) cyclize under both acidic and basic conditions, and thermally, to afford simple anthranil derivatives (**130**) (Table XVIII).[162–170] The sole structural requirement for the success of these cyclizations appears to be the presence of a moderately acidic benzylic C–H group. A recent study of the conversions of *o*-nitro-

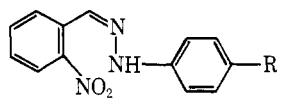
Table XVIII

Formation of Anthranils (130) from *o*-Nitrobenzylcarbonyl Compounds (129)

Starting material (129)	*Reaction conditions*	*Product (130)*	*Yield, %*	*Ref*
a	Concd H_2SO_4/105–110°/3 hr	**b**	50	162
d	Concd H_2SO_4/130°/2 hr	**b**	32	164
c	Concd H_2SO_4/130°/2 hr	**a** 19 **c** 34		165
d	Concd H_2SO_4/120–130°/2 hr	**b** 23 **d** 47		165
e	PCl_5–benzene/reflux/1 hr	**e**	59	167
f	PCl_5–benzene/reflux/1 hr	**f**	78	167
g	4% aq NaOH/reflux/50 hr	**h**	31	167, 168
h	150–190°/2.5 mm	**i**	*a*	170
i	120–160°/2 mm	**j**	40–50	170

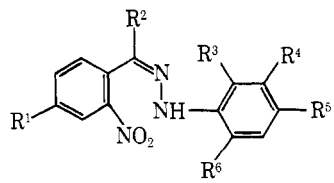
[a] No yield quoted.

and 2,4-dinitrophenylacetic acids[164] (**129c,d**) in hot concentrated sulfuric acid into anthranil and 6-nitroanthranil (**130a,b**), respectively, has demonstrated[165] the intermediate formation of the anthranil-3-carboxylic acids (**130c,d**). Cyclization of the ethylamides **129e,f** to the corresponding anthranils **130e,f** is catalyzed by phosphorus pentachloride in benzene.[167] Base-catalyzed cyclization is exemplified by the conversion[168] of 3,4-dimethoxy-2-nitrophenylacetic acid (**129g**) in warm aqueous alkali to 6,7-dimethoxyanthranil (**130h**) (Table XVIII); the acid (**130g**) is a probable intermediate in

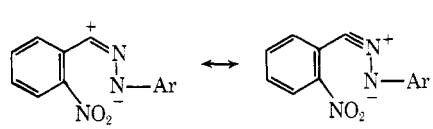


R

125a H
b Cl
c Me
d NO_2



	R^1	R^2	R^3	R^4	R^5	R^6
126a	H	Br	H	H	Br	H
b	H	Br	H	H	Me	H
c	H	Br	H	H	NO_2	H
d	H	Br	Br	H	Br	H
e	H	Br	Br	H	Me	H
f	H	Br	Br	H	NO_2	H
g	H	Br	Cl	H	Cl	Cl
h	H	Br	H	Me	Br	Br
i	H	Cl	Cl	H	Me	H
j	H	Cl	Cl	H	Me	Cl
k	NO_2	Br	Br	H	Me	H



127

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(154) F. D. Chattaway and A. B. Adamson, *ibid.*, 157 (1930).
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(162) S. S. Joshi and I. R. Gambhir, *J. Amer. Chem. Soc.*, **78**, 2222 (1956).
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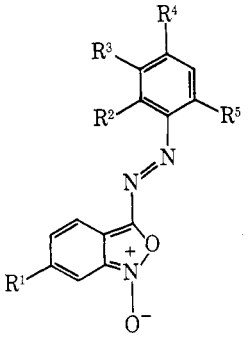
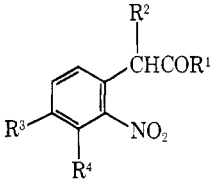
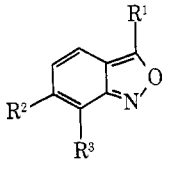


	R^1	R^2	R^3	R^4	R^5
128a	H	H	H	H	H
b	H	H	H	Cl	H
c	H	H	H	Me	H
d	H	H	H	NO_2	H
e	H	H	H	Br	H
f	H	Br	H	Br	H
g	H	Br	H	Me	H
h	H	Br	H	NO_2	H
i	H	Cl	H	Cl	Cl
j	H	H	Me	Br	Br
k	H	Cl	H	Me	H
l	H	Cl	H	Me	Cl
m	NO_2	Br	H	Me	H

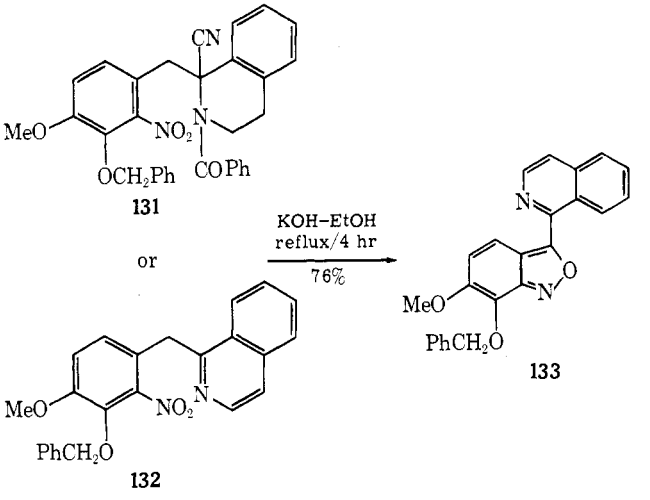


	R^1	R^2	R^3	R^4
129a	Me	H	NO_2	H
b	Me	COMe	NO_2	H
c	OH	H	H	H
d	OH	H	NO_2	H
e	$NH(CH_2)_2Ph$	H	MeO	MeO
f	$NHPr^i$	H	MeO	MeO
g	OH	H	MeO	MeO
h	EtO	CO_2Et	H	H
i	EtO	CN	H	H



	R^1	R^2	R^3
130a	H	H	H
b	H	NO_2	H
c	CO_2H	H	H
d	CO_2H	NO_2	H
e	$CONH(CH_2)_2Ph$	MeO	MeO
f	$CONHPr^i$	MeO	MeO
g	CO_2H	MeO	MeO
h	H	MeO	MeO
i	CO_2Et	H	H
j	CN	H	H

this reaction. Analogous cyclizations are the base-catalyzed conversions[169] of the *o*-nitrobenzylisoquinoline derivatives **131** and **132** to the 3-(1-isoquinolyl)anthranil (**133**). These reactions are probably mechanistically related to the base-catalyzed cyclization of *o*-nitrotoluene to anthranilic acid (see section III.C).



The thermal conversion of *o*-nitrobenzyl derivatives into anthranils is illustrated by the formation[170] of 3-ethoxycarbonyl- (**130i**) and 3-cyanoanthranil (**130j**) on attempted distillation of diethyl *o*-nitrophenylmalonate (**129h**) and ethyl *o*-nitrophenylcyanoacetate (**129i**), respectively (Table XVIII). These reactions are analogous to the pyrolytic cyclizations of *N*-*o*-nitrophenylurethanes to benzofurazans[171] (*cf.* section II.C.2) and may involve a related mechanism.

Anthranil-3-carboxylic acid (**130c**) is obtained (75%) by warming *o*-nitrophenacyl chloride with aqueous alkali.[35] This unusual anthranil synthesis can be explained by the intermediate formation and rearrangement of 1-hydroxyisatin.[35]

6. *Benzothiazoles*

Benzothiazoles and 2,2′-bibenzothiazolyls are among the products of the base-catalyzed and thermal transformations of compounds containing an *o*-nitroarylthio substituent. However, yields are low and complex mixtures are often obtained. Consequently processes of this type offer no advantage over conventional synthetic methods for benzothiazoles[172] and their dimers.[173,174]

o-Nitrophenylphenacyl sulfide (**134**) reacts with alkali[175] to give a complex mixture containing at least 12 compounds, three of which have been characterized as benzothiazole derivatives (**135a–c**). Under certain conditions the procedure affords 2-benzoylbenzothiazole in moderate yield (see Table XIX). The mechanism of benzothiazole formation is unclear particularly in relation to the nature and timing of the reduction process which must be involved. The efficient conversion[175] of 2-benzoylbenzothiazole into benzothiazole by treatment with potassium *tert*-butoxide in *tert*-butyl alcohol accounts for its presence in the reaction product.

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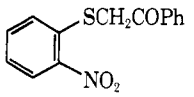
Table XIX

Effect of Reaction Conditions on the Formation of Benzothiazole Derivatives in the Alkaline Decomposition of *o*-Nitrophenylphenacyl Sulfide[176]

Reagent	Solvent	Temp, °C	Reaction time, hr	Product yield, % 135a	135b	135c
KOH	MeOH	65	0.5	4.7	3.0	30.6
KOMe	MeOH	65	0.5	6.7	0.7	27.0
KO-*t*-Bu	*t*-BuOH	82	0.5	18.9	1.8	6.5



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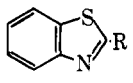
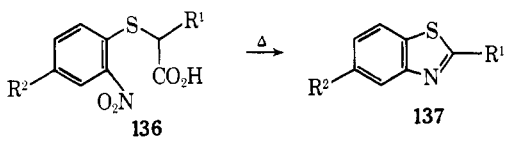


R

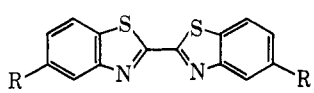
135a H
b Ph
c PhCO

Benzothiazoles (**137**) and bibenzothiazolyls (**138**) are among the products (*cf.* section II.E.7) of the thermolysis[129] of *o*-nitrophenylthioacetic acid and its derivatives (**136**). Analogous



136 137

	R^1	R^2	Reaction temp, °C	Yield, %
a	H	H	210	5
b	Me	H	215	4
c	H	NO_2	220	25
d	Me	NO_2	220	18

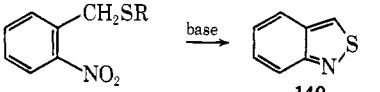


	R	Yield, %
138a	H	6 (from **136a**)
b	NO_2	9 (from **136c**), 12 (from **136d**)

products are formed[93] by pyrolysis of *o*-nitroaryl derivatives of α-amino acids (see section II.B.2) and *o*-nitroaryloxyacetic acids (see section II.B.4).

7. 2,1-Benzisothiazoles (Thioanthranils)

In general, the nature of the cyclizations leading to anthranils (*cf.* section II.B.5) precludes their use for the synthesis of thioanthranils. Thioanthranil (**140**) itself is formed in low yield when the thiol **139a** is treated with alkali or acid[176] or when *o*-nitrobenzylthioacetic acid (**139b**) is distilled with aqueous alkali.[177] However, the precise course of these reactions is not clear, although the formation of thioanthranil infers that interaction between the nitro group and the ortho side chain occurs at some stage.



139a H
b CH_2CO_2H

140

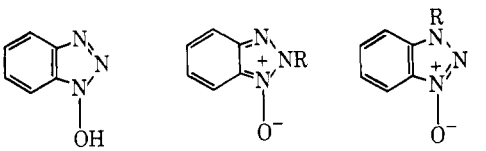
C. FIVE-MEMBERED HETEROCYCLES CONTAINING THREE HETEROATOMS

1. Benzo-1,2,3-triazoles

With only a few exceptions,[178] *o*-nitrobenzene derivatives are key starting materials for the synthesis of benzotriazoles and benzotriazole *N*-oxides. Reductive cyclization using sodium or ammonium sulfide or zinc and alkali of *o*-nitroazo- or azoxybenzenes affords 2-substituted benzotriazoles or their 1-*N*-oxides.[179]

The base-catalyzed cyclization of *o*-nitrophenylhydrazines to afford 1-hydroxybenzotriazoles (**141**) [which are tautomeric with benzotriazole *N*-oxides (**143**, R = H)] was discovered by Freund[180] and by Willgerodt[181] and was later clarified by Nietzki and Braunschweig.[182] Subsequently, related procedures involving *in situ* generation of the hydrazine derivative have been widely used to prepare 1-hydroxybenzotriazoles.

N- and N-substituted *o*-nitroarylhydrazines also cyclize readily, providing synthetic routes to 2- and 3-substituted benzotriazole *N*-oxides **142** and **143**, respectively. Representative examples of this type of cyclization are shown in Table XX although it should be noted that yields are often difficult to ascertain from the early literature. It should also be borne in mind that the list is not comprehensive; a survey of the early literature has been provided by Katritzky and Lagowski[183a] and further selected examples are given in ref 184.



141 142 143

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(177) Y. Iskander and Y. Riad, *J. Chem. Soc.*, 2054 (1951).
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(179) For a summary of synthetic routes to benzotriazoles, see "Chemistry of Carbon Compounds," E. H. Rodd, Ed., Vol. IVA, Elsevier, Amsterdam, 1964, pp 449–450; *cf.* also F. R. Benson and W. L. Savell, *Chem. Rev.*, **46**, 1 (1950); N. Zinin, *Justus Liebigs Ann. Chem.*, **114**, 217 (1860); A. Werner and E. Stiasny, *Chem. Ber.*, **32**, 3256 (1899); E. Bamberger and R. Hübner, *ibid.*, **36**, 3822 (1903); K. Fries, W. Franke, and W. Bruns, *Justus Liebigs Ann. Chem.*, **511**, 241 (1934).
(180) M. Freund, *Chem. Ber.*, **22**, 1663 (1889).
(181) C. Willgerodt and M. Ferko, *J. Prakt. Chem.*, **37**, 345 (1888).
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(185) E. Müller and G. Zimmermann, *J. Prakt. Chem.*, **111**, 277 (1925).
(186) O. M. Shemyakina, B. M. Bogoslovskii, and M. M. Shemyakin, *Zh. Obshch. Khim*, **26**, 1940 (1956); *J. Gen. Chem. USSR*, **26**, 2165 (1956).
(187) N. J. Leonard and K. Golankiewicz, *J. Org. Chem.*, **34**, 359 (1969).
(188) T. Curtius and M. Mayer, *J. Prakt. Chem.*, **76**, 369 (1907).
(189) A. K. Macbeth and J. R. Price, *J. Chem. Soc.*, 1637 (1934).
(190) O. L. Brady and J. N. E. Day, *ibid.*, **123**, 2258 (1923).
(191) B. Vis, *Recl. Trav. Chim. Pays-Bas*, **58**, 847 (1939).

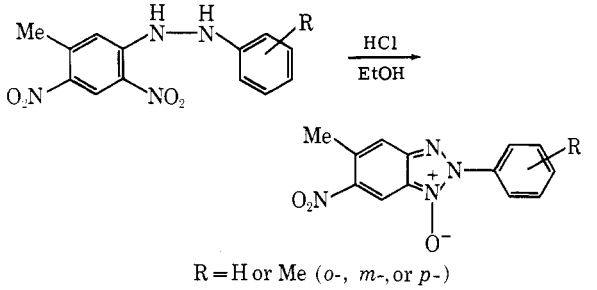
Table XX

Formation of 1-Hydroxy-1,2,3-benzotriazoles by the Base-Catalyzed Cyclization of *o*-Nitroarylhydrazines[a]

Product, 1-hydroxy-1,2,3-benzotriazole deriv (**141**)	*Yield, %*	*Ref*
Unsubstituted	90[187]	182, 185-187
6-Nitro	14,[186] 70[189]	186, 188, 189
5-Methyl-6-nitro		190
4-Methyl-6-nitro		190
6-Chloro	64[b]	191
6-Bromo	66[187]	187, 191
3-Methyl-4,6-dichloro	43	191
3-Methyl-4,6-dibromo		191
5-Halogeno	68 (for Br)	192
5-Halogeno-6-methyl		192
5,6-Dihalogeno	66[187] (for Cl)	187, 192
4,6-Dibromo		192
4,5-Dichloro	85	187
4,5,6-Trichloro	67	187
4,6,7-Trichloro	6	187
4,5,6,7-Tetrachloro	40	187
4-, 5-, 6-, and 7-substituted 2-(*p*-sulfamylphenyl)[c]	50–71	193
5-Chloro-6-nitro-2-phenyl		194
4,5-Dichloro-6-nitro-2-phenyl		194
4-Chloro-5-bromo-6-nitro-2-phenyl		194
5-Methyl-6-nitro-2-phenyl		195
5-Methyl-6-nitro-2-tolyl (*o*-, *m*- and *p*-)		195

[a] The *o*-nitroarylhydrazines are often generated *in situ* from *o*-halogeno-[185,187] *o*-nitro-,[191] and *o*-methoxynitroarenes.[190] [b] As the hydrazine salt. [c] Substituents at positions 4, 5, 6, and 7 include NO_2, Me, and halogen.

A related, though less thoroughly investigated, procedure involves the acid-catalyzed conversion of *o*-nitrohydrazobenzene derivatives into *N*-arylbenzotriazole *N*-oxides, *e.g.*, eq 6 (see ref 195) and 7. Cyclization of *o*-nitrohydrazobenzenes

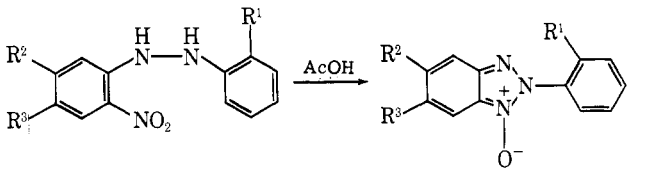


(6)

R = H or Me (*o*-, *m*-, or *p*-)

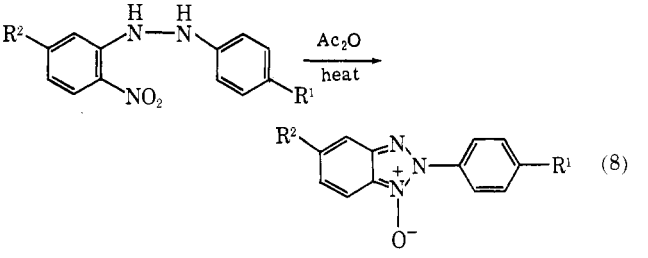
to *N*-arylbenzotriazole *N*-oxides can also be achieved by warming with acetic anhydride (eq 8).

The formation[198] of benzotriazole *N*-oxides (**145**) from acid-catalyzed reaction of the β-hydroxy ketones **144** with 2,4-dinitrophenylhydrazine is considered[188a] to involve the intermediate formation of pyrazoline derivatives. The *N*-oxide **145a** is also produced (56% yield)[198] in a similar reaction of 2,4-dinitrophenylhydrazine with a mixture of cyclohexyloxybutanone and 4-*n*-butoxybutanone, and an analogous product (**145b**) is formed in 49% yield using 1-ethoxypentan-3-one; the function of the mixed reagent has not been clarified.[198]



(7)

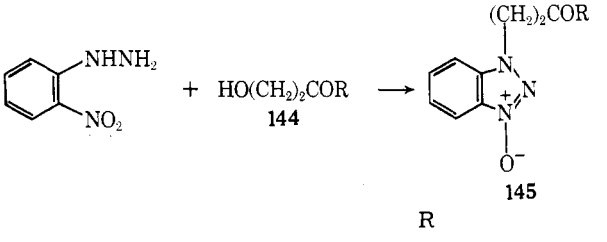
	R^1	R^2	R^3	Ref
a	SO_2NH_2	H	H	193
b	Me	Cl	NO_2	194



(8)

	R^1	R^2	Ref
a	H	Cl	196
b	NO_2	Cl	197

yields not quoted



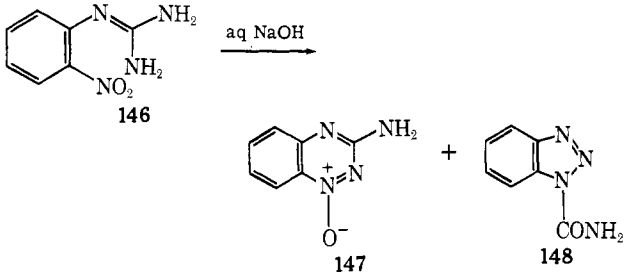
145

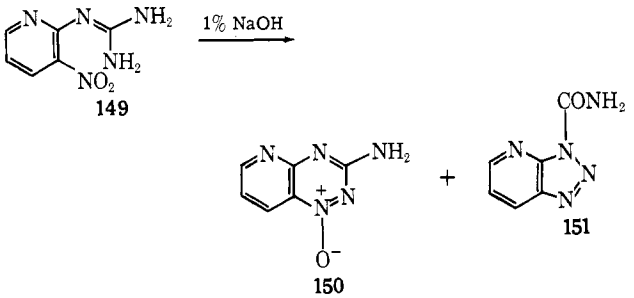
R	
a	Me (26% yield)
b	Et (46% yield)

Benzotriazoles, rather than 1-*N*-oxides, are obtained when *o*-nitrohydrazobenzene derivatives or their precursors are heated under reflux in ethanol[193,194,199] or are treated with potassium iodide in acetic acid.[200]

Benzotriazole derivatives (**148**) are also formed as secondary products in the course of the synthesis of benzo-1,2,4-triazine 1-*N*-oxides (**147**) by the base-catalyzed cyclization of *o*-nitrophenylguanidines (**146**) (*cf.* section II.F.1).[201] The triazole **148** has been shown[201a] to arise by base-catalyzed rearrangement of the N-oxide **147**. An analogous reaction (**149** → **150** + **151**) occurs in the pyridine series;[202] in a separate experiment it has been shown[202] that the N-oxide **150** is rapidly and efficiently (77% yield) converted to the triazole **151** under the

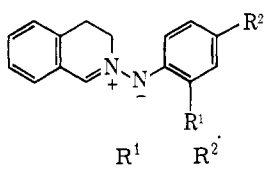
(192) H. Singh and R. S. Kapil, *J. Org. Chem.*, **25**, 657 (1960).
(193) A. Prakash and I. R. Gambhir, *J. Indian Chem. Soc.*, **41**, 845 (1964).
(194) R. S. Kapil and S. S. Joshi, *ibid.*, **36**, 417 (1959).
(195) M. Giua and M. Giua, *Gazz. Chim. Ital.*, **53**, 165 (1923).
(196) A. Mangini and C. Deliddo, *ibid.*, **65**, 214 (1935).
(197) A. Mangini, *ibid.*, **65**, 1191 (1935).
(198) H. J. Shine, L.-T. Fang, H. E. Mallory, N. F. Chamberlain, and F. Stehling, *J. Org. Chem.*, **28**, 2326 (1963).
(199) T. Zincke and E. Scharff, *Justus Liebigs Ann. Chem.*, **370**, 297 (1909).
(200) C. Willgerodt and H. Klein, *J. Prakt. Chem.*, **60**, 97 (1899).
(201) (a) J. A. Carbon, *J. Org. Chem.*, **27**, 185 (1962); (b) *ibid.*, **26**, 455 (1961).
(202) J. A. Carbon and S. H. Tabata, *ibid.*, **27**, 2504 (1962).





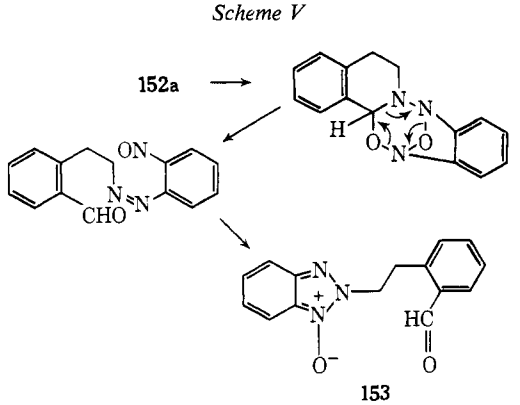
influence of more concentrated alkali (5% aqueous sodium hydroxide).

A number of reactions leading to benzotriazole derivatives have been rationalized on the basis of the intramolecular cycloaddition of an *o*-nitro group to an azomethine-imine or nitrile-imine side chain. Treatment of 2-(*o*-nitrophenylamino)-3,4-dihydroisoquinolinium bromide with pyridine generates the 1,3-dipole **152a** which can be trapped with phenyl isocyanate.[203] However, whereas the ylide **152b** dimerizes in the absence of dipolarophiles, the isomer **152a** is transformed into the benzotriazole **153** in 86% yield; the mechanism in Scheme V has been suggested.[203]

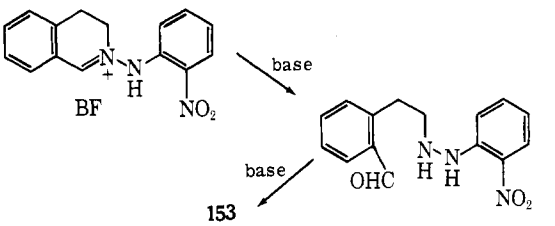


	R^1	R^2
152a	NO_2	H
b	H	NO_2
c	NO_2	NO_2

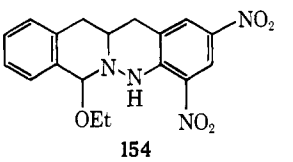
Scheme V



Scheme VI

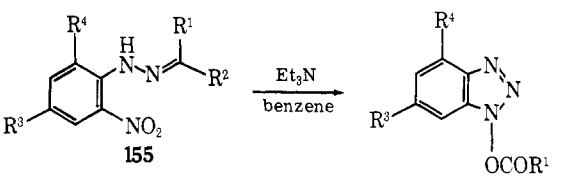


The alternative mechanism[6] in Scheme VI is not excluded by the available evidence, however. The nitro analog of **153** is formed almost quantitatively from the ylide **152c** in similar fashion, as well as by thermolysis of the closely related ethoxyisoquinoline derivative **154**.[203]

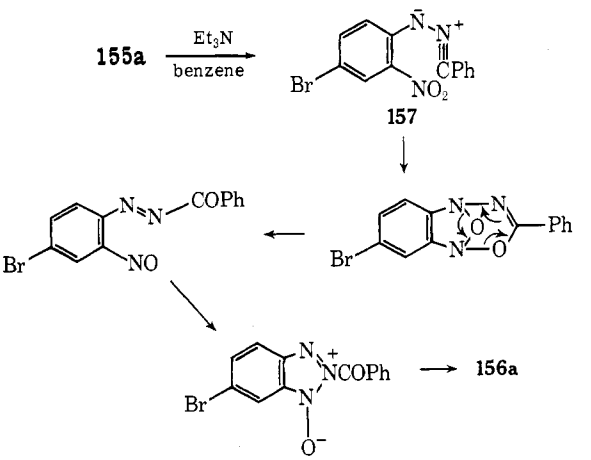


154

In closely related procedures, the hydrazidic halides **155a,b** are converted by treatment with triethylamine into the benzotriazoles **156a,b** in 20 and 71% yields, respectively.[204,205] A mechanism invoking the intermediacy of a nitrile-imine (*e.g.*, **157**) has been suggested,[204,205] although such an intermediate could not be trapped (at least in the case of **155a**[204]) by treatment with phenyl isocyanate.



	R^1	R^2	R^3	R^4	Ref
a	Ph	Br	Br	H	204
b	*s*-$(MeO)_3C_6H_2$	Cl	NO_2	NO_2	205

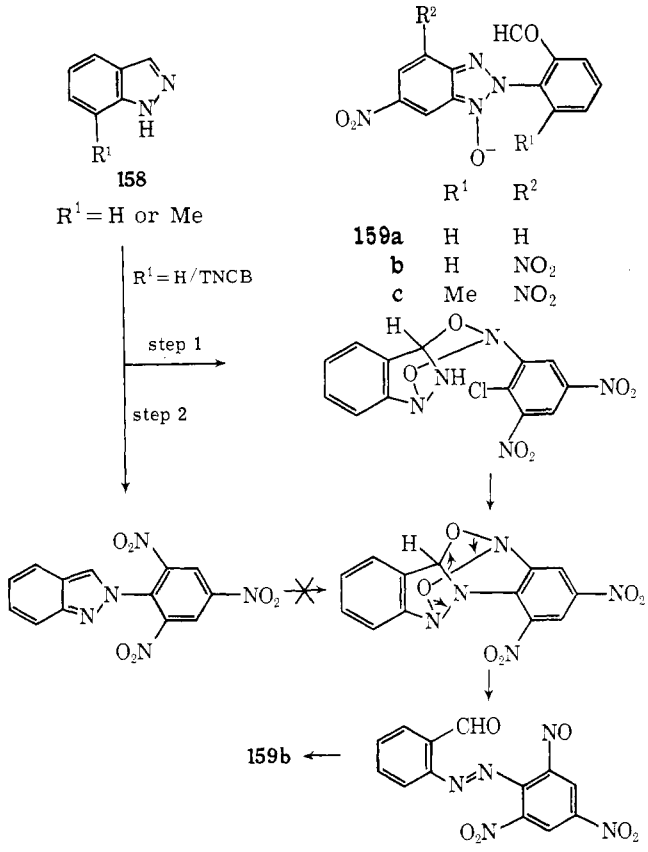


(203) R. Grashey, *Angew. Chem. Int. Ed. Engl.*, **1**, 158 (1962).

(204) M. S. Gibson, *Chem. Ind. (London)*, 1699 (1965).

(205) R. Huisgen and V. Weberndörfer, *Chem. Ber.*, **100**, 71 (1967).

Scheme VII



The recently reported[206,207] synthesis of 2-(2′-formylaryl)-substituted benzotriazole 1-*N*-oxides (**159**) by the reaction of indazoles **158** with 2,4-dinitrofluorobenzene (DNFB) or 2,4,6-trinitrochlorobenzene (TNCB) is also considered[207] to involve a cycloaddition step which precedes intramolecular nucleophilic displacement of chlorine (step 1 rather than step 2 in Scheme VII).

2. *Benzo-2,1,3-oxadiazoles (Benzofurazans)*

Benzofurazans are normally prepared by the reduction of benzofuroxans with, for example, hydroxylamine in alkaline solution[208a] or with trimethyl phosphite.[208b] Recently a useful synthetic method (*cf.* **160** → **161**) involving the thermolysis of methyl *N*-(*o*-nitroaryl)carbamates has been reported.[171] The yields are not particularly high (Table XXI), but the method is direct and the starting materials are readily available.

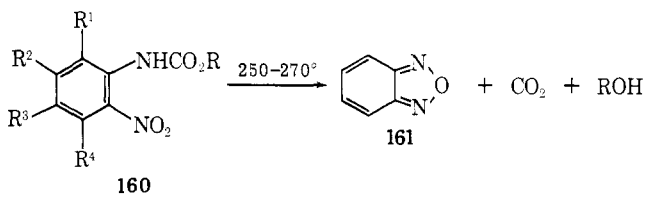


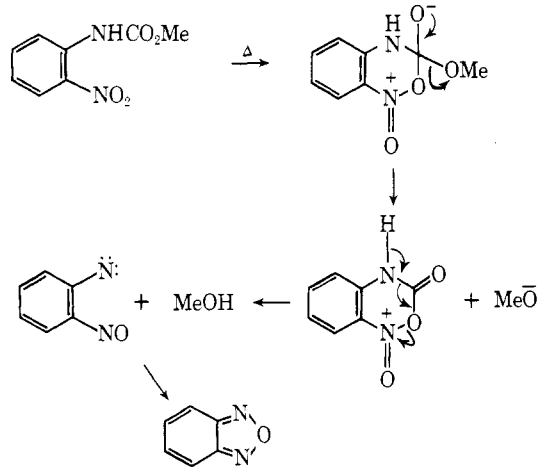
Table XXI

Benzofurazans (161) from the Thermolysis of Methyl *N*-(*o*-Nitroaryl)carbamates (160, R = Me) at 250–270°[171]

Compound 160				Product 161,
R^1	R^2	R^3	R^4	% yield
Me	H	H	H	30
MeO	H	H	H	30
H	MeO	H	H	20
H	Me	H	H	50
H	H	H	H	50
H	Cl	H	H	40
H	NO_2	H	H	35
H	Me	Me	H	48
H	H	Me	H	46
H	H	Cl	H	20
H	H	H	Me	50

The benzofurazans probably arise directly from the carbamate esters rather than from an intermediate *o*-nitroaryl isocyanate since pyrolysis of *o*-nitrophenyl isocyanate under conditions identical with those used for the carbamates gave a much reduced yield (20%) of benzofurazan.[171] The preferred substrate in these reactions is the methyl ester (**160**, R = Me) rather than the homologous esters (**160**, R = Et, *i*-Pr) which on pyrolysis produce undesirable by-products containing alkenes; the use of aryl carbamates (**160**, R = Ph, *p*-$MeOC_6H_4$, *p*-$O_2NC_6H_4$) resulted either in noticeably lower yields of benzofurazans or complete inhibition of the reaction. Attempts to obtain kinetic data in a variety of solvents were unsuccessful, but the mechanism in Scheme VIII has been proposed.[171]

Scheme VIII



3. *Benzo-2,1,3-oxadiazole 1-N-Oxides (Benzofuroxans)*

With few exceptions the available methods[209] for the synthesis of benzofuroxans involve nitro-group side-chain interactions. Excellent yields of benzofuroxans are obtained by oxidizing *o*-nitroaniline derivatives with aqueous alkaline hypochlo-

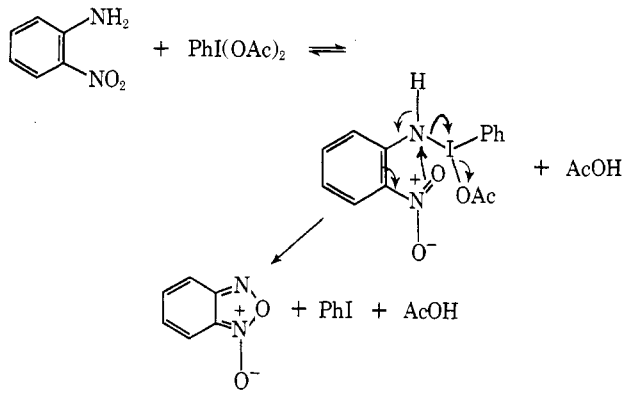
(206) J. Elguero, A. Fruchier, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 2619 (1967).

(207) J. Elguero, A. Fruchier, R. Jacquier, and U. Scheidegger, *ibid.*, 3331 (1968).

(208) (a) R. J. Gaughran, J. P. Picard, and J. V. R. Kaufman, *J. Amer. Chem. Soc.*, 76, 2233 (1954); (b) A. J. Boulton, A. C. Gripper-Gray, and A. R. Katritzky, *J. Chem. Soc.*, 5958 (1965).

(209) A. J. Boulton and P. B. Ghosh, *Advan. Heterocycl. Chem.*, 10, 1 (1969).

Scheme IX



rite;[210] phenyliodoso acetate in benzene solution[211] has also been used as an oxidant, but this procedure is occasionally unsatisfactory. For example,[211a] oxidation of 3-chloro-, 3-methyl-, and 3-methoxy-2-nitroanilines gives a mixture of the benzofuroxan, azo compound, and tars; 4-methoxy-2-nitroaniline yields tars and a small quantity of azo compound; the 6-methoxy analog gives tars and a low yield of benzofuroxan; and 6-methyl-2-nitroaniline affords only tars. When the solvent is changed from benzene to acetic acid, all substituted 2-nitroanilines yield azo compounds and/or tars, and no product of oxidative cyclization can be isolated.

The mechanism originally proposed[211a,b] for benzofuroxan formation has recently been considerably modified[212] (*cf.* Scheme IX) in the light of kinetic investigations. This modified mechanism is in accord with the behavior[213] of 2-nitroiodobenzene dichloride in which the nitro group acts as a neighboring nucleophile in the displacement of chlorine.

Benzofuroxans can also be prepared, often in good yields, by the thermolysis or photolysis of *o*-nitroarylazides (*e.g.*, **162 → 163**)[214] and (**164 → 165**); some representative examples are shown in Table XXII (*cf.*, also ref 183c).

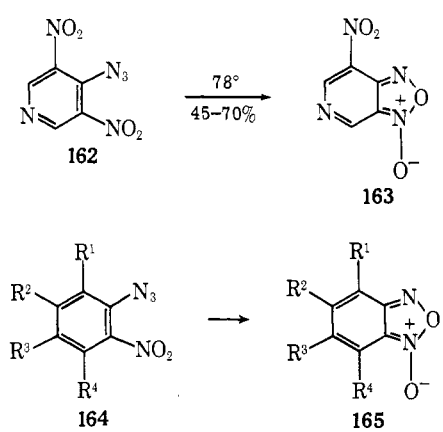


Table XXII

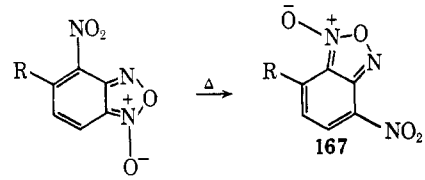
Benzofuroxan Derivatives (165) from Thermolysis of *o*-Nitroarylazides (164)

Compound 164				Pyrolysis temp, °C	Yield of benzofuroxan derivative (165), %	Ref
R^1	R^2	R^3	R^4			
H	H	H	H	100	80	215
Ph	H	H	H	120	55[a]	216
Ph	H	NO_2	H	120	83[a]	216
H	H	NO_2	H	75	93	217
H	N_3	NO_2	H	80–85	*b*	217
H	Cl	NO_2	H	100	*b*	218
H	NO_2	NO_2	H	100	50	218
H	Cl	Cl	H	Not quoted	64	219
H	H	NHAc	H	118	90	220
H	H	CO_2H	H	110	70	220
H	NMe_2	H	H	110	88	220
H	NMe_2	Cl	H	110	95	220
Br	Br	H	H	110	88	221
Br	H	Br	H	110	82	221
Br	H	H	Br	110	71	221

[a] Also obtained in similar yields by photolysis. [b] Yield not quoted.

The lower temperatures (<120°) required to effect thermolysis of *o*-nitroaryl azides, as compared with aryl azides in general (140–170°), have been rationalized[222] in terms of a mechanism involving participation by the *o*-nitro group in the expulsion of nitrogen from the azide side chain. Such a concerted process is in accord with the low entropies of activation observed[223] for pyrolyses of this type.

A closely related process is presumably involved in the thermal isomerization of nitrobenzofuroxans (**166 → 167**). A related rearrangement is involved in the conversion of the



R	Yield, %	Ref
Me	75	224
Cl	72	225

(210) A. G. Green and F. M. Rowe, *J. Chem. Soc.*, **101**, 2443 (1912); F. M. Rowe and J. S. H. Davies, *ibid.*, **117**, 1344 (1920).

(211) (a) L. K. Dyall and K. H. Pausacker, *Aust. J. Chem.*, **11**, 491 (1958); (b) K. H. Pausacker and J. G. Scroggie, *J. Chem. Soc.*, 4499 (1954); (c) K. H. Pausacker, *ibid.*, 1989 (1953).

(212) L. K. Dyall and J. E. Kemp, *Aust. J. Chem.*, **20**, 1625 (1967); L. K. Dyall, J. O. M. Evans, and J. E. Kemp, *ibid.*, **21**, 409 (1968).

(213) L. J. Andrews, R. M. Keefer, and E. A. Jeffrey, *J. Org. Chem.*, **30**, 617 (1965).

(214) A. S. Bailey, M. W. Heaton, and J. I. Murphy, *J. Chem. Soc. C*, 1211 (1971).

(215) P. A. S. Smith and J. H. Boyer, *Org. Syn.*, **31**, 14 (1951).

(216) P. A. S. Smith and B. B. Brown, *J. Amer. Chem. Soc.*, **73**, 2435 (1951).

(217) R. J. Gaughran, J. P. Picard, and J. V. R. Kaufman, *ibid.*, **76**, 2233 (1954).

(218) A. S. Bailey and J. R. Case, *Tetrahedron*, **3**, 113 (1958).

(219) A. J. Boulton, A. C. Gripper-Gray, and A. R. Katritzky, *J. Chem. Soc. B*, 909 (1967).

(220) A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *J. Chem. Soc. C*, 971 (1966).

(221) W. Moje, *J. Org. Chem.*, **29**, 3722 (1964).

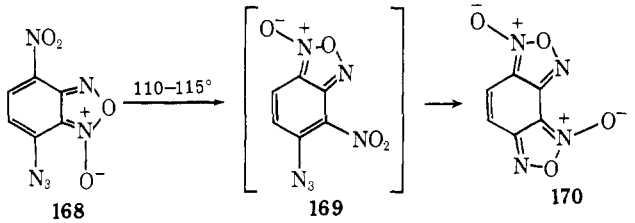
(222) *Cf.* ref 89 and references cited therein.

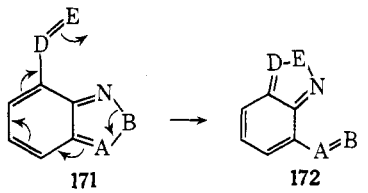
(223) *Cf.* R. A. Abramovitch and E. P. Kyba in "Chemistry of the Azido Group," S. Patai, Ed., Wiley-Interscience, New York, N. Y., 1971, p 261.

(224) (a) A. J. Boulton and A. R. Katritzky, *Proc. Chem. Soc., London*, 257 (1962); (b) *Rev. Chim., Acad. Repub. Pop. Roum.*, **7**, 691 (1962).

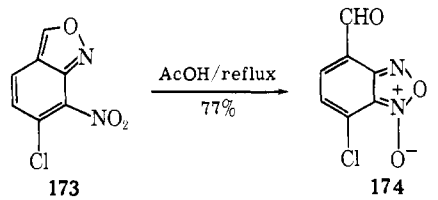
(225) A. J. Boulton, A. C. Gripper-Gray, and A. R. Katritzky, *J. Chem. Soc.*, 5958 (1965).

azide **168** at 110–115° into the furoxanobenzofuroxan **170**.[225] The azidobenzofuroxan **169** is a plausible intermediate in this reaction. Rearrangements of the type **166** → **167** are members of a general type of process that can be represented[224b] by **171** → **172** where A and D may be N, N^+–O^-, or CR and B and E may be O, NR, or CHR (*cf.* ref 226).





A large number of new benzofuroxans of the types **166** and **167** (R = substituted amino) have now been prepared,[227] and their behavior in relation to the Boulton–Katritzky rearrangement[224] has been evaluated. The recently reported[228] thermal rearrangement of 6-chloro-7-nitroanthranil (**173**) into 7-chloro-4-formylbenzofuroxan (**174**) provides the first example of a benzofuroxan being formed by an isomerization of the general type not involving another benzofuroxan.



D. SIX-MEMBERED HETEROCYCLES CONTAINING ONE HETEROATOM

1. Quinolines

Treatment of the *o*-nitrobenzylidene derivatives (**175**) of a variety of active methylene compounds with aqueous ethanolic potassium cyanide affords, in addition to 1-hydroxyindoles (*cf.* section II.A.1), moderate yields of otherwise inaccessible quinoline *N*-oxides (**177**) (Table XXIII).[13–15] In general, the use of strongly basic catalysts and the presence of powerfully electron-withdrawing substituents in the *o*-nitrobenzylidene derivative favor the formation of the quinoline *N*-oxide as opposed to formation of the 1-hydroxyindole in such reactions. As in the reactions leading to 1-hydroxyindoles (*cf.* section II.A.1), the quinoline *N*-oxides (**177**) are probably formed by the base-catalyzed cyclization of hydrogen cyanide adducts (**176**) which are not normally isolated. This course is supported by the smooth cyclization of the preformed adducts **176a** and **176g** in warm aqueous ethanolic potassium cyanide to the quinoline *N*-oxides **177a** and **177g**. The hydrolysis of the cyano group implicit in the formation of the latter product is also a feature of the reactions[15] **175d** → **177c** and **175f** → **177e** (Table XXIII). In the reactions of the compounds **175e** and **175g** with aqueous ethanolic potassium cyanide, the expected nitriles **177d** and **177f** are accompanied by the imides **178a,b** which are presumably formed by cyclization of intermediate amido esters (*i.e.*, **177d** and **177f**, $CONH_2$ for CN).

Table XXIII

Base-Catalyzed Transformation of *o*-Nitrobenzylidene Derivatives and Related Compounds into Quinoline *N*-Oxides

Starting material	*Reaction conditions*	*Product*	*Yield, %*	*Ref*
175a	KCN–H_2O–EtOH/reflux/15 min	**177a**	27	13
175b	50% aq KCN–EtOH/100°/10 min	**177b**	46	14
175c	50% aq KCN–EtOH/100°/10 min	**177b**	20	14
175d	50% aq KCN–EtOH/room temp/20 min	**177c**	41	15
175e	20% aq KCN–EtOH/warm	**177d**	3	15
		178a	68	
175f	20% aq KCN–EtOH/reflux/30 min	**177e**	*a*	15
175g	10% aq KCN–EtOH/reflux/0.5 hr	**177f**	8	15
		178a	54	
176g	NaOEt–EtOH/room temp/15 hr	**177g**	56	15

[a] Yield not quoted.

Conversion of the adducts **176** into quinoline *N*-oxides (**177**) is thought to involve the cyclization of intermediate hydroxylaminobenzenes produced by an intramolecular redox process.[6] The transformations[229] **179** → **180a** or **180b**, on the other hand, represent simple intramolecular aldol-type processes which have their counterparts in the cyclizations of nitrobiphenyl derivatives discussed later. A closely related process is the base-catalyzed conversion of *o*-nitroveratryl-idenesuccinic acid (**181**) into the quinoline *N*-oxide **182**.[230]

In addition to the indoxylic acid (**18**) (*cf.* section II.A.3), the base-catalyzed condensation of *o*-nitrobenzaldehyde with 1-indanone affords[31] the quinolinoindanone *N*-oxide (**183**) (yield 50%).

Tautomeric 1-hydroxyquinolin-4(1*H*)-ones (**186**) are obtained in excellent yield by condensing *o*-nitrobenzaldehydes (**184**) with certain activated methylene compounds (**185**) in inert solvents using hydrogen halides as catalysts (Table XXIV).[141,231] The *o*-nitrobenzylidene derivatives (*i.e.*, **187**) are probable intermediates in these reactions and in certain cases (*cf.* **187a–c**) are converted under similar conditions into the corresponding *N*-hydroxyquinolones (Table XXIV).[141,231] The use of hydrogen chloride as the catalyst results in chlorination of the 6 position in the product **186**.

When this position is blocked, substitution takes place at the 8 position (Table XXIV).[141,231] In contrast, hydrogen bromide, or hydrogen chloride in the presence of a mild reducing agent such as quinol, promotes condensation without entry of halogen (Table XXIV).[141] Mechanistically these

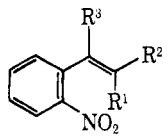
(226) (a) A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *Angew. Chem., Int. Ed. Engl.*, **3**, 693 (1964); (b) *J. Chem. Soc. B*, 1004 (1966); (c) *ibid.*, 1011 (1966).
(227) P. B. Ghosh, *ibid.*, 334 (1968).
(228) A. J. Boulton and R. C. Brown, *J. Org. Chem.*, **35**, 1662 (1970).
(229) A. Zaki and Y. Iskander, *J. Chem. Soc.*, 68 (1943); J. P. Cairns, J. D. Loudon, and A. S. Wylie, unpublished work; *cf.* ref 6.
(230) Y. Ahmad and S. A. Shamsi, *Bull. Chem. Soc. Jap.*, **39**, 195 (1966).
(231) J. D. Loudon and I. Wellings, *J. Chem. Soc.*, 3470 (1960).

Table XXIV

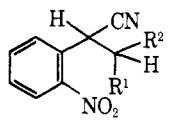
N-Hydroxyquinolin-4(1H)-ones 186 and 189

Starting material	*Reaction conditions*[d]	*Product*	*Yield, %*	*Ref*
184a + 185a	HCl–ether/8 hr	**186b**	*a*	231
184a + 185a	HBr–ether/48 hr	**186a**	60	141
187a	HCl–ether/8 hr	**186b**	*a*	231
187a	HBr–ether/48 hr	**186a**	60	141
187b	HCl–quinol–THF/48 hr	**186c**	90	141
184b + 185b	HCl–ether/48 hr	**186d**[c]	60	141
188a	HCl–ether/24 hr	**189b**	43	232
188a	HCl–ether/20 hr	**189b**	69[b]	233
188a	HBr–ether/48 hr	**189a**	31	232

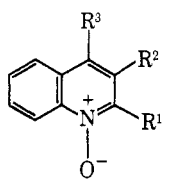
[a] Based on starting materials consumed. [b] Hydrochloride. [c] **187c** also isolated in 30% yield. [d] Room temperature in each case.

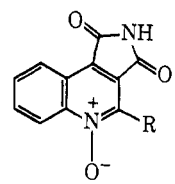


	R^1	R^2	R^3
175a	CO_2Et	CO_2Et	H
b	Ph	CN	H
c	Ph	H	CN
d	COMe	COMe	H
e	COMe	CO_2Et	H
f	COPh	COPh	H
g	COPh	CO_2Et	H



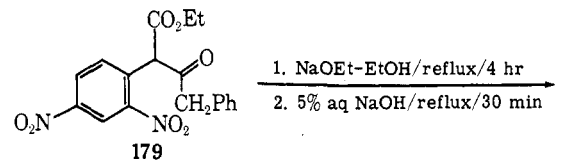
	R^1	R^2
176a	CO_2Et	CO_2Et
b	Ph	CN
c	COMe	COMe
d	COMe	CO_2Et
e	COPh	COPh
f	COPh	CO_2Et
g	COPh	CH_2COPh





	R^1	R^2	R^3		R
177a	OH	CO_2Et	CN	**178a**	Me
b	NH_2	Ph	CN	**b**	Ph
c	Me	COMe	$CONH_2$		
d	Me	CO_2Et	CN		
e	Ph	COPh	$CONH_2$		
f	Ph	CO_2Et	CN		
g	Ph	CH_2COPh	$CONH_2$		

cyclization reactions are analogous to the Zincke–Siebert anthranil synthesis (*cf.* section II.B.5).[6] In closely related processes the substituted *trans-o*-nitrophenylethylene oxides (**188a,c**) are converted in ethereal hydrogen chloride to the



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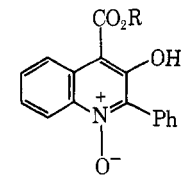
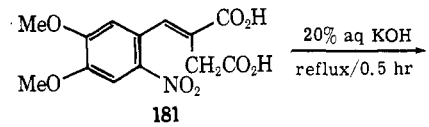


	R	Yield, %
180a	H	not quoted
b	Et	



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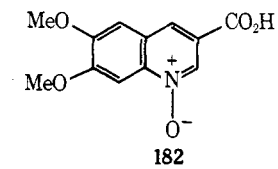

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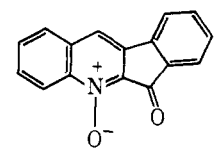
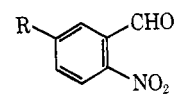
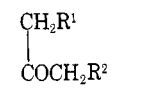


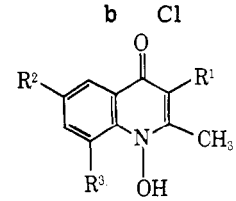
183



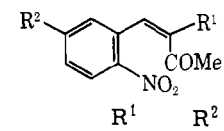
	R
184a	H
b	Cl



	R^1	R^2
185a	COMe	H
b	CO_2Et	H



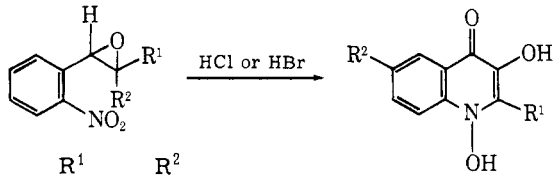
	R^1	R^2	R^3
186a	COMe	H	H
b	COMe	Cl	H
c	CO_2Et	H	H
d	CO_2Et	Cl	Cl



	R^1	R^2
187a	COMe	H
b	CO_2Et	H
c	CO_2Et	Cl
d	CO_2Et	Br

chlorinated *N*-hydroxyquinolones (**189b,d**).[232,233] The use of hydrogen bromide or hydrogen chloride–quinol as the catalyst in these reactions again gives chlorine-free products (*e.g.*, **189a** and **189c**) (Table XXIV).[232,233] A marked enhancement in yield is observed[232] in the conversion of the cis epoxide **188b** to the *N*-hydroxyquinolone **189b**. The diacyl epoxides **188d,e** likewise afford high yields of the chloro-*N*-hydroxy-

(232) T. W. M. Spence and G. Tennant, *Chem. Commun.*, 1100 (1970); *J. Chem. Soc. C*, 3712 (1971).
(233) I. P. Sword, *ibid.*, 820 (1971).

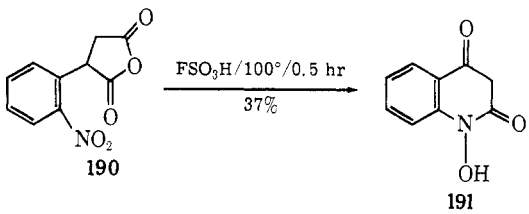


	R^1	R^2
188a	COPh	H
b	H	COPh
c	COMe	H
d	COMe	COMe
e	COPh	COMe

	R^1	R^2
189a	Ph	H
b	Ph	Cl
c	Me	H
d	Me	Cl

quinolone **189d** (Table XXIV).[232] The increased efficiency of these reactions compared with those of the trans epoxides **188a,c** (Table XXIV) is attributed to the steric effect of the *cis*-acyl group in compounds **188b** and **188d,e**.

o-Nitrophenylsuccinic anhydride (**190**) reacts with fluorosulfonic acid to give, in addition to 3-carboxymethylanthranil (*cf.* section II.B.5), the quinoline hydroxamic acid (**191**) which is probably derived by subsequent rearrangement of the anthranil product.[166]



190 **191**

2. Isoquinolines

Simple isoquinoline derivatives are not available by processes involving substituent interaction in ortho-substituted nitrobenzene derivatives. However, Kröhnke[234] has recently reported a number of cyclizations to polycyclic isoquinoline systems which involve the novel intramolecular displacement of aromatic nitro groups by nucleophilic carbon. Reactions 9 and 10 are typical examples of these cyclizations which proceed in excellent yield with a wide variety of heterocyclic substrates.

In general these cyclizations are carried out by treating the requisite substrate in dimethyl sulfoxide at room temperature for 3 hr with piperidine.[234]

3. Acridines

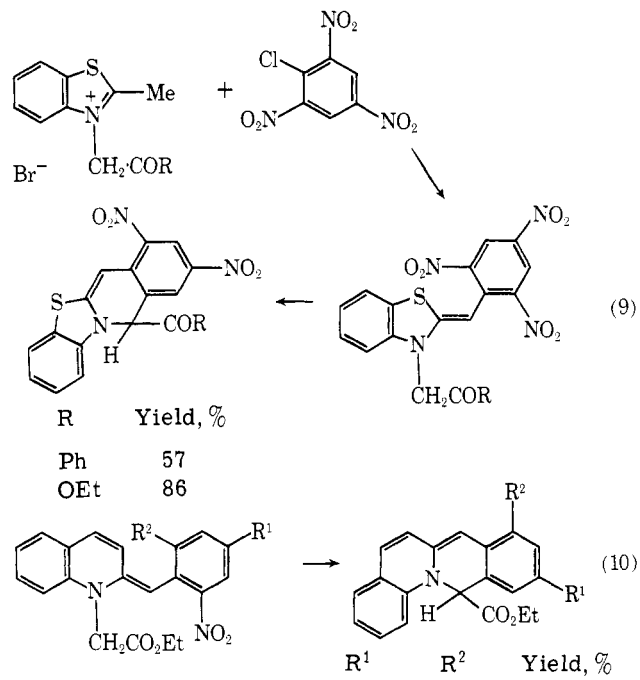
In addition to anthranils (*cf.* section II.B.5) the condensation of *o*-nitrobenzaldehydes (**192**) with aromatic hydrocarbons (**193**) in cold concentrated sulfuric acid affords low yields of the corresponding acridones (**195**)[135,137,138,235–237] and alkali-soluble products[137,138,139,238,239] formulated[134,240] as *N*-hydroxyacridones (**195**) (Table XXV). However, acridones (**194**)

Table XXV

Formation of Acridones (194) and *N*-Hydroxyacridones (195) by the Acid-Catalyzed Condensation of *o*-Nitrobenzaldehydes (192) with Benzene Derivatives (193)

Starting material	*Reaction conditions*	*Product*	*Yield, %*	*Ref*
192a + 193a	Concd H_2SO_4/24°/24 hr	**195a**	7	134
192a + 193a	Concd H_2SO_4/24°/5 hr	**195a**	14	238
192a + 193a	Concd H_2SO_4–$NaNO_2$/24°/120 hr	**194a**	42	241
192a + 193a	Polyphosphoric acid/96–100°/5 hr	**194a**	17	245
192a + 193d	Concd H_2SO_4/24°/5 hr	**195b**	*b*	238
192b + 193a	Concd H_2SO_4/24°/24 hr	**194b**	80	135, 235
192b + 193b	*a*	**195c**	*b*	139
192b + 193b	Concd H_2SO_4/24°/24 hr	**194c**	*b*	237
192b + 193c	Concd H_2SO_4/24°/24 hr	**194d**	38	236
192b + 193d	Concd H_2SO_4/24°/24 hr	**194e**	*b*	235, 237
192b + 193e	Concd H_2SO_4–$NaNO_2$/24°/48 hr	**194f**	25	138
		195d	17	
192b + 193f	*a*	**194g**	19	137
		195e	*b*	
192c + 193d	Concd H_2SO_4/24°/24 hr	**195f**	*b*	239
192c + 193e	Concd H_2SO_4/24°/24 hr	**195g**	*b*	239

[a] Data not available. [b] Yield not quoted.



are obtained in moderate to good yield in these reactions in the presence of sodium nitrite (Table XXV).[138,241] Acridone formation almost certainly involves rearrangement of intermediate anthranils catalyzed by sodium nitrite.[147,236,241–244a] These reactions are of considerable mechanistic interest in

(234) D. B. Reuschling and F. Kröhnke, *Chem. Ber.*, **104**, 2110 (1971).
(235) I. Tanasescu, *Bull. Soc. Chim. Fr.*, **41**, 528 (1927).
(236) K. Lehmstedt, *Chem. Ber.*, **65**, 999 (1932).
(237) I. Tanasescu and M. Macarovici, *Bull. Soc. Chim. Fr.*, **53**, 372 (1933).
(238) I. Tanasescu and E. Ramontianu, *ibid.*, **1**, 547 (1934).
(239) I. Tanasescu and M. Macarovici, *ibid.*, **4**, 240 (1937).
(240) A. Kliegl and A. Fehrle, *Chem. Ber.*, **47**, 1629 (1914); A. Kliegl and A. Brosamle, *ibid.*, **68**, 197 (1935); K. Lehmstedt, *ibid.*, **68**, 1455 (1935); **70**, 172 (1937).
(241) K. Lehmstedt, *ibid.*, **65**, 834 (1932).
(242) E. Bamberger, *ibid.*, **42**, 1707 (1909).
(243) F. R. Bradbury and W. H. Linnell, *J. Chem. Soc.*, 377 (1942).
(244) (a) A. Kliegl, *Chem. Ber.*, **42**, 591 (1909); (b) R. Kwok and P. Pranc, *J. Org. Chem.*, **33**, 2880 (1968).

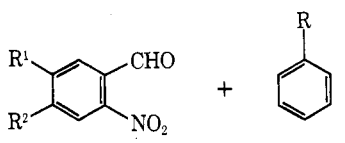
Table XXVI

Formation of Acridones (197) from *o*-Nitrodiphenylmethane Derivatives (196)

Starting material (196)	*Reaction conditions*	*Product* (197)	*Yield*, %	*Ref*
b	Concn H_2SO_4–$NaNO_2$/room temp/few min	a	70	147
a	Liq paraffin/heat	a	35–38	244
c	Liq paraffin/210°/15 min	b	30	148
c	Liq paraffin/300–360°/30 min	b	88	148

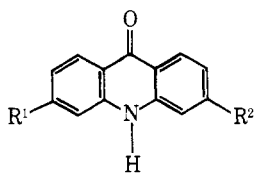
view of the recently reported[244b] thermal isomerization of 3-arylanthranils to acridones *via* nitrene intermediates.

Treatment of *o*-nitrobenzhydrol (**196b**) in concentrated sulfuric acid with sodium nitrite, in contrast to treatment with sulfuric acid alone (*cf.* section II.B.5), affords acridone (**197a**) in good yield[147] (Table XXVI). Polyphosphoric acid alone is reported[245] to promote the condensation of *o*-nitrobenzaldehydes with benzene derivatives to afford acridones (Table XXV) and has been used to prepare benzacridones (*e.g.*, **192a** + **198** → **199**). Acridones are also formed, albeit in variable yield (Table XXVI), by the pyrolysis of *o*-nitrodiphenylmethane derivatives (*e.g.*, **196a,c** → **197a,b**).[148,244]

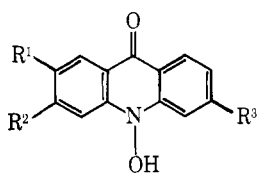


	R^1	R^2
192a	H	H
b	H	NO_2
c	Cl	H

	R
193a	H
b	Me
c	F
d	Cl
e	Br
f	I



	R^1	R^2
194a	H	H
b	NO_2	H
c	NO_2	Me
d	NO_2	F
e	NO_2	Cl
f	NO_2	Br
g	NO_2	I



	R^1	R^2	R^3
195a	H	H	H
b	H	Cl	H
c	H	NO_2	Me
d	H	NO_2	Br
e	H	NO_2	I
f	Cl	H	Cl
g	Cl	H	Br

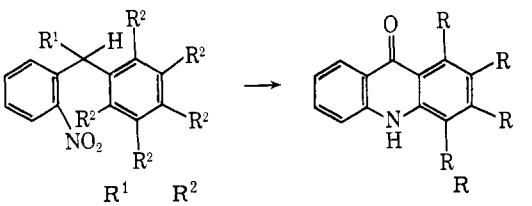
4. *Phenanthridines*

The base-catalyzed cyclization of 2-nitrobiphenyl derivatives (**200**) having an activated methylene group in the 2′ position provides a valuable synthetic route to phenanthridine *N*-oxides (**201**) (Table XXVII).[246,247] Only strong bases catalyze

Table XXVII

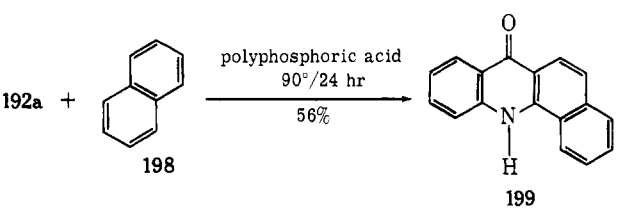
The Base-Catalyzed Cyclization of *o*-Nitrobiphenyl Derivatives (200) to Phenanthridine *N*-Oxides (201)

Starting material 200	*Reaction conditions*	*Product*	*Yield*, %	*Ref*
b	NaOH–MeOH/room temp/20 min	**201a**	82	247
b	NaOH–MeOH/reflux/1 hr	**201a**	88	247
c	NaOMe–MeOH/reflux/10 min	**201c**	55	246
c	NaOH–MeOH/reflux/5 min	**201a**	43	246
e	NaOH–MeOH/33°/8 min	**201e**	87	246
f	NaOH–MeOH/reflux/10 min	**201f** 20 **201a** 61		246
i	KCN–H_2O–EtOH/reflux/0.5 hr	**201e**	64	246
g	NaOH–MeOH/100°/1.5 hr	**202**	80	247

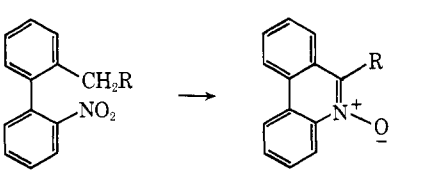


	R^1	R^2
196a	H	H
b	OH	H
c	OH	F

	R
197a	H
b	F



these cyclizations which proceed in moderate to good yield. Weak bases (*e.g.*, ammonia) and mineral acids are without effect.[246] Cyclization of the ketone **200b** proceeds with loss of the benzoyl group giving phenanthridine *N*-oxide (**201a**) in good yield (Table XXVII).[247] At high base concentrations the ester **200c** is likewise converted to phenanthridine *N*-oxide (**201a**) presumably by hydrolysis and decarboxylation of the ester *N*-oxide **201c** which can be isolated at low base concentrations.[246] Cyclization of the benzenesulfonyl derivative **200g** also fails to afford the expected sulfone **201g**. Instead the

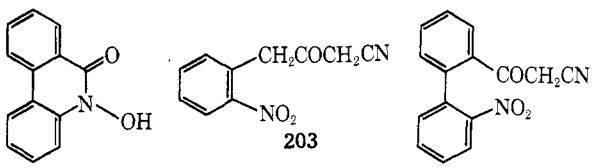


	R
200a	H
b	COPh
c	CO_2Me
d	CO_2H
e	CN
f	$CONH_2$
g	SO_2Ph
h	OH
i	Br
j	NO_2
k	Ph

	R
201a	H
b	COPh
c	CO_2Me
d	CO_2H
e	CN
f	$CONH_2$
g	SO_2Ph

(245) I. Tanasescu, M. Ionescu, I. Goia, and H. Mantsch, *Bull. Soc. Chim. Fr.*, 698 (1960).
(246) C. W. Muth, J. C. Ellers, and O. F. Folmer, *J. Amer. Chem. Soc.*, **79**, 6500 (1957).
(247) C. W. Muth, N. Abraham, M. L. Linfield, R. B. Wotring, and E. A. Pacovsky, *J. Org. Chem.*, **25**, 736 (1960).

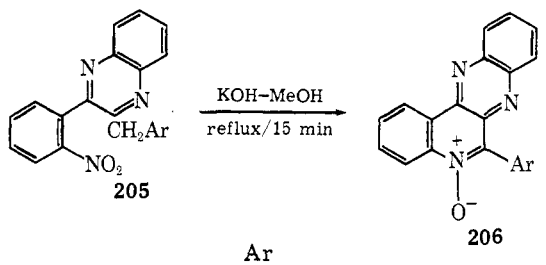
product is the cyclic hydroxamic acid **202** derived by nucleophilic displacement of the benzenesulfonyl group in the sulfone **201g**. As might be expected, the nitrile **200e** undergoes cyclization at a somewhat faster rate than the amide **200f**.[246] In both cases the expected phenanthridine *N*-oxides **201e,f** are obtained (Table XXVII).[246] The formulation of these cyclizations as intramolecular aldol-type condensations is supported by the structures of the products and by the requirement for successful cyclization of powerful electron withdrawal by the substituent R in **200**. Thus, cyclization fails in the case of the biphenyl derivatives **200a**, **200d**, and **200h–k**.[246,247] The failure of the nitro derivative **200j** to undergo cyclization is surprising, but this result should be treated with reserve since there is some doubt[246] as to the identity of the compound subjected to cyclization. Attempts to extend the cyclization **200** → **201** to the nitro compounds **203** and **204** were unsuccessful.[247]



202 **203** **204**

Cyclization procedures that are closely related to the biphenyl type **200** → **201** are the base-catalyzed transformations of *o*-nitrophenylquinoxalines (**205**) into quinolino[3,4-*b*]-quinoxaline *N*-oxides (**206**).[248]

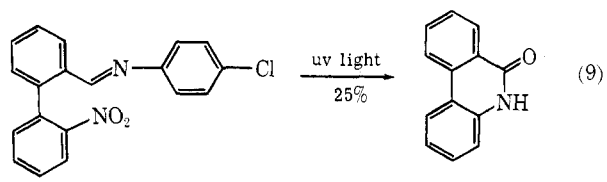
Phenanthridine derivatives are also formed in moderate yield by the photocyclization of *o*-nitrobiphenyl derivatives[249] as exemplified by reactions 9 and 10. The mechanisms of these reactions and the role of oxazetidine intermediates in process 10 have been discussed.[249,250]



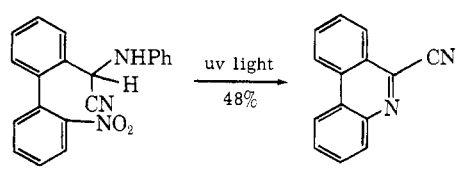
205 **206**

Ar

- **a** mesityl
- **b** *p*-tolyl
- **c** *p*-chlorophenyl
- **d** *o*-chlorophenyl
- **e** phenyl



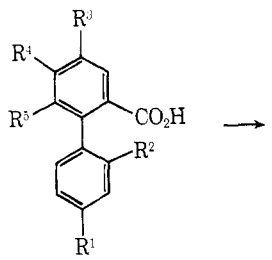
(9)



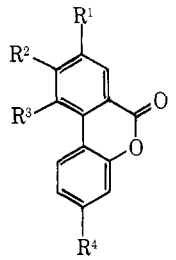
(10)

5. *Benzo[c]coumarins*

A novel route to benzo[*c*]coumarins (**208**) was discovered by Hey, *et al.*,[251] in the course of their studies on the decarboxylation of biphenylcarboxylic acids (**207**). In contrast to the behavior of 4,4′-dinitrobiphenyl-2-carboxylic acid (**207a**) which undergoes decarboxylation in conventional fashion, the 2′,4-dinitro isomer (**207b**) when boiled with copper chromite in quinoline affords 3-nitrobenzo[*c*]coumarin (**208a**) in moderate yield (Table XXVIII). Benzo[*c*]coumarin (**208b**) is similarly obtained from 2′-nitrobiphenyl-2-carboxylic acid (**207c**). Subsequent experiments demonstrated that these novel intramolecular nucleophilic displacements occur in boiling quinoline alone, or in boiling xylene or tetralin in the presence of piperidine. More recently, another example of a cyclization of this type (*i.e.*, **207d** → **208c**) has been reported.[252] In support of the contention that these reactions are examples of the intramolecular nucleophilic displacement of aromatic nitro groups, the sodium salt of the acid **207c** is cyclized thermally to afford the benzocoumarin **208b** in high yield.[251] In contrast the acid **207c** is thermally stable.[251] The readiness with which the cyclizations **207** → **208** take place is ascribed[251] to the favorable juxtaposition of the nitro and carboxyl groups. In this respect, it is noteworthy that attempted[253] cyclizations of



	R^1	R^2	R^3	R^4	R^5
207a	NO_2	H	NO_2	H	H
b	H	NO_2	NO_2	H	H
c	H	NO_2	H	H	H
d	MeO	NO_2	MeO	MeO	MeO



	R^1	R^2	R^3	R^4
208a	NO_2	H	H	H
b	H	H	H	H
c	MeO	MeO	MeO	MeO

(248) R. P. Barnes, J. H. Graham, and M. A. Salim Qureshi, *J. Org. Chem.*, **28**, 2890 (1963).

(249) E. C. Taylor, B. Furth, and M. Pfau, *J. Amer. Chem. Soc.*, **87**, 1400 (1965).

(250) E. C. Taylor and R. E. Buntrock, *J. Org. Chem.*, **36**, 634 (1971).

(251) D. H. Hey, J. A. Leonard, and C. W. Rees, *J. Chem. Soc.*, 4579 (1962).

(252) K. B. L. Mathur and K. P. Sarbhai, *Tetrahedron Lett.*, 1743 (1964).

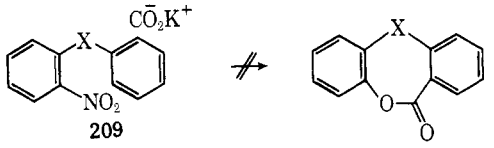
(253) D. M. Collington, D. H. Hey, and C. W. Rees, *J. Chem. Soc. C*, 1030 (1968).

Table XXVIII

Base-Catalyzed Formation of Benzo[c]coumarins (208) from 2′-Nitrobiphenyl-2-carboxylic Acids (207)

Starting material (207)	*Reaction conditions*	*Product* (208)	*Yield,* %	*Ref*
b	Copper chromite–quinoline/reflux/3 hr	a	49	251
c	Copper chromite–quinoline/reflux/0.5 hr	b	83	251
c	Quinoline/reflux/30 min	b	88	251
c	5% piperidine–xylene/reflux/24 hr	b	98	251
c	5% piperidine–tetralin/reflux/3 hr	b	60	251
d	Quinoline/reflux/1 hr	c	50	252

the type **209** → **210** failed to occur, presumably due to the less favorable steric situation.



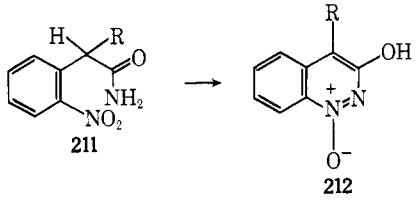
209 **210**

X = O, S, NMe

E. SIX-MEMBERED HETEROCYCLES CONTAINING TWO HETEROATOMS

1. Cinnolines

4-Cyano-3-hydroxycinnoline 1-*N*-oxide (**212b**) is obtained by the base-catalyzed cyclization of *o*-nitrophenylcyanoacetamide (**211b**).[254] Intramolecular aldol condensations of this type have not been exploited to any extent in the benzene

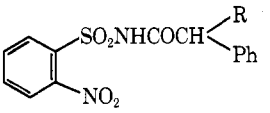


211 **212**

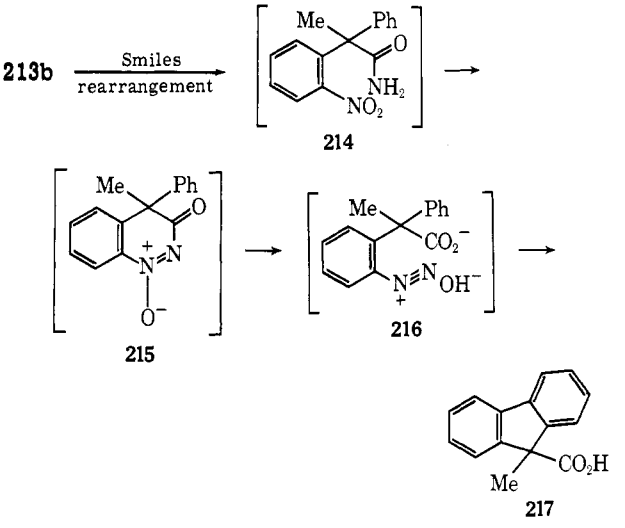
a, R = H; **b**, R = CN; **c**, R = Ph

series despite the fact that the method represents a potentially general route to otherwise inaccessible cinnoline *N*-oxides. However, similar cyclizations have been used for the synthesis of benzo[c]cinnoline *N*-oxides (see later). The success of the cyclization **211** → **212** appears to depend markedly on the mobility of the benzylic hydrogen. Thus, *o*-nitrophenylacetamide (**211a**) fails to cyclize[247] to the corresponding cinnoline *N*-oxide (**212a**). However, the N-oxide **212c** derived from the amide **211c** may be an intermediate in the base-catalyzed transformation of α-phenyl-*N*-(*o*-nitrobenzenesulfonyl)cyanoacetamide (**213a**) into 3-phenylindazole.[6,255]

A cinnoline *N*-oxide (**215**) is also postulated[256] as an intermediate in the base-catalyzed conversion of the sulfonamide **213b** into the fluorenecarboxylic acid **217**.



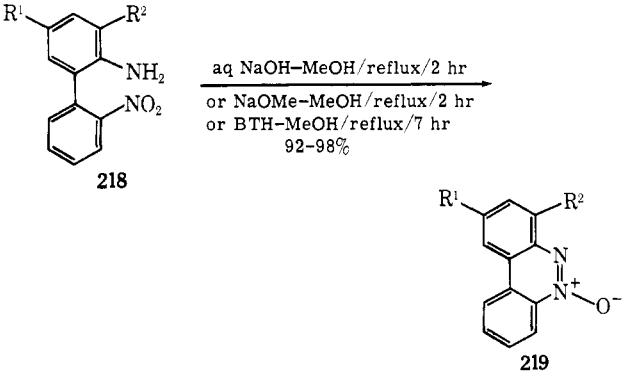
213a, R = H
b, R = Me



213b **214** **215** **216** **217**

Reaction conditions	Yield, % (**217**)
10% aq NaOH	30
$NaNH_2$–liq NH_3	43
t-BuOK–*t*-BuOH	67

Aldol-type condensation between amino and nitro groups in biphenyl derivatives provides a fairly general synthetic route to benzo[c]cinnoline *N*-oxides. Heating 2-amino-2′-nitrobiphenyl (**218a**) with aqueous or methanolic sodium hydroxide affords benzo[c]cinnoline *N*-oxide (**219a**) in high yield.[247] The biphenyl derivative **218b** is similarly cyclized to the benzo[c]cinnoline *N*-oxide (**219b**).[257,258] Cyclizations of this type are subject to steric hindrance and are also inhibited by base-weakening substituents (*e.g.*, nitro) in the amino-



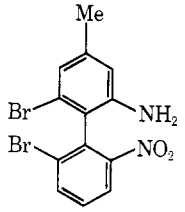
218 **219**

aq NaOH–MeOH/reflux/2 hr
or NaOMe–MeOH/reflux/2 hr
or BTH–MeOH/reflux/7 hr
92–98%

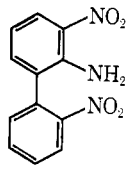
	R^1	R^2
a	H	H
b	Br	Br
c	NO_2	H

(254) J. P. Cairns, Ph.D. Thesis, Glasgow, 1964.
(255) T. Naito, R. Dohmori, and O. Nagase, *J. Pharm. Soc. Jap.*, **74**, 593 (1954); *Chem. Abstr.*, **48**, 10647 (1954).
(256) R. J. Sundberg and D. E. Blackburn, *J. Org. Chem.*, **34**, 2799 (1969).
(257) J. F. Corbett and P. F. Holt, *J. Chem. Soc.*, 5029 (1961).
(258) J. W. Barton and M. A. Cockett, *ibid.*, 2454 (1962).

phenyl nucleus. Thus, the biphenyl derivatives **220** and **221** fail to cyclize under a variety of basic conditions.[257,259] The inhibiting effect of a nitro group has been overcome in one

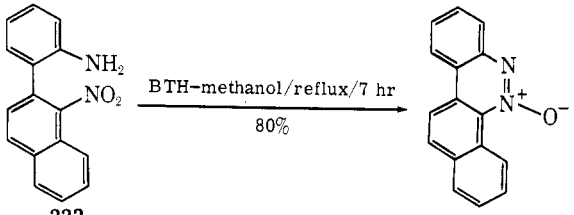


220



221

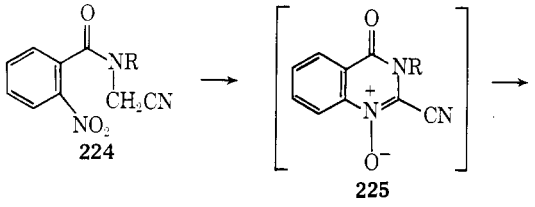
instance (**218c** → **219c**) by the use of benzyltrimethylammonium hydroxide (BTH) as catalyst.[259] BTH has also been used to good effect in the synthesis of the dibenzocinnoline *N*-oxide (**223**) from the nitro amine **222**.[260]



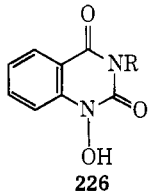
222 **223**

2. Quinazolines

1-Hydroxyquinazoline-2,4-diones (**226b–d**) are formed in high yield by heating N-substituted *o*-nitrobenzoylaminoacetonitriles (**224b–d**) under reflux with ethanolic sodium ethoxide[261] (Table XXIX). Cyclizations of this type are also catalyzed by aqueous ethanolic sodium or potassium hydroxide.



224 **225**



226

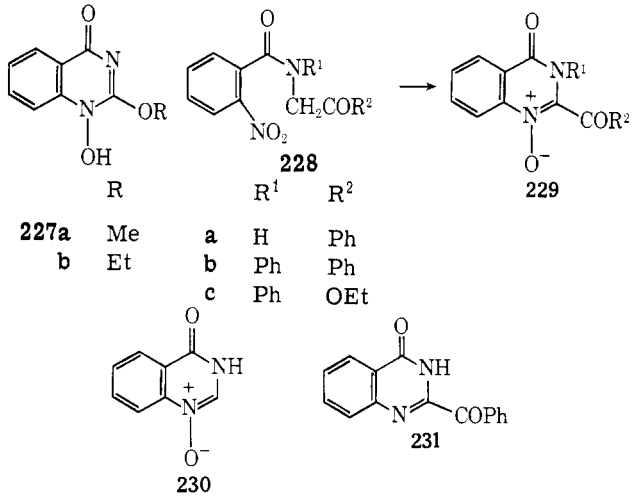
a, R = H **c**, R = CH_2Ph
b, R = Me **d**, R = Ph

The corresponding 2-cyanoquinazoline *N*-oxides (**225b–d**)—the initial products of intramolecular aldol condensation in the amides (**224b–d**)—are probable intermediates in these reactions.[261] Attempts to isolate the quinazoline *N*-oxide intermediates have been largely unsuccessful. *o*-Nitrobenzoylaminoacetonitrile (**224a**) heated with potassium *tert*-butoxide in *tert*-butyl alcohol affords the *N*-hydroxyquinazolinedione (**226a**) in low yield (Table XXIX).[262] Likewise, the use of methanolic sodium methoxide or ethanolic sodium ethoxide as the base in this reaction affords the ethers **227a,b** in low yield (Table XXIX).[262] The poor yields observed in these reactions are attributed[262] to the low methylene reactivity of the side chain in the amide **224a** and the presence of a competing nucleophilic center. However, the base-catalyzed conversion of the *o*-nitrobenzamide derivative **228a** to the N-oxide **230** and/or 2-benzoylquinazolin-4(3*H*)-one (**231**) provides evidence for the intermediate formation of the quinazolone *N*-oxide (**229a**).[262] Correspondingly, the conversion of the amides **228b,c** in warm ethanolic sodium ethoxide to 2-phenylindazolone (*cf.* section II.B.1) is explicable[261] by the intermediate formation and subsequent transformation in the basic medium, of the N-oxides **229b,c**. Heating the methyl-substituted amide **232a** under reflux with ethanolic sodium ethoxide gives the quinazolone *N*-oxide (**233a**) in moderate yield (Table XXIX).[261] The 2-methylquinazolin-4(3*H*)-one 1-*N*-oxides (**233b,c**) are also the presumed[261] intermediates in the

Table XXIX

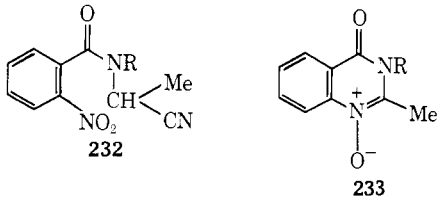
Base-Catalyzed Conversion of N-Substituted *o*-nitrobenzamides 224, 228, and 232 into *N*-Hydroxyquinazolones (226) and Related Products

Starting material	*Reaction conditions*	*Product*	*Yield, %*	*Ref*
224b	NaOEt–EtOH/reflux/1 hr	**226b**	93	261
224b	10% aq NaOH–EtOH/reflux/0.5 hr	**226b**	85–95	261
224c	NaOEt–EtOH/reflux/1 hr	**226c**	85	261
224d	NaOEt–EtOH/reflux/1 hr	**226d**	76	261
224a	NaOEt–EtOH/reflux/1 hr	**227b**	32	262
224a	NaOMe–MeOH/reflux/1 hr	**227a**	30	262
224a	*t*-BuOK–*t*-BuOH/reflux/1 hr	**226a**	28	262
228a	NaOEt–EtOH/room temp/1.25 hr	**230** / **231**	9 / 10	262
228a	NaOEt–EtOH/reflux/1 hr	**230**	56	262
228a	8% aq NaOH–EtOH/reflux/0.5 hr	**231**	16	262
232a	NaOEt–EtOH/reflux/1 hr	**233a**	39	261



227a R = Me; **b** R = Et
228 **a** R^1 = H, R^2 = Ph; **b** R^1 = Ph, R^2 = Ph; **c** R^1 = Ph, R^2 = OEt
229

230 **231**



232 **233**

a, R = H; **b**, R = CH_2Ph; **c**, R = Ph

(259) J. W. Barton and J. F. Thomas, *J. Chem. Soc.*, 1265 (1964).
(260) W. H. Poesche, *J. Chem. Soc. C*, 890 (1966).
(261) T. W. M. Spence and G. Tennant, *ibid.*, 97 (1972); *Chem. Commun.*, 194 (1969).
(262) G. Tennant and K. Vaughan, *J. Chem. Soc. C*, 2287 (1966).

Table XXX

Base-Catalyzed Cyclization of α-Acyl-*o*-nitroacetanilides (236) to Quinoxalin-3(4*H*)-one 1-*N*-Oxides (237–239)

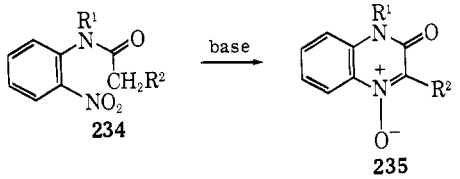
Starting material	*Reaction conditions*	*Product*	*Yield, %*	*Ref*
236a	4% aq NaOH/boil/few min	**237a**	34	263
236b	4% aq NaOH/reflux/0.5 hr	**237b**	75	263
236a	20% aq KOH/reflux/1 hr	**239a**	70	263
236b	20% aq KOH/reflux/1 hr	**239a**	74	263
236b	NaOPr^n–*n*-PrOH/boil/few min	**239a**	88	264
236c	*a*	**239a**	*b*	264
236d	NaOEt–EtOH/reflux/1 hr	**239b**	50	264
236e	NaOEt–EtOH/reflux/briefly[c] or 8% aq NaOH/reflux/15 min	**238a**	83[d]	264, 266
236f	8% aq NaOH–EtOH/reflux/1 hr	**238b**	84	267
236g	8% aq NaOH–EtOH/reflux/1 hr	**238c**	61	267
236h	8% aq NaOH–EtOH/reflux/1 hr	**238d**	94	267
236i	8% aq NaOH–EtOH/reflux/1 hr	**238e**	75	267
236j	8% aq NaOH–EtOH/reflux/1 hr	**238f**	56	267
236k	8% aq NaOH–EtOH/reflux/1 hr	**238g**	73	267
236l, **241**	0.4 *M* NaOEt–EtOH/reflux/0.5 hr	**237c**, **239a**	32, 16	266
236n	0.4 *M* NaOEt–EtOH/reflux/0.5 hr	**239a**	46	266
236m	NaOEt–EtOH/reflux/1 hr	**239b**	*b*	264

[a] Data not available. [b] Yield not quoted. [c] Method used in ref 266. [d] Yield from ref 268; no yield quoted in ref 266.

base-catalyzed transformations of the amides **232b,c** into indazolones or azo- and azoxybenzene derivatives, respectively[261] (*cf.* sections II.B.1 and III.B).

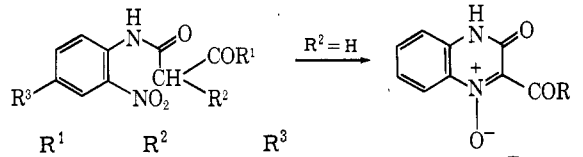
3. Quinoxalines

The base-catalyzed cyclization of α-substituted *o*-nitroacetanilides (**234**) is a valuable general method for the synthesis of otherwise inaccessible quinoxalin-3(4*H*)-one 1-*N*-oxides (**235**). Cyclization can be effected by a variety of basic catalysts and often occurs under relatively mild conditions (Table XXX).



234 **235**

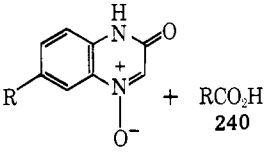
The yields obtained in these intramolecular aldol-type condensations are high, and the sole requirement for successful cyclization appears to be activation of the methylene group in **234** by electron withdrawal in R^2. Heating the α-acyl-*o*-nitroacetanilides (**236a,b**) with 4% aqueous sodium hydroxide affords the quinoxaline *N*-oxides **237a,b** (Table XXX).[263,264] The low yield of the cyclized product **237a** obtained from the anilide **236a** is due to the intervention of side reactions.[265] The use of 20% aqueous potassium hydroxide[263] or ethanolic sodium ethoxide to effect cyclization results in deacylation, giving the corresponding parent N-oxides **239** (*e.g.*, **236a–d** → **239a,b**) in high yield (Table XXX).[263,264] Deacylation also plays a key role in the base-catalyzed cyclization of α-alkyl-*o*-nitroacetanilides (*e.g.*, **236e–k**) which provides a valuable general synthetic route to 2-alkylquinoxalin-3(4*H*)-one 1-*N*-oxides (*e.g.*, **238a–g**) (Table XXX).[264,266,267] In contrast to the ketones **236a,b** the ester **236l**, the dianilide **241**, and the acid **236n** are converted in warm ethanolic sodium ethoxide into



	R^1	R^2	R^3
236a	Me	H	H
b	Ph	H	H
c	*i*-Bu	H	H
d	Me	H	Me
e	Ph	Me	H
f	Ph	Et	H
g	Ph	*n*-Pr	H
h	Ph	*n*-Bu	H
i	Ph	*n*-Pent	H
j	Ph	*n*-Hex	H
k	Ph	*n*-Hept	H
l	OEt	H	H
m	OEt	H	Me
n	OH	H	H

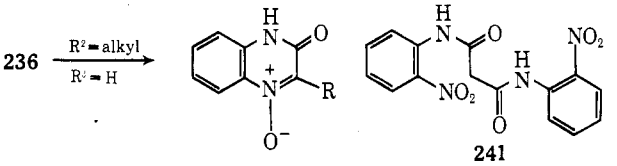
R

237a Me
b Ph
c OEt



R

239a H
b Me



R

238a Me
b Et
c *n*-Pr
d *n*-Bu
e *n*-Pent
f *n*-Hex
g *n*-Hept

2-ethoxycarbonylquinoxalin-3(4*H*)-one 1-*N*-oxide (**237c**) and/or the N-oxide **239a** (Table XXX).[266] The homolog **239b** is obtained similarly from the anilide **236m**.[264] The application of the α-acyl-*o*-nitroacetanilide cyclization to cycloalkanone and thioacetanilide derivatives is illustrated by reactions 11 and 12.[264]

Cyclization of the corresponding α-cyano-*o*-nitroacetanilides (**242**) with ethanolic sodium ethoxide,[266] aqueous barium hydroxide,[264] or 4% aqueous sodium hydroxide in pyridine[268] provides an excellent method for the synthesis of 2-cyanoquinoxalin-3(4*H*)-one 1-*N*-oxides (**243**) (Table XXXI). In contrast, heating the anilides **242a,f** with aqueous sodium or potassium hydroxide or ethanolic sodium ethoxide results in the loss of the cyano group to afford the *N*-hydroxyquinoxalinediones (**244a,b**) in high yield (Table XXXI).[266]

Despite the low reactivity of the methylene center in the side chain, α-aryl-*o*-nitroacetanilides (**245**) cyclize readily on

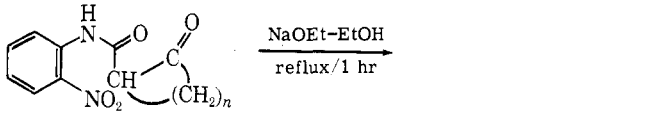
(263) G. Tennant, *J. Chem. Soc.*, 2428 (1963).
(264) R. Fusco and S. Rossi, *Gazz. Chim. Ital.*, **94**, 3 (1964).
(265) G. Tennant, *J. Chem. Soc.*, 1986 (1964).
(266) G. Tennant, *ibid.*, 2666 (1964).
(267) G. Tennant, *ibid.*, 2285 (1966).
(268) Y. Ahmad, M. S. Habib, and Ziauddin, *Tetrahedron*, **20**, 1107 (1964).

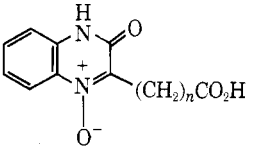
Table XXXI

The Base-Catalyzed Cyclization of α-Cyano-*o*-nitroacetanilides (242) to Quinoxalin-3(4*H*)-one 1-*N*-Oxides (243)

Starting material (242)	*Reaction conditions*	*Product*	*Yield, %*	*Ref*
a	Aq $Ba(OH_2)$/60–70°/few min[a]	**243a**	50–58	264
	0.4 *M* NaOEt–EtOH/reflux/0.5 hr		42–53	266
	4% NaOH–pyridine/24°/1 hr		64	268
b	Aq $Ba(OH)_2$/60–70°/few min	**243b**	80	264
	4% NaOH–pyridine/24°/1 hr		65	268
c	Aq $Ba(OH)_2$/60–70°/few min	**243c**	63	264
d	Aq $Ba(OH)_2$/60–70°/few min	**243d**	55	264
	4% NaOH–pyridine/24°/1 hr		60	268
e	Aq $Ba(OH)_2$/60–70°/few min	**243e**	61	264
f	15% NaOH–EtOH/reflux/few min	**243f**	*b*	264
	$NaCN–H_2O$/100°/10 min		70	266
g	15% NaOH–EtOH/reflux/few min	**243g**	*b*	264
a	4% aq NaOH/reflux/0.5 hr or 20% aq KOH/reflux/0.5 hr	**244a**	84	266
f	0.4 *M* NaOEt–EtOH/reflux/0.5 hr or 20% aq KOH or 4% NaOH/reflux/0.5 hr	**244b**	50	266

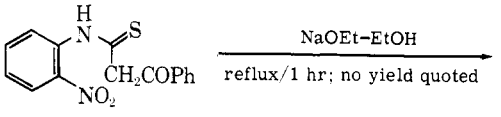
[a] Also formed in 17% yield by warming α-chloro-*o*-nitroacetanilide (**242a**, Cl for CN) with aqueous sodium cyanide.[167] [b] Yield not quoted.

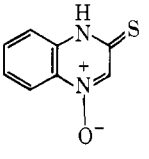




(11)

n	Yield, %
3	61
4	no yield quoted
5	
6	





(12)

warming with aqueous alkali in pyridine, affording good yields of 2-arylquinoxalin-3(4*H*)-one 1-*N*-oxides (**246**) (Table XXXII).[264,269] On the other hand, treatment of α-phenyl-*o*-nitroacetanilide (**245a**) with warm ethanolic sodium ethoxide affords 2-phenylquinoxalin-3(4*H*)-one 1-*N*-oxide (**246a**) in very low yield owing to competing solvolysis of the side chain.[266] In contrast, similar treatment of the *N*-methyl derivative **245l** gives the *N*-methyl *N*-oxide **246l** in high yield,[266] presumably owing to the enhanced methylene reactivity and increased resistance to solvolysis of the amide side chain. In accord with their greater methylene reactivity, nitrophenyl derivatives (*e.g.*, **245f–k**) cyclize more readily and afford higher yields of quinoxaline *N*-oxides (*e.g.*, **246f–k**) than the corresponding unnitrated compounds (Table XXXII).

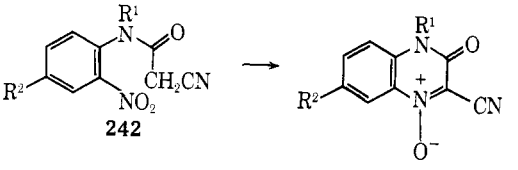
Cyclization of pyridinium salts of the types **247a,b** in warm methanolic piperidine is accompanied by scission of the pyridine ring, affording moderate yields of 2-aminoquinoxalin-3(4*H*)-one 1-*N*-oxides (*e.g.*, **248a,b**).[263,266] A subsequent study[270] demonstrated the intermediate formation of anils isolated as the sodium salts (**249**) in such cyclizations.

Table XXXII

Base-Catalyzed Cyclization of α-Aryl-*o*-nitroacetanilides (245) to 2-Arylquinoxalin-3(4*H*)-one 1-*N*-Oxides (246)

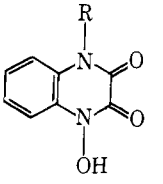
Starting material (245)	*Reaction conditions*	*Product* (246)	*Yield, %*	*Ref*
a	20% KOH–pyridine/100°/1 hr	**a**	78	269
a	0.4 *M* NaOEt–EtOH/reflux/0.5 hr	**a**	8	266
b	20% KOH–pyridine/100°/1 hr	**b**	72	269
c	20% KOH–pyridine/100°/1 hr	**c**	74	269
d	20% KOH–pyridine/100°/1 hr	**d**	72	269
e	20% KOH–pyridine/100°/1 hr	**e**	70	269
f	4% NaOH–pyridine/24°/15 min	**f**	88	269
f	*a*	**f**	*b*	264
g	4% NaOH–pyridine/24°/15 min	**g**	84	269
h	4% NaOH–pyridine/24°/15 min	**h**	78	269
i	4% NaOH–pyridine/24°/15 min	**i**	81	269
j	4% NaOH–pyridine/24°/15 min	**j**	73	269
k	*a*	**k**	*b*	264
l	4% aq NaOH–MeOH/reflux/0.5 hr 0.4 *M* NaOEt–EtOH/24°/1 hr	**l**	86	266

[a] Details not given. [b] Yields not quoted.



242 **243**

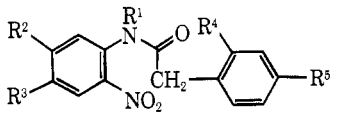
	R^1	R^2
a	H	H
b	H	Cl
c	H	OEt
d	H	OMe
e	H	Me
f	Me	H
g	CH_2Ph	H



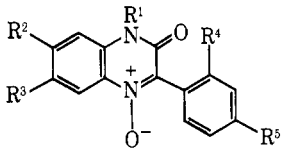
244a, R = H; **b**, R = Me

(269) Y. Ahmad, M. S. Habib, Ziauddin, and N. Bashir, *Tetrahedron*, **21**, 861 (1965).

(270) R. Fusco, S. Rossi, and S. Maiorana, *Gazz. Chim. Ital.*, **95**, 1237 (1965).



245



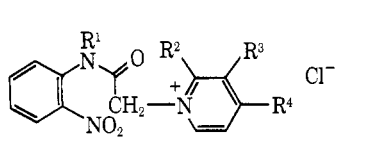
246

	R^1	R^2	R^3	R^4	R^5
a	H	H	H	H	H
b	H	H	Cl	H	H
c	H	H	EtO	H	H
d	H	H	MeO	H	H
e	H	Cl	Cl	H	H
f	H	H	H	H	NO_2
g	H	H	Cl	H	NO_2
h	H	H	EtO	H	NO_2
i	H	H	MeO	H	NO_2
j	H	Cl	Cl	H	NO_2
k	H	H	H	NO_2	NO_2
l	Me	H	H	H	H

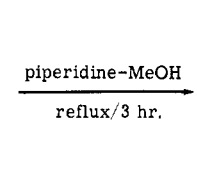
amines with ferrous oxalate[272] provides a useful direct synthesis of phenazines. Subsequent to this work it has been shown[273] that phenazine can be obtained in poor yield (15%) by heating 2-nitrodiphenylamine in sand at 300° in the absence of a reductant, and more recently the base- and acid-catalyzed cyclization of 2-nitrodiphenylamines to phenazines and/or phenazine *N*-oxides has been investigated[274] (Tables XXXIII and XXXIV, respectively).

The exclusive formation of phenazine *N*-oxides in the acid-catalyzed process is particularly noteworthy. Although the yields are variable (Table XXXIV) this method offers an attractive alternative to the Wohl–Aue reaction[8a] and peracid oxidation[2b] as methods for the synthesis of phenazine *N*-oxides.

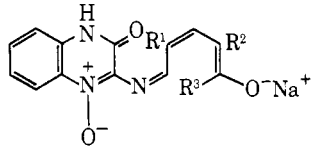
Nitrophenazines (**254**) are obtained by the base-catalyzed[275-277] or thermal[275] cyclization of polynitrodiphenylamines (**253**) (Table XXXV). These reactions are analogous to similar processes leading to phenoxazines and phenothiazines (*cf.* sections II.E.6 and II.E.8) and involve the intramolecular nucleophilic displacement of aromatic nitro groups. Base-catalyzed cyclization fails[275,278] for the case of the unsubstituted amino derivative **253a**, although it is cyclized to the phenazine **254a** in low yield by heating in naphthalene at 200°. The products **254** are highly colored solids and may in



	R^1	R^2	R^3
247a	H	H	H
b	Me	H	H
c	H	Me	H
d	H	H	Me



	R	Yield, %
248a	H	40
b	Me	53



	R^1	R^2	R^3	Yield, %
249a	H	H	H	Not quoted
b	H	H	Me	Not quoted
c	Me	H	H	mixture obtained from **247d** in quantitative yield
d	H	Me	H	

4. *Phenazines*

Phenazines have frequently[8b,271] been prepared by the condensation of *o*-phenylenediamines with either *o*-benzoquinones or catechols, or by the Wohl–Aue condensation[8a] of nitrobenzenes with arylamines. Unfortunately none of these procedures is entirely satisfactory: the latter method, although utilizing readily available starting materials, often gives poor yields and several side products; the first two methods employ the less accessible catechols and the frequently labile *o*-benzoquinones. The reductive cyclization of 2-nitrodiphenyl-

fact be phenazyls[8c] rather than simple phenazine derivatives.

In reactions formally analogous to the phenazine syntheses described before, 4-chloro-1,2-dimethyl-5-nitrouracil (**255**)

(271) British Patent 1,086,522 (1967); *Chem. Abstr.*, **65**, 2279 (1966).

(272) H. C. Waterman and D. L. Vivian, *J. Org. Chem.*, **14**, 298 (1949); D. L. Vivian and J. L. Hartwell, *ibid.*, **18**, 1065 (1953).

(273) R. H. Smith and H. Suschitzky, *Tetrahedron*, **16**, 80 (1961).

(274) B. Cross, P. J. Williams, and R. E. Woodall, *J. Chem. Soc. C*, 2085 (1971); B. Cross and P. J. Williams, British Patent, 1,091,618 (1967); *Chem. Abstr.*, **69**, 43939 (1968).

(275) F. Kehrmann and J. Messinger, *Chem. Ber.*, **26**, 2372 (1893).

(276) F. Kehrmann and J. R. y Punti, *ibid.*, **44**, 2622 (1911).

(277) F. Kehrmann and Y. Effront, *Helv. Chim. Acta*, **4**, 517 (1921).

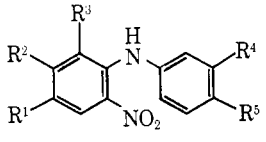
(278) H. Leemann and E. Grandmougin, *Chem. Ber.*, **41**, 1306 (1908).

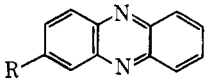
Table XXXIII

Potassium Hydroxide Catalyzed Cyclization of 2-Nitrodiphenylamines (250)[a,b]

Starting material (250)	*Solvent*	*Temp, °C*	*Time, hr*	*Product*	*Yield, %*
a	Decalin	190	1	**251a**	22
				252a	0
b	Xylene	136	48	**251b**	0
				252b	36
b	Chlorobenzene	132	36	**251b**	15
				252b	30
b	Cumene	152	16	**251b**	0
				252b	39
b	1,2-Dichlorobenzene	179	1	**251b**	19
				252b	0
b	Decalin	190	1	**251b**	48
				252b	0

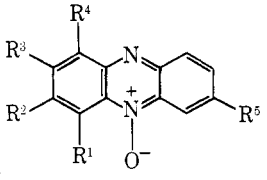
[a] Carried out heterogeneously using a 5–10 molar equiv excess of powdered KOH. [b] Reference 274.





	R^1	R^2	R^3	R^4	R^5
250a	H	H	H	H	H
b	Cl	H	H	H	H
c	H	H	H	H	Cl
d	Cl	H	H	H	Cl
e	H	Cl	H	H	Cl
f	H	H	Cl	H	Cl
g	Cl	H	H	Cl	H
h	Cl	Cl	H	H	H
i	Cl	H	H	H	Me
j	H	Cl	H	H	Me

	R
251a	H
b	Cl



	R^1	R^2	R^3	R^4	R^5
252a	H	H	H	H	H
b	H	Cl	H	H	H
c	H	Cl	H	H	Cl
d	H	H	Cl	H	Cl
e	H	H	H	Cl	Cl
f	Cl	H	H	H	Cl
g	H	Cl	Cl	H	H
h	H	Cl	H	H	Me
i	H	H	Cl	H	Me

reacts with aminouracils **256** and **258** in uncatalyzed reactions affording high yields (Table XXXVI) of pyrimido[4,5-*g*]-pteridine *N*-oxides (**257** and **259**).[279] These reactions are thought[279] to involve the intermediate formation and cyclization of nitropyrimidylamino derivatives (*e.g.*, **260** and **262**) either by intramolecular nucleophilic displacement of the nitro group (*cf.* **260** → **261** → **257**) or by condensation involving the nitro group (*cf.* **262** → **263** → **257**) and should provide a general route to heteroaromatic N-oxides of potential biological importance.

(279) Y. Maki, M. Sako, and E. C. Taylor, *Tetrahedron Lett.*, 4271 (1971).

Table XXXIV

Conversion of 2-Nitrodiphenylamines (250) to Phenazine *N*-Oxides (252) in Oleum[a,b]

Starting material (250)	*Product* (252)	*Yield, %*
a	a	18
b	b	Trace
c	b	64
d	c	77
e	d	54
f	e	80
g	f, d	45
h	g	5
i	h	37
j	i	24

[a] Carried out by dissolving the amine in concentrated sulfuric acid, adding 20% oleum, and maintaining the temperature below 40°. [b] Reference 274.

Table XXXV

Formation of Nitrophenazines (254) from Polynitrodiphenylamines (253)

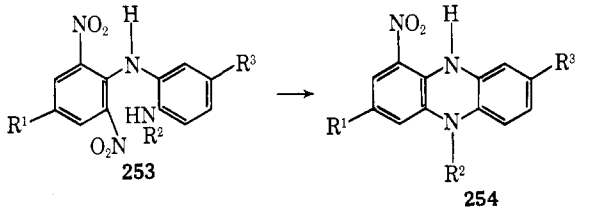
Starting material (253)	*Reaction conditions*	*Product* (254)	*Yield, %*	*Re*
a	Naphthalene/200°	a	25	275
b	NaOAc–EtOH/reflux	b	*a*	275
c	NaOAc–EtOH/reflux	c	*a*	275
d	NaOAc–EtOH/reflux	d	*a*	275
e	NaOH–EtOH/100°	e	*a*	275
f	NaOH–EtOH/room temp/2 hr	f	*a*	276
g	NaOH–EtOH/reflux/few min	g	*a*	277
h	Quinoline/reflux/few min	h	*a*	277

[a] Yield not quoted.

Table XXXVI

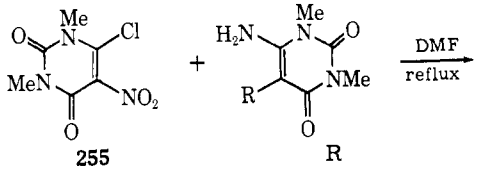
Synthesis of Pyrimido[4,5-*g*]pteridine *N*-Oxides (257, 259) from the Thermal Reactions of 4-Chloro-1,2-dimethyl-5-nitrouracil (255) with Aminouracils (256 and 258)

Reactant	*Reaction time, hr*	*Product*	*Yield, %*
256a	0.5	**257**	90
256b	1.0	**257**	50
258a	0.5	**259a**	80
258b	1.0	**259a**	70
258c	0.5	**259b**	55
258d	0.5	**259c**	90
258e	1.0	**259c**	75
258f	0.5	**259d**	35

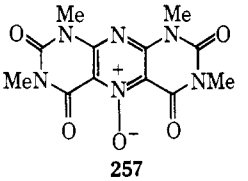


253 254

	R^1	R^2	R^3
a	NO_2	H	H
b	NO_2	Me	H
c	NO_2	Et	H
d	NO_2	CH_2Ph	H
e	NO_2	Ph	H
f	NO_2	Ph	NO_2
g	H	Me	H
h	H	Ph	H



255 256a NO
256b H



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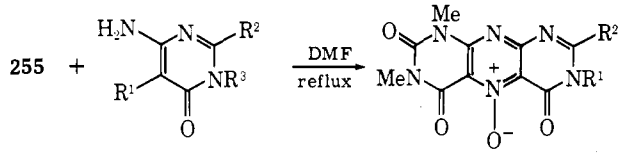
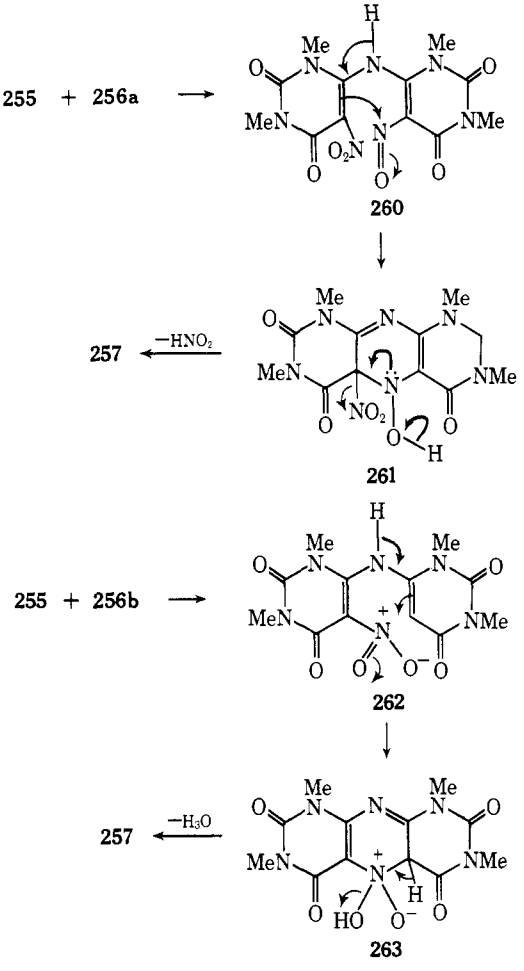


	R^1	R^2	R^3		R^1	R^2
258a	NO	Ph	Me	**259a**	Me	Ph
b	H	Ph	Me	**b**	H	Ph
c	NO	Ph	H	**c**	Me	SMe
d	NO	SMe	Me	**d**	H	SMe
e	H	SMe	Me			
f	NO	SMe	H			

5. *Benzoxazines*

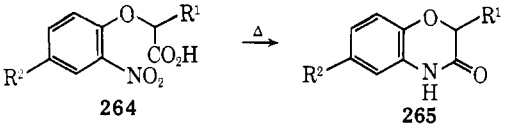
2*H*-1,4-Benzoxazin-3(4*H*)-one (**265a**) and its 2-methyl derivative (**265b**) are obtained[129] in low yield (25%) by thermolysis of *o*-nitrophenoxyacetic (**264a**) and propionic acids (**264b**), respectively. No attempt was made[129] to maximize the yields in these reactions, but a disappointing feature is the absence of the corresponding cyclized products **265c,d** from thermolysis of the dinitro compounds **264c,d**, respectively. Probably such reactions will find only limited synthetic use despite the ready availability of the starting materials.[129,280,281]

From the synthetic viewpoint the conversion[282] of *o*-nitro-



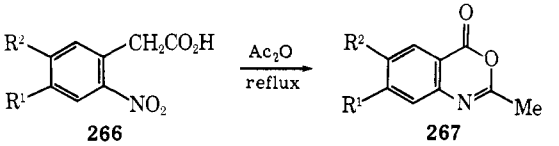
260 261 262 263

aryl derivatives of acetic acid (**266a,b**) into 2-methyl-1,3-benzoxazin-4-ones (**267a,b**) by acetic anhydride is considerably more promising. The products **267** almost certainly



264 265

	R^1	R^2
a	H	H
b	Me	H
c	Me	NO_2
d	Ph	NO_2



266 267

	R^1	R^2	Yield, %
a	H	H	41
b	MeO	MeO	52

arise by acid-catalyzed conversion of the carboxylic acids **266** into the anthranil (*cf.* ref 165 and section II.B.5) followed by subsequent reaction with acetic anhydride.

(280) N. V. Hayes and G. E. K. Branch, *J. Amer. Chem. Soc.*, **65**, 1555 (1943).
(281) P. H. McFarlane and D. W. Russell, *Chem. Commun.*, 475 (1969).
(282) G. N. Walker, *J. Amer. Chem. Soc.*, 77, 6698 (1955).

Table XXXVII

Synthesis of Phenoxazines by Base-Catalyzed Reaction of *o*-Chloronitroarenes (268) with *o*-Aminophenols (269)

Starting materials 268	269	*Reaction conditions*	*Product* (270)	*Yield*, %	*Ref*
a	a	NaOH–EtOH/warm	a	70	284
b	a	NaOAc–EtOH/reflux	b	84	285
c	a	NaOH–aq EtOH/reflux	c	*a*	285
c	b	NaOAc–NaOH–EtOH/reflux	d	19	286
c	c	NaOAc–NaOH–EtOH/reflux	e	23	286
c	d	NaOAc–NaOH–EtOH/reflux	f	19	286
c	e	NaOAc–NaOH–EtOH/reflux	g	16	286
c	f	NaOAc–NaOH–EtOH/reflux	h	9	286
d	g	NaOH–aq EtOH/reflux	i	83	287
d	h	NaOH–aq EtOH/reflux	j	69	287
b	h	Pyridine/100°	k	35	288
e	a	Aq NaOAc/heat	l	93	289

[a] Yield not quoted.

Table XXXVIII

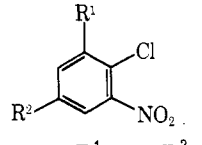
Synthesis of Phenoxazines by the Base-Catalyzed Cyclization of 2-Hydroxy-2′-nitrodiarylamines

Starting material (271)	*Reaction conditions*	*Product* (272)	*Yield*, %	*Ref*
a	5% aq NaOH/reflux	a	95	289
b	5% aq NaOH/reflux	b	>95	289
c	5% aq NaOH/warm	c	*a*	289
d	5% aq NaOH/reflux	d	94	289
e	1% aq NaOH/reflux	e	97	289
f	NaOAc–glycerin/200°	f	*a*	290
g	18% NH_4OH–EtOH/room temp	g	>95	291
h	Aq NaOH/reflux	h	*c*	292
i	Aq NaOH/reflux	i	*c*	292
k	Aq NaOH/reflux	k	*c*	292
l	K_2CO_3–Cu–DMF/reflux	l	43	293
m[b]	KOH–EtOH/reflux	m	78	291

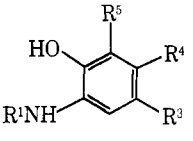
[a] Yield not quoted. [b] Starting material actually **271e**; *p*-$MeC_6H_4SO_2O$ for HO. [c] Yields not quoted but reported[292] to be "excellent."

6. *Phenoxazines*

A number of phenoxazine derivatives (**270**) have been synthesized by the base-catalyzed reaction of *o*-chloronitroarenes (**268**) with *o*-aminophenols (**269**) (the Turpin reaction); some examples of this type of condensation are given in Table XXXVII (*cf.* also ref 283).

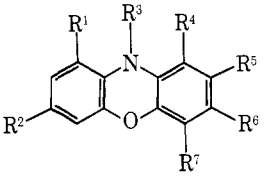


	R^1	R^2
268a	NO_2	NO_2
b	NO_2	Cl
c	Me	NO_2
d	H	NO_2
e	SO_3H	NO_2



	R^1	R^2	R^3	R^4	R^5
269a	H	H	H	H	H
b	H	Me	H	H	H
c	H	H	Me	H	H
d	H	H	H	Me	H
e	H	H	H	H	Me
f	H	Me	H	MeO	H
g	$PhCH_2$	H	H	H	H
h	$PhCH_2$	H	Cl	H	H

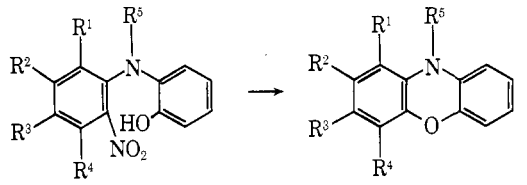
The intermediacy of diarylamines in the Turpin reaction is suggested by the facile base-catalyzed cyclization of 2-hydroxy-2′-nitrodiarylamines (*cf.* **271** → **272**; Table XXXVIII); analogous intramolecular nucleophilic substitution reactions have been used for the synthesis of phenazines, phenothiazines, dibenzodioxans, and phenoxathiins (see section II.E.4, 8, 9, and 10, respectively).



	R^1	R^2	R^3	R^4	R^5	R^6	R^7
270a	NO_2	NO_2	H	H	H	H	H
b	NO_2	Cl	H	H	H	H	H
c	Me	NO_2	H	H	H	H	H
d	Me	NO_2	H	Me	H	H	H
e	Me	NO_2	H	H	Me	H	H
f	Me	NO_2	H	H	H	Me	H
g	Me	NO_2	H	H	H	H	Me
h	Me	NO_2	H	Me	H	MeO	H
i	H	NO_2	$PhCH_2$	H	H	H	H
j	H	NO_2	$PhCH_2$	H	Cl	H	H
k	NO_2	Cl	$PhCH_2$	H	Cl	H	H
l	SO_3H	NO_2	H	H	H	H	H

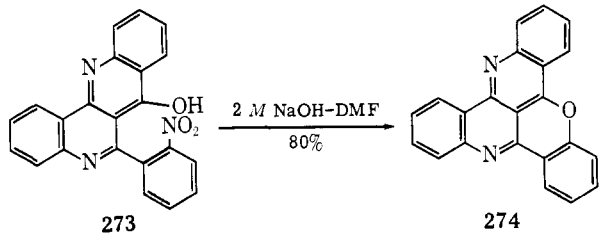
The displacement of nitrite ion by oxyanion implicit in these cyclizations[294] also operates in the conversion of 7-hydroxy-6-*o*-nitrophenyl-5,12-diazabenz[*a*]anthracene (**273**) into 5-oxa-10,15-diazabenzo[*a*]naphth[1,2,3-*de*]anthracene (**274**).[295]

(283) H. Goldstein and A. Warnéry, *Helv. Chim. Acta*, **11**, 489 (1928).
(284) G. S. Turpin, *J. Chem. Soc.*, **59**, 714 (1891).
(285) F. Ullmann and S. M. Sané, *Chem. Ber.*, **44**, 3730 (1911).
(286) H. Musso and P. Wager, *ibid.*, **94**, 2551 (1961).
(287) B. Boothroyd and E. R. Clark, *J. Chem. Soc.*, 1499 (1953).
(288) M. F. Grundon and W. L. Matier, *J. Chem. Soc. B*, 267 (1966).
(289) F. Ullman, G. Engi, N. Wossnesensky, E. Kuhn, and E. Heine, *Justus Liebigs Ann. Chem.*, **366**, 79 (1909).
(290) F. Kehrmann and M. Ramm, *Chem. Ber.*, **53**, 2265 (1920).
(291) E. Misslin and A. Bau, *Helv. Chim. Acta*, **2**, 285 (1919).
(292) O. L. Brady and C. Waller, *J. Chem. Soc.*, 1218 (1930).
(293) G. E. Bonvicino, L. H. Yogodzinski, and R. A. Hardy, *J. Org. Chem.*, **26**, 2797 (1961).
(294) F. Kehrmann and A. van Baerle, *Chem. Ber.*, **56**, 2385 (1923).
(295) M. W. Partridge, J. M. Sprake, and H. J. Vipond, *J. Chem. Soc. C*, 1245 (1966).



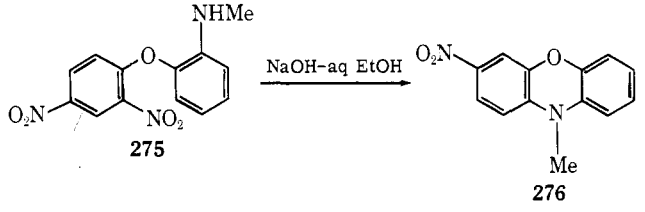
271 272

	R^1	R^2	R^3	R^4	R^5
a	CO_2H	H	NO_2	H	H
b	NO_2	H	CO_2H	H	H
c	NO_2	H	PhCO	H	H
d	NO_2	H	SO_3H	H	H
e	NO_2	H	H	H	H
f	H	H	NO_2	H	H
g	H	H	NO_2	H	Ac
h	MeO	H	NO_2	MeO	H
i	NO_2	H	Me	H	H
j	NO_2	Me	H	H	H
k	NO_2	H	H	Me	H
l	H	Cl	H	H	$(CH_2)_3NMe_2$
m	NO_2	H	NO_2	H	H



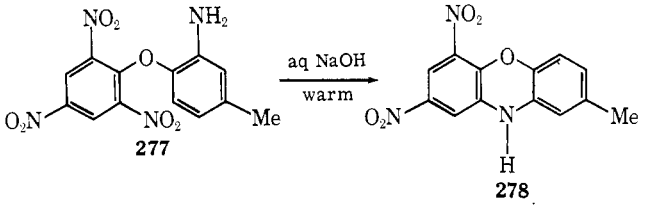
273 274

2-Amino-2′-nitrodiaryl ethers have also been used as substrates for this type of intramolecular displacement reaction, although in these cyclizations phenoxazine formation may (*e.g.*, **275** → **276**) or may not (*e.g.*, **277** → **278**) be preceded by Smiles rearrangement (*cf.* also ref 296). See eq 13[297] and 14.[298]



275 276

(13)

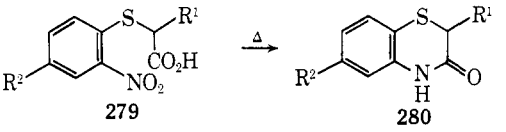


277 278

(14)

7. Benzothiazines

2*H*-1,4-Benzothiazin-3(4*H*)-ones (**280a–c**) are obtained[129] among other products (see section II.B.6) in low yield (10–30%) by pyrolysis of *o*-nitroarylthio derivatives of acetic and propionic acids (**279a–c**). However, thermal reactions of this kind are difficult to control and loss of material is considerable because of carbonization; they offer no advantage over conventional benzothiazine syntheses[299] employing reductive cyclization of the nitro compounds (**279**) with sodium borohydride/palladium–charcoal.



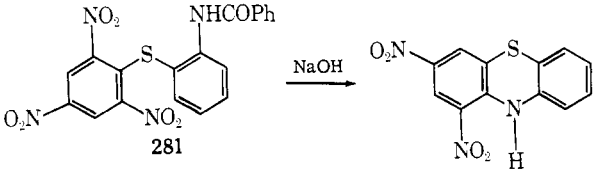
279 280

	R^1	R^2
a	H	H
b	Me	H
c	H	NO_2

2*H*-1,4-Benzothiazin-3(4*H*)-one (**280a**) is also formed[175] among other products (see section II.B.6) by the action of alkali on *o*-nitrophenylphenacyl sulfide. However, the yield is extremely low (<2%) and the process clearly has no synthetic value.

8. Phenothiazines

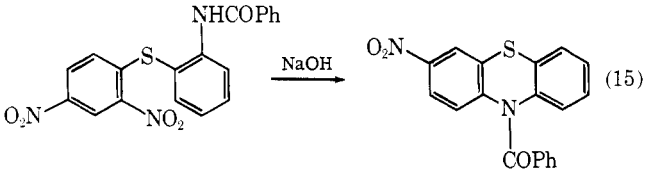
A number of reports on the synthesis of phenothiazines in the early literature[276, 288, 300–305] (*e.g.*, **281** → **282**)[303] were clarified when Smiles and his coworkers[306–308] found that rearrangements of 2-nitro-2′-acylaminodiphenyl sulfides to 2′-mercapto-2-nitro-*N*′-acyldiphenylamines occurred readily in alkaline media, and that these compounds in turn lose nitrous acid to form phenothiazines. The scope of the reaction has



281 282

subsequently been investigated by Smiles, *et al.*, and also by other workers;[309] some typical examples of this type of phenothiazine synthesis are shown in eq 15,[308] 16,[310–312] 17,[311] 18,[313] and 19.[314]

(296) K. C. Roberts and C. G. M. de Worms, *J. Chem. Soc.*, 1309 (1935).
(297) K. C. Roberts and H. B. Clark, *ibid.*, 1312 (1935).
(298) K. C. Roberts and C. G. M. de Worms, *ibid.*, 727 (1934).
(299) R. T. Coutts, D. L. Barton, and E. M. Smith, *Can. J. Chem.*, **44**, 1733 (1966).
(300) F. Kehrmann and L. Schild, *Chem. Ber.*, **32**, 2605 (1899).
(301) F. Kehrmann and J. Steinberg, *ibid.*, **44**, 3011 (1911).
(302) F. Kehrmann and O. Nossenko, *ibid.*, **46**, 2809 (1913).
(303) F. Kehrmann and F. Ringer, *ibid.*, **46**, 3014 (1913).
(304) J. Pollak, E. Riesz, and Z. Kahane, *Monatsh. Chem.*, **49**, 213 (1928).
(305) R. Möhlau, H. Beyschlag, and H. Köhres, *Chem. Ber.*, **45**, 131 (1912).
(306) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 181 (1925).
(307) W. J. Evans and S. Smiles, *ibid.*, 1263 (1935).
(308) C. F. Wight and S. Smiles, *ibid.*, 340 (1935).
(309) R. Baltzly, M. Harfenist, and F. J. Webb, *J. Amer. Chem. Soc.*, **68**, 2673 (1946).
(310) A. Roe and W. F. Little, *J. Org. Chem.*, **20**, 1577 (1955).
(311) A. J. Saggiomo, M. Asai, and P. M. Schwartz, *J. Heterocycl. Chem.*, **6**, 631 (1969).
(312) R. L. Mital and S. K. Jain, *J. Chem. Soc. C*, 2148 (1969).
(313) R. J. Galbraith and R. K. Ingham, *J. Org. Chem.*, **23**, 1804 (1958).
(314) F. A. Davis and R. B. Wetzel, *Tetrahedron Lett.*, 4483 (1969).



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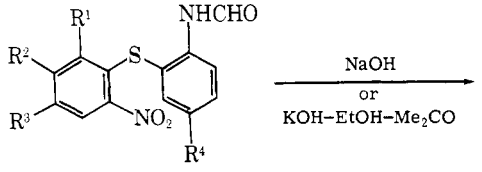
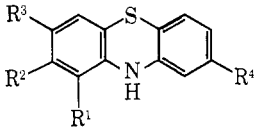
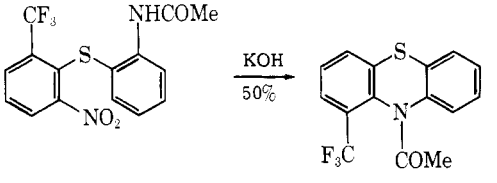


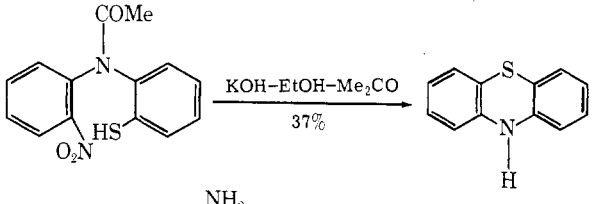


(16)

	R^1	R^2	R^3	R^4	Yield, %
a	H	H	CF_3	H	52
b	H	CF_3	H	H	59
c	H	H	F	H	43
d	CF_3	H	H	H	88
e	H	H	Br	Cl	86
f	H	H	NO_2	H	46
g	H	H	NO_2	NO_2	55
h	H	H	NO_2	Cl	23



(17)



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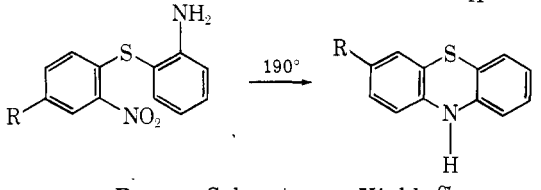
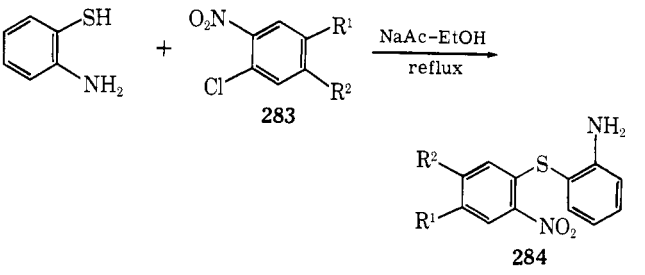


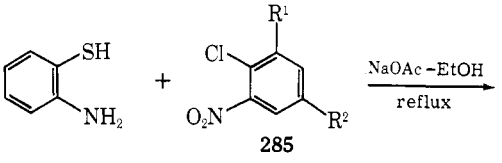
(19)

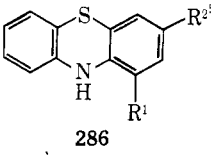
R	Solvent	Yield, %
H	CH_3CONMe_2	31
H	None	17
Me	CH_3CONMe_2	24
Me	None	18

These phenothiazine syntheses appear to be sensitive to the nature of the substituents present. For example, when the nitrated ring contains halogen (Cl), rearrangement and cyclization occur,[307] but when halogen (Br) is in the unnitrated ring, no reaction occurs.[309] However, even when the unnitrated ring is substituted by halogen, the presence of two nitro groups promotes cyclization.[309] In an effort to clarify these substituent effects, Sharma, *et al.*, have recently[315] examined



	R^1	R^2	Yield (**284**), %
a	Cl	H	65
b	NO_2	H	85
c	NO_2	Me	70

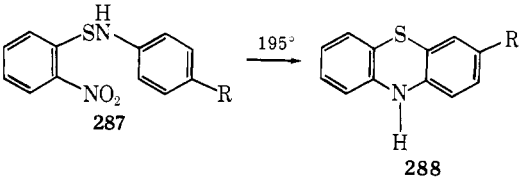




	R^1	R^2	Yield (**286**), %
a	NO_2	H	68
b	NO_2	NO_2	95
c	NO_2	Cl	90

the reactions of *o*-aminothiophenol with a number of *o*-chloronitrobenzenes (**283** and **285**). The results of their studies on the reactions **283** → **284** and **285** → **286** indicate that phenothiazines are formed only when the positions ortho to the activated halogen atom in the halonitrobenzenes are substituted by either two nitro groups or a nitro group and a halogen atom. These results are rationalized on the basis of steric effects in relation to alignment of the aryl substituent within an intermediate diaryl sulfide. (The work of Okamoto and Bunnett[316] on substituent effects on the rate of the Smiles rearrangement of 2-hydroxy-2′-nitrodiaryl sulfones to 2-(*o*-nitrophenoxy)arenesulfinic acids is also relevant in this context.)

Smiles rearrangements of intermediate diaryl sulfides are almost certainly responsible for the formation,[317] among other products (see section III.E), of phenothiazines **288** in the thermal reactions of *o*-nitrosulfenanilides (**287**) (Table XXXIX).



a, R = H; **b**, R = Me

(315) H. L. Sharma, V. N. Sharma, and R. L. Mital, *Aust. J. Chem.*, **21**, 3081 (1968); *Tetrahedron Lett.*, 1657 (1959).

(316) T. Okamoto and J. F. Bunnett, *J. Amer. Chem. Soc.*, **78**, 5363 (1956).

(317) F. A. Davis, R. B. Wetzel, T. J. Devon, and J. F. Stackhouse, *J. Org. Chem.*, **36**, 799 (1971); *Chem. Commun.*, 687 (1970).

Table XXXIX

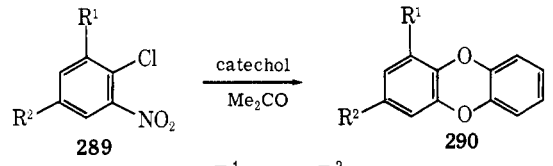
Phenothiazines from the Thermolysis of Nitrobenzenesulfenanilides[a]

Starting material (287)	*Solvent*	*Product* (288)	*Yield,* %
a	Aniline	**a**	3
a	*p*-Toluidine	**b**	12
b	Aniline	**a**	3
b	*p*-Toluidine	**b**	14

[a] The sulfenanilides were heated with an excess of the amine at 195° for *ca.* 15 hr.

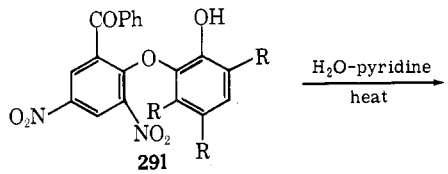
9. Dibenzodioxans

Dibenzodioxans (**290a–c**) are obtained[318] when *o*-chloronitrobenzene derivatives (**289a–c**) are treated with catechol in warm acetone. The presence of a 6-substituent appears to be mandatory for the success of this type of condensation which fails in the case of 2,4-dinitrochlorobenzene (**289d**) (similar restrictions apply to related syntheses of phenoxazines and phenothiazines; *cf.* sections II.E.6 and II.E.8). Reactions of the type **289** → **290** almost certainly proceed by a mechanism involving intramolecular nucleophilic displacement of the nitro group in an intermediate diaryl ether as evidenced[318] by the conversion of the 2-nitro-2′-hydroxydiaryl ethers (**291**) into the dibenzodioxans (**292**) under basic conditions. On this basis these reactions are closely related to the conversions of 2-nitro-2′-hydroxydiarylamines and of 2-nitro-2′-acylaminodiaryl sulfides into phenoxazines and phenothiazines, respectively (*cf.* section II.E.6 and II.E.8).



289 290

	R^1	R^2
a	NO_2	H
b	NO_2	NO_2
c	PhCO	NO_2
d	H	NO_2



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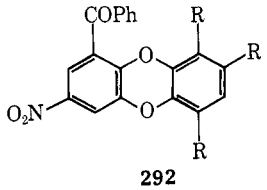
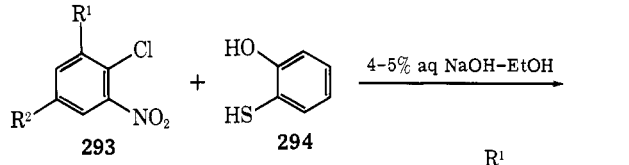


292

R = H or Me

10. Phenoxathiins

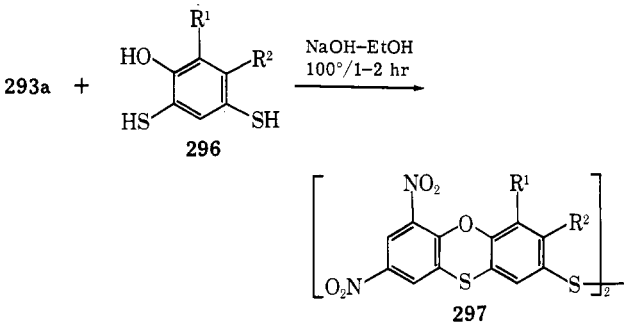
The formation of phenoxathiins (*e.g.*, **295**, **297**) by the reaction of *o*-chloronitroarenes (**293**) with *o*-mercaptophenol (**294**) and its derivatives (**296**) was first reported by Mauthner[319,320] and later by Pollak and Riesz.[321,322] However, no attempt was made to establish the orientation of the phenoxathiin products.



293 294 295

	R^1	R^2	Yield, %	Ref
a	NO_2	NO_2	59	319
b	CO_2H	NO_2	62	320

The problem of orientation was clarified by Stevenson and Smiles[323] who demonstrated that the intramolecular displacement of the nitro group implicit in these reactions is effected by the hydroxy rather than the thiol group (*cf.* **298** → **299** and **300** → **299**).

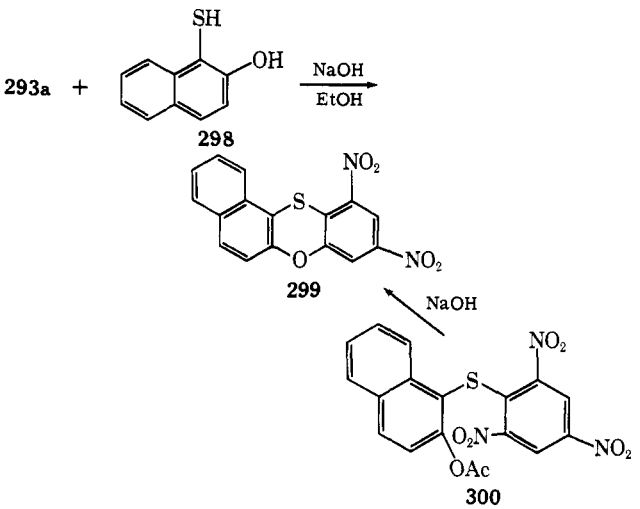


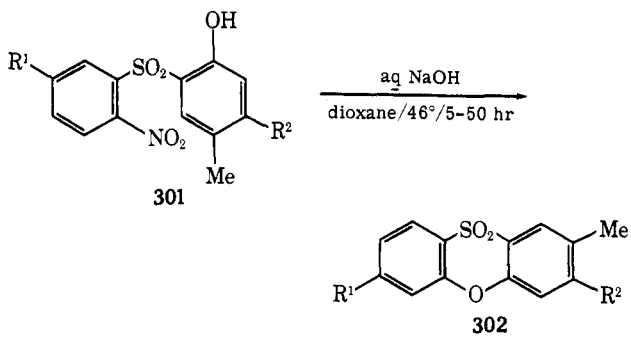
296 297

	R^1	R^2	Ref
a	Me	H	321
b	H	Me	321
c	H	H	322

The intramolecular displacement of a nitro group is almost certainly involved in the formation of phenoxathiin 10-dioxides (**302**) from 2-hydroxy-2′-nitrodiaryl sulfones (**301**), although here displacement is preceded by Smiles rearrangement. In general, however, low yields are obtained and this reaction is unlikely to have any synthetic value for the otherwise readily accessible[324] phenoxathiin *S*-dioxides.

(318) J. D. Loudon and F. McCapra, *J. Chem. Soc.*, 1899 (1959).
(319) F. Mauthner, *Chem. Ber.*, **38**, 1411 (1905).
(320) F. Mauthner, *ibid.*, **39**, 1340 (1906).
(321) J. Pollak and E. Riesz, *Monatsh. Chem.*, **50**, 251 (1928).
(322) J. Pollak and E. Riesz, *ibid.*, **53**, 90 (1929).
(323) H. A. Stevenson and S. Smiles, *J. Chem. Soc.*, 718 (1931).
(324) D. S. Breslow and H. Skolnik in "Chemistry of Heterocyclic Compounds," Part 2, A. Weissberger, Ed., Wiley, New York, N. Y., 1966, p 868.





	R^1	R^2	Yield, %	Ref
a	Cl	H	Not quoted	325
b	H	H	<5	326
c	H	Cl	<5	326
d	H	Br	<5	326

F. SIX-MEMBERED HETEROCYCLES CONTAINING THREE HETEROATOMS

Benzo-1,2,4-triazines

The base-catalyzed cyclization of *o*-nitrophenylguanidines, *o*-nitrophenylureas, and related compounds provides probably the best general method for the synthesis of 3-substituted benzo-1,2,4-triazine 1-*N*-oxides. These cyclizations are analogous to the type already described for the synthesis of cinnoline *N*-oxides (*cf.* section II.E.1). Warming *o*-nitrophenylguanidine (**305a**) with aqueous alkali yields 3-aminobenzo-1,2,4-triazine 1-*N*-oxide (**306a**) in high yield (Table XL).[327] The scope of this reaction has been modified and extended to include a variety of *o*-nitrophenylguanidine derivatives (**305**) (Table XL) which are prepared *in situ* by the acid-catalyzed condensation of an *o*-nitroaniline derivative (**303**) with cyanamide (**304**), or the cheaper sodium cyanamide, and subsequently cyclized to benzo-1,2,4-triazine *N*-oxides (**306**) under alkaline conditions.[328,329] Typical reaction conditions and yields are shown in Table XL. Owing to the exothermic nature of the *o*-nitroaniline–cyanamide condensation, large-scale reactions are best carried out in a solvent such as acetic acid.[328] The limiting factor in this benzo-1,2,4-triazine *N*-oxide synthesis is the ease of formation of the nitrophenylguanidine. In difficult cases, treating the *o*-nitroaniline derivative with cyanamide dihydrochloride at elevated temperature is recommended (Table XL).[328] However, even these conditions fail to convert the weakly basic 2,4-dinitroaniline (**303e**) into 7-nitrobenzo-1,2,4-triazine 1-*N*-oxide (**306e**). However, the latter compound is readily synthesized by the base-catalyzed cyclization of 2,4-dinitrophenylguanidine (**305e**) prepared by an alternative method.[332] Enhanced yields (Table XL) of 3-aminobenzo-1,2,4-triazine 1-*N*-oxides are obtained by using an excess of cyanamide.[330] N-Substituted *N'*-*o*-nitrophenylguanidines also undergo base-catalyzed cyclization to the corresponding benzo-1,2,4-triazine *N*-oxide (*e.g.*, **307** →

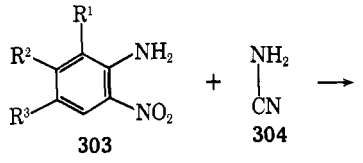
Table XL

Base-Catalyzed Cyclization of *o*-Nitrophenylguanidine Derivatives (305) to 3-Aminobenzo-1,2,4-triazine 1-*N*-Oxides (306)

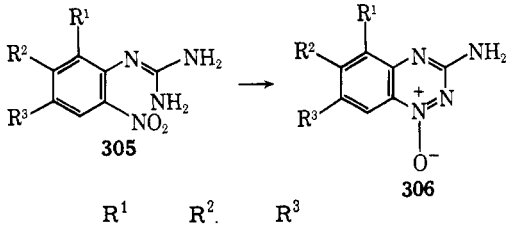
Starting material	*Reaction conditions*	*Product*	*Yield, %*	*Ref*
305a	Aq NaOH/boil briefly	**306a**	*a*	327
303a	1. Sodium cyanamide/concn HCl/heat 2. 40% NaOH/100°/0.5 hr	**306a**	44	329
303a	1. NH_2CN/100° 2. Concd HCl/100°/few min 3. 40% NaOH/100°/0.5 hr	**306a**	80	330
309a	4% aq NaOH/boil/2 min	**306a**	85	331
303b	1. NH_2CN/concd HCl/heat 2. 30% aq NaOH/100°/5 min	**306b**	26	328
303b	*b*	**306b**	*a*	329
303b	1. NH_2CN/100° 2. Concd HCl/100°/few min 3. 40% aq NaOH/100°/0.5 hr	**306b**	39	330
303c	1. NH_2CN/concn HCl–AcOH/reflux/25 min 2. 30% aq NaOH/boil/10 min	**306c**	47	328
303d	1. $NH_2CN(HCl)_2$/180–190°/10 min 2. 30% aq NaOH/boil/few min	**306d**	64	328
303f	*b*	**306f**	*a*	329
303f	1. NH_2CN/100° 2. Concd HCl/100°/few min 3. 40% aq NaOH/100°/0.5 hr	**306f**	81	330
303g	40% aq NaOH/100°/0.5 hr	**306g**	66	330
303h	*b*	**306h**	*a*	329
303i	*b*	**306i**	*a*	329
303j	1. NH_2CN/100° 2. Concd HCl/100°/few min 3. 40% aq NaOH/100°/0.5 hr	**306j**	75	330
303k	*b*	**306k**	*a*	329
305e	8% aq NaOH/reflux/4 min	**306e**	50	332
307	Aq NaOH/reflux	**308**	Quant	333
309b	4% aq NaOH/reflux/5 min	**311**	94	331

[a] Yield not quoted. [b] No details given.

(325) B. A. Kent and S. Smiles, *J. Chem. Soc.*, 422 (1934).
(326) T. Okamoto and J. F. Bunnett, *J. Amer. Chem. Soc.*, **78**, 5357 (1956).
(327) F. Arndt, *Chem. Ber.*, **46**, 3522 (1913).
(328) F. J. Wolf, K. Pfister, R. M. Wilson, and C. A. Robinson, *J. Amer. Chem. Soc.*, **76**, 3551 (1954).
(329) J. Jiu and G. P. Mueller, *J. Org. Chem.*, **24**, 813 (1959).
(330) J. C. Mason and G. Tennant, *J. Chem. Soc. B*, 911 (1970).
(331) H. J. Backer and H. D. Moed, *Recl. Trav. Chim. Pays-Bas*, **66**, 689 (1947).
(332) H. Dolman, H. A. Peperkamp, and H. D. Moed, *ibid.*, **83**, 1305 (1964).
(333) F. Arndt and B. Rosenau, *Chem. Ber.*, **50**, 1248 (1917).



303 304

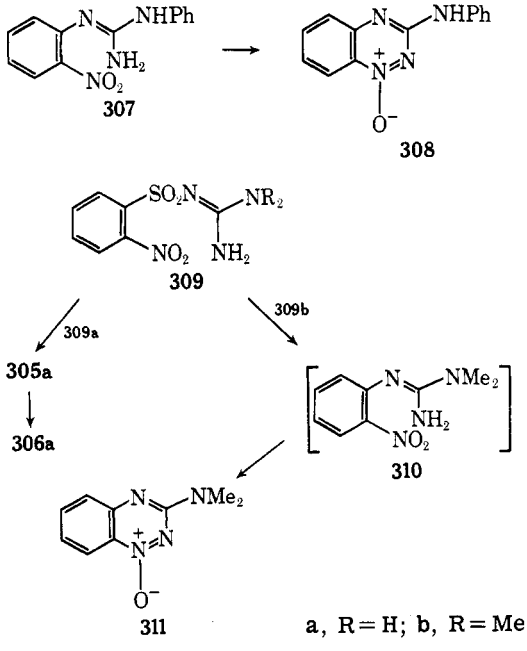


305 306

	R^1	R^2	R^3
a	H	H	H
b	H	H	Cl
c	H	H	Br
d	H	Cl	Cl
e	H	H	NO_2
f	H	H	MeO
g	H	H	Me
h	H	H	EtO
i	H	H	Ph
j	H	Me	Me
k	Me	H	Me

308);[333] Table XL). The *o*-nitrophenylguanidine derivative can also be generated *in situ* by the Smiles rearrangement of an *o*-nitrophenylsulfonylguanidine as exemplified by the base-catalyzed transformations **309a** → **305a** → **306a** and **309b** → **310** → **311** (Table XL).[331]

The nitrophenylguanidine cyclization has also been applied to heterocyclic derivatives. Base-catalyzed cyclization of the nitropyridylguanidines (**312a–c**) affords moderate to good



a, R = H; b, R = Me

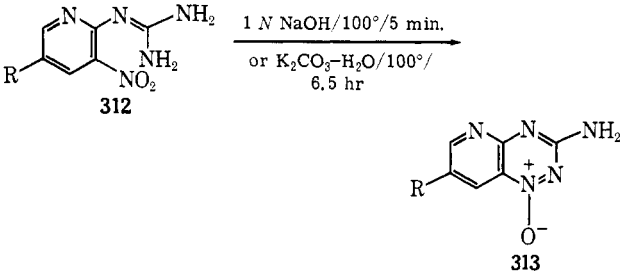
yields of pyrido[2,3-*e*]-*as*-triazine *N*-oxides (**313a–c**).[202] The best yields in these reactions are obtained using aqueous potassium carbonate at 100° for 6.5 hr. Under these conditions subsequent ring contraction of the triazine product to a triazole derivative (see section II.C.1) is kept to a minimum. No cyclization occurs when <1% aqueous sodium hydroxide is used as catalyst, while the use of >5% aqueous sodium hydroxide causes extensive triazole formation.[202] Isomeric pyrido[4,3-*e*]-*as*-triazine *N*-oxides (*e.g.*, **315**) are available[334] by the corresponding base-catalyzed cyclization of nitropyridylguanidines of the type **314**. In contrast, attempts[201b] to effect the base-catalyzed cyclization of the nitroimidazolyl-

Table XLI

Base-Catalyzed Cyclization of *o*-Nitrophenylureas (318, X = O) and *o*-Nitrophenylthioureas (318, X = S) to Benzo-1,2,4-triazine 1-*N*-Oxides (319, X = O or S)

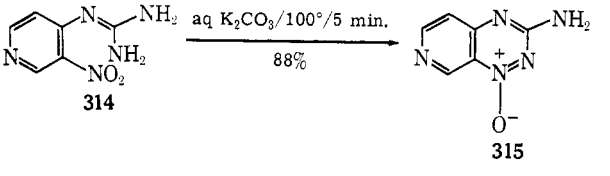
Starting material	*Reaction conditions*	*Product (319)*	*Yield, %*	*Ref*
318a	10% aq KOH/heat	**a**	*a*	327
318b	30% aq NaOH/90–95°/0.5 hr	**b**	88	335
318c	Aq NaOH/reflux/1 min	**c**	89	332
320a	8% aq NaOH/reflux/5 min	**a**	45	336

[a] Yield not quoted.



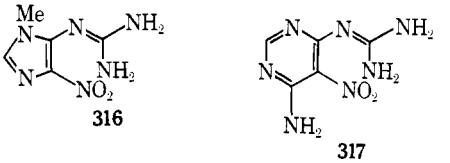
312 313

	R	Yield, %
a	H	40
b	Me	83
c	Cl	39



314 315

and nitropyrimidylguanidines (**316** and **317**) resulted in the complete degradation of the starting material.

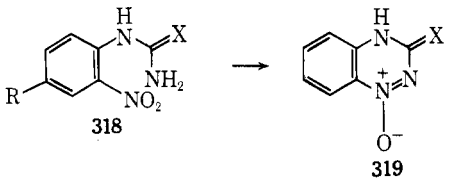


316 317

Closely related to the *o*-nitrophenylguanidine cyclizations are the base-catalyzed transformations of *o*-nitrophenylureas (**318**, X = O) and thioureas (**318**, X = S) into benzotriazinone *N*-oxides (**319**, X = O) and benzotriazinethione *N*-oxides (**319**, X = S).[327,332,335] Typical examples are given in Table XLI.

The *o*-nitrophenylurea can be generated *in situ* by Smiles rearrangement (see before) as in the conversion[336] of *o*-nitrophenylsulfonylurea (**320a**) into the benzotriazinone **319a**

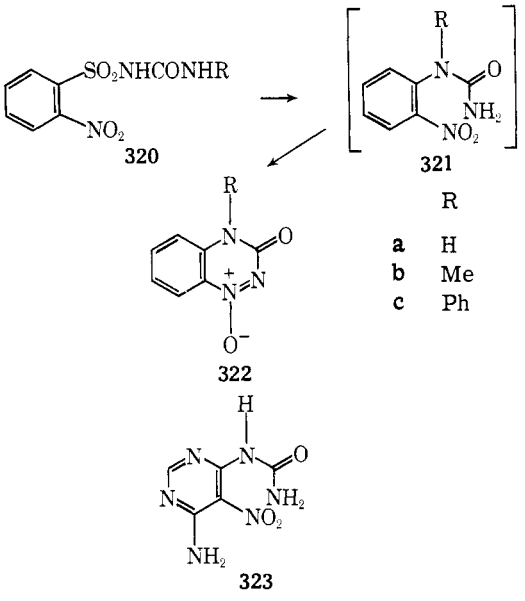
(334) A. Lewis and R. G. Shepherd, *J. Heterocycl. Chem.*, **8**, 47 (1971).
(335) F. J. Wolf, A. M. Wilson, J. K. Pfister, and M. Tishler, *J. Amer. Chem. Soc.*, **76**, 4611 (1954).
(336) H. J. Backer and J. Groot, *Recl. Trav. Chim. Pays-Bas*, **69**, 1323 (1950).



318 319

	R	X
a	H	O
b	Cl	O
c	H	S

(Table XLI). The N-substituted *o*-nitrophenylsulfonylureas (**320b,c**) heated with 0.1–2 *N* aqueous sodium hydroxide undergo Smiles rearrangement to afford the N-substituted *o*-nitrophenylureas (**321b,c**) which resist cyclization to the corresponding benzotriazinone *N*-oxides (**322b,c**).[336]



320 321 322 323

	R
a	H
b	Me
c	Ph

Heating the nitropyrimidylurea (**323**) with aqueous alkali resulted in degradation of the starting material rather than cyclization.[201b]

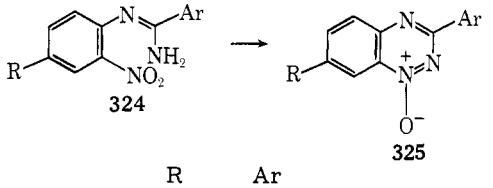
N-*o*-Nitrophenylamidines (**324**) cyclize on warming with 2 *N* aqueous sodium hydroxide or ethanolic sodium ethoxide providing a convenient general route to 3-arylbenzo-1,2,4-triazine 1-*N*-oxides (**325**) (Table XLII).[337,338] Similar cyclization of the hetarylamidines (**326**) affords 3-(thiazol-4-yl)benzo-1,2,4-triazine 1-*N*-oxides (**327**).[339]

Table XLII

Base-Catalyzed Cyclization of *N*-(*o*-Nitrophenyl)arylamidines (324) to 3-Arylbenzo-1,2,4-triazine 1-*N*-Oxides (325)

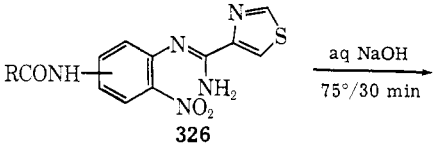
Starting material (324)	*Reaction conditions*	*Product* (325)	*Yield, %*	*Ref*
a	8% aq NaOH/100°/5 min	a	2.2	337, 338
b	NaOR–ROH/heat	b	*a*	338
c	NaOR–ROH/heat	c	*a*	338
d	NaOR–ROH/heat	d	58	338
e	NaOR–ROH/heat	e	80	338
f	NaOR–ROH/heat	f	*a*	338
g	NaOR–ROH/heat	g	60	338
h	NaOR–ROH/heat	h	*a*	338

[a] Yield not quoted.



324 325

	R	Ar
a	H	Ph
b	Me	Ph
c	Cl	Ph
d	MeO	Ph
e	H	*p*-$NO_2C_6H_4$
f	H	*p*-ClC_6H_4
g	H	*p*-$MeOC_6H_4$
h	H	CH=CHPh



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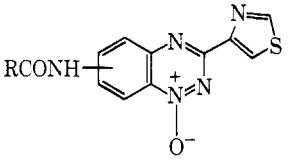


327

R = *i*-PrO, Ph, *p*-FC_6H_4 (yields not quoted)

III. Formation of Uncyclized Products

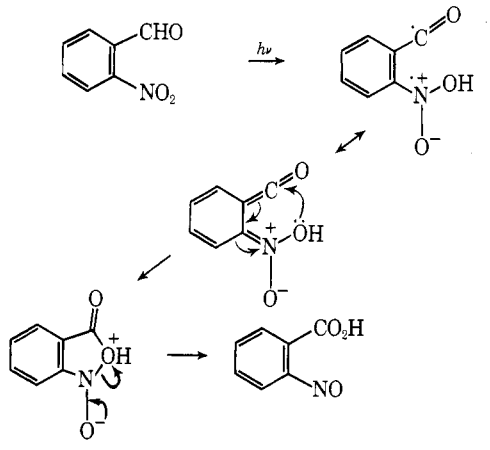
A. AROMATIC NITROSO COMPOUNDS

Aromatic nitroso compounds remain difficult to prepare despite the wide variety of synthetic routes available.[340] The synthesis of nitrosoarenes by photochemical transformation of *o*-nitrobenzene derivatives has been known since 1901, the earliest reported example being the conversion[341] of *o*-nitrobenzaldehyde to *o*-nitrosobenzoic acid (eq 20). Reactions of this type have been discussed in a recent review;[5] other examples are illustrated in reactions 21–25.

The efficiency of typical examples from the early literature is difficult to assess, but more recent examples (eq 22 and 23) suggest that the yields of nitroso products are high. Clearly such reactions will be of only limited use in synthesis: although they have the advantage of occurring in neutral media, they suffer from an obvious limitation in relation to the presence of other photosensitive functional groups in the molecule. However, an important indirect application is in the design of photosensitive protecting groups for carboxylic acids (*cf.* (eq 26 and 27). The undesirable side reaction of the liberated amine with *o*-nitrosobenzaldehyde in reaction 27 is avoided

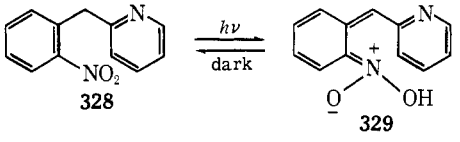
(337) R. F. Robbins and K. Schofield, *J. Chem. Soc.*, 3186 (1957).
(338) R. Fusco and G. Bianchetti, *Rend. Ist. Lomb. Sci. Lett., Cl. Sci. Mat. Natur.*, **91**, 963 (1957); *Chem. Abstr.*, **53**, 9243 (1959).
(339) R. L. Ellsworth, D. F. Hinkley, and E. F. Schoenewaldt, French Patent 2,014,422; *Chem. Abstr.*, **74**, 76423 (1971).
(340) J. H. Boyer in "The Chemistry of the Nitro and Nitroso Groups," H. Feuer, Ed., Interscience, New York, N. Y., pp 215–299.
(341) G. Ciamician and P. Silber, *Chem. Ber.*, **34**, 2040 (1901).

Scheme IX



by the use of the corresponding 2,2′-dinitrodiphenylmethyloxycarbonyl derivatives.[342]

Very little attention has been paid to the mechanism[343,344] of the photoisomerization of *o*-nitrobenzaldehyde. One possibility[345] is that N–O bond cleavage followed by subsequent oxygen atom insertion into the C–H bond of the aldehyde side chain occurs. Alternatively,[4,346,347] the benzylic hydrogen atom may be abstracted by the photoexcited nitro group (Scheme IX). Circumstantial evidence in support of the latter mechanism is provided by the photochromic behavior[348a] of a number of compounds containing an *o*-nitrobenzyl substituent. It has been established that the colored species formed have *aci*-nitro structures (*e.g.*, **328** ⇌ **329**). It should be noted,



328 **329**

however, that *p*-nitrobenzaldehyde can be converted photochemically to *p*-nitrosobenzoic acid, and the possibility of an intermolecular mechanism for the *o*-nitrobenzaldehyde rearrangement has not been ruled out.

The isomerization of *o*-nitrobenzaldehyde to *o*-nitrosobenzoic acid can also be effected[352] through the formation of intermediate cyanohydrins. Yields are high and the generality of the reaction has been demonstrated[352] using *o*-nitropiperonal and 2-nitro-5-chloro- and 2,4-dinitrobenzaldehyde.

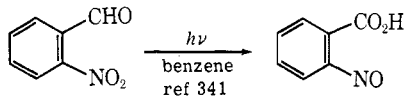
Photolysis of the readily available[120] *o*-nitroaryl derivatives of α-amino acids **330** in neutral or alkaline solution provides a valuable synthetic route to *o*-nitrosoarylamines (**331**);[353–356] in acid solution, however, the major products are benzimidazole *N*-oxides (see section II.B.3). Some examples of this type of transformation are shown in Table XLIII. *o*-Nitrosoarylamines have also been obtained,[357] although in low yield, by irradiation of *N*-alkyl-*o*-nitroanilines (*cf.* **332** → **333**, yield *ca.* 5%).

Table XLIII

Formation of *o*-Nitrosoarylamines in the Photolysis of *N*-(2,4-Dinitrophenyl)-α-amino Acids

Starting material (330)	*Product* (331)	*Yield, %*	*Ref*
a	**a**	67	355
b	**a**	*a*	356
c	**a**	76	101
d	**a**	*a*	356
e	**b**	84	354

[a] Yield not quoted.



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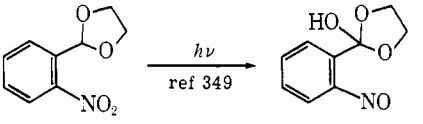

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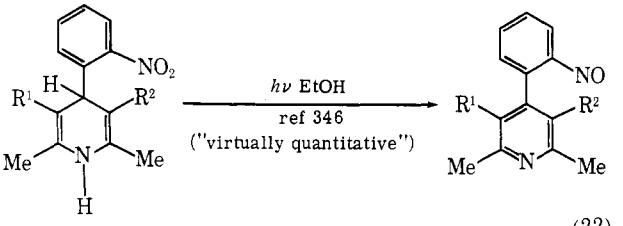
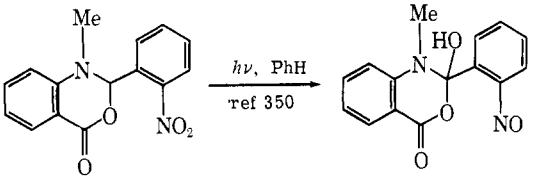


(22)

$R^1 = R^2 = CO_2Et$
$R^1 = R^2 = COMe$
$R^1 = COMe;\ R^2 = CO_2Et$

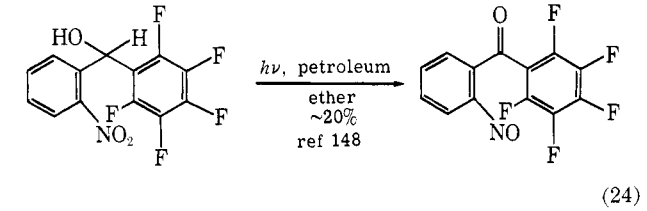


(23)

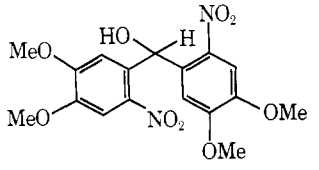
A related procedure is the photolytic conversion[358] of the sodium salt of 2-deoxy-2-(2,4-dinitroanilino)-D-gluconic acid (**334**) in aqueous solution into 4-nitro-2-nitrosoaniline together with D-arabinose (**335**).

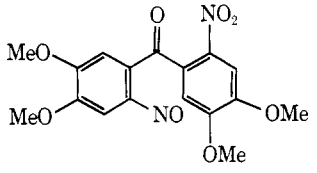
In contrast to the salt **334** the alditol derivative **336** is photochemically stable under similar conditions. This difference in reactivity may prove to be useful as a diagnostic tool in structure determination. Oxidation of the *N*-(2,4-dinitrophenyl)

(342) A. Patchornik, B. Amit, and R. B. Woodward, *J. Amer. Chem. Soc.*, **92**, 6333 (1970).
(343) P. Leighton and F. Lucy, *J. Chem. Phys.*, **2**, 756 (1934).
(344) H. Mauser and H. Heitzer, *Z. Naturforsch.*, **21b**, 109 (1966).
(345) J. G. Calvert and J. N. Pitts, "Photochemistry," Wiley, New York, N. Y., 1966, p 478.
(346) J. A. Berson and E. Brown, *J. Amer. Chem. Soc.*, **77**, 447 (1955).
(347) I. Tanasescu, *Bull. Soc. Chim. Fr.*, **29**, 1443 (1926).
(348) (a) R. Exelby and R. Grinter, *Chem. Rev.*, **65**, 247 (1965); J. Weinstein, A. Bluhm, and J. Sousa, *J. Org. Chem.*, **31**, 1983 (1966); (b) J. Reisch and K. G. Weidmann, *Arch. Pharm. (Weinheim)*, 906 (1971).
(349) I. Tanasescu and H. Tanasescu, *Bull. Soc. Stiinte Cluj.*, **2**, 369 (1925); *Chem. Abstr.*, **20**, 749 (1926).
(350) M. A. Hems, *Tetrahedron Lett.*, 375 (1969).
(351) J. A. Barltrop, P. J. Plant, and P. Schofield, *Chem. Commun.*, 822 (1966).
(352) G. Heller, *Chem. Ber.*, **39**, 2334 (1906); **43**, 2829 (1910); *J. Prakt. Chem.*, **106**, 1 (1923); S. Ekecrantz and A. Ahlquist, *Chem. Ber.*, **41**, 878 (1908).
(353) D. W. Russell, *Biochem. J.*, **83**, 8 (1962).
(354) D. W. Russell, *J. Chem. Soc.*, 2829 (1964).
(355) D. W. Russell, *ibid.*, 874 (1963).
(356) D. W. Russell, *Biochem. J.*, **87**, 1 (1963).
(357) R. E. McMahon, *Tetrahedron Lett.*, 2307 (1966).
(358) A. E. El Ashmawy, D. Horton, and K. D. Philips, *Carbohyd. Res.*, **9**, 350 (1969).

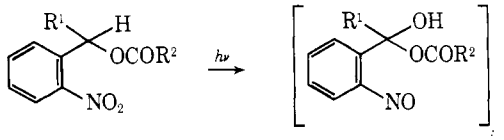


(24)

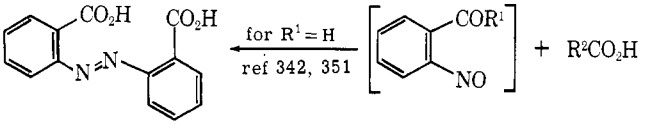


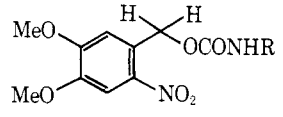


(25)

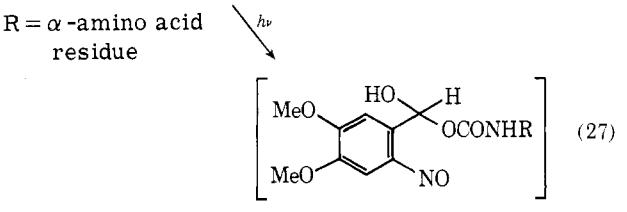


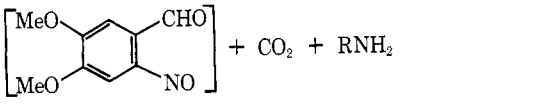
R^1 = H, Ph; R^2 = Ph, $PhCH_2$, H_2NCH_2 (26)

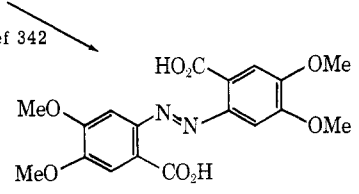




R = α-amino acid residue

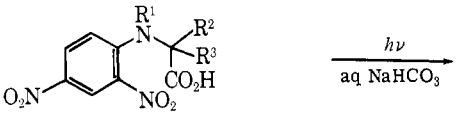




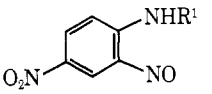


derivative to the aldonic acid followed by photolysis may likewise find use as a method for the stepwise degradation of 2-amino-2-deoxyaldoses.

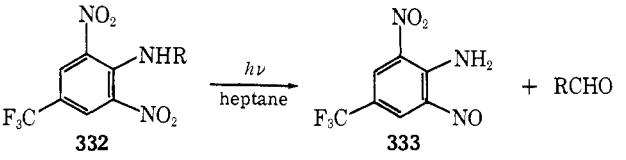
In reactions analogous to the amino acid decompositions (**330** → **331**; **332** → **333**), photolysis of *o*-nitroaryloxyacetic acids (**337**) affords good yields (*ca.* 65%) of *o*-nitrosophenols (**338**).[359] This synthetic method is an attractive one since it



	R^1	R^2	R^3
330a	H	H	*i*-Bu
b	H	H	H
c	H	Me	H
d	H	*i*-Pr	H
e	Me	H	*i*-Bu

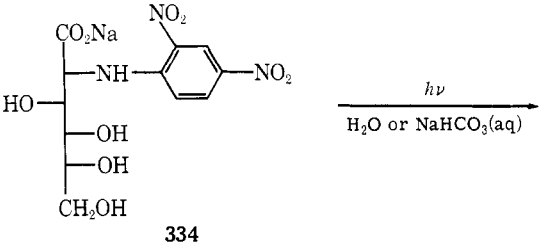


	R^1
331a	H
b	Me



332 **333**

	R
a	H
b	*n*-Pr



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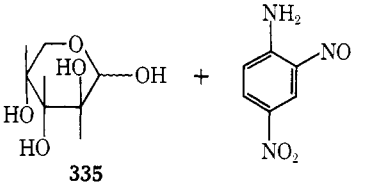

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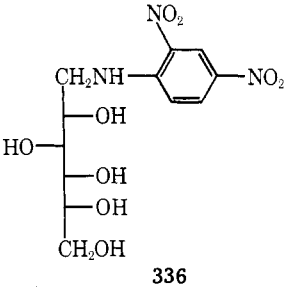
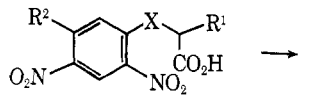


336

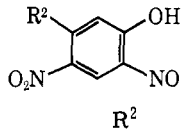
offers an alternative to the Baudisch oxidative nitrosation procedure;[360] indeed an attempted[359] synthesis of 4-nitro-2-nitrosophenol by either the Baudisch method or by reduction[360c] of 2,4-dinitrophenol was unsuccessful. An attempt to extend the photochemical nitrosophenol synthesis to obtain the unknown *o*-nitrosothiophenol and its derivatives (*e.g.*,

(359) P. H. McFarlane and D. W. Russell, *Chem. Commun.*, 475 (1969).

(360) (a) O. Baudisch, *J. Amer. Chem. Soc.*, **63**, 622 (1941); (b) G. Cronheim, *J. Org. Chem.*, **12**, 1, 7, 20 (1947); (c) K. Murayama, I. Tanimoto, and R. G. Goto, *J. Org. Chem.*, **32**, 2516 (1967).



	X	R^1	R^2
337a	O	Me	H
b	O	H	O-alkyl

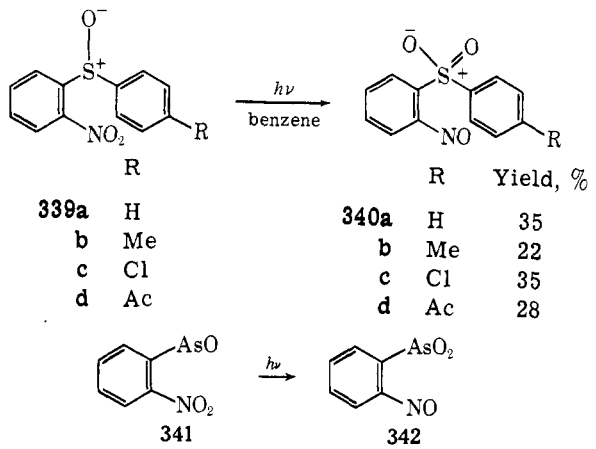


+ CO_2 + R^1CHO

	R^2
338a	H
b	O-alkyl

using (**337**) X = S; R^1 = H, alkyl, or Ph; R^2 = H) was unsuccessful.[361] Apparently[361] nitroso compounds are formed in these reactions but undergo further transformation on work-up to give complex, inseparable mixtures.

The photochemical conversion of (2-nitrophenyl)aryl sulfoxides (**339**) to (2-nitrosophenyl)aryl sulfones (**340**) has recently been reported.[362] The preliminary work[362] indicates that these photochemical reactions are specific for sulfoxides and cannot be applied to the corresponding nitrodiaryl sulfides. The photochemical process **339** → **340** is inhibited by benzophenone and cannot be effected thermally. A formally analogous photochemically induced oxygen transfer process is the conversion of the arsenic derivative **341** into the nitroso compound **342**.[363]

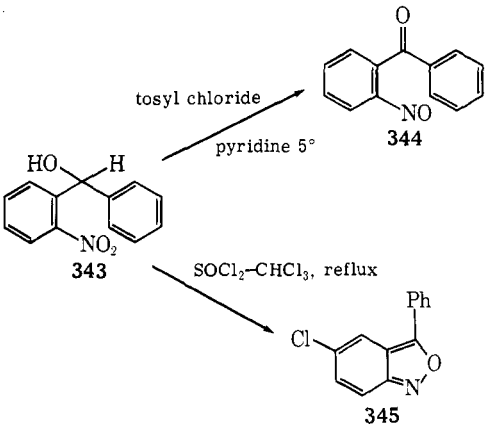


	R
339a	H
b	Me
c	Cl
d	Ac

	R	Yield, %
340a	H	35
b	Me	22
c	Cl	35
d	Ac	28

341 **342**

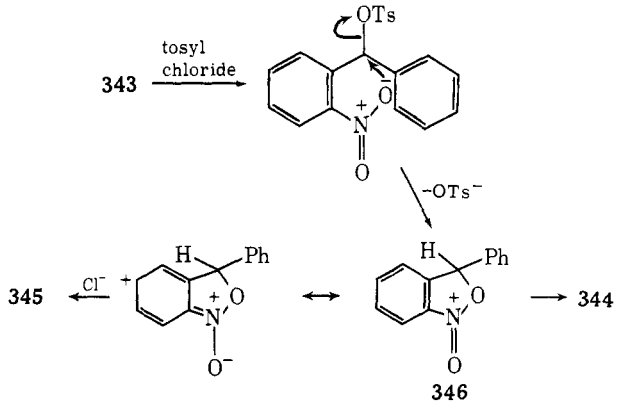
An alternative route to aromatic nitroso compounds involves the acid-catalyzed transformations of *o*-nitrobenzhydrol and its derivatives. Thus *o*-nitrobenzhydrol (**343**) is converted in high yield (78%) by treatment with *p*-toluenesulfonyl chloride to *o*-nitrosobenzophenone (**344**) or to 5-chloro-3-phenyl-2,1-benzisoxazole (**345**) by treatment with thionyl chloride[364] (see section II.B.5). The method is useful for the synthesis of *o*-nitrosoaryl ketones since conventional approaches from the appropriate amine, or from the anthranil,[365] involve vigorous oxidation. The reactions are presumed[364] to involve an intramolecular nucleophilic displacement of a tosylate or chlorosulfonate ester by the nitro group followed



343 **344** **345**

by subsequent conversion of an intermediate (**346**) into either the nitroso ketone or the anthranil. More recently it has been shown[150,151] that the nitroso ketone is formed solvolytically from *o*-nitrobenzydryl bromide in acetic acid providing sufficient sodium acetate is present to prevent accumulation of hydrogen bromide; when the latter is present at moderate concentration, the solvolysis product is exclusively 5-bromo-3-phenyl-2,1-benzisoxazole (*cf.* section II.B.5). The suggested[364] neighboring group participation by the nitro group is supported[150] by kinetic data which indicate a 1500-fold solvolytic rate difference for the ortho-, relative to the para-substituted nitro derivative.

In a reaction closely analogous to transformations of *o*-nitrobenzhydrol and its derivatives (*cf.* **343** → **344**), *o*-nitrophenylcyclopropane (**347**) is converted[366] to *o*-nitrosophenyl ethyl ketone (**348**). Under identical experimental conditions,

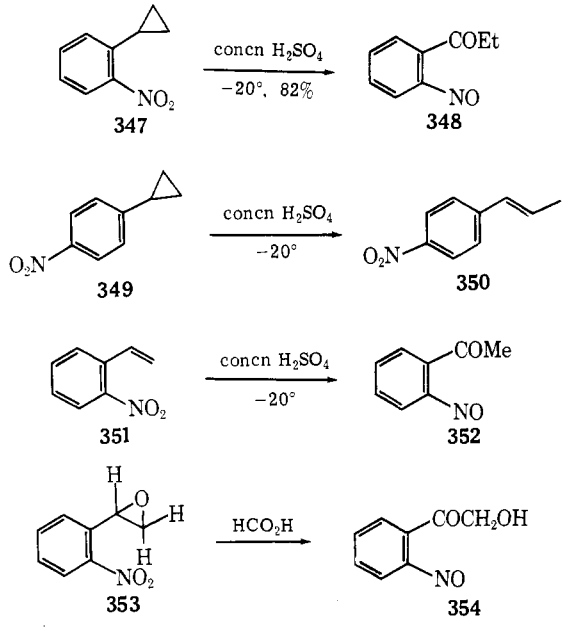


345 **346**

the *p*-nitro isomer **349** undergoes ring opening to afford the alkene **350**. A transformation related to the reaction **347** → **348** is the acid-catalyzed conversion of 2-nitrophenylethylene (**351**) to *o*-nitrosoacetophenone (**352**). A process which is formally analogous to the *o*-nitrophenylcyclopropane reactions (*i.e.*, **347** → **348**) is the acid-catalyzed transformation[70,367,368] of *o*-nitrophenylethylene oxide (**353**) to *o*-nitrosobenzoylmethanol (**354**).

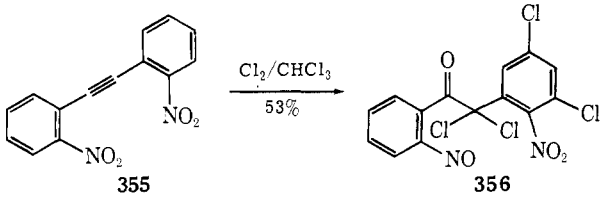
The conversion[369] of 2,2′-dinitrotolan (**355**) into the nitro-

(361) R. S. Goudie and P. N. Preston, *J. Chem. Soc. C*, 3081 (1971).
(362) R. Tanikaga, Y. Higashio, and A. Kaji, *Tetrahedron Lett.*, 3273 (1970).
(363) P. Karrer, *Chem. Ber.*, **47**, 1783 (1914).
(364) W. B. Dickinson, *J. Amer. Chem. Soc.*, **86**, 3580 (1964).
(365) G. Heller, *J. Prakt. Chem.*, **77**, 166 (1908).
(366) Y. S. Shabarov, S. S. Mochalov, and I. P. Stepanova, *Dokl. Akad. Nauk. SSSR*, **189**, 1028 (1969); *Chem. Abstr.*, **72**, 66523 (1970).
(367) F. Arndt, B. Eistert, and W. Partale, *Chem. Ber.*, **61**, 1107 (1928).
(368) S. H. Nicolson and G. Tennant, unpublished results.
(369) P. Ruggli, H. Zaeslin, and F. Lang, *Helv. Chim. Acta*, **21**, 1240 (1938).



347 348 349 350 351 352 353 354

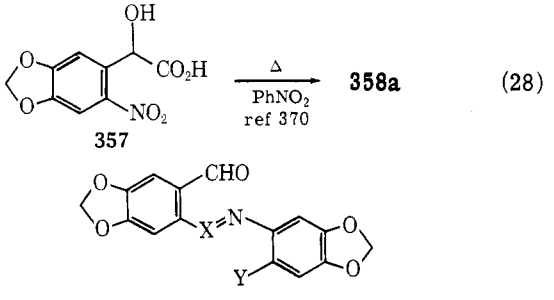
sobenzil derivative **356** by chlorine is a remarkable example of an *o*-nitro substituent interaction, the mechanism and scope of which have not been investigated.



355 356

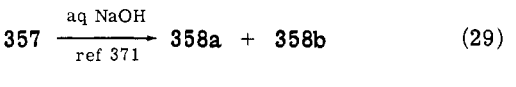
B. AZO AND AZOXY COMPOUNDS

Azo- and azoxybenzene derivatives are produced in thermal, photochemical, and base-catalyzed transformations of ortho-substituted nitrobenzene derivatives; many of these involve intramolecular oxidation of the side chain by the *o*-nitro group. Except for a few notable cases, however, yields are either poor or difficult to ascertain from the literature; unless yields are moderate to good, therefore, they are not quoted below. Processes leading to azo- and azoxybenzene derivatives are exemplified by reactions 28–33.

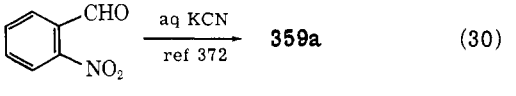


357 **358a** (28)

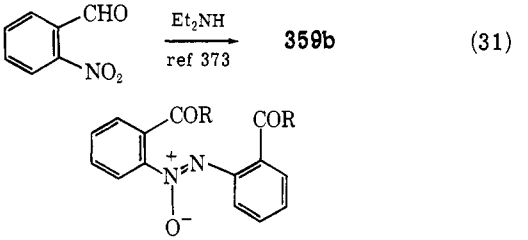
358a X = N; Y = CO_2H
b X = $\overset{+}{N}$—$\overset{-}{O}$; Y = CHO



357 → **358a** + **358b** (29)

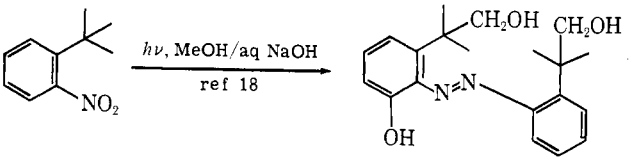


359a (30)

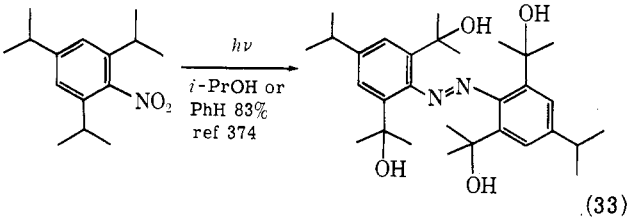


359b (31)

359a, R = OH
b, R = NEt_2

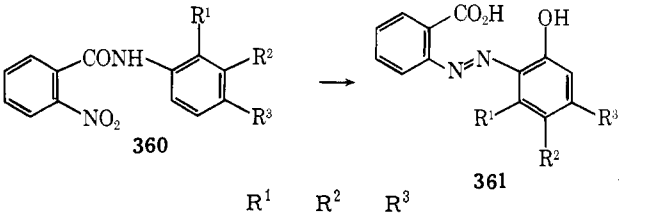


(32)



(33)

Photochemical transformation of the N-substituted *o*-nitrobenzamides (**360** and **362**) into the hydroxyazobenzenecarboxylic acids (**361** and **363**)[375] occurs in the solid phase, or in solution by irradiation with ultraviolet light or bright sunlight. However the yields in these reactions (**360** → **361**, **362** → **363**) are poor perhaps because of competitive light absorption by the azobenzene products. The overall efficiency can be increased, however, by continuously cycling the photolysate through alumina which adsorbs the azobenzene products. *o*-Nitrobenzamide and *N*-alkyl (Me, Et, *i*-Pr, $PhCH_2$, $PhCH_2CH_2$) derivatives are photochemically stable. Although azoxy compounds could not be isolated,[375] their intermediacy in these reactions is in accord with the well-known[376] azoxybenzene–hydroxyazobenzene rearrangement.



360 361

	R^1	R^2	R^3
a	H	H	H
b	Me	H	H
c	Cl	H	H
d	H	H	Cl
e	H	Me	H

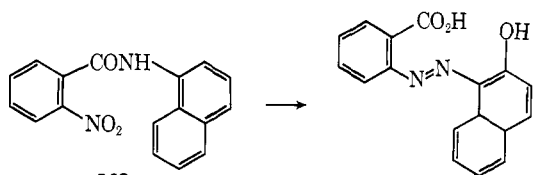
(370) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **105**, 1456 (1914).
(371) G. M. Robinson, *ibid.*, **111**, 109 (1917).
(372) B. Homolka, *Chem. Ber.*, **17**, 1902 (1884); *cf.* also G. Lock, *ibid.*, **63**, 855 (1930); P. Carré, *Compt. Rend.*, **140**, 633 (1905).
(373) H. Dickhauser and F. Kröhnke, *Chem. Ber.*, **103**, 320 (1970).
(374) Y. Kitaura and T. Matsuura, *Tetrahedron*, **27**, 1583 (1971).
(375) B. C. Gunn and M. F. G. Stevens, *Chem. Commun.*, 835 (1972).
(376) G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970).

Table XLIV

Products from the Pyrolysis of Nitrotoluenes in the Presence of Methanol[a,b]

Products	*Nitrotoluene isomer pyrolyzed* *Ortho*	*Meta*	*Para*
Toluidine	100	100	100
Aniline	385	6	4
Cresol	67	62	38
N-Methyltoluidine	31	29	17
Methyl anthranilate	369		
Bibenzyl and isomers	3	73	17

[a] Conditions: 400°, 16-sec contact time; N_2 at 20 ml min^{-1}; molar ratio nitrotoluene: methanol = 1:100. [b] Figures quoted are relative yields as estimated mass spectrometrically.



362 363

Azo- and azoxybenzene derivatives are also formed in a number of reactions discussed elsewhere in this review [see sections III.D (ref 361 and 377), III.E (ref 378), II.B.1 (ref 70), and III.A (ref 342 and 351)].

C. ARYLAMINES

The thermal behavior of the nitrotoluenes has been investigated[379] at 400–600° in the presence of benzene, benzene-d_6, chlorobenzene, and methanol. A noteworthy feature of these reactions is the considerable difference in behavior of the ortho compared with the meta and para isomers. For example, the products from the last two substrates in the presence of benzene are generally similar, although relative yields differ. Other than biphenyl, which is also formed from benzene alone, the major products are methylbiphenyls which probably arise from arylation of benzene by tolyl radicals. However, under the same conditions the ortho isomer gives aniline as the major product, together with smaller quantitites of *o*-methylbiphenyl and its dehydrogenation product, fluorene. The origin of the aniline was clarified by pyrolysis of the nitrotoluenes in methanol (Table XLIV) from which it appears that methyl anthranilate is formed from the ortho isomer in a yield about equal to that of aniline. Evidently at high temperatures in the absence of methanol, *o*-nitrotoluene undergoes intramolecular oxidation–reduction to give anthranilic acid which decarboxylates to give aniline. Substituted methyl anthranilates can be obtained from *o*-nitrotoluene analogs, and, although yields are not particularly high (Table XLV), the route is of synthetic interest since the reactions can be carried out in a single step.

The formation of aniline from *o*-nitrotoluene in the absence of methanol also has obvious synthetic implications, exploitation of which (Table XLVI) indicates that this direct route may be useful for the synthesis of the frequently inaccessible meta-substituted arylamines.

Table XLV

Synthesis of Methyl Anthranilates by Pyrolysis of *o*-Methylnitroarenes in the Presence of Methanol

o-Methylnitroarene	*Product*	*Yield, %*
o-Nitrotoluene	Methyl anthranilate	38
4-Chloro-2-nitrotoluene	Methyl 4-chloroanthranilate	36
4-Fluoro-2-nitrotoluene	Methyl 4-fluoroanthranilate	21
Nitro-*p*-xylene	Methyl 4-methylanthranilate	25
5-Nitropseudocumene	Methyl 3,4-dimethylanthranilate	20
Methyl 3-nitro-4-methylbenzoate	Dimethyl 2-aminoterephthalate	6
	Methyl anthranilate	37
2-Methyl-1-nitronaphthalene	Methyl 1-amino-2-naphthoate	11

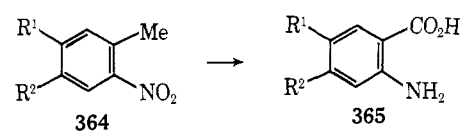
Table XLVI

Synthesis of Arylamines by the Pyrolysis of *o*-Methylnitroarenes[a] in the Presence of Benzene

o-Methylnitroarene	*Product*	*Yield, %*
o-Nitrotoluene	Aniline	57
Nitro-*p*-xylene	*m*-Toluidine	59
4-Chloro-2-nitrotoluene	*m*-Chloroaniline	15
4-Fluoro-2-nitrotoluene	*m*-Fluoroaniline	27
5-Nitropseudocumene	4-Amino-*o*-xylene	19
Methyl 3-nitro-4-methylbenzoate	Methyl 3-aminobenzoate	32
2-Methyl-1-nitronaphthalene	1-Naphthylamine	70

[a] Conditions: 600°; contact time 20 sec; mole ratio of nitro compound: benzene = 1:4.

o-Aminobenzoic acid derivatives are also formed in variable yields in the reactions of *o*-nitrotoluene derivatives with alkali; typical examples are represented by the reaction **364** → **365**.



364 365

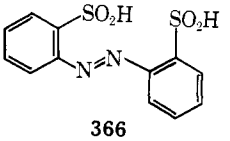
R^1	R^2	Conditions	Product (**365**), % yield	Ref
H	H	KOH/Δ	22	380
SO_3H	H	Aq NaOH/Δ	45	381
H	NO_2	KOH-*i*-PrOH/Δ	Not quoted	382

D. SULFINIC ACIDS

Synthetic routes to the relatively labile aromatic sulfinic acids are well established,[383] and the formation of such compounds from ortho-substituted nitrobenzene derivatives is of mechanistic interest only.

(377) C. Simons and L. G. Ratner, *J. Chem. Soc.*, 421 (1944).
(378) D. H. R. Barton, T. Nakano, and P. G. Sammes, *J. Chem. Soc. C*, 322 (1968).
(379) E. K. Fields and S. Meyerson, *J. Org. Chem.*, **33**, 4487 (1968).
(380) G. Lock, *Chem. Ber.*, **73**, 1377 (1940).
(381) E. N. Shagova, *Anilinokrasochnaya Prom.*, **4**, 264 (1934); *Chem. Abstr.*, **28**, 7254 (1934).
(382) K. G. Rosdahl, Swedish Patent, 128,380; *Chem. Abstr.*, **44**, 9480 (1950).
(383) W. E. Truce and A. M. Murphy, *Chem. Rev.*, **48**, 69 (1951).

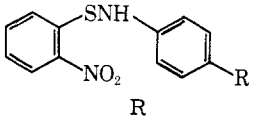
o-Nitrothiophenol when heated with sodium pentyl oxide in pentyl alcohol affords the sodium salt of the sulfinic acid **366**



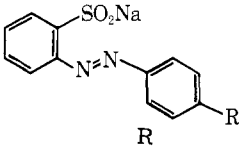
366

in 32% yield although under the same conditions the corresponding methylthio ether is simply reduced to the corresponding azo or azoxy compound.[377]

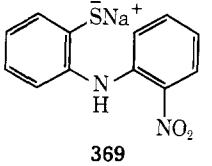
Base-catalyzed reaction of 2-nitrobenzenesulfenanilide (**367a**) affords the sodium salt of azobenzene-2-sulfinic acid (**368a**)[384] and not the *o*-nitroaniline derivative (**369**) as reported by previous workers.[385]



	R
367a	H
b	MeO
c	NO_2
d	Me



	R
368a	H
b	NHPh



369

The mechanism proposed[384] for the formation of the sulfinate **368a** was shown to be unacceptable by Brown[386] on the grounds that both the oxygen atoms in the product originate from the nitro group as evidenced by labeling studies. Kinetic data[386] indicate that the reactions **367** → **368** are first order in sulfenanilide and in hydroxide ion with the methoxy derivative (**367b**) rearranging at a slightly faster rate than **367a**. These observations, coupled with the failure of the nitro derivative (**367c**) to undergo rearrangement, have been rationalized[386] in terms of a mechanism involving an intramolecular oxygen-transfer process (Scheme X).

A remarkably similar transformation of the anilide **367a** occurs[861] under the influence of light from a sun lamp. Under these conditions the sulfinic acid **368b** (SO_2H for SO_2Na) is formed in moderate yield (37%) together with 2,2′-dinitrodiphenyl disulfide (<5%) and aniline (10%). This behavior contrasts with the results observed when the anilide **367a** is pyrolyzed[317] (see section III.E). Formation of the sulfinic acid appears to have precise structural requirements since such products are not observed[861] on photolysis of the *N*-methylanilide **367a** (NMe for NH).

E. SULFONIC ACIDS AND DERIVATIVES

Orthanilic acid or its derivatives are formed among other products in a number of reactions (*cf.* **370** → **371**; Table XLVII) involving derivatives of *o*-nitroarylsulfenic acids.

Scheme X

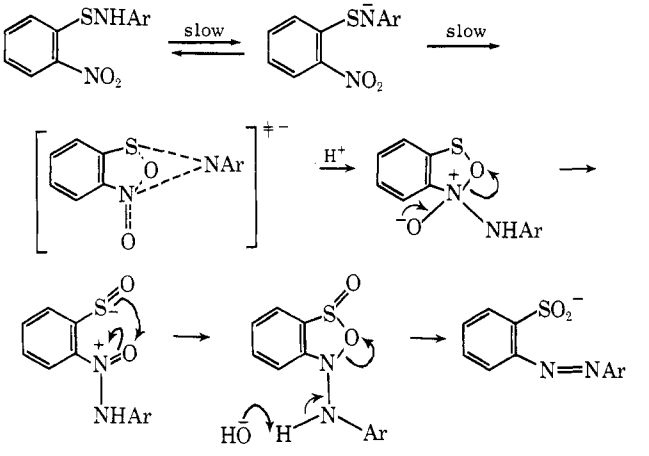


Table XLVII

Formation of Orthanilic Acid and 2-Amino-4-nitrobenzenesulfonic Acid from Derivatives of *o*-Nitrobenzenesulfenic Acid

Starting material (370)	*Reaction conditions*	*Product* (371)	*Yield*, %	*Ref*
a	Aq MeOH/heat	**a**	33	388
b	(i) AcOH, (ii) PhH/80°	**b**	2	389
c	MeOH/HCl/H_2O/heat	**b**	70	389
b	MeOH/HCl/H_2O/heat	**b**	40	389
d	MeOH/HCl/H_2O/heat	**b**	20	389
e	*hν*/benzene	**b**	*a*	378
f	*hν*/benzene	**b**	*a*	378
d	*hν*/benzene	**b**	*a*	378, 390
g	*hν*/benzene	**b**	19	387a

[a] Yield not determined.

Orthanilic acid itself is formed in the reaction of *o*-nitrophenylsulfonylacetic acid (**372**) with aqueous sodium hydroxide.[387b]

The mechanisms of these reactions (**370** → **371**) have not been established although the conversion **370b** → **371b** is apparently[391] in part photochemical and proceeds by way of the 2-acetoxyamino compound **371** (NHOAc for NH_2). Reactions of this type may find some application for the synthesis of orthanilic acids; certainly the process **370c** → **371b** is a superior route compared with an alternative procedure employing fuming sulfuric acid.[389]

Studies[385,392] of the thermolysis of 2-nitrobenzenesulfenanilides (**373**) in amine solvents have recently been reinvestigated by Davis and his coworkers.[317] A variety of products are obtained including diaryl sulfides, phenothiazines (*cf.* section II.E.8), and aminoarylsulfonamides (**374**) (*cf.* Table XLVIII). In general yields are poor, but it is noteworthy that

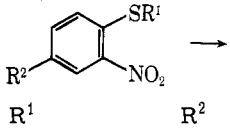
(384) M. P. Cava and C. E. Blake, *J. Amer. Chem. Soc.*, **78**, 5444 (1956).
(385) M. L. Moore and T. B. Johnson, *ibid.*, **57**, 2235 (1935).
(386) C. Brown, *Chem. Commun.*, 100 (1969); *J. Amer. Chem. Soc.*, **91**, 5832 (1969).
(387) (a) D. H. R. Barton, Y. L. Chow, A. Cox, and G. W. Kirby, *J. Chem. Soc.*, 3571 (1965); (b) K. B. Shaw and R. K. Miller, *Can. J. Chem.*, **48**, 1394 (1970).
(388) T. Zincke and F. Farr, *Justus Liebigs Ann. Chem.*, **391**, 57 (1912).
(389) N. Kharasch, W. King, and T. C. Bruice, *J. Amer. Chem. Soc.*, 77, 931 (1955).
(390) R. S. Goudie, Ph.D. Thesis, Heriot-Watt University, Edinburgh, 1971.
(391) F. Kaluza and G. W. Perold, *J. S. Afr. Chem. Inst.*, **13**, 89 (1960); *Chem. Abstr.*, **55**, 11346 (1961).
(392) M. L. Moore and T. B. Johnson, *J. Amer. Chem. Soc.*, **57**, 1517 (1935); **58**, 1091, 1960 (1936).

Table XLVIII

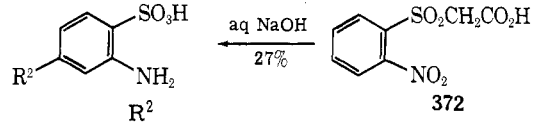
2-Aminobenzenesulfonamides from the Thermal Decomposition of 2-Nitrobenzenesulfenamides in Arylamines[a]

Starting material (373)	*Solvent*	*Product* (374)	*Yield, %*
a	Aniline	a	37
	p-Toluidine	b	53
b	Aniline	a	35
	p-Toluidine	b	55
	p-Toluidine[b]	b	60

[a] The sulfenamides were heated in amine solvents in sealed tubes at 195° for *ca.* 15 hr. [b] Degassed.

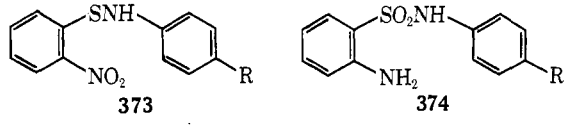


	R^1	R^2
370a	Cl	H
b	Cl	NO_2
c	MeO	NO_2
d	PhNH	NO_2
e	$PhCH_2O$	NO_2
f	p-MeC_6H_4O	NO_2
g	AcO	NO_2



	R^2
371a	H
b	NO_2

372



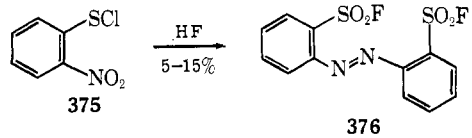
373 374

a, R = H; b, R = Me

the procedure provides a simple route to sulfonamides under neutral conditions. The oxygen transfer process inherent in the transformation **373** → **374** is almost certainly intramolecular since pyrolysis[317] of 3-nitrobenzenesulfenanilides in aniline gave none of the sulfonamide.

Bis(2,2′-difluorosulfonyl)azobenzene (**376**), rather than the expected *o*-nitrobenzenesulfenyl fluoride, is formed[393] in low yield when *o*-nitrobenzenesulfenyl chloride (**375**) is treated with anhydrous hydrogen fluoride alone, or in carbon tetrachloride solution. Despite the low yield, this route is a useful one since products of the type **376** are inaccessible.

An unusual oxygen-transfer process has been observed by Barton, *et al.*,[378] in connection with their investigations of the



375 376

(393) D. L. Chamberlain, D. Peters, and N. Kharasch, *J. Org. Chem.*, **23**, 381 (1958).

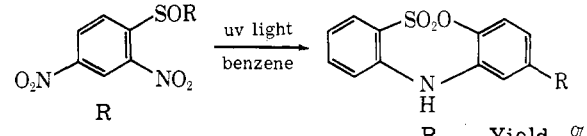
Table XLIX

Products from the Aluminum Chloride Catalyzed Reaction of Benzene with Nitrobenzenesulfonyl Chlorides

Position of nitro group(s)	*Mol of $AlCl_3$*	*Time, hr*	*Aryl halide, %*	*Sulfone, %*	*Sulfinic acid, %*	*Recovered sulfonyl chloride*
2	1	5	41	1.5	38	50
2	2	5	89	0.5	82	0
3	1	19	15	7	20	67
3	2	19	75	5	72	15
4	1	24	0	2.5	Trace	94
4	2	24	41	4	43	45
2,4	1	5	36	0	*a*	47
2,4	2	5	85	0	*a*	6

[a] Sulfinic acid too unstable for isolation.

photolysis of compounds containing an *o*-nitroarylthio substituent. Solutions of the esters **377** in benzene are decomposed by ultraviolet light to give among other products low yields of the cyclic sulfonates **378**.

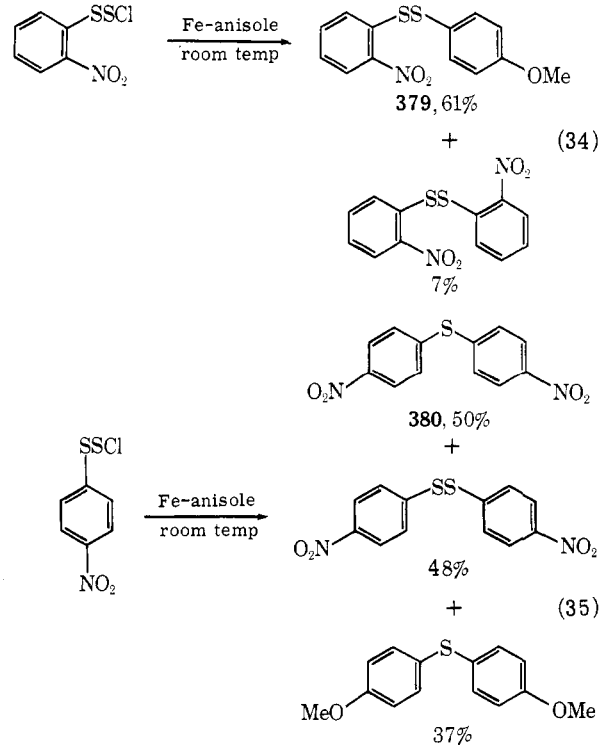


	R
377a	p-MeC_6H_4
b	Ph

	R	Yield, %
378a	Me	23
b	H	20

IV. Miscellaneous Compounds

In all of the reactions discussed so far, interaction between the ortho side chain and the nitro group is accompanied by chemical modification of the latter. However, it is now well known that nitro groups can exert a more subtle influence on the re-



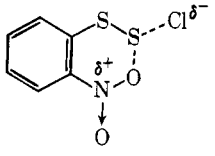
379, 61% (34)

7%

380, 50%

48% (35)

37%



381

$$ArSO_2Cl \xrightarrow{AlCl_3\text{–}Ar'H} ArSO_2{\cdot}AlCl_3 + Ar'Cl + HCl \quad (36)$$

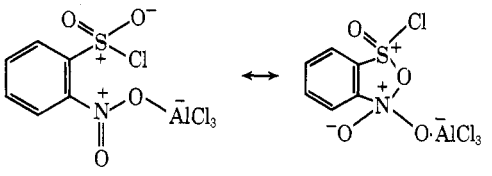
$$ArSO_2{\cdot}AlCl_3 \xrightarrow{H_2O} ArSO_2H$$

activity of an ortho side chain without becoming chemically involved. Perhaps the best examples of processes of this type are to be found in reactions involving "participation" by ortho nitro groups in the reactions of sulfur side chains.

Intramolecular interaction between the β-sulfur atom in the side chain and the ortho nitro group has been proposed[394] to account for the difference in reactivity of *o*- and *p*-nitrobenzenethiosulfenyl chlorides in their iron-catalyzed reactions with anisole (*cf.* reactions 34 and 35, respectively).[394]

The preferential formation of the disulfide **379** from the ortho isomer (*cf.* eq 34) as opposed to the sulfide **380** from the para isomer (*cf.* eq 35) is attributed[394] to stabilization of the disulfide side chain by the ortho nitro group in a complex of the type **381**.

Participation between an aromatic nitro group and an ortho side chain has also been suggested[395] to account for the greater efficiency of *o*-nitrobenzenesulfonyl chloride as opposed to the meta and para isomers in the aluminum chloride catalyzed chlorination of aromatic hydrocarbons (Table XLIX) (*cf.* eq 36). The greater efficiency of *o*-nitrobenzenesulfonyl chloride is attributed[395] to the enhanced electrophilicity of the chlorine atom in a complex of the type **382**.



382

Aluminum chloride catalyzed chlorination of aromatic hydrocarbons in the presence of *o*-nitrobenzenesulfonyl chloride is attractive as a route to aryl chlorides although the scope of such reactions has not been investigated.[396]

(394) T. Fujisawa, T. Kobori, and G. Tsuchihashi, *Tetrahedron Lett.*, 4291 (1969).

(395) E. C. Dart, G. Holt, and K. D. Jeffreys, *J. Chem. Soc.*, 5663 (1964).

(396) Since submission of this article, new information concerning this work has appeared in the literature, and an Appendix has been prepared which will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number CR-72-627.