957. *The Bromination of the Nitronaphthylamines and their N-Acyl Derivatives.*

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Molecular bromination of the nitronaphthylamines and of their *N*-acetyl and *N*-arylsulphonyl derivatives under a variety of conditions has been studied. The reactivity and mode of substitution of these compounds have been compared with those for the parent naphthylamines and with the results obtained in the corresponding nitration studies.[1] Mechanisms are suggested for results classified as abnormal.

The bromination of several of the nitronaphthylamines and their *N*-acyl derivatives has been reported previously, notably by Hodgson and his co-workers, but an overall picture of orientation and reactivity-determining factors could not previously be obtained. We now report results for all the nitronaphthylamines and their *N*-acetyl derivatives permitting a more detailed analysis.

Bromination of the *N*-acetyl derivatives is considered first since this may be compared with their nitration described earlier [1] and does not involve the abnormal reaction that apparently occurs in the bromination of the free amines in chloroform and other solvents. The solvent selected was 85% acetic acid since kinetic investigations [2] have been carried out in this medium, good yields of *N*-acetyl derivatives can be obtained by crystallisation from this solvent, and considerable amounts of sodium acetate can be introduced (to reduce developed acidity) without the reaction's becoming heterogeneous, and reactions can be carried out at *ca.* 100° without much loss of solvent. " Cold " conditions were used wherever possible, " hot " ones only for unreactive substrates.

Bromination of amines or substituted amines in chloroform solution has proved an excellent preparative method. The amines are readily soluble in the cold solvent; the hydrobromic acid liberated forms the insoluble hydrobromide of most of the product. This can be removed by filtration, usually in high yield, and invariably in a high state of purity since non-basic side-products remain in solution. For the present investigations it was essential that the whole product be examined; even so the amounts of by-products separated by chromatography were small. A few results for other solvents are available for comparison, as are others for temperatures above 20°; in no case was there any improvement; often yields were reduced.

Thirteen nitronaphthylamines and their *N*-acetyl derivatives have been studied. 1-Nitro-2-naphthylamine has been omitted since preliminary experiments indicated that its behaviour is unique and requires a separate study.

Only a few isomers among the *N*-arylsulphonamides were examined, in order to specify " normal " and " abnormal " brominations of these derivatives. Previous reports of bromination in pyridine have been confirmed, extended, and compared with the " normal " reaction observed in acetic acid. Yields of product from these derivatives were variable and rarely quantitative.

The following Tables list the results of the present and some previous investigations. A single entry under " yield " is that for purified reaction product, usually after chromatography in the case of the amine studies, but for unpurified product in the case of the derivatives. In all cases the yields were calculated on the basis of the composition determined subsequently.

Discussion.—Monobromination of the *N*-acetyl derivatives is readily brought about in the cold for those isomers not suffering strong deactivation by the nitro-group. In accordance with the greater selectivity of molecular bromine than of the nitronium ion,

[1] Ward and Wells, preceding paper.
[2] Brown and Stock, *J. Amer. Chem. Soc.*, 1957, **79**, 1421.

substitution in only one nuclear position is observed whereas nitration generally produces a mixture of isomers.[1] As our chromatographic method reveals the presence of >1% of a second isomer,[3] it can be estimated that the 4-position of the α-naphthylamine series and the 1-position in the β-series are the most reactive by a factor of at least 100. *N*-Acetyl-4-nitro-1-naphthylamine is, of course, an exception: it reacts in the only unoccupied reactive position, with difficulty. The 5-nitro-isomer is also unreactive, substitution occurring with difficulty in the 2-position, owing to a steric effect of the *peri*-nitro-group on the 4-position; it is pertinent that this substance gives an exceptionally high ratio of 4- : 2-nitration,[1] which was interpreted in terms of a dipolar activating effect that would not operate for the neutral reagent of bromination.[4] As would be expected from the deactivating effect of the nitro-group on the ring to which it is attached, the 2- and the 3-nitro-isomer are also unreactive, especially the latter where there are also serious steric restrictions. Vigorous conditions are required for the latter bromination. In the

TABLE 1.

Bromination of *N*-acetyl derivatives in aqueous acetic acid.

Position of NHAc	Position of NO_2	Br_2 (mol.)	Temp.*	Posn. of substitn.	Yield (%)	Notes & refs.
1	—	1	C	4	97	*a*
1	—	2	C	4	(107)	i
1	—	2	H	2,4	77	
1	2	1	C	4 †	80	ii
1	3	5	H	2; 2,4	46	iii
1	4	1	C	2 †	95	iv
1	5	1	H	2 †	85	iii
1	5	2	H	2,4 ‡	51	
1	6	1	C	4	93	
1	6	2	H	2,4	80	
1	7	1	C	4	84	v, *b*
1	7	2	H	2,4	76	v, *b*
1	8	1	H	4	80	vi, *c*
1	8	2	H	2,4	—	*c*
2	—	2	H	1	99	vii, *d*
2	3	1	C	1	96	*e*
2	4	1	H	1 †	87	viii
2	5	1	—	1	—	v, *f*
2	6	1	C	1	91	
2	7	1	C	1	77	

* C = At 20° or 0°; H = at 100°. † Also unchanged material. ‡ Also a trace of 2-bromo-derivative.

Notes: (i) High apparent yield may indicate some 5% of dibromination. (ii) 4-Substitution in glacial acetic acid reported by Hodgson and Elliott (*J.*, 1935, 1850). (iii) No reaction at 20°. (iv) 85% Yield of monobromo-compound at 100°. (v) In glacial acetic acid. (vi) Lower yield in aqueous acetic acid. (vii) The reported formation of the 1,6-dibromo-compound could not be repeated. (viii) Complete bromination was only achieved with an excess of reagent.

References: (*a*) Cf. Perconito, *Gazzetta*, 1935, **65**, 689. (*b*) Hardy, Ward, and Day, *J.*, 1956, 1979. (*c*) Hodgson and Crook, *J.*, 1936, 1338. (*d*) Cf. Consiner, *Ber.*, 1881, **14**, 58; Claus and Philipson, *J. prakt. Chem.*, 1891, **43**, 47. (*e*) Ward, Coulson, and Wells, *J.*, 1957, 4816. (*f*) Veselý and Dvorak, *Chem. Listy*, 1923, **17**, 163.

β-series reactivity differences can be distinguished only between *N*-acetyl-4-nitro-2-naphthylamine (which is unreactive) and the other isomers. In this compound the nitro-group is placed so that its greatest influence is felt at the reaction site, *i.e.*, the *para*-position. Even under the " hot " conditions the β-derivatives were not dibrominated. On the other hand, all the α-derivatives are sufficiently reactive for bromination at positions 2 and 4 (if free). " Cold " conditions do not, however, seem sufficient for this further reaction except perhaps in the case of *N*-acetyl-1-naphthylamine itself.

The outstanding feature of the bromination of the amines in chloroform is that although monobromination and, for some isomers, dibromination can be cleanly effected in the

[3] Cf. Ward, Johnson, and Day, *J.*, 1959, 487.
[4] Wells and Ward, *Chem. and Ind.*, 1958, 1172.

TABLE 2.

Bromination of nitronaphthylamines in chloroform solution.

Position of NH_2	Position of NO_2	Br_2 (mol.)	Temp.	Posn. of substitn.	Yield (%)	Notes & refs.
			(A) *Nitro-1-naphthylamines*			
1	—	1	20°	2,4 *	99	
1	—	2	20	2,4	88	i
1	2	1	20	4	—	ii, iii
1	3	1	20	2,4 *	98	
1	3	2	50	2,4	100	*g*
1	4	1	20	2	92·5	ii, iv
1	5	1	20	2; 2,4	92	v
1	5	2	20	2,4	100	vi
1	6	1	−5	2,4 *	58	*h*
1	6	2	−5	2,4	100	*h*
1	7	1	20	2,4 *	—	*b*
1	7	2	20	2,4	90	*b*
1	8	1	0	2,4 *	—	vii, *c*
1	8	2	0	2,4	100	vii, *c*
			(B) *Nitro-2-naphthylamines*			
					Yield (%) crude	Yield (%) pure	
2	—	1	20	1	99	96	
2	—	2	20	1,6	92	—	
2	3	1	20	1	100	95	*e*
2	3	2	20	1,6	88	—	*e*
2	4	1	50	1	100	—	*i*
2	4	2	20	1,6	93	—	
2	5	1	20	1	92	89	viii
2	6	1	20	1	95	85	viii
2	7	1	50	1	90	—	viii, *j*
2	8	1	20	1	98	96	
2	8	2	20	1,6	80	—	

* Also unchanged material.

Notes: (i) Consden and Kenyon [k] report a quantitative yield in acetic acid at 100°. (ii) With an excess of bromine 2,4-dibromonaphthalene-1-diazonium perbromide is formed.[k] (iii) Similar results are reported for acetic acid or nitrobenzene solution.[l] (iv) 50% Yield in acetic acid at 100°; [k] 35% Yield in nitrobenzene at 20°.[m] (v) Hodgson and Turner [n] found only the 2-bromo-compound. (vi) Hodgson and Turner [n] report 58% yield at 50°. (vii) Similar results reported for carbon tetrachloride and nitrobenzene solutions. (viii) No dibromination even at 50°.

References: (*b*, *c*, *e*) See Table 1. (*g*) Hodgson and Hathaway, *J.*, 1944, 21. (*h*) Hodgson and Dean, *J.*, 1950, 822. (*i*) Hodgson and Hathaway, *J.*, 1944, 385. (*j*) Hodgson and Ward, *J.*, 1947, 327. (*k*) Consden and Kenyon, *J.*, 1935, 1591. (*l*) Hodgson and Elliott, *J.*, 1935, 1850. (*m*) Veselý and Chudozilov, *Chem. Listy*, 1925, **19**, 260; Hodgson and Elliott, *J.*, 1934, 1705. (*n*) Hodgson and Turner, *J.*, 1942, 723.

TABLE 3.

Bromination of *N*-*p*-toluenesulphonyl derivatives.

Position of NHTos	Position of NO_2	Solvent	Temp.	Posn. of substitn.	Yield (%)	Notes & refs.
1	—	Chloroform	" Cold "	4	" Good "	i, *k*
1	—	Pyridine	" Cold "	2,4	" Good "	*k*
1	3	Acetic acid	20°	4 *	84	
1	3	Pyridine	20	4; 2,4	80	
1	4	Chloroform	" Cold "	N.R.†		*k*
1	4	Pyridine	—	2	—	*k*
1	5	Acetic acid	20°	4; 2,4	90	ii
1	5	Pyridine	20	N.R.†	—	
1	8	Acetic acid	20	4	94	iii
1	8	Pyridine	20	N.R.†		
2	—	Chloroform	" Hot "	1,6	" Poor "	*o*
2	—	Pyridine	" Cold "	1,3	—	*o*
2	1	Pyridine	" Cold "	3	—	
2	6	Pyridine	" Cold "	1	" Good "	*j*
2	7	Pyridine	" Cold "	1	" Good "	*j*

* Also unchanged material. † No reaction.

Notes: (i) *N*-*m*-Nitrobenzenesulphonyl derivative. (ii) Whitehurst (*J.*, 1951, 222) reports a 10% yield of the 4-bromo-compound in acetic acid at 95°. (iii) *Idem* (*ibid.*) reports a 56% yield in acetic acid at 50°.

References: (*k*, *j*) See Table 2. (*o*) Bell, *J.*, 1932, 2732.

β-series, yet in the α-series, despite the use of a deficiency of reagent, the dibromo-compound is generally the only product obtained. This type of behaviour, classified as " abnormal," has been noted before, not only in bromination but also in other reactions.[5] One explanation,[5] which seems to be generally favoured, requires that the unsubstituted compound, being the stronger base, becomes protonated, and hence removed from reaction so much more completely than the monobromo-compound that reaction takes place preferentially through the latter. However, it has been shown [6] that even when the two brominations compete with equal rate constants the final reaction mixture contains comparable quantities of monobromo- and dibromo-compound and unchanged material. Hence to account for the experimental result of no detectable monosubstitution this type of explanation requires that decreased basicity must more than compensate for decreased reactivity. This seems most unlikely since the 2-position of these substrates must be less reactive than the 4-position (the *N*-acetyl results suggest a factor of at least 1/100), without account being taken of the deactivating effect of the bromine. The latter factor alone appears to make the explanation untenable since Hammett's ρ values indicate that reactivity towards bromination would be reduced more by a *m*-bromo-atom than basicity would be reduced by a *p*-bromo-atom ($\sigma_{p\text{-Br}} = 0{\cdot}23$; [7] $\sigma^*_{m\text{-Br}} = 0{\cdot}40$; [8] $\rho = 2{\cdot}77$ for the acid dissociation of the anilinium ions; [9] $\rho = -11{\cdot}35$ for halogenation in acetic acid [8]).

TABLE 4.

Bromination of other *N*-toluene-*p*-sulphonyl derivatives in pyridine.

NHTos	Position of X	Posn. of substitn.	Yield (%)	Refs.
1 *	4-Br	2	—	*k*
2 *	1,5-$(NO_2)_2$	3	83	*p*
2	1,6-$(NO_2)_2$	3	—	*k*
2	1-Cl	3	—	*q*
2	1-Br	3	—	*o*
2	1,6-Br_2	3	—	*o*

* *N*-*m*-Nitrobenzenesulphonyl derivative.

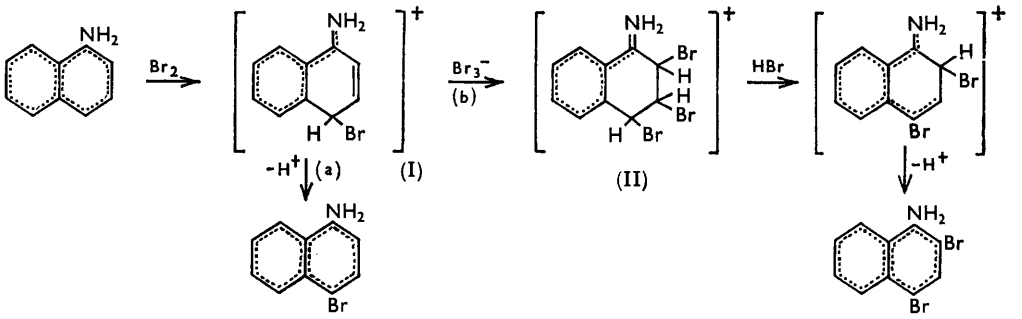
References: (*k*) See Table 2. (*o*) See Table 3. (*p*) Hodgson and Dean, *J.*, 1950, 820. (*q*) Bell, *J.*, 1950, 3035.

The results require that the formation of the 2,4-dibromo-compound shall be considerably faster than monobromination. Clearly this cannot be electrophilic substitution.

Clues to the nature of this reaction are provided by the bromination of the 3- and 5-nitro-amine and by the further reactions of the bromination products of the 2- and the 4-isomer. " Abnormal " behaviour is observed for 3-nitro-1-naphthylamine with no apparent reduction in reactivity despite the deactivating nitro-group (cf. the bromination of the *N*-acetyl derivative). 5-Nitro-1-naphthylamine, on the other hand, is the only member of the α-series that can be monobrominated, and here reaction occurs in the 2- instead of the usually more reactive 4-position. With an excess of bromine in chloroform, 4-bromo-2- and 2-bromo-4-nitro-1-naphthylamine are both converted into 2,4-dibromonaphthalene 1-diazoperbromide.[10] This product arises by nucleophilic displacement of the nitro-group as nitrite which subsequently, under the acid conditions, diazotises the amino-group. Such a displacement is not a usual reaction and requires the presence of some powerful nucleophilic bromide-ion equivalent, such as Br_3^-. These facts suggest a mechanism similar to that proposed by Robertson [11] for chlorination of 2-naphthol. It it is supposed that the first step is electrophilic bromination in the 4-position, to yield the intermediate (I), then nucleophilic addition (path b), the reagent being Br_3^-, could

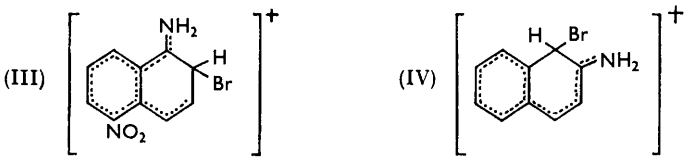
[5] de le Mare and Ridd, " Aromatic Substitution," Butterworths, London, 1959, pp. 48, 106.
[6] Wells, *J. Phys. Chem.*, 1959, **63**, 1978.
[7] McDaniel and Brown, *J. Org. Chem.*, 1958, **23**, 420.
[8] Brown and Okamoto, *J. Amer. Chem. Soc.*, 1957, **79**, 1913.
[9] Jaffe, *Chem. Rev.*, 1953, **53**, 191.
[10] Consden and Kenyon, *J.*, 1935, 1591.
[11] Robertson, *J.*, 1956, 1883.

compete very favourably with the usual second step of proton loss (path a) and give the addition compound (II). Loss of hydrogen bromide and then a proton from the intermediate (II) would yield the 2,4-dibromo-compound. A highly nucleophilic bromide-containing species is present in the reaction mixture and a nitro-group would assist, instead of retarding, the key step in this mechanism. The intermediate (III) that will be



formed from 5-nitro-1-naphthylamine, which reacts first in the 2-position, would have a styrene-like structure instead of one having an activated 2,3-double bond as (I). It, and for the same reason the nitro-amines (IV) of the β-series, will tend to follow path a and yield monobromination products.

If the above considerations are correct, then the results for the β-series are for true electrophilic substitutions uncomplicated by addition–elimination. The 1-position, as indicated by the *N*-acetyl results, is so much the most reactive that only one monobromination product is detected. The next most reactive position is 6, and in dibromination this position (when unoccupied) will be the site of further substitution provided there is no "*ortho*"-nitro-group, as in the 5- and the 7-isomer. For bromination, unlike nitration, there is no indication of activation of the 8-position. Polar activation of positions 6 and 8 may be comparable but the *peri*-bromo-group would be expected effectively to block approach of the large bromine molecule to the latter reaction site.



Only a few selected *N*-arylsulphonamides were examined in these studies, principally to throw light on the effect of pyridine. Unusual orientation, specifically reaction in the 3-position of some β-derivatives, has been known for some time. Bell [12] suggested that pyridine abstracts a proton from the weakly acidic derivative, to yield a negatively charged nitrogen species that reacts readily with the polarized bromine in the presumably inductively activated 3-position. It would be expected, however, that such a substituent would activate the 6-position (where reaction normally occurs in other solvents) as strongly as, if not more strongly than, the 3-position, and thus lead to the usual product at a faster rate. Furthermore, reaction in the 3-position has not been observed for β-naphthyl oxides with, for example, diazotized amines. This almost unique orientation has been attributed [13] to a mechanism very similar to that suggested above for "abnormal" bromination of amines. The base, pyridine, facilitating the removal of hydrogen bromide from the addition product, will favour the addition–elimination mode of introduction of

[12] Bell, *J.*, 1950, 3035.
[13] Panizzon-Favre, *Gazzetta*, 1924, **54**, 838.

bromine. In support of this we have found that, while the *N*-toluene-*p*-sulphonyl derivatives of 3-, 5-, and 8-nitro-1-naphthylamine behave as do their *N*-acetyl derivatives in acetic acid, the 3-isomer is more reactive in pyridine than in acetic acid, while the 5- and the 8-isomer are more reactive in acetic acid. Presumably the addition–elimination mechanism is not operative for these two substances but can be utilised for readier reaction by the 3-isomer (and also the 4-isomer).

Experimental

M. p.s are corrected.

Bromination: General Procedures.—In chloroform. The nitronaphthylamine in cold chloroform (30 c.c./g.) was treated at room temperature (*ca.* 20°), with a 10% w/v solution of bromine in chloroform (8·6 c.c./g. for monobromination, or 17·1 c.c./g. for dibromination). The hydrobromide, which immediately began to separate, was collected after 24 hr. and washed with chloroform (5 c.c.). After removal of the chloroform *in vacuo*, this product was suspended in ice-water and treated with ammonia (*d* 0·88), to liberate the free amine. This material usually constituted 50—80% of the total product and was invariably of extremely high purity. The residual chloroform solution and washings yielded, on evaporation, the remaining bromoamine. In all experiments the two fractions were combined and chromatographed on alumina with benzene–ethyl acetate. All mixtures were readily separated; the minor amounts of by-products remained at the top of the columns.

In " cold " aqueous acetic acid. The *N*-acetyl or *N*-toluene-*p*-sulphonyl derivative (0·5 g.) was dissolved in the minimum of cold 85% v/v aqueous acetic acid (0·15M in sodium acetate) and treated at room temperature with the equivalent quantity of bromine (0·05M in the above solvent). The mixture was set aside for 24 hr. in a stoppered dark bottle, then the product was precipitated by addition of ice (in many cases considerable quantities of the product crystallised during the reaction). After being washed with water and dried at *ca.* 50° *in vacuo*, the products were hydrolysed as previously described [1] and chromatographed on alumina. The strongly adsorbed by-products were generally in greater, though still small, amounts than in bromination of amines in chloroform; products crystallising from the reaction solution were, however, always of high purity.

In " hot " aqueous acetic acid. The *N*-acetyl derivative (0·5 g.) was dissolved in the minimum of the warm solvent, heated on a boiling-water bath and treated dropwise with the reagent during 60—90 min. After a further 1—3 hr. at this temperature and ~12 hr. at room temperature, the mixture was worked up as described for the " cold " reaction. The crystalline material obtained on cooling was generally very pure, but chromatography of the hydrolysed material revealed appreciable quantities of by-products.

In pyridine. The *N*-toluene-*p*-sulphonyl derivative (1·0 g.) was set aside for 24 hr. with bromine (1·0 g., 2·1 equiv.) in pyridine, (25 c.c.). Addition to ice precipitated the product

Table 5.

Position of NH_2	Position of NO_2	Br	M. p.	Found (%) C	Found (%) H	Found (%) Br	Formula	Required (%) C	Required (%) H	Required (%) Br
Bromo-nitronaphthylamines										
1	3	2	113°	45·1	3·0	29·7	$C_{10}H_7BrN_2O_2$	45·0	2·3	29·9
1	6	4	214	45·1	3·0	—	,,	,,	,,	,,
2	4	1,6	177	—	—	46·3	$C_{10}H_6Br_2N_2O_2$	34·7	1·75	46·2
2	8	1,6	139	34·4	1·6	46·6	,,	,,	,,	,,
N-*Acetyl-bromo-nitronaphthylamines*										
1	3	2	246	—	—	26·0	$C_{12}H_9BrN_2O_2$	46·6	2·9	25·85
1	6	4	269	46·4	2·8	—	,,	,,	,,	,,

which was washed with dilute hydrochloric acid, followed by water, and dried at *ca.* 50° *in vacuo*. The sulphonamide was hydrolysed as previously described [1] and the resulting amine chromatographed on alumina.

New Compounds.—See Table 5. 4-Bromo-3-nitro-1-naphthylamine has m. p. 143°, and its *N*-toluene-*p*-sulphonyl derivative, m. p. 230°.

Orientations.—2-Bromo- was different (mixed m. p.) from 4-bromo-3-nitro-1-naphthylamine

obtained from N^1-acetyl-3-nitro-1,4-naphthylenediamine by Sandmeyer reaction as reported by Panizzon-Favre.[13] Both bromo-amines gave the 2,4-dibromo-compound on further bromination in chloroform. 4-Bromo-6-nitro-1-naphthylamine was diazotised by the method of Hodgson and Turner,[14] and the resulting diazonium solution added to a suspension of cuprous oxide in ethanol. After initial reaction had subsided, further cuprous oxide was added and the mixture left for 10 min. before addition to ice. The red-brown solids were dried and extracted with boiling benzene, to yield, by concentration and two recrystallisations, pale yellow needles, m. p. 132°, of 1-bromo-7-nitronaphthalene, undepressed on admixture with an authentic specimen. 1,6-Dibromo-8-nitro-2-naphthylamine was deaminated as above, to give 1,6-*dibromo*-8-*nitronaphthalene* as buff needles, m. p. 97° (from benzene) (Found: C, 36·6; H, 1·7. $C_{10}H_5Br_2NO_2$ requires C, 36·3; H, 1·5%). This (0·1 g.) was ground with hydrated stannous chloride (1 g.) and cautiously warmed for 1 hr. with concentrated hydrochloric acid (2 c.c.). After dilution with cold water (50 c.c.), the solids were collected and air-dried for 2 days. Extraction with hot ethanol and evaporation gave 3,8-dibromo-1-naphthylamine as a brown semi-solid material that did not crystallise from the usual organic solvents. The crude bromo-amine was dissolved in sulphuric acid (5 c.c.; *d* 1·84), diazotised, and deaminated as described above, to yield white crystals, m. p. and mixed m. p. 61°, of 1,6-dibromonaphthalene. Insufficient 1,6-dibromo-4-nitro-2-naphthylamine was available for similar reactions.

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[14] Hodgson and Turner, *J.*, 1943, 86.