Reaction of Benzofurazan *N*-Oxide with Secondary Aliphatic Amines; Preparation of *NN*-Dialkyl-*N'*-(*o*-nitrophenyl)hydrazines †

By **David W. S. Latham, Otto Meth-Cohn,* and Hans Suschitzky,** The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT, Lancashire

The interaction of benzofurazan *N*-oxide with a variety of secondary aliphatic amines in the cold gives *NN*-dialkyl-*N'*-(*o*-nitrophenyl)hydrazines by attack on the hetero-ring. At higher temperatures, dialkylaminobenzofurazans are obtained by attack on the benzene ring. Substituents in the benzofuran *N*-oxide exerting $-I$ and $-M$ effects slow down both processes. The interaction of various *NN*-dialkylhydrazines with chloronitrobenzenes and polynitrobenzenes gives either nitrophenyldialkyl-amines or -hydrazines in a predictable manner, for which a mechanistic rationale is proposed, involving charge-transfer complex formation when polynitrobenzenes are used.

As an extension of our studies of *ortho*-substituted dialkylanilines [1] (' the tertiary-amino-effect ') we initiated a study of the analogous hydrazines [*e.g.* (1)]. Preliminary experiments suggested a novel route to these compounds, involving the attack of simple secondary amines on benzofurazan *N*-oxide (9) (Scheme 1). This reaction seemed feasible on the basis of the well known tendency of benzofurazan *N*-oxides to undergo nucleophilic attack at the 3-position under mild conditions, whereas vigorous conditions tend to cause substitution in the benzene ring.[2] Indeed, addition of benzofurazan *N*-oxide to an excess of the amine at 0 °C resulted in an exothermic reaction to give, in many cases, the required hydrazine. Since this was a rare example [2] of the ring-opening of a benzofurazan *N*-oxide to give a nitro-compound we undertook a thorough study of this reaction.

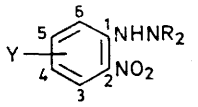
A variety of secondary amines gave the corresponding hydrazines in reasonable yields (Table 1), but larger ring

† Preliminary communication, D. W. S. Latham, O. Meth-Cohn, and H. Suschitzky, *Tetrahedron Letters*, 1973, 5635.

[1] O. Meth-Cohn and H. Suschitzky, *Adv. Heterocyclic Chem.*, 1972, **14**, 211.

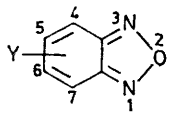
[2] *E.g.* A. J. Boulton and P. B. Ghosh, *Adv. Heterocyclic Chem.*, 1969, **10**, 2.

amines (perhydro-azepine and -azocine) gave no hydrazine, and primary aliphatic amines gave no definable



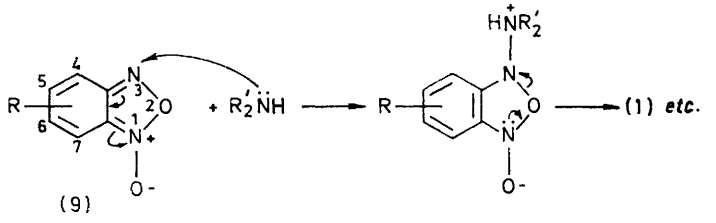
(1) R = Me
(2) R = Et
(3) $R_2 = [CH_2]_4$
(4) $R_2 = [CH_2]_5$
(5) $R_2 = [CH_2]_2 \cdot O \cdot [CH_2]_2$
(6) $R_2 = [CH_2]_2 \cdot NMe \cdot [CH_2]_2$
(7) R_2 = Ph, Me
(8) $R_2 = [CH_2]_6$

products. Use of solvents gave either intractable mixtures or lower yields. The weaker base morpholine reacted slowly at 0 °C, and even at 50 °C required 2 days to consume the benzofurazan *N*-oxide, giving the hydrazine (5; Y = H) mixed with a morpholinobenzofurazan (10; Y = morpholino) (10%). Both 4- and 5-morpholinobenzofurazan (10; Y = morpholino) were readily synthesised from the corresponding chlorobenzofurazans (10; Y = 4- or 5-Cl, respectively) by the action of morpholine in dimethyl sulphoxide, and the 4-isomer was identical with the product from the *N*-oxide. This reaction is readily rationalised, by analogy with known *N*-oxide substitutions,[3] as shown in Scheme 2.



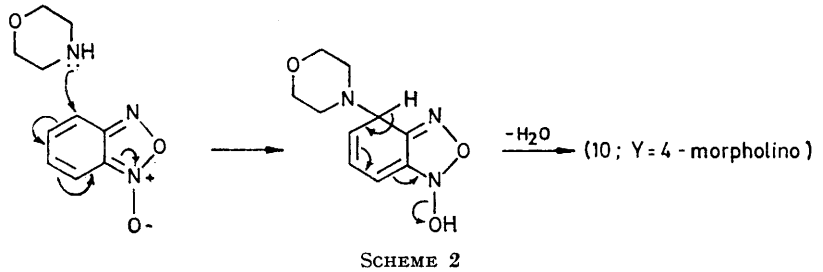
(10)

In order to discover the effect of substituents in the benzofurazan *N*-oxide on the course of the reaction, 5(6)-chloro-, -trifluoromethyl-, -ethoxycarbonyl-, -methoxy-, and -nitro-benzofurazan *N*-oxide and 4(7)-nitro-benzofurazan *N*-oxide were treated with secondary amines. As the benzofurazan *N*-oxide is made increasingly electrophilic (by electron-withdrawing substituents) so the reactivity with secondary amines and the tendency to give hydrazines diminishes and attack at the benzene ring dominates. Thus the methoxybenzofurazan *N*-oxide [9; R = 5(6)-OMe] reacts readily at 0 °C to give unidentified, unstable purple products together with a little hydrazine, probably (4; Y = 5-OMe). 5(6)-Chlorobenzofurazan *N*-oxide gave two hydrazines (4; Y = 5-Cl or 5-piperidino), both resulting formally from attack of piperidine on the 5-chlorobenzofurazan *N*-oxide (known to be the preferred isomer both in solution[4] and in the solid state[5]) with no trace of products from attack of the 6-chloroisomer. The 2-nitro-5-piperidinophenylhydrazine (4; Y = 5-piperidino) is the expected product of nucleophilic substitution of the activated halide. Perhydroazepine again did not give a hydrazine. 5(6)-Trifluoromethylbenzofurazan *N*-oxide gave a mixture of the 2-nitro-4-trifluoromethylphenylhydrazine (4; Y = 4-CF_3) (25%) and 5-piperidino-6-trifluoromethylbenzofurazan (10; 36%) by the action of piperidine at 50 °C. At 0 °C or ambient temperature the reaction was sluggish.



(9)

SCHEME 1



SCHEME 2

As with the 6(5)-nitro- and 6(5)-ethoxycarbonylbenzofurazan *N*-oxides,[4] this derivative probably exists largely

[3] *E.g.* R. Fielden, O. Meth-Cohn, and H. Suschitzky, *J.C.S. Perkin I*, 1973, 705.

[4] A. J. Boulton, A. R. Katritzky, M. J. Sewell, and B. Wallis, *J. Chem. Soc.* (*B*), 1967, 914.

[5] D. Britton and W. E. Noland, *J. Org. Chem.*, 1962, **27**, 3218.

as the 6-isomer, whereby the *N*-oxide oxygen atom is able to compensate for the strong $-I$ effect of the CF_3 groups. Substitution of the 6-isomer would lead to the above products by analogy with Scheme 1 for the hydrazine and according to Scheme 3 for the furazan.

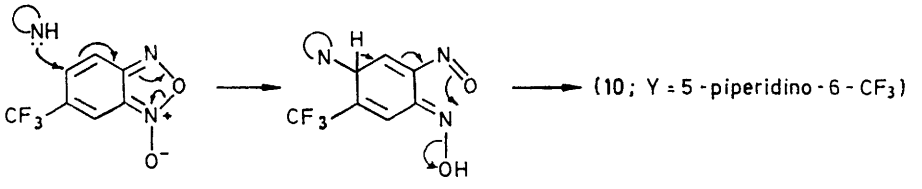
The 6(5)-ethoxycarbonylbenzofurazan *N*-oxide [**9**; R = 6(5)-CO_2Et], with a $-I$, $-M$ substituent, in fact gives no hydrazine and requires a temperature of 50 °C for smooth reaction to give the 5-ethoxycarbonyl-6-piperidinobenzofurazan (10), analogous to the product from the trifluoromethyl derivative. However, 6-nitrobenzofurazan *N*-oxide was a highly reactive system and even at −20 °C in dilute solution gave only intractable material with piperidine. Nevertheless 4(7)-nitrobenzofurazan *N*-oxide, which exists solely as the 4-isomer,[6] reacted smoothly with piperidine, morpholine, perhydroazepine or n-butylamine to give the 4-amino-7-nitrobenzofurazans (10) at ambient temperatures. Finally, the interaction of 3,4-diphenylfurazan *N*-oxide (11) and the naphthofurazan *N*-oxide (12) with piperidine was examined. Even under reflux these *N*-oxides were unreactive. Other workers comment on this inertness towards nucleophiles.[7]

The only reported methods for the synthesis of *NN*-dialkyl-*N'*-(*o*-nitrophenyl)hydrazines [*e.g.* (1)] involve treatment of picryl chloride[8] or 1-chloro-2,4-dinitrobenzene[9] with *NN*-dimethylhydrazine. This type of reaction is, however, not of general applicability. Thus, whereas polynitro-compounds prove satisfactory starting materials, mononitro-halogenobenzenes, the obvious starting materials for *o*-nitrophenylhydrazines, give primarily *NN*-dialkyl-*o*-nitroanilines (14) (Scheme 4 and Table 2).

TABLE 1

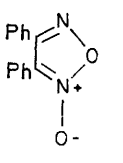
Reaction of benzofurazan *N*-oxides (9) with aliphatic amines

Reactants		Conditions		Product(s)			
Benzofurazan *N*-oxide (9)	R'_2NH	Time (days)	Temp. (°C)	No.	Y	%	M.p. (°C)
R = H	R'_2 = Me_2	5	20	(1)	H	5	(Oil)
H	Et_2	5	20	(2)	H	10	(Oil)
H	$[CH_2]_4$	3	0	(3)	H	44	64
H	$[CH_2]_5$	5	0	(4)	H	48	97
H	$[CH_2]_2$·O·$[CH_2]_2$	1	50	(5)	H	12	123.5
				(10)	4-C_4H_8NO	10	107
H	$[CH_2]_2$·NMe·$[CH_2]_2$	5	20	(6)	H	10	100
5-Cl	$[CH_2]_5$	4	0	(4)	5-Cl	50	117
				(4)	5-$C_5H_{10}N$	7	141
5-CF_3	$[CH_2]_5$	0.5	50	(4)	5-CF_3	25	88
				(10)	5-CF_3–6-$C_5H_{10}N$	36	64
5-CO_2Et	$[CH_2]_5$	4	20	(10)	5-CO_2Et–6-$C_5H_{10}N$	26	95
5-OMe	$[CH_2]_5$	7	0				
5-NO_2	$[CH_2]_5$		−20 to −30				
4-NO_2	$[CH_2]_5$	1	20	(10)	4-$C_5H_{10}N$–7-NO_2	37	169
4-NO_2	$[CH_2]_6$	1	20	(10)	4-$C_6H_{12}N$–7-NO_2	18	124
4-NO_2	$[CH_2]_2$·O·$[CH_2]_2$	1	20	(10)	4-C_4H_8NO–7-NO_2	26	221
4-NO_2	H, Bu	1	20	(10)	4-NHBu–7-NO_2	28	94

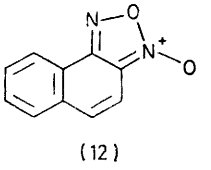


SCHEME 3

The use of protic (methanol, ethanol, or an excess of the hydrazine) or aprotic (benzene, dimethylformamide



(11)



(12)

[6] R. K. Harris, A. R. Katritzky, S. Øksne, A. S. Bailey, and W. G. Paterson, *J. Chem. Soc.*, 1963, 197.

[7] N. A. Mufarry, M. J. Haddadin, C. H. Issidorides, J. W. McFarland, and J. D. Johnston, *J.C.S. Perkin I*, 1972, 965.

[8] H. J. Bocker, *Rec. Trav. chim.*, 1912, **31**, 152.

[9] B. Vis, *Rec. Trav. chim.*, 1939, **58**, 747.

or dimethyl sulphoxide) solvents, various temperatures, a nitrogen atmosphere, or a base (sodium carbonate or diazabicyclo-octane) did not yield more hydrazine.

salt (Scheme 4) which by loss of the elements of a halogenoamine yields the aniline. Although the formation of halogenoamines was not confirmed, this mechanism is

TABLE 2

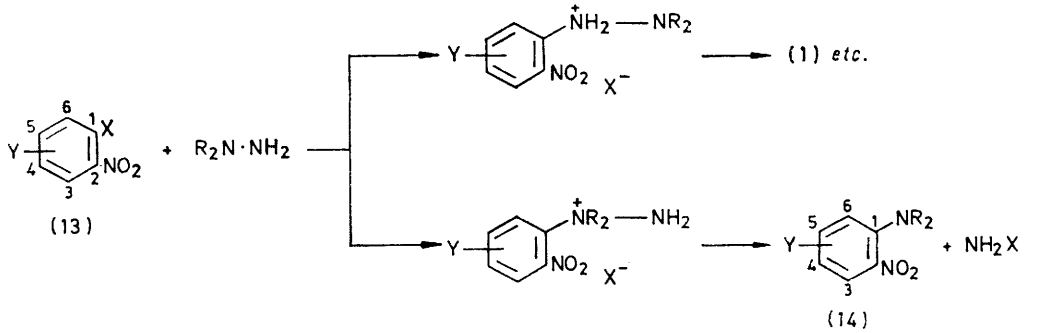
Products from the action of nitrobenzenes (13) on *NN*-dialkylhydrazines

Reactants			Product(s)						
			Phenylhydrazine [(1)—(8)]				Aniline (14)		
(13)		$H_2N{\cdot}NR_2$	Cpd.	Y	%	M.p. (°C)	R^2	Y	%
X = F	Y = H	R_2 = Me_2	(1)	H	5	(Oil)	Me_2	H	80
F	H	$[CH_2]_5$					$[CH_2]_5$	H	83
F	H	Ph, Me	(7)	H	37	91 [a]			
Cl	4-NO_2	Me_2	(1)	4-NO_2	75	117			
Cl	4-NO_2	$[CH_2]_4$	(3)	4-NO_2	62	170			
F	4-NO_2	$[CH_2]_5$	(4)	4-NO_2	83	175—176			
Cl	4-NO_2	$[CH_2]_5$	(4)	4-NO_2	81	175—176			
Cl	4-NO_2	$[CH_2]_6$	(8)	4-NO_2	57	168			
Cl	4-NO_2	$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	(5)	4-NO_2	73	191			
Cl	4-CF_3	Me_2	(1)	4-CF_3	72	88	Me_2	4-CF_3	15
Cl	4-CF_3	$[CH_2]_4$	(3)	4-CF_3	34	(Oil)	$[CH_2]_4$	4-CF_3	Trace
Cl	4-CF_3	$[CH_2]_5$	(4)	4-CF_3	58	88	$[CH_2]_5$	4-CF_3	Trace
Cl	4-CF_3	$[CH_2]_6$	(8)	4-CF_3	46	78	$[CH_2]_6$	4-CF_3	Trace
Cl	4-CF_3	$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	(5)	4-CF_3	32	106—108	$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	4-CF_3	Trace
Cl	4-CO_2Et	Me_2	(1)	4-CO_2Et	67	100	Me_2	4-CO_2Et	18
Cl	4-CO_2Et	$[CH_2]_6$	(8)	4-CO_2Et	41	95			
NO_2	H	Me_2	(1)	H	33	(Oil)	Me_2	H	40
NO_2	H	$[CH_2]_5$	(4)	H	9	97	$[CH_2]_5$	H	9
NO_2	H	$[CH_2]_6$	(8)	H	15		$[CH_2]_6$	H	15
NO_2	5-Cl	Me_2	(1)	5-Cl	45	118			
NO_2	5-Cl	$[CH_2]_5$	(4)	5-Cl	42	117			
NO_2	5-Cl	$[CH_2]_6$	(8)	5-Cl	38	(Oil)			
NO_2	5-Cl	$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	(5)	5-Cl	26	154			
NO_2	4-NO_2	Me_2	(1)	4-NO_2	86	117			
NO_2	4-NO_2	$[CH_2]_5$	(4)	4-NO_2	86	175—176			
Cl	4,6-$(NO_2)_2$	Me_2	(1)	4,6-$(NO_2)_2$	82	136 [b]			

[a] Lit. 90° (G. R. Clemo and T. B. Lee, *J. Chem. Soc.*, 1954, 2417). [b] Lit. 136° (H. J. Bocker, *Rec. Trav. chim.*, 1912, **31**, 152).

Thus *o*-fluoronitrobenzene with 1-aminoperhydro[2.2.2]-diazepine gave the aniline (14; Y = H, R_2 = $[CH_2]_5$) (60%) and no hydrazine, whereas with *NN*-dimethylhydrazine the aniline (14; Y = H, R = Me) (80%) and

supported by the observations of Nagarajan and his co-workers,[10] who showed that the action of benzyl bromide on *NN*-dimethylhydrazine or *N*-aminopiperidine gave a quaternary salt (15). They also showed that 2-chloro-



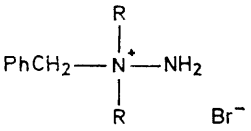
SCHEME 4

the hydrazine (1; Y = H) (5%) were isolated. The nucleophilicity of the tertiary nitrogen atom of the dialkylhydrazines is greater than that of the primary nitrogen, resulting in the initial formation of a quaternary

benzoxazole or -benzothiazole (16) with dimethylhydrazine gave a mixture of amine (17) and hydrazine

[10] K. Nagarajan, C. L. Kulkarni, and R. K. Shah, *Indian J. Chem.*, 1971, **9**, 748.

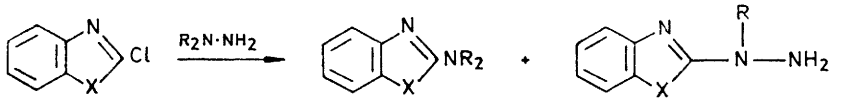
(18), whereas *N*-aminopiperidine gave only (17), both products being derived from an intermediate salt analogous to (15) (Scheme 5). As would be expected on



(15)

this basis, *N*-methyl-*N*-phenylhydrazine reacted with *o*-fluoronitrobenzene solely at the primary nitrogen atom, this being the more basic.

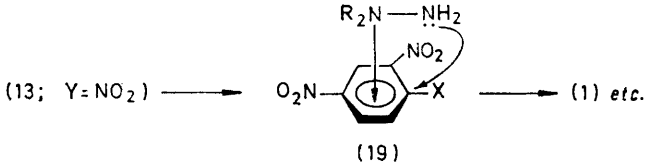
The above results do not, however, explain the dichotomy between mono- and poly-nitrobenzenes in their mode of reaction with *NN*-dialkylhydrazines. This



(16) (17) (18)

SCHEME 5

situation is understandable when one considers the role of polynitro-compounds as 'π-acids'. Thus aliphatic tertiary amines are noted for their ability to form charge-transfer (CT) complexes with polynitrobenzenes.[11] If nucleophilic substitution in the polynitrohalogenobenzenes is thus preceded by formation of a CT complex (19) with the more nucleophilic site of the hydrazine (the tertiary nitrogen), the less nucleophilic nitrogen is thus conveniently available for substitution (*e.g.* Scheme 6), leading to the required *o*-nitrophenylhydrazine. If this postulate is correct, there are several corollaries. With the polynitro-compounds: (1) the reaction should proceed with *o*-dinitrobenzenes leading to *o*-nitrophenyl-



(19)

SCHEME 6

hydrazines by substitution of a nitro-group; (2) the reaction should proceed more efficiently the more electron-withdrawing substituents are attached to the ring; and (3) hydrazine formation should be favoured the more nucleophilic the tertiary nitrogen atom of the hydrazine. These factors indeed operate in the examples examined (Table 2). Thus, whereas *o*-nitrohalogenobenzenes give *o*-nitroanilines as the major (or sole) product with various hydrazines, the *o*-dinitro-analogues give increasing quantities of the *o*-nitrophenylhydrazines as the ring is further substituted with electron-withdrawing substituents. Indeed, *o*-nitrohalogenobenzenes containing an extra electron-withdrawing group (other than nitro, *e.g.* 4-CF_3 or 4-CO_2Et) good yields of the required hydrazines.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 257, ^1H n.m.r. spectra with a Varian A60A or HA100, and mass spectra with an A.E.I. MS12 or MS902 instrument. Light petroleum refers to the fraction of b.p. 60—80° unless otherwise stated.

Furazan N-*Oxides*.—The benzofurazan *N*-oxides (9) were prepared by oxidation of suitable *o*-nitroanilines with hypochlorite [for (9; R = H [12], Cl [13], Br [14], OMe [15], or CF_3 [7])] or by thermal decomposition of the appropriate *o*-nitrophenyl azide [for (9; R = H [12], Cl [13], 5(6)-NO_2 [16], 5(6)-CO_2Et [4])]. 4(7)-Nitrobenzofurazan *N*-oxide was prepared by nitration of benzofurazan *N*-oxide.[17] Literature methods were also employed for naphtho[1,2-*c*]furazan *N*-oxide [18] and 3,4-diphenylfurazan *N*-oxide.[7]

Benzofurazans.—4-Chlorobenzofurazan [19] was prepared by condensation of 2,6-dichloro-1-nitrosobenzene [20] with sodium azide in dimethyl sulphoxide at 100 °C (70%); 5-chlorobenzofurazan [21] was obtained from 5(6)-chlorobenzofuroxan by deoxygenation with triethyl phosphite (68%). The 4- and 5-chlorobenzofurazans (2.0 g) were separately treated in dimethyl sulphoxide (20 ml) with morpholine (1.5 g) at 100 °C for 24 h. The mixtures were poured onto water and the precipitates were filtered off, washed with water, dried, and recrystallised from light petroleum (b.p. 80—100°) to give yellow needles of 4-*morpholinobenzofurazan* (53%), m.p. 107° (Found: C, 58.1; H, 5.7; N, 20.8. $C_{10}H_{11}N_3O_2$ requires C, 58.5; H, 5.4; N, 20.5%), M^+ 205, $\lambda_{max.}$ 232 and 392 nm; τ ($CDCl_3$), 6.28 (m, NCH_2), 5.99 (m, OCH_2), 3.58 (t, *J* 4 Hz, 6-H), and 2.68 (d, *J* 4 Hz, 5- and 7-H); or 5-*morpholinobenzofurazan* (61%), m.p. 129—130° (Found: C, 58.5; H, 5.3; N, 20.7%), M^+ 205, τ ($CDCl_3$) 6.65 (m,

[11] P. A. S. Smith, 'Open Chain Nitrogen Compounds,' Benjamin, New York, 1965, p. 23.
[12] P. A. S. Smith and J. H. Boyer, *Org. Synth.*, Coll. Vol. IV, 1963, p. 75.
[13] A. G. Green and F. M. Rowe, *J. Chem. Soc.*, 1913, **103**, 897.
[14] M. O. Forster and M. F. Barker, *J. Chem. Soc.*, 1913, **103**, 1918.
[15] R. J. Gaughran, J. P. Picard, and J. V. R. Kaufmann, *J. Amer. Chem. Soc.*, 1954, **76**, 2233.
[16] A. S. Bailey and J. R. Case, *Tetrahedron*, 1958, **3**, 113.
[17] A. G. Green and F. M. Rowe, *J. Chem. Soc.*, 1913, **103**, 2023.
[18] A. G. Green and F. M. Rowe, *J. Chem. Soc.*, 1917, **111**, 612.
[19] A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1966, 1004.
[20] R. R. Holmes and R. P. Bayer, *J. Amer. Chem. Soc.*, 1960, **82**, 3454.
[21] A. J. Boulton, A. C. Gripper-Gray, and A. R. Katritzky, *J. Chem. Soc.*, 1965, 5958.

NCH_2), 6.04 (OCH_2), 3.18 (d, *J* 2 Hz, 4-H), 2.62 (dd, *J* 10 and 2 Hz, 6-H), and 2.17 (d, *J* 10 Hz, 7-H).

Hydrazines.—The *NN*-disubstituted hydrazines were prepared by reduction of the appropriate *N*-nitroso-amines with zinc and acetic acid,[22] and were distilled under water-pump vacuum prior to use.

Nitrobenzenes (13).—1,2-Dinitrobenzene,[23] 1-chloro-3,4-dinitrobenzene,[24] and ethyl 4-chloro-3-nitrobenzoate [25] were prepared by literature methods and the remaining nitrobenzenes were purchased from Koch–Light.

Interaction of Benzofurazan N-*Oxides* (9) *with Amines.*—The benzofurazan *N*-oxide (9) (2.0 g) and the amine (10 ml) were kept for up to 7 days (monitored by t.l.c. for consumption of benzofurazan *N*-oxide) at the appropriate temperature (see Table 1). The mixture was poured into water (200 ml) and thoroughly extracted with ether; the extract was washed, dried ($MgSO_4$), and evaporated. The residue was chromatographed through a column of alumina with benzene–light petroleum (1 : 1) yielding the hydrazine [(1)—(8); Tables 1 and 3].*

Interaction of the Nitrobenzenes (13) *with Hydrazines.*—The nitrobenzene (13) (0.02 mol), the hydrazine (0.025 mol), and sodium hydrogen carbonate (2 g) in a suitable solvent were heated as indicated (Table 4) * until the amount of nitrobenzene remaining was minimal (t.l.c.), and the mixture was poured into water. If a solid precipitated it was filtered off and recrystallised; oils were chromatographed on alumina with light petroleum–benzene as eluant to give the products (Tables 2 and 4).*

We thank the S.R.C. for a grant (to D. W. S. L.) and Mrs. S. Bogle for ^1H n.m.r. spectra.

[6/588 *Received*, 29*th March*, 1976]

* Tables 3 and 4 (analytical and spectral data) are available as Supplementary Publication No. SUP 21829 (4 pp.). For details see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

[22] W. W. Hartmann and L. J. Roll, *Org. Synth.*, Coll. Vol. II, 1950, p. 460; H. Zimmer, L. F. Audrieth, M. Zimmer, and R. A. Rowe, *J. Amer. Chem. Soc.*, 1955, **77**, 790.

[23] W. D. Emmons and A. F. Ferris, *J. Amer. Chem. Soc.*, 1953, **75**, 4623.

[24] L. H. Welsh, *J. Amer. Chem. Soc.*, 1941, **63**, 3276.

[25] H. Hübner, *Annalen*, 1884, **222**, 166.