Proximity Effects in Diaryl Derivatives. Part 7.[1] Mechanism of Base-catalysed Rearrangement of 2-(Hydroxyamino)aryl Phenyl Sulphones to 2-Hydroxy-2'-(phenylsulphonyl)azoxybenzenes

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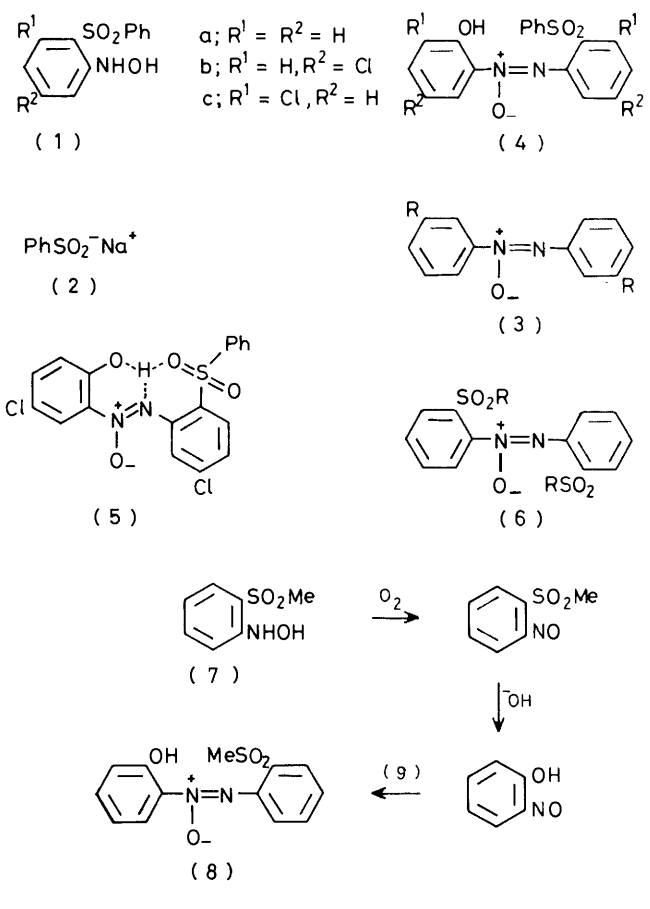
Base-catalysed rearrangement of a 2-(hydroxyamino)aryl phenyl sulphone (1b) to the 2-hydroxy-2'-(phenylsulphonyl)azoxybenzene (4b) was shown by isolation and kinetic studies to be a rapid reaction requiring oxygen; in the absence of oxygen the sulphur-free azoxybenzene (3; R = Cl) was the only product isolated from the reaction of (1c). A mechanism for the formation of 2-hydroxyazoxybenzenes (4) is proposed (Scheme 2) involving dimerization of a nitrosoaryl radical anion (9) to the dianion of an *NN*-diol (10), and displacement of a phenylsulphonyl group by intramolecular transfer of oxygen from a nitrogen atom. A similar study of the base-catalysed reactions of a 2-(hydroxyamino)aryl phenyl sulphide (12) in the presence of oxygen showed that with a poorer leaving group the bis(phenylthio)azoxybenzene (11; R = SPh) is formed. An improved procedure for the preparation of *N*-arylhydroxylamines from nitrobenzenes is described.

In Parts 4 [2] and 6 [1] we showed that treatment of 2-(hydroxyamino)aryl phenyl sulphones (1a—c) with base at ambient temperature resulted in the loss of phenylsulphonyl groups to give sodium benzenesulphinate (2) and mixtures of sulphur-free azoxybenzenes (3) (2—54% yield) and 2-hydroxy-2'-(phenylsulphonyl)azoxybenzenes (4a—c) (19—57% yield). Structures of the latter compounds were confirmed by *X*-ray crystallographic examination [3] of compound (4b), which was shown to contain a (*Z*)-azo-group and a bifurcated hydrogen bond as indicated in (5).

A study of the reaction of 4-chloro-2-(hydroxyamino)-phenyl phenyl sulphone (1b) with alkoxides in anhydrous solvents showed that 2-hydroxyazoxybenzene derivatives (4) are formed by intra- or inter-molecular rearrangements, the hydroxy-oxygen being derived from the sulphone or 2-hydroxyamino-group rather than from the solvent. 2,2'-Bis(phenylsulphonyl)azoxybenzene (6; R = Ph) was stable to aqueous sodium hydroxide and is not, therefore, an intermediate in the rearrangement reactions.[1]

In an independent investigation, Shaw *et al.*[4] showed that reaction of 2-(hydroxyamino)phenyl methyl sulphone (7) with aqueous sodium hydroxide in air at ambient temperature gave 2-hydroxy-2'-(methylsulphonyl)azoxybenzene (8) and 2,2'-bis(methylsulphonyl)azoxybenzene (6; R = Me) as major products; it is likely that the reactions of methyl and phenyl sulphones with base occur by analogous routes, although they were studied under different conditions. Several mechanisms for the formation of the azoxybenzenes (8) were discussed, and the one preferred (Scheme 1) involved oxidation of the hydroxylamine to a nitroso-derivative from which a methylsulphonyl group is displaced by hydroxide ion; the nitrosophenol so formed then reacts with the starting hydroxylamine. Since this route is inconsistent with the results obtained with phenyl sulphones, we decided to study further the mechanism of the reaction.



Scheme 1

Results and Discussion

Preparation of N-*Arylhydroxylamines.*—In our earlier work,[2] 2-(hydroxyamino)aryl phenyl sulphones (1) were obtained by catalytic reduction of the corresponding nitrobenzenes, but this method was less satisfactory on a larger scale since the product was contaminated by the nitro- and the amino-derivatives. Reduction of aromatic nitro-compounds with zinc in solutions kept near neutrality by addition of ammonium chloride has been employed frequently, but has been described as 'frustratingly erratic and may be entirely unsatisfactory in some cases '.[5] We have studied reduction of nitrobenzenes by this method in order to find optimum conditions for the preparation of *N*-arylhydroxylamines.

On addition of zinc dust to the yellow solutions of 4-chloro-2-nitrodiphenyl sulphide in aqueous ethanol containing ammonium chloride stirred at 20 °C, the solution became

Table 1. Kinetics of reaction of (1b) in aqueous ethanol (20% H_2O v/v) at 24 °C

λ/nm	10^5 [(1b)]/ M	[NaOH]/ M	10^3 k/s^{-1}	$t_{\frac{1}{2}}$/s	Correlation coefficient
438	6.6	0.05	7.65	90.6	0.999
300	6.6	0.05	8.10	85.6	0.990
438	6.6	0.025	5.81	119	0.997
300	3.3	0.025	6.07	114	0.998
438	3.3	0.01	2.41	288	0.997
300	3.3	0.01	2.32	298	0.999

colourless in 2 min, at which point the unchanged zinc particles tended to become suspended and its temperature rose to *ca.* 40 °C; immediate filtration led to the isolation of the hydroxylamine in 76% yield. The key to the success of the method apparently is to stop the reaction as soon as reduction is complete; for colourless reactants, optimum times were determined by other means (see Experimental section). A number of *N*-arylhydroxylamines have been obtained in yields of 48—83% by the new procedure (Table 2), and although substituent effects have not been fully examined, it appears that electron-attracting groups promote rapid reduction and the presence of the electron-donating *p*-methyl substituent results in slower reduction.

The Role of Oxygen in the Reaction of 2-*(Hydroxyamino)aryl Phenyl Sulphones with Base.*—In the formation of azoxybenzenes (3) and (4) from 2-(hydroxyamino)aryl phenyl sulphones (1), the reactions were carried out ' under nitrogen ' for 2—24 h.[1] The corresponding rearrangements of the methyl sulphone (7), however, occurred in air, but not in a nitrogen atmosphere.[4] Our first objective was to resolve this apparent dichotomy by studying the role of oxygen in the base-catalysed reactions of the sulphones (1).

Treatment of 4-chloro-2-(hydroxyamino)diphenyl sulphone (1b) with sodium methoxide in methanol for 1 min with exclusion of oxygen and then acidification led to recovery of the hydroxylamine almost quantitatively; after a reaction time of 12 h, the 2-hydroxyazoxybenzene (4b) was obtained (37% yield). In the presence of oxygen, however, the rearrangement product (4b) was isolated in 83% yield after a reaction time of 1 min. It appears, therefore, that the rearrangement requires oxygen and that the slow formation of the 2-hydroxyazoxybenzenes (4) under nitrogen was due to the presence of residual oxygen in the solution.

Similar experiments were carried out with 6-chloro-2-(hydroxyamino)diphenyl sulphone (1c). This compound reacted with base to give substantial quantities of the azoxybenzene derivative (3; R = Cl) as well as the 2-hydroxyazoxybenzene (4c) [1] and provided an opportunity to determine the effect of oxygen on both rearrangement reactions. In the reaction of compound (1c) with sodium methoxide in methanol or with potassium t-butoxide in t-butyl alcohol in the presence of oxygen only the 2-hydroxyazoxybenzene (4c) was isolated, whereas when the latter reaction was carried out with the exclusion of oxygen, the sulphur-free azoxybenzene (3; R = Cl) (74%) was the sole product isolated. These results confirm that oxygen is required for the formation of 2-hydroxyazoxybenzenes (4) but not for the competing rearrangement giving compounds (3); this conclusion is in accord with the intramolecular nucleophilic mechanism proposed for the latter reaction.[2]

Kinetics of Reaction of Arylhydroxylamine (1b) *with* RO^-–ROH.—Upon addition of (1b) (3×10^{-5}M) to aqueous ethanol (20% H_2O v/v) containing sodium hydroxide (0.01—0.05M) there follows a rapid reaction ($t_{\frac{1}{2}}$ 300—100 s at 24 °C) which has been monitored by recording the time dependence of the u.v.–visible absorption spectrum. The changes in absorption at 438 (increase) and 300 nm (decrease) follow identical pseudo-first-order kinetics (Table 1) and the rate constant (or the pseudo-first-order rate constant) is independent of [(1b)] but dependent upon [HO^-]. The base dependence is almost linear in the hydroxide concentration range 0.01—0.025M but at 0.05M the rate of reaction is *ca.* 30% less than expected on the basis of linear extrapolation. This may be a consequence of appreciable ionisation of (1b) at high base concentration; thus, if the reactive species is the conjugate base (S^-) of the substrate (SH) we obtain reaction (1) for

$$SH + \text{base} \overset{K}{\rightleftharpoons} S^- \xrightarrow{k} P \qquad (1)$$

which equation (2) obtains. Thus, k_{obs} becomes linearly

$$\frac{d[P]}{dt} = \frac{-d[SH + S^-]}{dt} = \frac{k}{(1 + 1/K[\text{base}])}[SH + S^-] = k_{obs}[SH + S^-] \qquad (2)$$

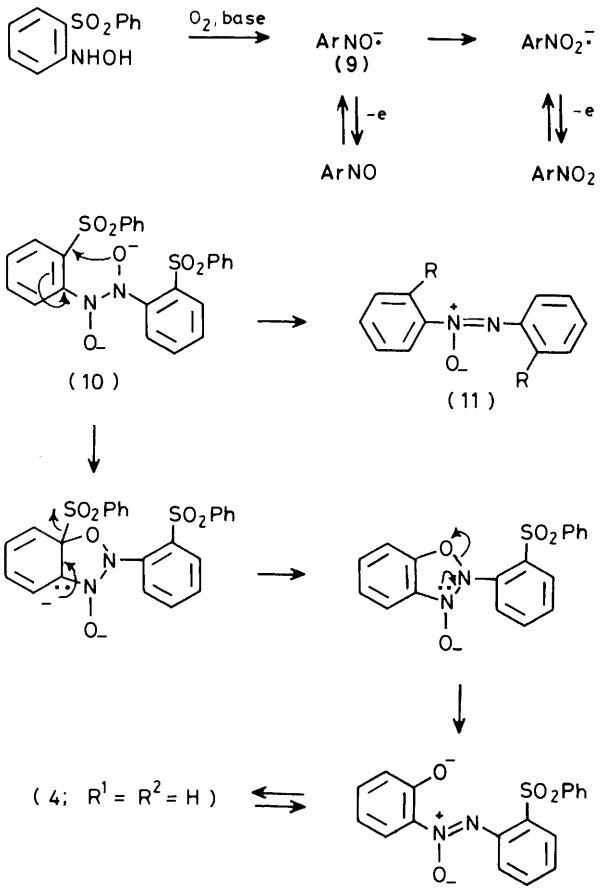
dependent on [base] only when $1/K[\text{base}] \geqslant 1$ and the pK_a of the substrate is much greater than the pH of the reaction medium. However, it is probable that the substrate (1b) will have a pK_a of 12—13 and that the base dependence of k_{obs} will become non-linear at the highest base concentration used.

It is apparent from the results in Table 1 that reaction of (1b) is complete within minutes. The product mixture under kinetic conditions has $\lambda_{max.}$ 214 and 436 nm (acidic medium); although the spectral data are not identical with that of the 2-hydroxyazoxybenzene (4b), the major product of reaction at higher concentration, the pH dependence in both cases is characteristic of the presence of a phenolic group. Reaction of the hydroxylamine (1b) (3×10^{-5}M) in methanolic sodium methoxide (0.0275M) was found to reach completion within a few minutes to give a product with $\lambda_{max.}$ 235 and 430 nm (basic solution) and 235 and 330 nm (acidic solution); the spectral characteristics are again consistent with formation of an azoxyphenol, in accord with the earlier report [1] that conversion of 2-(hydroxyamino)diaryl sulphones into azoxyphenols is not dependent on the use of hydroxide ion as base.

The kinetic results indicate the rapidity of the reaction and the dependence on [OH^-]. Although the dependence of the rate of reaction on [O_2] was not investigated, the use of solutions saturated with air ensured that the oxygen concentration was essentially constant and did not therefore affect the kinetic results. It is clear that oxygen is required for the reaction, suggesting that a reactive intermediate, for example a radical anion, is generated prior to coupling. Because of the complexity of the reaction and in particular the difficulty in identifying the products formed at low concentrations, extension of the kinetic study was not attempted.

Mechanism of Formation of 2-*Hydroxy*-2′-*phenylsulphonylazoxybenzenes* (4).—A possible mechanism for the base-catalysed rearrangement is illustrated for compound (1a) in Scheme 2.

Reaction of phenylhydroxylamine with base in the presence of air is believed to give the radical anions $PhNO^{\cdot-}$ and $PhNO_2^{\cdot-}$.[6,7] An analogous reaction is suggested as the first step in the reaction of compounds (1) with base, and is supported by the need for oxygen, by the kinetic studies indicating that ionisation of the hydroxyamino-group is involved, and by the isolation of 2-nitroaryl phenyl sulphones as minor products of the reaction.[2]



Scheme 2

Dimerization of the nitrosoaryl radical anion (9) or reaction of the anion of the hydroxylamine with the corresponding nitroso compound to give the dianion (10) of a symmetrical *N*,*N*-diol is regarded as the second stage of the reaction. A similar intermediate was proposed for the reaction of phenylhydroxylamine with nitrosobenzene in aqueous sodium hydroxide, the product, azoxybenzene, being formed from the partially protonated dianion in an elimination reaction.[6,8] The corresponding symmetrically substituted azoxybenzenes (11; R = SO_2Ph) were not detected in the reaction of 2-(hydroxyamino)aryl phenyl sulphones (1) with base, although 2,2′-bis(methylsulphonyl)azoxybenzene (6; R = Me) was the major product from the methyl sulphone (7).[4]

Since the hydroxy-group in product (4) is not derived from solvent and since the *N*-oxide group in compound (4) is adjacent to the ring bearing the hydroxy-function, the most likely mechanism for loss of a phenylsulphonyl group involves transfer of oxygen from the nitrogen atom furthest away from the ring under attack in intermediate (10); a mechanism satisfying these conditions and in accord with the stereochemistry of the final product, *cf.* (5), is proposed in Scheme 2.

Reaction of 4-*Chloro*-2-(*hydroxyamino*)*diphenyl Sulphide with Base.*—Kinetic results indicate that a phenylsulphonyl substituent is a remarkably effective leaving group in the base-catalysed rearrangement of 2-(hydroxyamino)aryl phenyl sulphones (Scheme 2). It was thus of interest to study a related compound containing a poorer leaving group; 4-chloro-2-(hydroxyamino)diphenyl sulphide (12) was chosen for this purpose.

The sulphide (12) was unaffected by sodium methoxide in methanol in the absence of oxygen. The introduction of oxygen resulted in the precipitation of the azo-derivative (13), but the major product of the reaction was shown by elemental analysis, i.r., and mass spectroscopy (see Experimental section) to be the bis(phenylthio)azoxybenzene (14); this was the sole product obtained from reaction of the hydroxyamino-derivative (12) with aqueous sodium hydroxide.

The u.v. spectrum of the hydroxyamino-derivative (12) in methanol showed no absorbance above 350 nm, but on the addition of sodium methoxide (0.01M) absorption occurred immediately at 436 nm and reached maximum intensity after *ca.* 5 min; this absorption then diminished in intensity and shifted hypsochromically giving after *ca.* 3 h a spectrum showing a maximum at 380 nm almost identical with the spectrum of the azoxy-derivative (14). Thus, the reaction of the hydroxyamino-sulphide (12) with base occurs at a lower rate than that of the sulphone (1b) and involves the formation of an intermediate ($\lambda_{max.}$ 436 nm), possibly a nitroso-derivative, from which the product is obtained by a much slower process.

In summary, the study of the mechanism of the rearrangement of 2-(hydroxyamino)aryl phenyl sulphones to 2-hydroxy-2′-(phenylsulphonyl)azoxybenzenes indicates that a fast reaction with oxygen and base to give a radical anion is followed by dimerization and then intramolecular displacement of the phenylsulphonyl group (Scheme 2); with a poor leaving group (PhS) the dimer is converted into the azoxybenzene derivative (11; R = SPh). We are now investigating the mechanism of displacement of the phenylsulphonyl group.

Experimental

I.r. spectra were recorded on a Perkin-Elmer 457 instrument, u.v. spectra on a Unicam SP800 or a Perkin-Elmer 402 instrument, and mass spectra on an AEI MS9 spectrometer.

N-Arylhydroxylamines.—A solution of ammonium chloride (5 g) in water (20 ml) was added to the corresponding nitrobenzene (8.02 mmol) in ethanol (50 ml). Zinc dust (4 g) was added to the vigorously stirring solution, its temperature rising to *ca.* 40 °C. When formation of the hydroxylamine was complete [determined by the solution becoming colourless or by monitoring with t.l.c. on silica with chloroform–ethyl acetate (9 : 1)] the mixture was filtered immediately and the filtrate added to water (500 ml). The hydroxylamines (Table 2) were recovered with dichloromethane and crystallised from ether–light petroleum (b.p. 40—60 °C) or from light petroleum (b.p. 40—60 °C).

5,5′-*Dichloro*-2-*hydroxy*-2′-(*phenylsulphonyl*)*azoxybenzene* (4b).—(a) A solution of sodium methoxide (0.012 mol) in anhydrous methanol (15 ml) was added to a nitrogen-flushed solution of the hydroxylamine (1b) (1.42 g, 0.005 mol) in

Table 2. Preparation of arylhydroxylamines by reduction of nitrobenzenes with zinc and ammonium chloride

Precursor	Reaction time (min)	Yield (%) of ArNHOH	M.p. (°C) of ArNHOH	Lit. m.p. (°C) of ArNHOH
4-Chloro-2-nitrodiphenyl sulphide	2	76	71—72 [a]	
4-Chloro-2-nitrodiphenyl sulphone	0.75	83	170—171	170—171 [9]
6-Chloro-2-nitrodiphenyl sulphone	0.75	81	119—120	120—121 [1]
3-Bromonitrobenzene	10	62	66—68	65.5 [10]
4-Bromonitrobenzene	15	60	90—92	91—92 [11]
2-Chloronitrobenzene	20	70	52—54	[54 [12]]
3-Chloronitrobenzene	10	67	48—50	49 [10]
4-Chloronitrobenzene	17	61	87—89	86.5 [10]
2,5-Dichloronitrobenzene	20	68	92—94	93 [13]
4-Methylnitrobenzene	60	48	97—99	98 [10]

[a] Found: C, 57.0; H, 4.0; N, 5.55. $C_{12}H_{10}ClNOS$ requires C, 57.0; H, 4.0; N, 5.6%.

anhydrous methanol (50 ml), kept under nitrogen for 12 h, evaporated and the residue was treated with water. Extraction with dichloromethane and crystallisation from methanol gave the azoxybenzene (4b) (0.3 g, 37%), m.p. 151—153 °C, identical with an authentic sample.[2]

(b) The hydroxylamine (1b) (0.56 g, 2×10^{-3} mol) in methanol–acetonitrile (5 ml, 1 : 1) was added to an oxygen-flushed solution of sodium methoxide in methanol (90 ml, 1M). After 1 min, the solution was acidified with hydrochloric acid and the azoxybenzene (4b) (0.35 g, 83%) was isolated in the normal way; 4-chloro-2-nitrodiphenyl sulphone (0.04 g, 7%), m.p. 120—122 °C (lit.,[14] 121 °C), was also obtained.

Repetition with a solution flushed with nitrogen instead of oxygen resulted in recovery of the hydroxylamine almost quantitatively, although the azoxybenzene (4b) was detected by t.l.c.

Reactions of 6-Chloro-2-(hydroxyamino)phenyl Phenyl Sulphone with Sodium Methoxide and with Sodium t-Butoxide.—(a) Reaction of 6-chloro-2-(hydroxyamino)phenyl phenyl sulphone (1c) (0.1g) with an oxygen-flushed solution of sodium methoxide in methanol as described for the 4-chloro-derivative in (b) above gave the azoxybenzene (4c) (0.06 g, 80%), m.p. 180 °C, identical with an authentic sample.[2] Repetition of the reaction with sodium t-butoxide in t-butyl alcohol gave the azoxybenzene (4c) (34%).

(b) Reaction of the hydroxylamine (1c) (0.2 g) with sodium t-butoxide in nitrogen-flushed t-butyl alcohol gave 3,3′-dichloroazoxybenzene (0.07 g, 74%), m.p. and mixed m.p. 95—97 °C.

Reactions of 4-Chloro-2-(hydroxyamino)phenyl Phenyl Sulphide (12) *with Bases.*—(a) Sodium methoxide in methanol (5 ml, 1M) was added to an oxygen-flushed solution of the hydroxylamine (12) (0.5 g) in methanol (20 ml). After 1 min, an orange-red precipitate of 5,5′-dichloro-2,2′-bis(thiophenoxy)-azobenzene (13) (0.05 g, 12%), m.p. 115—117 °C (lit.,[1] 117—119 °C), was removed. Dilution of the filtrate with water gave *5,5′-dichloro-2,2′-bis(thiophenoxy)azoxybenzene* (14) (0.16 g, 34%) separating from methanol in orange plates, m.p. 109—110.5 °C, $\lambda_{max.}$ 380 nm (MeOH), $\nu_{max.}$ (KBr) 1 517 and 1 130 cm^{-1} (N–O), *m/z* 482 (M^+) and 373 ($M^+ - C_6H_5S$) (Found: C, 59.1; H, 3.4; N, 5.9. $C_{24}H_{16}Cl_2N_2OS_2$ requires C, 59.4; H, 3.3; N, 5.8%).

Repetition of the reaction with nitrogen instead of oxygen flushing resulted after 15 min in recovery of the hydroxylamine (12) almost quantitatively.

(b) Addition of aqueous sodium hydroxide (10 ml, 1M) to an oxygen-flushed solution of the hydroxylamine (12) (0.5 g) in methanol (20 ml) and dilution with water gave the azoxybenzene (14) (0.24 g, 50%).

Kinetics of Reaction of Hydroxylamine (1b) *with* RO^-–ROH.—Reactions were initiated by adding a solution (10—30 μl) of the hydroxylamine (0.02M) in acetonitrile to the base solution (3 ml) contained in a quartz cuvette and thermostatted within the cell compartment of a u.v.–visible spectrometer (Perkin-Elmer model 402). Reactions were monitored by scanning the spectrum repetitively, in the usual way, and a least-squares analysis was used to determine the rate constants for the pseudo-first-order reactions observed (Table 1).

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References

1 Part 6, M. F. Grundon, D. J. Maitland, and W. L. Matier. *J. Chem. Soc. C*, 1971, 654.
2 M. F. Grundon, B. T. Johnston, and W. L. Matier, *J. Chem. Soc. B*, 1966, 260.
3 T. S. Cameron, R. J. Cummings, M. F. Grundon, and A. C. Knipe, *Cryst. Struct. Commun.*, 1974, **3**, 423.
4 K. B. Shaw, R. M. Heggie, and R. K. Millar, *Can. J. Chem.*, 1970, **48**, 1404.
5 P. A. S. Smith, ' The Chemistry of Open-chain Organic Nitrogen Compounds,' Benjamin, New York, 1966, vol. II, p. 15.
6 G. A. Russell and E. J. Geels, *J. Am. Chem. Soc.*, 1965, **87**, 122.
7 P. B. Ayscough, F. P. Sargent, and R. Wilson, *J. Chem. Soc. B*, 1966, 903.
8 M. M. Shemyakin, U. I. Maimind, and B. K. Vaichunaite, *Bull. Acad. Sci., U.S.S.R. Div. Chem. Sci.*, 1957, 1284.
9 M. F. Grundon and B. T. Johnston, *J. Chem. Soc. B*, 1966, 255.
10 A. Lapworth and L. Pearson, *J. Chem. Soc.*, 1921, **119**, 765, 768.
11 E. Bamberger, *Ber.*, 1895, **28**, 1221.
12 K. Brand and J. Mahr, *J. prakt. Chem.*, 1931, **131**, 97, 114.
13 T. Debrauw, *Recl. Trav. Chim. Pays-Bas*, 1931, **50**, 753.
14 R. J. W. LeFèvre, D. D. Moir, and E. E. Turner, *J. Chem. Soc.*, 1927, 2337.

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