Quinoxalines and Related Compounds. Part IX.[1] Preparation of 2-Aryloxyquinoxalines and their Cyclisation to Benzofuro[2,3-*b*]quinoxalines †

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When 2-chloroquinoxaline is treated with a sodium aryloxide in an excess of the corresponding phenol, a mixture of the expected quinoxalinyl ether and the corresponding benzofuro[2,3-*b*]quinoxaline is obtained. Polyphosphoric acid has been found to be the best reagent for the cyclisation of the isolated quinoxalinyl ethers to the benzofuroquinoxalines.

THIS paper reports the preparation of 2-aryloxyquinoxalines and their cyclisation to benzofuro[2,3-*b*]quinoxalines. Some derivatives of the latter system, prepared by other methods, have been described previously.[2,3]

The required quinoxalinyl ethers were prepared by reactions of 2-chloroquinoxaline with phenol and its homologues, with *m*-methoxyphenol, and with 1- and 2-naphthol (see Table 1). However when the displacement of chloride ion with phenoxide ion was carried out in an excess of the phenol as solvent, benzofuro[2,3-*b*]quinoxalines were also formed. As the nucleophilicity of the phenol was increased (see Table 2), *i.e.* by methyl or methoxy-substitution, the ratio of cyclised material to ether in the crude product usually increased. Since we were unable to demonstrate that the pre-formed ether cyclised to a benzofuro[2,3-*b*]quinoxaline under our

† A preliminary account of this work was presented at the Heterocyclic Discussion Group meeting of the Chemical Society at Glaxo, Greenford, in May 1971.

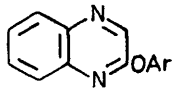
[1] G. W. H. Cheeseman and M. Rafiq, *J. Chem. Soc.* (*C*), 1971, 452.

[2] J. C. E. Simpson, 'Condensed Pyridazines and Pyrazine Rings,' in 'The Chemistry of Heterocyclic Compounds,' ed. A. Weissberger, Interscience, New York, 1953, p. 298.

[3] M. J. Haddadin, J. J. Zamet, and C. H. Issidorides, *Tetrahedron Letters*, 1972, 3653.

TABLE 1

2-Aryloxyquinoxalines

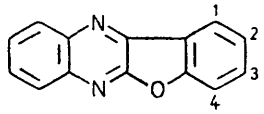


Ar	Method of preparation	Yield (%)	M.p. (°C)	Purification: Crystallisation solvent	Purification: Sublimation or distillation conditions	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
Ph	1 [a]	68	99—100	MeOH	90°, 0·5 mmHg	75·4	4·5	12·5	$C_{14}H_{10}N_2O$	75·6	4·5	12·6
2-MeC_6H_4	1	66	87—88	EtOH	100°, 0·5 mmHg	75·9	5·1	11·6				
4-MeC_6H_4	1	72	90—92	MeOH	100°, 0·2 mmHg	76·0	5·1	11·9				
	1 [b]	63										
3-MeC_6H_4	2 [c]	10	100—102	MeOH		75·9	5·0	11·8	$C_{15}H_{12}N_2O$	76·3	5·1	11·9
	3	60										
3-MeO·C_6H_4	1	18	120	EtOH	100°, 0·2 mmHg	71·4	4·9	11·6	$C_{15}H_{12}N_2O_2$	71·4	4·8	11·1
	2	79										
2,3-$Me_2C_6H_3$	1	51 [d]										
	2	49	124—125	MeOH	100°, 0·2 mmHg	76·7	5·5	10·6				
	4 [e]	29										
2,5-$Me_2C_6H_3$	1	39										
	2	44	82	MeOH	100°, 0·2 mmHg	77·0	5·6	11·0	$C_{16}H_{14}N_2O$	76·8	5·6	11·2
3,5-$Me_2C_6H_3$	1 [b]	58	72—73	MeOH	100°, 0·2 mmHg	77·2	5·4	11·1				
	2	56										
1-$C_{10}H_7$	2	41	118	MeOH	100°, 0·05 mmHg	79·2	4·6	10·4	$C_{18}H_{12}N_2O$	79·4	4·4	10·3
2-$C_{10}H_7$	2	61	145—147	MeOH	120°, 0·2 mmHg	78·8	4·6	10·4				

[a] The reaction mixture was poured into an excess of 2N-sodium hydroxide and the precipitated ether was filtered off, washed with water, dried, and purified. [b] The crude product was extracted into chloroform and the residue obtained by evaporation of the dried (Na_2SO_4) extracts was triturated with a *little* methanol. The crude product was filtered off, washed with a little methanol, then light petroleum (b.p. 40°), dried, and purified. [c] The phenol was treated with ethanolic sodium ethoxide (1 mol); 50% of 2-ethoxyquinoxaline was isolated as a by-product. [d] Shown to contain 30% of cyclised material by ^{1}H n.m.r. analysis. [e] Quinoxaline-2(1*H*)-one (50%) isolated from the mother liquors.

TABLE 2

Benzofuro[2,3-*b*]quinoxalines



Substituent	Method of preparation	Yield (%)	M.p. (°C)	Cryst. solvent(s)	Analysis: Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
None	*a*	50 [c]						$C_{14}H_8N_2O$			
3-Me	*b*	1·4	172	MeOH or CCl_4	76·7	4·3	12·0	$C_{15}H_{10}N_2O$ [d]	76·9	4·3	12·0
	a	65 [c,e]									
3-MeO	*b*	36	196	C_6H_6	72·2	4·1	10·9	$C_{15}H_{10}N_2O_2$	72·0	4·0	11·2
	a	80 [c,f]									
1,3-Me_2	*b*	16	206—207	EtOAc	77·2	5·1	11·1				
	a	70 [c]						$C_{16}H_{12}N_2O$	77·4	4·9	11·3
1,4-Me_2	*b*	2·4	188—189	EtOAc	77·4	5·2	11·0				
3,4-Me_2	*b*	15 [c]						$C_{16}H_{12}N_2O$ [g]			
	a	8 [c]									

[a] Prepared by polyphosphoric acid cyclisation of the quinoxalinyl aryl ether. [b] Isolated from the corresponding quinoxalinyl ether preparation (method 1). [c] Yield based on integration of the ^{1}H n.m.r. spectrum of the crude reaction mixture. [d] M^+ 234·0797 ($C_{15}H_{10}N_2O$ requires *M*, 234·0793). [e] The 100 MHz ^{1}H n.m.r. spectrum of 3-methylbenzofuroquinoxaline showed δ 9·10 (d, J_{ortho} 7·0 Hz, H-1), 7·20 (dd, J_{ortho} 7·0, J_{meta} 1·0 Hz, H-2), and 7·38 (d, J_{meta} 1·0 Hz, H-4). Irradiation at the methyl frequency (δ 2·57) sharpened the absorptions of H-2 and H-4. If the isomeric 1-methylbenzofuroquinoxaline had been formed, irradiation at the methyl group frequency would have sharpened the absorption of only one proton. [f] ^{1}H N.m.r. spectrum indicated the presence of a mixture of cyclised products, probably the 3- and 1-methoxy-compounds. [g] M^+ 248·0994 ($C_{16}H_{12}N_2O$ requires *M*, 248·0950).

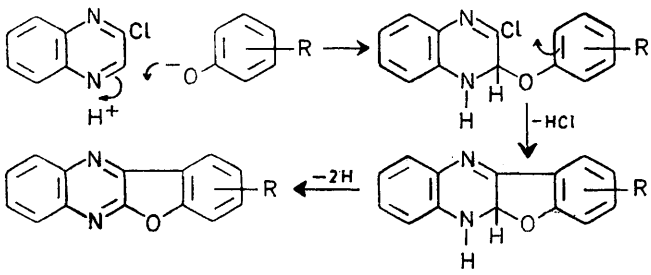
experimental conditions, we suggest that the cyclic material is formed as a result of an initial addition of a molecule of phenol to the C(3)–N(4) bond of 2-chloroquinoxaline. The subsequent stages are formalised in the Scheme. The terminal oxidation to the fully aromatic benzofuroquinoxaline would be expected to occur readily.*

When 2,3-dichloroquinoxaline was treated with 1 mol. equiv. of sodium *m*-cresolate in an excess of *m*-cresol under the same conditions, the product was 2,3-bis-(3-methylphenoxy)quinoxaline. Our results parallel those of Lockhart and Turner,[4] who failed in their attempts to convert 2,3-dichloroquinoxaline into 2-chloro-3-phenoxyquinoxaline, and instead obtained 2,3-diphenoxyquinox-

* *Cf.* J. Pinson and J. Armand, *Coll. Czech. Chem. Comm.*, 1971, **36**, 584, who found that various 1,2-dihydroquinoxalines are readily oxidised in air.

[4] D. Lockhart and E. E. Turner, *J. Chem. Soc.*, 1937, 424.

aline. This suggests that nucleophilic substitution of the chlorine atom leads to the ether, whereas addition yields a dihydro-intermediate which gives rise to cyclised species. An alternative possibility is that the aryloxide



SCHEME

ion is acting as an ambident nucleophile and that benzofuroquinoxaline is the result of *C*- rather than *O*-substitution of the phenol.

In view of the difficulties encountered in our initial attempts to prepare 2-aryloxyquinoxalines, alternative procedures were developed for ether formation (see Experimental section, methods 2—4). No cyclised products were obtained when an equimolecular mixture of 2-chloroquinoxaline and the pre-formed sodium aryloxide were fused together, or when the chloro-compound was condensed with the phenol in the presence of potassium carbonate in carbon tetrachloride or sodium hydroxide in aqueous ethanol.

We made attempts to cyclise 2-aryloxyquinoxalines to benzofuro[2,3-*b*]quinoxalines based on known procedures for dehydrogenative ring closure (*e.g.* thermal reaction[5] or treatment with aluminium chloride,[6] copper powder,[7] or palladium–charcoal [8]). Treatment with polyphosphoric acid at 140—160° gave the most satisfactory yields (Table 2). Both methyl and methoxy-groups facilitated cyclisation, which then took place preferentially *para* with respect to the activating substituent. The acidic reagent presumably acted by increasing the electrophilicity of the quinoxaline ring at C-3 by protonation at N-4.

Benzofuroquinoxalines were not obtained if the 3-position of the quinoxaline was blocked. Thus 2-phenoxy-3-phenylquinoxaline and 2-methyl-3-phenoxyquinoxaline were unaffected by polyphosphoric acid.

The ether derived from 2-chloroquinoxaline and 2-naphthol also cyclised in polyphosphoric acid to give the known naphtho[1′,2′:4,5]furo[2,3-*b*]quinoxaline.[9]

2-Benzyloxyquinoxaline and 2-phenylthioquinoxaline [10] were synthesised but attempts to cyclise these compounds with polyphosphoric acid were not successful. No tetracyclic products were detected as by-products during their preparation.

EXPERIMENTAL

2-Quinoxalinyl Aryl Ethers (*Table* 1).—*Method* 1. Sodium (0·05 mol) was dissolved in the phenol (0·25 mol) at 90—100°. More phenol was added if necessary so that the mixture could be stirred, and then 2-chloroquinoxaline (0·05 mol) was added. The bath temperature was raised to 120—140° and kept there for 10—20 h. Excess of phenol was then removed by either distillation or sublimation under water-pump vacuum. The residue was triturated with water and the crude product was filtered off, washed with water, dried, and purified.

Method 2. Sodium (0·02 mol) was dissolved in dry methanol (50 cm³). The phenol (0·02 mol) was added and the solution was heated under reflux for 1 h, cooled, and evaporated to dryness under water-pump vacuum over a boiling water-bath. 2-Chloroquinoxaline (0·02 mol) was added to the hot residue and the mixture was fused with a free flame until reaction occurred (150—200°). The melt was heated at 140—160° for 12 h, then cooled and stirred with water. The crude product was filtered off, washed with water, dried, and purified.

Method 3. A mixture of 2-chloroquinoxaline (0·02 mol), the phenol (0·02 mol), and anhydrous potassium carbonate (0·04 mol) in carbon tetrachloride (10 cm³) was refluxed with stirring until carbon dioxide ceased to be evolved (*ca.* 4 h). Inorganic salts were filtered off and washed with hot carbon tetrachloride (3 × 10 cm³). The combined filtrate and washings were evaporated to dryness and the residue was stirred with a little methanol. The crude ether was filtered off and purified.

Method 4. 2-Chloroquinoxaline (0·025 mol) in ethanol (10 cm³) was treated with the phenol (0·025 mol) in aqueous sodium hydroxide (10%; 10 cm³). The mixture was stirred and refluxed for 7 h, then cooled, and the crude ether was filtered off, washed with water, dried, and purified. The filtrate yielded quinoxalin-2(1*H*)-one on acidification.

2,3-Bis-(3-methylphenoxy)quinoxaline.—2,3-Dichloroquinoxaline [11] was treated with sodium *m*-cresolate in an excess of *m*-cresol by method 1. The *diether* (59%) had m.p. 142—143° (from ethanol) (Found: C, 77·5; H, 5·7; N, 7·9%; *M*, 342. $C_{22}H_{18}N_2O$ requires C, 77·1; H, 5·3; N, 8·2%; *M*, 342).

Benzofuro[2,3-b]*quinoxalines* (*Table* 2).—The quinoxalin-2-yl aryl ether (1·0 g) was treated with polyphosphoric acid (20 g). The mixture was heated at 140—160° for 6 h, then cooled and neutralised with sodium hydrogen carbonate solution. The product was filtered off, washed with water, dried, and purified.

2-Phenoxy-3-phenylquinoxaline.—The ether was prepared by method 1 from 2-chloro-3-phenylquinoxaline (see footnote *a* to Table 1) and purified chromatographically (Al_2O_3–C_6H_6) giving a white *solid* (95%), m.p. 152—153° (Found: C, 80·5; H, 5·1; N, 9·1. $C_{20}H_{14}N_2O$ requires C, 80·5; H, 4·7; N, 9·4%).

2-Methyl-3-phenoxyquinoxaline.—The ether was prepared by method 1 from 2-chloro-3-methylquinoxaline (see footnote *a* to Table 1) and purified chromatographically (Al_2O_3–C_6H_6) giving a white *solid* (98%), m.p. 101—102° (Found: C, 76·3; H, 4·9; N, 11·8. $C_{15}H_{12}N_2O$ requires C, 76·3; H, 5·1; N, 11·9%).

2-Benzyloxyquinoxaline.—Sodium (1·2 g) was dissolved in benzyl alcohol (25 cm³). 2-Chloroquinoxaline (4·0 g) was added and the mixture was stirred and heated at 110° for 5 h, cooled, poured into water (50 cm³), and extracted with

[5] C. Graebe and F. Ullmann, *Ber.*, 1896, **29**, 1876.
[6] M. H. Palmer and N. M. Scollick, *J. Chem. Soc.* (*C*), 1968, 2838.
[7] J. von Braun and J. Nelles, *Ber.*, 1937, **70**, 1760.
[8] N. W. Zelinskii, I. Titz, and M. Gaverdovskaya, *Ber.*, 1926, **59**, 2590.
[9] K. Fries and E. Pusch, *Annalen*, 1925, **442**, 272.
[10] F. Cuiban, M. Ionescu, H. Bala, and M. Steresco, *Bull. Soc. chim. France*, 1963, 356.
[11] R. D. Haworth and S. Robinson, *J. Chem. Soc.*, 1948, 777.

benzene (4 × 50 cm³). The benzene layers were combined and washed with water until neutral, dried (Na_2SO_4), and evaporated. The excess of benzyl alcohol was removed at 60° and 0·2 mmHg. The residue (3·8 g) solidified on cooling and recrystallisation from methanol (15 cm³) gave *2-benzyloxyquinoxaline* as shiny white plates (3·0 g, 51%), m.p. 49—51° (Found: C, 76·6; H, 5·1; N, 11·7. $C_{15}H_{12}N_2O$ requires C, 76·3; H, 5·1; N, 11·9%).

Naphtho[1′,2′:4,5]*furo*[2,3-b]*quinoxaline.*—2-(2-Naphthyloxy)quinoxaline was treated with polyphosphoric acid by the method described above, but the product was isolated from the neutralised reaction mixture by extraction with chloroform. The extract was dried (Na_2SO_4) and evaporated, and the residue (60%) crystallised from glacial acetic acid to give yellow needles, m.p. 217—218° (lit.,[9] 218°), δ ($CDCl_3$) 9·2—9·4 (1H, q, J_{ortho} 7·5, J_{meta} 1·5 Hz, H-1) and 7·4—8·5 (9H, m, quinoxaline and naphthalene protons).

Mass spectra were measured either on an A.E.I. MS9 spectrometer (ionising voltage of 70 eV) operated by the University of London Intercollegiate Research Services Scheme under the supervision of Dr. B. J. Millard, or on a similar instrument at the P.C.M.U., Harwell. We thank Mr. C. J. Turner and the P.C.M.U., Harwell, for the measurement of ^1H n.m.r. spectra (Perkin-Elmer R10 spectrometer operating at 60 MHz and Varian HA-100D spectrometer operating at 100 Hz). We also thank Ward, Blenkinsop, and Co. Ltd. for financial support, and Queen Elizabeth College for a Student Demonstratorship (to R. K. A.).

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