Reaction of Benzofurazan Oxides with Benzofuran-3(2*H*)-ones, and a New Synthesis of Benzofuro[2,3-*b*]quinoxalines

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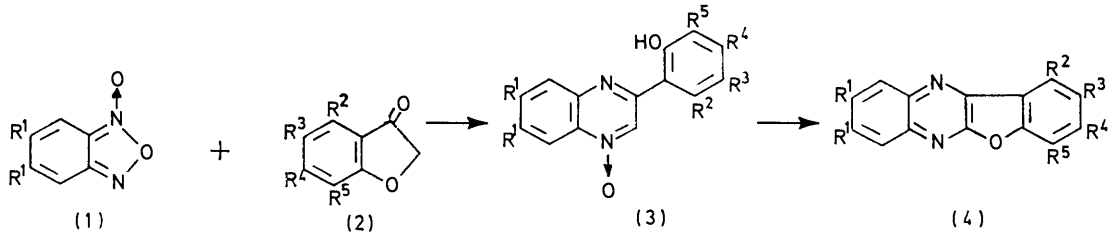
Reaction of benzofurazan oxides (1) with benzofuran-3(2*H*)-ones (2) provides a general, one-step synthesis of 3-(*o*-hydroxyaryl)quinoxaline 1-oxides (3). Cyclization of the products in refluxing acetic anhydride to give benzofuro[2,3-*b*]quinoxalines (4) constitutes a practicable route to a heterocyclic system for which no convenient synthetic methods are available.

In a preliminary communication,[1] we reported the unexpected formation of 3-(*o*-hydroxyphenyl)quinoxaline 1-oxide (3a) from benzofurazan 1-oxide (1a) and benzofuran-3(2*H*)-one (2a). We now present details of this reaction, evidence of its generality, and examples of its utility as a route to a heterocyclic system (4) for which no convenient synthetic methods are available (Table 1).

TABLE 1

Preparation of 3-(*o*-hydroxyaryl)quinoxaline 1-oxides (3) and cyclization to benzofuro[2,3-*b*]quinoxalines (4)



(1) (2) (3) (4)

Starting materials (1), (2)	R¹	R²	R³	R⁴	R⁵	Product (3)	M.p. (°) (solvent) *	Yield (%)	Product (4)	M.p. (°) (solvent) *	Yield (%)
(1a),[a] (2a) [b]	H	H	H	H	H	(3a)	229—230 (decomp.) (A)	78	(4a)	171—172 [c] (F)	70
(1a), (2b) [d]	H	H	Me	H	H	(3b)	253—254 (decomp.) (B)	71	(4b)	165—167 (G)	75
(1a), (2c) [d]	H	H	H	Me	H	(3c)	240—241 (decomp.) (C)	80	(4c)	174—175 (G)	70
(1a), (2d) [e]	H	H	H	H	Me	(3d)	217—218 (C)	71	(4d)	159—160 (G)	70
(1a), (2e)	H	H	Br	H	H	(3e)	268—269 (decomp.) (B)	70			
(1a), (2f) [d]	H	Me	H	Me	H	(3f)	205—206 (C) [f]	55	(4f)	205—206 [g] (D)	75
(1a), (2g) [h]	H	H	Br	H	Br	(3g)	281—282 (D)	68	(4g)	219—220 (H)	75
(1a), (2h)	H	H	CH=CH–CH=CH–		H	(3h)	255—256 [i] (decomp.) (E)	70	(4h)	247—248 (G)	60
(1b),[j] (2a)	Me	H	H	H	H	(3i)	247—248 (C)	50	(4i)	190—192 (G)	60
(1b), (2c)	Me	H	H	Me	H	(3j)	249—250 (C)	50	(4j)	253—254 (G)	60
(1c),[j] (2a)	Cl	H	H	H	H	(3k)	300—302 (decomp.) (D)	80	(4k)	254—255 (H)	55

* A = C_6H_6–MeOH, B = C_6H_6–$CHCl_3$, C = $CHCl_3$–MeOH, D = HOAc, E = MeOH–dioxan, F = aq. EtOH, G = EtOH, H = EtOH–$CHCl_3$.

[a] Ref. 2*a*. [b] Ref. 3*a*. [c] Lit.,[7] 173·5°. [d] Ref. 3*b*. [e] K. V. Auwers, *Ber.*, 1916, **49**, 813. [f] Product chromatographed on alumina (grade II) and eluted with chloroform, before recrystallization. [g] Lit.,[12] 206° [h] K. Fries and L. Moskopp, *Annalen*, 1909, **372**, 197. [i] Analytical sample purified by chromatography on alumina (grade II), eluted by $CHCl_3$. [j] Ref. 2*b*.

The benzofurazan oxides used were prepared by alkaline hypochlorite oxidation of *o*-nitroanilines.[2] With one exception (2h),[3] the benzofuran-3(2*H*)-ones were obtained from phenols by esterification to the corresponding aryl chloroacetates, rearrangement of the esters by aluminum trichloride to ω-halogeno-*o*-hydroxyacetophenones, and cyclization of the halogeno-ketones by base to the desired products (2).[4]

The reaction of benzofurazan 1-oxide and benzofuran-3(2*H*)-one in methanolic potassium hydroxide occurs very rapidly and gives, after acidification, a yellow product which is formulated as 3-(*o*-hydroxyphenyl)-quinoxaline 1-oxide (3a) on the basis of the following evidence (Scheme 1).

(i) The elemental analysis of (3a) is compatible with the molecular formula $C_{14}H_{10}N_2O_2$. The mass spectrum shows a molecular ion at *m/e* 238 and an intense *M* − 16 peak suggestive of an *N*-oxide function. The presence of this group is corroborated by deoxygenation of (3a) with sodium dithionite to a product identical (m.p., i.r. spectrum) with an authentic sample [5] of 2-(*o*-hydroxyphenyl)quinoxaline (5a).

(ii) Oxidation of (5a) at room temperature by peracetic acid gives (3a) in good yield. During this oxidation, two nitrogen atoms (N-1 and N-4) of the quinoxaline are available for attack by the peracid. Of these, N-1 is sterically hindered by the substituent at position 2,

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

[2] (*a*) F. B. Mallory, *Org. Synth.*, 1957, **37**, 1; (*b*) F. B. Mallory and C. S. Wood, *J. Org. Chem.*, 1962, **27**, 4109.

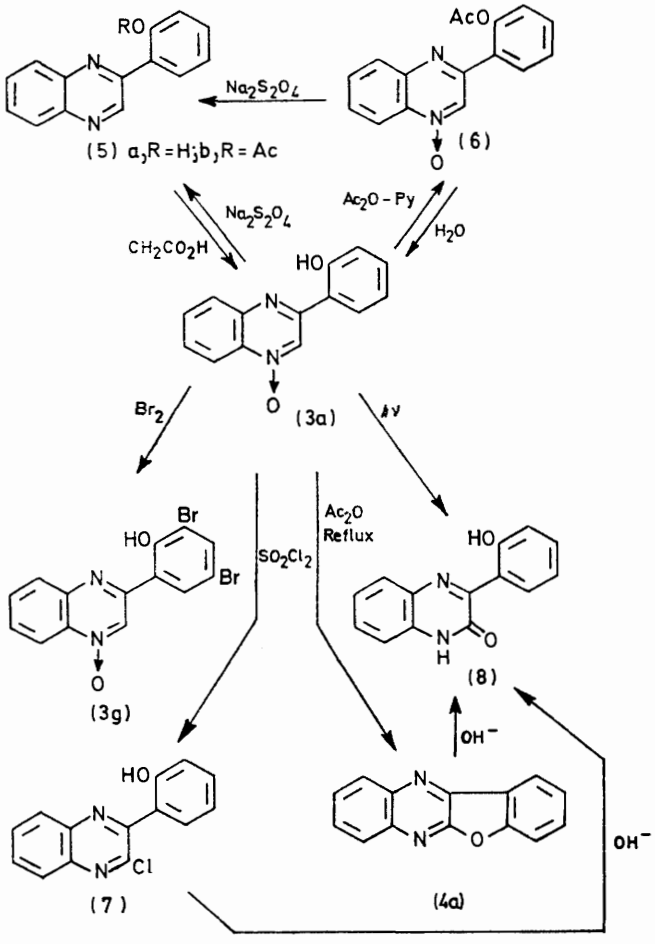
[3] P. Emmett and R. Livingstone, *J. Chem. Soc.*, 1958, 4629.

[4] (*a*) K. Fries and W. Pfaffendorf, *Ber.*, 1910, **43**, 212; (*b*) K. Fries and G. Finck, *ibid.*, 1908, **41**, 4271.

[5] K. Fries and K. Saftien, *Annalen*, 1925, **442**, 284.

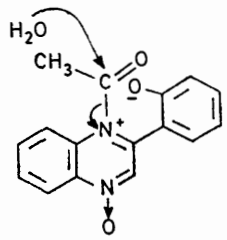
and by chelation with the phenolic proton. Electrophilic attack by the oxidant therefore takes place at N-4 giving (3a). The steric effect of aryl subtituents during peracid oxidations of quinoxalines and related compounds is well documented.[6] That chelation in (5a) contributes further in decreasing the reactivity at N-1 is suggested by the failure of (3a) to react under conditions reported [7] to give 2-phenylquinoxaline 1,4-dioxide from 3-phenylquinoxaline 1-oxide.

(iii) The presence of a phenolic function is compatible with the solubility of (3a) in aqueous alkali (from which it is reprecipitated by acid), and with the formation of a monoacetate [(6), acetic anhydride–pyridine at room temperature]. The acetate is so sensitive to hydrolysis that, unless filtered off immediately during the work-up, it reverts to starting material (see Experimental section).



SCHEME 1

The pronounced tendency of (6) to hydrolysis is possibly indicative of intramolecular catalysis by the nitrogen atom at position 4 (Scheme 2). When treated with sodium dithionite, (6) undergoes hydrolysis and deoxygenation to (5a).



SCHEME 2

(iv) Bromination of (3a) gives a dibromo-derivative (3g) identical with that obtained from 5,7-dibromobenzofuran-3(2*H*)-one and benzofurazan 1-oxide (Table 1).

(v) Treatment of (3a) with sulphuryl chloride at reflux gives the chloro-derivative (7) which is smoothly converted by refluxing aqueous sodium hydroxide into a product identical with an authentic sample [8] of 3-(*o*-hydroxyphenyl)quinoxalin-2(1*H*)-one (8). The validity of this diagnostic method for the position of the *N*-oxide function in quinoxaline 1-oxides carrying one *C*-substituent on the hetero-ring has been established.[6]

(vi) That (3a) is correctly formulated with the aryl substituent β to the *N*-oxide function is further corroborated by the isolation of quinoxalinone (8) as one of the products of the photolysis of (3a) in acetone solution. Kaneko and his co-workers have shown that quinoxaline 1-oxides bearing a 3-phenyl substituent give 3-phenylquinoxalin-2(1*H*)-one as one of the photoproducts, whereas those bearing the substituent at position 2 give only *N*-benzoyl-*N'*-formyl-*o*-phenylenediamine.[9]

(vii) The postulated structure (3a) is supported further by spectroscopic evidence. The n.m.r. spectrum of 3-(*o*-acetoxyphenyl)quinoxaline 1-oxide [(6) in CCl_4] shows a low-field singlet at τ 1·37 (1H) for the α-proton, and a multiplet at 1·50 (1H) for the proton at position 8. In the n.m.r. spectrum of 3-(o-acetoxyphenyl)quinoxaline (5b) the singlet for the α-proton shows a marked shift to τ 0·92. The downfield shift (τ 1·37 to 0·92) attending deoxygenation [(6) to (5b)] is compatible with structure (3a). The situation here is similar to that reported by Ochiai [10] for pyridine *N*-oxides in aprotic solvents: upon deoxygenation, protons α to the *N*-oxide function move downfield whereas β protons move upfield, without exception.

The reaction of benzofurazan 1-oxides (1) with benzofuran-3(2*H*)-ones (2) is unusual in that the products (3) (Table 1) are at an oxidation state two levels lower than expected [(4) as the di-*N*-oxide [1,11]]. Evidence that benzofuran-3(2*H*)-ones play the dual role of substrates as well as reductants during the reaction is provided by

[6] (*a*) A. R. Katritzky and J. M. Lagowski, 'Chemistry of the Heterocyclic *N*-Oxides,' Academic Press, London and New York, 1971, p. 71; (*b*) E. Ochiai, 'Aromatic Amine Oxides,' Elsevier, Amsterdam, 1967, pp. 45 and 68.

[7] Y. Ahmad, M. Habib, and Z. Bakhtiari, *J. Org. Chem.*, 1966, **31**, 2613.

[8] L. Marchlewski and J. Sosnovski, *Ber.*, 1901, **34**, 2294, 1108.

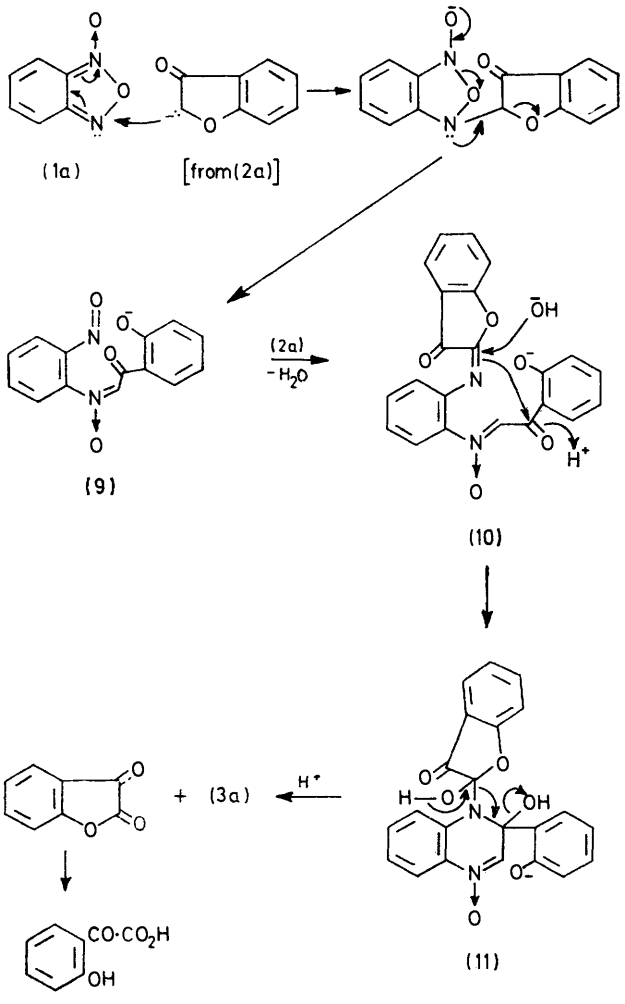
[9] (*a*) C. Kaneko, S. Yamada, I. Yokoe, and M. Ishikawa, *Tetrahedron Letters*, 1967, 1873; (*b*) G. G. Spence, E. L. Taylor, and O. Buchardt, *Chem. Rev.*, 1970, **70**, 254.

[10] Ref. 6*b*, p. 109.

[11] C. H. Issidorides and M. J. Haddadin, *J. Org. Chem.*, 1966, **31**, 3067.

the isolation of *o*-hydroxyphenylglyoxylic acid and of 4,6-dimethylbenzofuran-2,3-dione [12] as by-products from the reaction of (1a) with (2a) and with (2f) respectively. The *o*-hydroxyphenylglyoxylic acid evidently arises by hydrolysis of the unstable benzofuran-2,3-dione.[13]

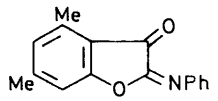
A plausible mechanism for the base-catalysed reaction of (1a) and (2a) is outlined in Scheme 3. The postulated mechanism provides a reasonable explanation not only for the formation of the observed by-products but also for the fact that the yields of (3) are optimum when (1) and (2) are employed in a 1 : 2 molar ratio, but fall off sharply with decreasing proportion of (2). The mechanism derives some further support from the following considerations: first, the analogous imine (12) [readily



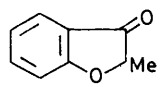
SCHEME 3

synthesized from (2f) and nitrosobenzene by a condensation similar to that postulated to occur between (2a) and the nitroso-intermediate (9)] is known to undergo hydrolysis in warm alkali to give 4,6-dimethylbenzofuran-2,3-dione.[12] Secondly, compound (13) [for which no imine intermediate of type (10) is possible] fails to react with benzofurazan oxide.

A remarkable reaction occurs when 3-(*o*-hydroxyaryl)-quinoxaline 1-oxides (3) are refluxed with acetic anhydride: deoxygenation is accompanied by cyclization to benzofuro[2,3-*b*]quinoxalines (4). The transformation



(12)



(13)

is quite general (Table 1) and evidently bears some mechanistic analogy to the reaction between pyridine *N*-oxide and acetic anhydride in the presence of anisole to give 2-(*o*-methoxyphenyl)pyridine.[14] A few benzofuro[2,3-*b*]quinoxalines had been hitherto available either from 3-(*o*-hydroxyphenylquinoxalin-2(1*H*)-ones by pyrolysis,[12] or from 2,2-dibromobenzofuran-3(2*H*)-one by condensation with *o*-phenylenediamine.[13] Of the two prior methods, the former works only in a few cases [8] whereas the latter gives impure products. The method described here provides a general and convenient route to (4).

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer model 257 spectrophotometer using potassium bromide discs, unless otherwise specified. ^{1}H N.m.r. were determined on a Varian A60-D spectrometer using tetramethylsilane as internal reference. Microanalyses were performed by F. Pascher, Mikroanalytisches Laboratorium, Bonn, Germany.

General Procedure for the Preparation of 3-(o-*Hydroxyphenyl*)*quinoxaline* 1-*Oxides* (3).—A solution of the benzofurazan 1-oxide (1) (0·01 mol) and the benzofuran -3(2*H*)-one (2) (0·02 mol) in methanol (15 ml) was treated with 5% methanolic potassium hydroxide (22·4 ml). A vigorous reaction ensued, and the resulting dark red mixture was allowed to stand at room temperature for 4 h. Acidification with glacial acetic acid gave a solid (usually yellow) which was collected by filtration and recrystallized [Table 1, (3a—k)].

Attempted Reaction between 2-*Methylbenzofuran*-3(2H)-*one* (13) *and* (1a).—A solution in methanol (10 ml) of (1a) (0·7 g) and (13) (1·47 g) was treated with 5% methanolic potassium hydroxide according to the general procedure for the preparation of (3). No precipitate was formed. The solvent was evaporated off under reduced pressure, aqueous potassium hydroxide was added to the residue, and the mixture was extracted with ether. Evaporation of the ether gave (1a) (0·56 g, 80% recovery). The aqueous layer after acidification, extraction with ether, and evaporation of the ether gave (13) (1·1 g, 78% recovery). When the same procedure was repeated at reflux temperature for 2 h, the recovery of (1a) and (13) was 78 and 75% respectively.

General Procedure for Acetylation of 3-(o-*Hydroxyaryl*)-*quinoxaline* 1-*Oxides* (3).—A solution of (3) (0·005 mol) in pyridine (10 ml) was treated with an excess of acetic anhydride (2 ml) and allowed to stand at room temperature for 15 h (during which a gradual change of the solution from yellow to colourless occurred). The solution was then poured onto ice and water, and the white precipitate was collected by filtration immediately to prevent hydrolysis of

[12] K. Fries and K. Bartens, *Annalen*, 1925, **442**, 257.
[13] K. Fries and W. Pfaffendorf, *Ber.*, 1912, **45**, 161.
[14] T. Cohen and G. L. Deets, *J. Org. Chem.*, 1972, **37**, 55.

the extremely labile acetate. The products (recrystallized from cyclohexane) showed carbonyl absorption at 1760 cm^{-1} (Table 2, Reaction A).

General Procedure for Deoxygenation of 3-(o-*Hydroxyaryl*)-*quinoxaline* 1-*Oxides* (3).—Deoxygenations were effected by dissolving the oxide (0·001 mol) in EtOH [30 ml for (3a)] or in 1 : 1 ethanol–dioxan [10 ml for (3b—d)] and adding to the solution sodium dithionite (0·003 mol) dissolved in warm water (5 ml). The mixture was refluxed [4 h for (3a), 12 h for (3b—d)] and then poured over ice. The yellow quinoxalines were recrystallized from ethanol (Table 2, Reaction B).

General Procedure for Brominations.—Bromine (in glacial acetic acid) was added slowly to a cold solution of (3) in glacial acetic acid. The mixture was allowed to stand at room temperature for 1 h, and the precipitated solid was collected. Dilution of the filtrate with water gave more product. The combined crops were recrystallized from glacial acetic acid (Table 2, Reaction C).

General Procedure for Preparation of Benzofuro[2,3-b]*quinoxalines* (4).—The mono-oxide (3) (0·001 mol; recrystallized, for best results) was refluxed [2 h for (3a), 7 h for (3b—j), 15 h for (3k)] in acetic anhydride (10—15 ml). The solution was poured onto ice–water and the resulting mixture was treated with potassium acetate and stirred. The resultant solid was recrystallized to give (4) [Table 1 (4a—k)].

2-(o-*Acetoxyphenyl*)*quinoxaline* (5b).—Acetylation of (5a) (0·23 g, 0·001 mol) was effected in a mixture of pyridine (5 ml) and acetic anhydride (2 ml) at room temperature for 12 h. The solution was poured onto ice, treated with sodium acetate, and stirred. The product (5b) was recrystallized from cyclohexane, 0·21 g (75%), m.p. 103—104°, $\nu_{max.}$ 1755, 1480, 1360, 1200, 1175, 1050, 1030, 1010, 950, 910, and 765 cm^{-1}, τ ($CDCl_3$) 0·92 (1H, s), 2·33 (8H, m), and 7·84 (3H, s).

3-(o-*Hydroxyphenyl*)*quinoxalin*-2(1H)-*one* (8).—*Method* (a). Sulphuryl chloride (7 ml) was added to (3a) (0·6 g, 0·0025 mol) and the mixture was refluxed for 2 h. The mixture was then poured into an evaporating dish and, after evaporation of the sulphuryl chloride, the residual solid was recrystallized from chloroform to give 2-chloro-3-(o-hydroxyphenyl)quinoxaline (7), 0·5 g (74% yield), m.p. 287—288°, $\nu_{max.}$ 1580, 1500, 1370, 1350, 1255, 1175, 965, 850, and 760 cm^{-1}, τ (CF_3CO_2H) 2·25 (m). This product (0·2 g, 0·0008 mol) was refluxed for 2 h with 10% aqueous sodium hydroxide (10 ml). Acidification gave a product (8) which was recrystallized from ethanol, 0·12 g (60%), m.p. 294—295°, $\nu_{max.}$ 1660, 1570, 1480, 1440, 1310, 1280, 1260, 1205, 1170, 1150, 865, 760, and 750 cm^{-1}. The product was identical with an authentic sample.[8]

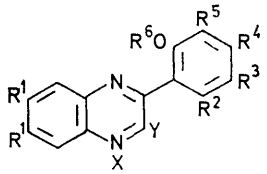
Method (b). A solution of (3a) (1·4 g, 0·01 mol) in acetone (500 ml) was irradiated for 48 h with a Hanovia 679A36 high pressure mercury lamp. Evaporation of the solvent and recrystallization of the resulting solid from ethanol gave (8) (0·18 g, 14% yield). When the photolysis was allowed to proceed for only 24 h, a mixture of (8) and the starting material was obtained.

Method (c). Compound (4a) (0·11 g, 0·0005 mol) was refluxed for 4 h with 10% aqueous sodium hydroxide (10 ml). The solution was then cooled and acidified with hydrochloric acid to give (8) (0·08 g, 66%), m.p. 294—295° (EtOH).

Isolation of By-products.—(a) *From the reaction of* (1a) *and* (2a). Benzofurazan 1-oxide (1a) (0·7 g, 0·005 mol) and benzofuran-3(2*H*)-one (2a) (1·34 g, 0·01 mol) were dissolved in methanol and treated with 5% methanolic potassium hydroxide (11 ml). After 4 h at room temperature, the precipitate was recrystallized from methanol–benzene to give (3a) (0·84 g, 72%). The mother liquor was evaporated to dryness under reduced pressure and the residual tarry solid was extracted with 10% aqueous potassium hydroxide (3 × 15 ml). The basic extracts were acidified with hydrochloric acid and extracted with ether. The ethereal solution was extracted with 10% sodium carbonate, and the carbonate layer was acidified and extracted with ether. Evaporation of the ether gave a dark brown oily compound (0·6 g) which failed to crystallize, but whose i.r. spectrum was identical with that of an authentic sample of 2-hydroxy-

TABLE 2

Derivatives of 3-(*o*-hydroxyaryl)quinoxaline 1-oxides



Starting material	Reaction *	Product X	Y	R^1	R^2	R^3	R^4	R^5	R^6	M.p. (°)
(3a)	A	O	H	H	H	H	H	H	Ac	100—101
(3b)	A	O	H	H	H	Me	H	H	Ac	124—125
(3c)	A	O	H	H	H	H	Me	H	Ac	154—155
(3d)	A	O	H	H	H	H	H	Me	Ac	140—141
(3k)	A	O	H	Cl	H	H	H	H	Ac	160—161
(3a)	B		H	H	H	H	H	H	H	189—190
(3b)	B		H	H	H	Me	H	H	H	191—192
(3c)	B		H	H	H	H	Me	H	H	177—178
(3d)	B		H	H	H	H	H	Me	H	167—168
(3a or e)	C	O	H	H	H	Br	H	Br	H	280—281
(3b)	C	O	H	H	H	Me	H	Br	H	281—282
(3c)	C	O	H	H	H	Br	Me	Br	H	286—287
(3d)	C	O	H	H	H	Br	H	Me	H	265—266

* A = acetylation, B = deoxygenation, C = bromination.

phenylglyoxylic acid.[8] The oily material (0·4 g, 0·0025 mol), when refluxed in glacial acetic acid (20 ml) with *o*-phenylenediamine hydrochloride (0·3 g, 0·0025 mol), gave (8) (0·4 g, 71%), identical with an authentic sample.[8]

(b) *From the reaction of* (1a) *and* (2f). Benzofurazan 1-oxide (1a) (0·7 g, 0·005 mol), and 4,6-dimethylbenzofuran-3(2*H*)-one (2f) (1·6 g, 0·01 mol) were dissolved in methanol (10 ml), treated with 5% methanolic potassium hydroxide (11 ml), and allowed to stand at room temperature for 4 h. The solution was then evaporated to dryness under reduced pressure and the residual solid was extracted with boiling benzene. The benzene extracts were chromatographed on alumina (grade II) to give (3f) (0·72 g, 55%). The solid residue which was insoluble in benzene in the previous step was dissolved in water. Acidification of the solution with hydrochloric acid gave a yellow solid which was recrystallized from ethanol. The compound obtained was identical (mixed m.p., i.r. spectrum) with an authentic sample [12] of 4,6-dimethylbenzofuran-2,3-dione; yield 0·46 g (53%), m.p. 144—146°, $\nu_{max.}$ (Nujol) 1820, 1730, 1630, 1595, 1330, 1250, 1210, 1140, 1135, 1025, 960, 865, and 750 cm^{-1}.

Peracid Oxidation of 2-(o-*Hydroxyphenyl*)*quinoxaline* (5a). —The quinoxaline (5a) (0·22 g, 0·001 mol) was dissolved in 40% peracetic acid (20 ml) and allowed to stand at room temperature for 24 h. Dilution with water gave (3a) (0·18 g, 75%), m.p. 227—228° (EtOH).

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