567. *Quinoxaline N-Oxides. Part I. The Oxidation of Quinoxaline and its Bz-Substituted Derivatives.*

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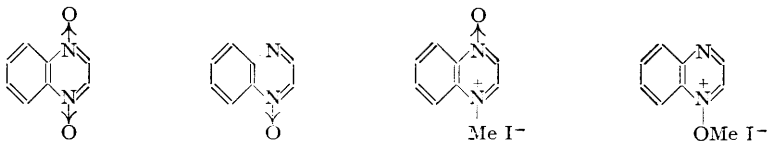
Quinoxaline and its *Bz*-alkyl, -alkoxy-, -halogeno-, and acylamino-derivatives are oxidised to mono- and di-*N*-oxides by organic peracids. Negative substituents promote the simultaneous formation of 2 : 3-dihydroxyquinoxaline derivatives. Resistance to *N*-oxidation, due to steric or polar influences, is encountered in 5- and 8-substituted quinoxalines. The reactions of some *N*-oxides with methyl iodide and with phosphoryl chloride are examined.

QUINOXALINE 1 : 4-DIOXIDE (I) and its 2-methyl-, 3-*n*-amyl-2-methyl-, and 2 : 3-tetramethylene derivatives were prepared by McIlwain (*J.*, 1943, 322) as possible antagonists of the *K* vitamins and related compounds and they have been shown to have moderate antibacterial activity *in vitro* (McIlwain, *loc. cit.*; Wiedling, *Acta Path. Microbiol. Scand.*, 1945, **22**, 379; Frisk, *Acta Med. Scand.*, 1946, **125**, 487; Iland, *Nature*, 1948, **161**, 1010). Some hydroxy- and methoxy-derivatives were synthesised by King, Clark, and Davis (*J.*, 1949, 3012) as possible antibacterials related to iodinin, and (I) and its 2-methyl-, 2-sulphanilamido-, and 2 : 3-diphenyl derivatives have been tested as antimalarials (Wiselogle, "Survey of Antimalarial Drugs, 1941—1945," Edwards, Ann Arbor, Mich., 1946, Vol. II, p. 1472) with negative results. During an investigation of quinoxaline derivatives as amœbicides it was found in these laboratories that 2-methylquinoxaline 1 : 4-dioxide was highly active against amœbiasis in rats, and this prompted a re-examination of this field from both the chemical and the biological standpoint. The preparation of some quinoline and quinoxaline *N*-oxides for examination as amœbicides was subsequently reported by Mamalis and Petrow (*J.*, 1950, 703) but no details were given.

Quinoxaline *N*-oxides have been made hitherto by oxidation with hydrogen peroxide in acetic acid. It is advantageous to use the 1·2M-solution of peracetic acid obtained by treating 30% hydrogen peroxide with acetic anhydride and sulphuric acid, the latter being neutralised by the subsequent addition of sodium acetate (Byers and Hickinbottom, *J.*, 1948, 286). Performic acid and concentrated peracetic acid (6·5 or 10M) are more potent but less controllable reagents. Hydrogen peroxide alone, or with sulphuric acid or phosphoric acid, oxidises quinoxaline to quinoxaline 1-oxide (II) together with much tar and insoluble, high-melting by-products, but organic peracids oxidise quinoxaline cleanly to either (I) or (II) according to the conditions.



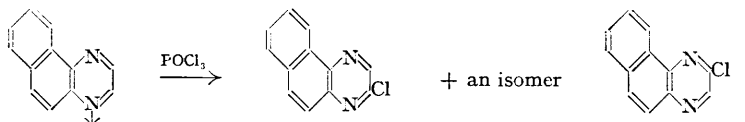
(I) (II) (III) (IV)

5-Substituted quinoxalines afford mono-*N*-oxides which are considered to be the 1-oxides, but with the exception of the 5-methoxy-compound they are highly resistant to further oxidation to di-*N*-oxides. This is attributable to steric hindrance (which is least with the methoxyl group) and to the reduced electron density at the tertiary nitrogen atom in the mono-*N*-oxides. No *N*-oxide is obtained from 5 : 8-dichloroquinoxaline, but 5 : 6 : 7 : 8-dibenzoquinoxaline (phenanthrapyrazine) gives a mono-*N*-oxide. Both mono- and di-*N*-oxides are obtained from 6- and 7-substituted quinoxalines, but 6-halogeno-compounds give mainly mono-*N*-oxides unless fairly drastic oxidation conditions (*e.g.*, performic acid) are used. Quinoxalines unsubstituted in the heterocyclic nucleus undergo simultaneous oxidation to 2 : 3-dihydroxy-derivatives; with 6-methylquinoxaline this is negligible (*ca.* 1%), but negative substituents favour the reaction, 6-halogenoquinoxalines

giving about 30% of the 2 : 3-dihydroxy-compounds while 6-nitro- and 6-cyano-quinoxaline give 50—60% with only traces of *N*-oxides. 2 : 3-Dihydroxyquinoxalines are conveniently characterised by boiling them with phosphoryl chloride and dimethylaniline, to give the 2 : 3-dichloro-derivatives; methylation to give 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxalines is not always satisfactory, 6-cyano-2 : 3-dihydroxy- and 2 : 3-dihydroxy-6-nitroquinoxaline, for example, giving monomethyl derivatives. Peracetic acid oxidation of 6-iodoquinoxaline and of 6 : 7-benzoquinoxaline is abnormal, possibly involving attack at the *meso*-positions in the latter case. 2 : 3-Dichloroquinoxaline is resistant to oxidation by peracetic acid, but 2-chloroquinoxaline is oxidised to a mono-*N*-oxide, which is regarded as 2-chloroquinoxaline 4-oxide.

With the foregoing exceptions quinoxaline mono-*N*-oxides are readily oxidised to di-*N*-oxides from which they are distinguished by lower melting points and greater solubility in non-polar solvents. Methyl iodide reacts with (II), but not with 5 : 6-benzoquinoxaline 1-oxide (V), to give a quaternary derivative. Of the alternative structures, 1-methylquinoxalinium 4-oxide iodide (III) and methoxyquinoxalinium iodide (IV), the former is preferred as the substance does not yield formaldehyde or quinoxaline on alkaline degradation. The yellow aqueous solution of (III) becomes deep blue-green on addition of sodium hydroxide, the colour fading on heating

Phosphoryl chloride reacts vigorously with (I) and (II), giving 2 : 3-dichloro- and 2-chloro-quinoxaline respectively. 5-Methylquinoxaline 1-oxide is converted into 2-chloro-5-methylquinoxaline, but two isomeric chlorobenzoquinoxalines are obtained from (V). Neither of these is identical with 3-chloro-5 : 6-benzoquinoxaline (VII), which was made by an unambiguous route from 2-carbethoxymethylaminonaphthalene. One of the isomers



(V) (VI) (VII)

was identified as 2-chloro-5 : 6-benzoquinoxaline (VI) by its reactivity with boiling piperidine, the other isomer being unaffected by this reagent. The unreactive isomer was not obtained by direct chlorination of 5 : 6-benzoquinoxaline in acetic acid, the product being a dichlorobenzoquinoxaline which also was unaffected by boiling piperidine.

Experimental

o-Phenylenediamines.—*3-Ethoxy-o-phenylenediamine.* 2 : 3-Dinitrophenetole (80 g.) dissolved in methanol (600 c.c.) was hydrogenated over Raney nickel at room temperature. Evaporation of the filtered solution under reduced pressure gave a dark oil (54 g.) which was used without further purification. The diamine formed a *picrate*, yellow needles (from ethanol), m. p. 210—212° (Found: C, 44·15; H, 4·0; N, 18·5. $C_8H_{12}ON_2,C_6H_3O_7N_3$ requires C, 44·1; H, 3·9; N, 18·4%).

4 : 5-*Diamino-2-bromotoluene.* (*a*) 2-Bromo-4-nitrotoluene (108 g.) was added during 45 min. to a mixture of sulphuric acid (465 c.c.; *d* 1·84) and nitric acid (150 c.c.; *d* 1·4) at 40—45°, and the mixture was heated at 90° for 2·25 hr., cooled, and poured on ice (3 kg.). The solid product was crystallised from ethanol, to give *2-bromo-4 : 5-dinitrotoluene* (55 g. of m. p. 92—94°), colourless leaflets, m. p. 94—95° (Found: N, 10·4. $C_7H_5O_4N_2Br$ requires N, 10·7%). This compound (108 g.), heated with ethanolic ammonia (600 c.c.; saturated at 0°) for 5 hr. at 120° (340 lb./sq. in.), gave 65 g. of mixed bromonitrotoluidines, m. p. 164—166°, which on reduction with zinc dust and sodium hydroxide in ethanol afforded 4 : 5-*diamino-2-bromotoluene*, faintly brown leaflets (from light petroleum), m. p. 140—141° (Found: N, 14·0. $C_7H_9N_2Br$ requires N, 13·9%). (*b*) 4-Acetamido-2-bromotoluene was nitrated and the product hydrolysed to 4-amino-2-bromo-5-nitrotoluene, m. p. 163—164°, which was reduced similarly to the diamine.

Quinoxalines.—The following general method of preparation was employed: glyoxal sodium bisulphite (0·25 mole), an *o*-phenylenediamine (0·25 mole), and water (300 c.c.) were stirred at 60° for 3 hr., more glyoxal sodium bisulphite (10% of the original charge) being added after 1 hr. The mixture was then made strongly alkaline with potassium hydroxide, and the

quinoxaline was isolated by filtration, steam-distillation, or extraction with ether. The following quinoxalines (colourless except as stated) were made by this method:

5-*Methylquinoxaline*, pale yellow, m. p. 20—21°, b. p. 120°/15 mm. (Found: N, 19·5. $C_9H_8N_2$ requires N, 19·45%), changing in moist air to a *hydrate*, m. p. 49—50° (Found: N, 17·1. $C_9H_8N_2,H_2O$ requires N, 17·3%).

5-*Ethoxyquinoxaline*, rhombs, m. p. 63—64°, b. p. 165—166°/18 mm. (Found: N, 16·2. $C_{10}H_{10}ON_2$ requires N, 16·1%).

5-*Chloroquinoxaline*, cream needles [from light petroleum (b. p. 40—60°)], m. p. 60—62° (Found: N, 17·3. $C_8H_5N_2Cl$ requires N, 17·0%).

6-*Iodoquinoxaline*, m. p. 114—115° (from benzene), steam-volatile (Found: N, 10·7. $C_8H_5N_2I$ requires N, 10·9%).

6-*Cyanoquinoxaline*, needles (from ethanol), m. p. 176—178° (Found: N, 26·6. $C_9H_5N_3$ requires N, 27·1%).

6 : 7-*Dimethylquinoxaline*, plates [from light petroleum (b. p. 80—100°)], m. p. 100—101° (Found: N, 17·7. $C_{10}H_{10}N_2$ requires N, 17·7%).

6 : 7-*Benzoquinoxaline*, needles [from light petroleum (b. p. 60—80°)], m. p. 125—126°, steam-volatile (Found: N, 15·55. $C_{12}H_8N_2$ requires N, 15·55%).

6-*Chloro*-7-*methylquinoxaline*, needles [from light petroleum (b. p. 100—120°)], m. p. 120—122° (Found: N, 15·8. $C_9H_7N_2Cl$ requires N, 15·7%).

6-*Bromo*-7-*methylquinoxaline*, needles [from light petroleum (b. p. 100—120°)], m. p. 127—128° (Found: N, 12·2. $C_9H_7N_2Br$ requires N, 12·55%).

6 : 7-*Dichloroquinoxaline*, laminæ [from light petroleum (b. p. 100—120°)], m. p. 210° (Found: C, 48·3; H, 2·0; N, 14·2. $C_8H_4N_2Cl_2$ requires C, 48·2; H, 2·0; N, 14·1%).

5 : 8-*Dichloroquinoxaline*, needles [from light petroleum (b. p. 100—120°)], m. p. 205—207° (Found: N, 13·9%).

5-Chloroquinoxaline and 6-iodoquinoxaline were also made in poor yield from 5- and 6-aminoquinoxaline by the Sandmeyer reaction.

6-*Bromoquinoxaline*. 6-Aminoquinoxaline (14·5 g.) in 10% hydrobromic acid (60 c.c.) was added to a stirred mixture of 48% hydrobromic acid (40 c.c.), ice (200 g.), and saturated sodium nitrite solution (from 10 g. of sodium nitrite). After 5 min. sulphamic acid was added to destroy nitrous acid, and the solution was added to an ice-cold solution of cuprous bromide (17 g.) in 48% hydrobromic acid (50 c.c.). After 16 hr. the mixture was heated at 100° for 1 hr. made alkaline, and steam-distilled. 6-*Bromoquinoxaline* (5·6 g.) was isolated from the distillate by extraction with benzene and distillation, and had b. p. 146—149°/18 mm., f. p. 48—49° (Found: N, 13·5. $C_8H_5N_2Br$ requires N, 13·4%).

6-*Acetamidoquinoxaline* (first made in these laboratories by Dr. A. F. Crowther). 6-Aminoquinoxaline (Hinsberg, *Annalen*, 1887, **237**, 345) (15 g.), acetic anhydride (13·5 c.c.), and benzene (200 c.c.) were boiled under reflux for 1·5 hr., and the *product* (18·1 g.; m. p. 196°) was collected when cold. It formed pale cream needles, m. p. 196·5°, from water (Found: C, 64·05; H, 5·05; N, 22·55. $C_{10}H_9ON_3$ requires C, 64·2; H, 4·7; N, 22·5%). 5-Acetamidoquinoxaline was made similarly from 5-aminoquinoxaline (Jensen, *Acta Chem. Scand.*, 1948, **2**, 91).

N-6-*Quinoxalylsuccinamic acid*. 6-Aminoquinoxaline (12·6 g.), succinic anhydride (8·7 g.), and dry toluene (400 c.c.) were boiled under reflux for 10 min., then cooled, and the toluene was decanted. The solid residue was extracted with 10% sodium carbonate solution (100 c.c.) and the filtered extract was acidified with hydrochloric acid. The *product* separated slowly as a red-brown solid [9·7 g.; m. p. 216—217° (decomp.)] which gave light brown crystals, m. p. 217°, from glacial acetic acid (Found: C, 58·5; H, 4·5; N, 17·2. $C_{12}H_{11}O_3N_3$ requires C, 58·8; H, 4·5; N, 17·1%).

N-*Oxides*.—*Quinoxaline* 1-*oxide*. Quinoxaline (32·5 g., 0·25 mole) and 1·2M-peracetic acid (210 c.c., 0·25 mole) were heated overnight at 50°, and the mixture was poured on ice (600 g.), neutralised with 40% sodium hydroxide solution, and extracted with chloroform. The dried (Na_2SO_4) extract was evaporated and the residue crystallised from *cyclo*hexane, giving *quinoxaline* 1-*oxide* (II) as colourless needles (20 g.), m. p. 122—123° (Found: C, 66·1; H, 4·1; N, 19·4. $C_8H_6ON_2$ requires C, 65·75; H, 4·1; N, 19·2%).

Quinoxaline 1 : 4-*dioxide* (I). Quinoxaline (50 g.) and 1·2M-peracetic acid (1 l.) were heated overnight at 50°, a slightly exothermic reaction being observed at first. The mixture was evaporated at 10—15 mm. on the water-bath to about 200 c.c., poured on ice (500 g.), and neutralised with 40% aqueous sodium hydroxide, care being taken to avoid excess of this reagent. The precipitate (40—50 g.) was collected and washed with water, and the mother-liquor was extracted with chloroform to recover a further 9 g. of crude quinoxaline 1 : 4-dioxide.

Two crystallisations from ethanol gave golden-yellow needles (30—39 g.), m. p. 241—243° (Found: C, 59·2; H, 4·0; N, 17·3. Calc. for $C_8H_6O_2N_2$: C, 52·25; H, 3·7; N, 17·3%). (Note: the m. p.s of quinoxaline dioxides are greatly depressed if the samples are heated slowly, or are kept for any length of time at an elevated temperature.)

Oxidation of 5-methylquinoxaline. (*a*) 5-Methylquinoxaline (7·2 g.) and 1·2M-peracetic acid (200 c.c.) were heated overnight at 50°, diluted with ice (300 g.), and neutralised with 40% aqueous sodium hydroxide. The precipitated *5-methylquinoxaline 1-oxide* (4·6 g.) was collected, extraction of the mother-liquor with chloroform yielding a further 1·7 g.; it crystallised from light petroleum (b. p. 100—120°) in colourless needles of the *hydrate*, becoming reddish-orange on exposure to light (see Table 1). (*b*) 5-Methylquinoxaline (7·2 g.) and concentrated peracetic acid (20 c.c. of 10M or 30 c.c. of 6·5M) were heated to 50° and then cooled in ice to control the violent exothermic reaction. The mixture was then heated overnight at 50°, cooled, neutralised with 40% aqueous sodium hydroxide and ice, and filtered from 5-methylquinoxaline 1-oxide (2·7 g.). The filtrate was extracted with chloroform, and the dried (Na_2SO_4) extract evaporated. The residue was extracted with boiling *cyclo*hexane to remove monoxide (0·5 g.), and the undissolved *5-methylquinoxaline 1 : 4-dioxide* (0·2 g.) was crystallised from ethanol (see Table 1).

TABLE 1. *N-Oxides of substituted quinoxalines.*

Substituent	Degree of oxidation	Formula	M. p.	Found, % C	Found, % H	Found, % N	Required, % C	Required, % H	Required, % N
5-Me	Mono	$C_9H_8ON_2,H_2O$	131—132°	—	—	15·7 [a]	—	—	15·7
	Di	$C_9H_8O_2N_2$	192—194	61·1	4·5	15·6	61·36	4·55	15·9
6-Me	Di	$C_9H_8O_2N_2$	218—219	61·4	4·5	15·7	61·36	4·55	15·9
6 : 7-Me_2	Di	$C_{10}H_{10}O_2N_2$	220	63·0	5·4	14·7	63·16	5·25	14·7
5 : 6-Benzo	Mono	$C_{12}H_8ON_2$	158—159	—	—	14·8	—	—	14·3
	Di	$C_{12}H_8O_2N_2$	215—216	67·8	4·0	13·0	67·9	3·8	13·2
5 : 6-7 : 8-Dibenzo	Mono	$C_{16}H_{10}ON_2$	243—244	77·1	4·1	10·7	78·0	4·05	11·4
5-MeO	Di	$C_9H_8O_3N_2$	222	56·5	4·4	14·8	56·2	4·2	14·6
5-EtO	Mono	$C_{10}H_{10}O_2N_2$	114—116	63·1	5·3	14·5	63·16	5·25	14·7
6-MeO	Di	$C_9H_8O_3N_2$	227—228 [b]	56·2	4·3	15·3	56·2	4·2	14·6
6-EtO	Di	$C_{10}H_{10}O_3N_2$	192—194	57·6	4·95	13·75	58·25	4·85	13·6
5 : 6-$(MeO)_2$	Mono	$C_{10}H_{10}O_3N_2$	138—140	57·95	5·0	13·8	58·25	4·85	13·6
	Di	$C_{10}H_{10}O_4N_2$	220—222	53·8	4·8	12·55	54·0	4·5	12·6
6 : 7-$(MeO)_2$	Di	$C_{10}H_{10}O_4N_2$	264—265 [c]	55·0	4·6	12·5	54·0	4·5	12·6
2-Cl	Mono	$C_8H_5ON_2Cl$	150—152	53·1	3·0	15·7	53·2	2·8	15·5
5-Cl	Mono	$C_8H_5ON_2Cl$	177—179	51·7	2·7	15·4	53·2	2·8	15·5
6-Cl	Mono	$C_8H_5ON_2Cl$	151—152	53·5	2·8	15·2	53·2	2·8	15·5
	Di	$C_8H_5O_2N_2Cl$	211—212	49·5	2·5	14·0	48·85	2·5	14·3
6-Br	Di	$C_8H_5O_2N_2Br$	223—225	39·7	2·0	11·7	39·9	2·1	11·6
6 : 7-Cl_2	Di	$C_8H_4O_2N_2Cl_2$	206—208	42·1	1·7	12·7	41·55	1·7	12·1
6-Cl-7-Me	Mono	$C_9H_7ON_2Cl$	166—168	—	—	14·1	—	—	14·4
	Di	$C_9H_7O_2N_2Cl$	227	51·45	3·45	13·0	51·3	3·3	13·3
6-Br-7-Me	Mono	$C_9H_7ON_2Br$	167—168	45·25	2·95	11·6	45·2	2·9	11·7
	Di	$C_9H_7O_2N_2Br$	222—224	42·35	3·0	10·45	42·3	2·75	11·0
5-NHAc	Mono	$C_{10}H_9O_2N_3$	175—178	59·0	4·6	20·3	59·1	4·4	20·7
	Di?	—	230—232	Insufficient for analysis					
6-NHAc	Di	$C_{10}H_9O_3N_3$	245—247	54·8	4·2	18·9	54·8	4·1	19·2
[d]	Di	$C_{12}H_{11}O_5N_3$	242—244	52·1	3·9	14·8	52·0	4·0	15·2

[a] Loss at 100°/0·05 mm., 10%. $1H_2O$ requires 10·1%. [b] Lit., m. p. 207—210° (decomp.). [c] Lit., decomp. at *ca.* 250°. [d] Substituent, 6-$HO_2C{\cdot}[CH_2]_2{\cdot}CO{\cdot}NH$.

Oxidation of 6-chloroquinoxaline. (*a*) 6-Chloroquinoxaline (8·2 g.), glacial acetic acid (200 c.c.), and 30% hydrogen peroxide (50 c.c.) were heated at 50° overnight, cooled, and filtered from 6-chloro-2 : 3-dihydroxyquinoxaline (3 g.). The filtrate was neutralised with 40% aqueous sodium hydroxide and ice, and was extracted with chloroform. Evaporation of the dried (Na_2SO_4) extract gave crude *6-chloroquinoxaline mono-N-oxide* (1·1 g.; m. p. 115°) which was crystallised repeatedly from ethanol (see Table 1). (*b*) Crude 6-chloroquinoxaline mono-*N*-oxide (2·6 g.) and 1·2M-peracetic acid (20 c.c.) were heated at 50° overnight, poured on ice (100 g.), and neutralised with 40% sodium hydroxide solution. The precipitated *6-chloroquinoxaline 1 : 4-dioxide* was collected, washed with water, and crystallised from ethanol. (*c*) 6-Chloroquinoxaline (3·1 g.), anhydrous formic acid (60 c.c.) (or 32 c.c. of 85% formic acid and 26 c.c. of acetic anhydride) and 30% hydrogen peroxide (20 c.c.) were heated cautiously to 40—50°, and the vigorous exothermic reaction was controlled by cooling to prevent the temperature exceeding 60°. When the reaction abated the mixture was heated at 50° overnight, cooled, filtered from 6-chloro-2 : 3-dihydroxyquinoxaline (0·8 g.), and evaporated at 15—20 mm.

to about 20 c.c. Neutralisation with 40% aqueous sodium hydroxide and ice precipitated crude di-*N*-oxide (1·75 g.).

Oxidation of 5 : 6-*benzoquinoxaline.* (*a*) 5 : 6-Benzoquinoxaline (9 g.), anhydrous formic acid (150 c.c.), and 30% hydrogen peroxide (50 c.c.) were heated at 50° overnight (the initial exothermic reaction being controlled by cooling), poured into ice-water (500 c.c.), and filtered from 5 : 6-*benzoquinoxaline* 1-*oxide* (V), (8·9 g.). The filtrate was neutralised at 0—10° with 40% sodium hydroxide solution and extracted with chloroform. The dried extract was evaporated, the residue was extracted with boiling light petroleum (30 c.c.; b. p. 100—120°) to remove 5 : 6-benzoquinoxaline 1-oxide, and the undissolved 5 : 6-*benzoquinoxaline* 1 : 4-*dioxide* (0·15 g.) was crystallised from ethanol (see Table 1). (*b*) (V) (7·2 g.) and 1·2M-peracetic acid (60 c.c.) were heated at 60° for 96 hr., further additions of peracetic acid (16 c.c. each) being made after 24 and 48 hr., and the mixture was then concentrated under reduced pressure and neutralised (pH 7·0) with sodium hydroxide solution and ice. The precipitated solid (5·9 g.) was extracted with light petroleum (b. p. 100—120°) to remove (V), and the residue was crystallised from ethanol, giving 5 : 6-benzoquinoxaline 1 : 4-dioxide (0·45 g.).

Details of substituted quinoxaline *N*-oxides prepared by the foregoing methods are given in Table 1. In all cases the preparation of di-*N*-oxides was attempted, and mono-*N*-oxides were isolated only when they were obtained in such experiments. Table 2 gives the yields of crude 2 : 3-dihydroxyquinoxalines obtained as by-products in these oxidations; the 2 : 3-dichloro-derivatives were obtained by boiling the 2 : 3-dihydroxy-compounds (1 g.) with phosphoryl chloride (5 g.) and dimethylaniline (0·5—1 g.) for 0·5—4 hr., pouring on ice, and crystallising the solid from light petroleum.

1-*Methylquinoxalinium iodide* 4-*oxide.* (*a*) The oxide (II) (2 g.) and methyl iodide (4 c.c.) in acetonitrile (20 c.c.) were set aside in the dark. After 36 hr. the product (0·5 g.) was filtered off; the mother-liquors slowly deposited more (1·5 g.). The *iodide* crystallised from ethanol in brown laminæ, m. p. 188—189° (Found: C, 38·0; H, 3·5; N, 9·6; I, 43·2. $C_9H_9ON_2I$ requires C, 37·5; H, 3·1; N, 9·7; I, 44·1%). (*b*) The oxide (II) (1·5 g.) and methyl iodide (1·5 c.c.) were mixed in a stoppered vessel protected from light. The mixture became brown and after 1 month the product was crystallised twice from ethanol (yield 1·5 g.; m. p. 187—188°).

TABLE 2. *Oxidation of quinoxalines to* 2 : 3-*dihydroxy-derivatives by peracetic or performic acid.*

Substituent	2 : 3-Dihydroxy-compounds, approx. yield (%)	2 : 3-Dichloroquinoxalines			
		Formula	M. p.	N, found, %	N, reqd., %
6-Me	1	$C_9H_6N_2Cl_2$	112° [a]	—	—
5-Cl	30	$C_8H_3N_2Cl_3$	142—143	12·2	12·0
6-Cl	15—30	$C_8H_3N_2Cl_3$	144 [b]	—	—
6-Br	28	$C_8H_3N_2Cl_2Br$	132 [c]	—	—
5 : 8-Cl_2	65	$C_8H_2N_2Cl_4$	160—161	10·7	10·45
6 : 7-Cl_2	43	$C_8H_2N_2Cl_4$	170—170·5	10·0	10·45
6-Cl, 7-Me	10	$C_9H_5N_2Cl_3$	172—173	11·4	11·3
6-Br, 7-Me	12—16	$C_9H_5N_2Cl_2Br$	160—161	9·5	9·6
6-CN	50	—	—	—	—
6-NO_2	60	$C_8H_3O_2N_3Cl_2$	150 [d]	—	—

Recorded m. p.s (*a*) 114°, (*b*) 143—144°, (*c*) 132°, (*d*) 152°.

Reaction of Phosphoryl Chloride with Quinoxaline N-*Oxides.*—(*a*) The oxide (II) (2 g.) was added cautiously to phosphoryl chloride (10 c.c.). The vigorous exothermic reaction was controlled by cooling, and the mixture was then boiled under reflux for 15 min., poured on crushed ice (150 g.), and made strongly alkaline with potassium hydroxide solution (cooling in ice). The product was extracted with ether, and the dried (Na_2SO_4) extract evaporated. The residue (2·1 g.), dissolved in light petroleum (b. p. 40—60°), was decolorised by passage through alumina, and the solution was concentrated to yield white needles, m. p. 46—48°, undepressed by admixture with authentic 2-chloroquinoxaline. Under the same conditions, (I) gave 2 : 3-dichloroquinoxaline, and 5-methylquinoxaline 1-oxide gave 2-chloro-5-methylquinoxaline, m. p. 95°, identical with a sample made from *N*-(6-nitro-*o*-tolyl)glycine (Me = 2) (Platt and Sharp, *J.*, 1948, 2129).

(*b*) The oxide (V) (7·2 g.) and phosphoryl chloride (35 c.c.) were boiled under reflux for 15 min., cooled, poured on ice (300 g.), and made alkaline with potassium hydroxide. The product was washed with water and dried at 40°. The solid (7·8 g.; m. p. 86—98°) was dissolved in 3 : 1 light petroleum (b. p. 60—80°)–benzene and chromatographed on alumina,

giving 2-*chloro*-5 : 6-*benzoquinoxaline* (4·4 g.), m. p. 120·5° (Found : C, 66·9; H, 3·3; N, 12·2. $C_{12}H_7N_2Cl$ requires C, 67·1; H, 3·25; N, 13·05%). Further elution of the alumina with 1 : 1 light petroleum–benzene gave a *chloro*-5 : 6-*benzoquinoxaline* (1·8 g.), m. p. 104—104·5° (Found : C, 67·1; H, 3·5; N, 12·3%).

2-*Chloro*-7 : 8-*benzoquinoxaline*. Ethyl 2-naphthylaminoacetate (7·7 g.), dissolved in ethanol (70 c.c.), was treated with a diazo-solution prepared from aniline (3·1 g.) in 2·5N-hydrochloric acid (30 c.c.) and sodium nitrite (2·4 g.) in water (7 c.c.), and then with sodium acetate trihydrate (1·6 g.). After 1 hour's stirring the product was collected, washed with 60% aqueous ethanol and with water, and crystallised from butanol, giving *ethyl* 1-*phenylazo*-2-*naphthylaminoacetate* (6·9 g.), red needles, m. p. 135—136° (Found : N, 12·1. $C_{20}H_{19}O_2N_3$ requires N, 12·6%). This compound (42 g.) in ethanol (500 c.c.) was hydrogenated over Raney nickel at 60°/50 atm., and evaporation of the resulting solution and extraction of the catalyst sludge with acetone gave 1 : 2 : 3 : 4-*tetrahydro*-2-*oxo*-7 : 8-*benzoquinoxaline* (20·5 g.), m. p. 197—198° (Found : C, 73·0; H, 5·2; N, 14·5. $C_{12}H_{10}ON_2$ requires C, 72·7; H, 5·05; N, 14·1%). This was dissolved in hot alkaline hydrogen peroxide (250 c.c. of 0·5N-sodium hydroxide and 60 c.c. of 6% hydrogen peroxide), and the solution was clarified with carbon, diluted to 500 c.c., and acidified with acetic acid, to precipitate 2-hydroxy-7 : 8-benzoquinoxaline (17·5 g.), which crystallised from dioxan as a *hydrate*, m. p. 275—275·5° (Found : C, 66·6; H, 4·2; N, 13·1. $C_{12}H_8ON_2,H_2O$ requires C, 67·3; H, 4·66; N, 13·1%). The hydroxy-compound (21 g.) and phosphoryl chloride (105 c.c.) were refluxed for 45 min. and poured on ice. The aqueous layer was decanted and the residue was treated with ice and potassium hydroxide solution until alkaline, filtered, and washed with water. Crystallisation of the dried solid from light petroleum (b. p. 80—100°) gave 2-*chloro*-7 : 8-*benzoquinoxaline* (15·1 g.) as pale yellow needles, m. p. 128—129° (Found : C, 67·3; H, 3·8; N, 12·1. $C_{12}H_7N_2Cl$ requires C, 67·1; H, 3·25; N, 13·05%).

1 : 2 : 3 : 4-*Tetrahydro*-5-*methyl*-2-*oxoquinoxaline*. *N*-(6-Nitro-*o*-tolyl)glycine (Me = 2) (4·6 g.) in ethanol (100 c.c.) was hydrogenated over Raney nickel at 60°/60 atm. Evaporation of the filtered solution and crystallisation from benzene gave the *product* (1·7 g.) as colourless needles, m. p. 177—180° (Found : C, 66·6; H, 6·3; N, 17·3. $C_9H_{10}ON_2$ requires C, 66·67; H, 6·16; N, 17·3%), which were readily oxidised to 2-hydroxy-5-methylquinoxaline, m. p. 282—283°.

2-*Piperidino*-7 : 8-*benzoquinoxaline*. 2-Chloro-7 : 8-benzoquinoxaline (1·5 g.) and piperidine (5 c.c.) were boiled under reflux for 1·5 hr., cooled, and diluted with water (25 c.c.) The *product* was collected, washed with water, dried, and crystallised from light petroleum (b. p. 60—80°), giving orange-yellow prisms (1·45 g.), m. p. 101·5—102·5° (Found : C, 77·8; H, 6·7; N, 15·9. $C_{17}H_{17}N_3$ requires C, 77·56; H, 6·45; N, 15·97%).

2-*Piperidino*-5 : 6-*benzoquinoxaline*, prepared similarly from 2-chloro-5 : 6-benzoquinoxaline, was purified by chromatography (benzene–light petroleum; alumina) and formed lemon-yellow rhombic prisms, m. p. 124—125° (Found : C, 77·9; H, 6·5; N, 15·7%).

Dichloro-5 : 6-*benzoquinoxaline*. Chlorine was passed slowly into 5 : 6-benzoquinoxaline (2·3 g.), dissolved in glacial acetic acid (10 c.c.), during 1 hr., and the solution was filtered from 5 : 6-benzoquinoxaline hydrochloride (0·2 g.) and diluted with water. The pasty precipitate was triturated with aqueous sodium carbonate and with water, and crystallised from benzene and then (twice) from *cyclo*hexane, to give a colourless *product*, m. p. 187—188° (Found : C, 57·9; H, 1·7; N, 11·0. $C_{12}H_6N_2Cl_2$ requires C, 57·8; H, 2·4; N, 11·25%).

3-*Hydroxy*-1-*methyl*-6- *or* -7-*nitroquinoxal*-2-*one*. 2 : 3-Dihydroxy-6-nitroquinoxaline (2·0 g.), 5% sodium hydroxide solution (115 c.c.), and methyl sulphate (5 c.c.) were stirred for 16 hr., and the sodium salt was collected after 48 hr., dissolved in boiling water (100 c.c.) (carbon), and precipitated with acetic acid. The *product* crystallised from dilute acetic acid as yellow crystals, m. p. 344° (Found : C, 48·7; H, 3·1; N, 18·8. $C_9H_9O_4N_3$ requires C, 48·87; H, 3·16; N, 19·0%).

Similarly, methylation of 6-cyano-2 : 3-dihydroxyquinoxaline (m. p. >360°) gave 6- or 7-*cyano*-3-*hydroxy*-1-*methylquinoxal*-2-*one*, colourless needles (from dilute acetic acid), m. p. 353—354° (Found : C, 59·3; H, 3·4; N, 20·6. $C_{10}H_7O_2N_3$ requires C, 59·7; H, 3·5; N, 20·9%).

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