403. *Quinoxaline* N-*Oxides. Part IV.* Derivatives of* Py-*Hydroxyalkyl-, -Aminoalkyl-, and -Carboxy-quinoxalines.*

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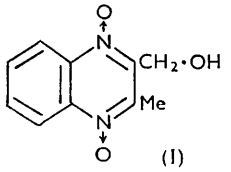
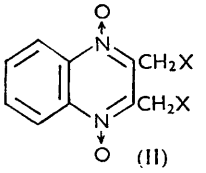
Quinoxaline *N*-oxides, bearing in the hetero-ring 1-hydroxyalkyl, bromomethyl, substituted aminoalkyl or carboxyl groups, and various functional derivatives of these groups, have been made in a search for compounds of improved antibacterial or antiprotozoal activity. Quinoxaline 1 : 4-dioxide and its 2-methyl and 2 : 3-dimethyl homologues formed bromine addition compounds, those from the homologues being converted into bromomethylquinoxaline dioxides.

A metabolite of 2 : 3-dimethylquinoxaline 1 : 4-dioxide with enhanced antibacterial activity has been identified as 2-hydroxymethyl-3-methylquinoxaline 1 : 4-dioxide (I),[1] and we have therefore prepared other quinoxaline di-*N*-oxides with hetero-ring substituents which might modify the pharmacological activity. 2-Hydroxymethylquinoxaline and 2-1′-hydroxyethyl-3-methylquinoxaline were obtained, as in the synthesis of the metabolite, by reduction of the corresponding carbonyl compounds, and after acetylation they were converted into the 1 : 4-dioxides by oxidation and hydrolysis. 2-Acetoxymethylquinoxaline (m. p. 49—51°) differs from the compound (m. p. 132—133°) prepared by Euler and Hasselquist[2] from acetylreductone and *o*-phenylenediamine. 2 : 3-Bishydroxymethylquinoxaline 1 : 4-dioxide was prepared by hydrolysis of the diacetoxy-compound obtained by treating 2 : 3-bisbromomethylquinoxaline 1 : 4-dioxide (II; X = Br) with silver acetate; it could not be obtained directly from the bromo-compound and silver oxide. 2-Ethoxymethylquinoxaline 1 : 4-dioxide was prepared from the known parent quinoxaline,[3] but the 3-methyl homologue gave no crystallisable product with peracetic or perphthalic acid, and 2-(1 : 2 : 3 : 4-tetra-acetoxybutyl)quinoxaline[4] resisted oxidation with peracetic acid.



(I)



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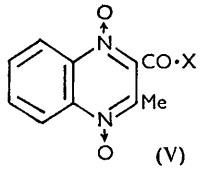

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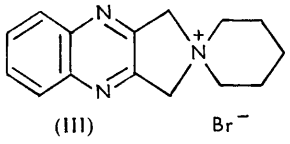

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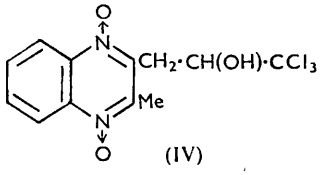

(IV)

2 : 3-Bisbromomethylquinoxaline 1 : 4-dioxide was a useful intermediate for the synthesis of bisaminomethyl derivatives. The parent quinoxaline was prepared from 1 : 4-dibromobutane-2 : 3-dione and *o*-phenylenediamine;[5] bromination of 2 : 3-dimethylquinoxaline in acetic acid afforded only 2 : 3-bisdibromomethylquinoxaline,[6] and, although the 2 : 3-bisbromomethyl compound was obtained by bromination in chloroform, the method was not reliable. Moreover, attempts to reduce the tetrabromo-compound with stannous bromide

* Part III, *J.*, 1953, 2830.

[1] Francis, Landquist, Levi, Silk, and Thorp, *Biochem. J.*, 1956, **63**, 455.
[2] Euler and Hasselquist, *Rec. Trav. chim.*, 1950, **69**, 402.
[3] Bradshaw, Stephen, and Weizman, *J.*, 1915, **107**, 810.
[4] Ohle, *Ber.*, 1934, **67**, 155.
[5] Wegmann and Dahn, *Helv. Chim. Acta*, 1946, **29**, 95.
[6] Bennett and Willis, *J.*, 1928, 1973.

or hydrogen and Adams's catalyst, or by heating it with *cyclo*hexane, tetralin, or 2 : 3-dimethylquinoxaline gave only dark oils or tars. It was also resistant to oxidation by peracetic acid.

With bromine in chloroform 2 : 3-dimethylquinoxaline 1 : 4-dioxide gave initially an unstable addition compound; this decomposed spontaneously into a mixture of products from which 2 : 3-bisbromomethylquinoxaline 1 : 4-dioxide was isolated in low yield. Quinoxaline 1 : 4-dioxide and the 2-methyl homologue formed more stable addition compounds which analysed as sesquibromides. 2-Methylquinoxaline 1 : 4-dioxide sesquibromide when heated in ethyl acetate brominated the solvent with regeneration of the dioxide, and when heated in chloroform gave a small yield of a bromo-derivative which is regarded as 2-bromomethylquinoxaline 1 : 4-dioxide. Quinoxaline 1 : 4-dioxide sesquibromide liberated bromine when boiled with water.

2 : 3-Bisaminomethylquinoxaline 1 : 4-dioxides (II; X = NR_2) were obtained when the bisbromomethyl compound was treated with dimethylamine, piperidine, aniline, or *p*-chloroaniline, in suitable solvents; trimethylamine, pyridine, and hexamine gave the bisquaternary salts (II; X = $\overset{+}{N}R_3$ Br^-) and thiourea gave a bisthiuronium salt [II; X = $SC(:NH)\cdot NH_2$]. Several of these compounds were too unstable for them to be recrystallised to analytical purity. An interesting property of 2 : 3-bispiperidinomethylquinoxaline 1 : 4-dioxide was the partly reversible purple coloration on exposure to light; after exposure the blue component of the colour faded in the dark, leaving a brown colour like that shown (after very much longer exposure) by most quinoxaline dioxides. When the hexamine compound was treated with dilute hydrochloric acid or aqueous hydroxylamine, or the thiuronium salt with alkali in presence or in absence of methyl sulphate, gross decomposition appeared to take place, giving dark red products which were not characterised. Similar red mixtures which did not yield the desired derivatives were formed when 2 : 3-bisbromomethylquinoxaline 1 : 4-dioxide was treated with ammonia, ethylamine, *iso*propylamine, benzylamine, ethylenediamine, or hydrazine in alcohol or dioxan solution. There was no reaction with ethanolamine or *p*-nitroaniline at ordinary temperatures. The reaction of piperidine with 2 : 3-bisbromomethylquinoxaline gave under appropriate conditions both 2 : 3-bispiperidinomethylquinoxaline and the *spiro*-quaternary salt (III) which would be formed from 2-bromomethyl-3-piperidinomethylquinoxaline by intramolecular quaternisation.

Despite the lack of reactivity of 2 : 3-dimethylquinoxaline 1 : 4-dioxide towards *p*-dimethylaminobenzaldehyde,[7] some reactions characteristic of activated methyl groups were found. A Mannich reaction with piperidine under suitable conditions gave 2 : 3-bis-2′-piperidinoethylquinoxaline 1 : 4-dioxide (II; X = $CH_2\cdot NC_5H_{10}$) and chloral gave a derivative (IV). Neutral formalin at 120° gave a dark oil, which evolved heat when mixed with piperidine, but neither the oil nor its reaction product was characterised. Attempted condensation with ethyl oxalate in presence of potassium ethoxide was unsuccessful.

By prolonging the period of oxidation it was possible to convert ethyl 3-methylquinoxaline-2-carboxylate[8] into the dioxide, whereas under the usual conditions the principal product was a monoxide, as might be expected with the electronegative ester group adjacent to a heteroatom; Yelina and Magidson[9] likewise obtained only the 4-oxide from ethyl quinoxaline-2-carboxylate. The ester dioxide was converted into the acid, the amide, and the hydroxamic acid, but decomposition accompanied its reactions with diethylamine and *iso*propylamine. Hydrazine reacted with evolution of nitrogen to give a mono-*N*-oxide; it is likely that the $N_{(1)}$-oxygen is less firmly bonded than that at $N_{(4)}$, and this product is believed to be 3-methylquinoxaline-2-carboxyhydrazide 4-oxide. Ethyl 3-methylquinoxaline-2-carboxylate was also converted into the amide, hydroxamic acid, and hydrazide.

Oxidation of 2 : 3-bis-*p*-tolylthioquinoxaline (from 2 : 3-dichloroquinoxaline and toluene-*p*-thiol) with performic acid gave 2 : 3-dihydroxyquinoxaline and toluene-*p*-sulphonic acid.

[7] Landquist and Stacey, *J.*, 1953, 2822.
[8] Wahl and Doll, *Bull. Soc. chim. France*, 1913, **13**, 469.
[9] Yelina and Magidson, *Zhur. obshchei Khim.*, 1955, **25**, 161.

Experimental

1-Ethoxy-3-hydroxyiminobutan-2-one.—Ethyl γ-ethoxy-α-methylacetoacetate[3] (84 g.), water (960 c.c.), and potassium hydroxide (31·5 g.) were stirred overnight in a closed flask. Sodium nitrite (39 g.), dissolved in water (126 c.c.), was added and the solution was cooled in ice and acidified at <10° by dropwise addition of 20% sulphuric acid. After 30 min. the mixture was made alkaline (Brilliant-yellow) with sodium hydroxide and extracted with ether. The ether was washed with N-sodium hydroxide until the extract was no longer yellow. The combined aqueous solutions were cooled, acidified, and extracted with ether, and the extract was washed with water, dried (Na_2SO_4), and evaporated to yield *1-ethoxy-3-hydroxyiminobutan-2-one* (57·7 g.), thin platelets, m. p. 87—88° [from light petroleum (b. p. 40—60°)] (Found : N, 10·2. $C_6H_{11}O_3N$ requires N, 9·65%).

2-Ethoxymethyl-3-methylquinoxaline.—*o*-Phenylenediamine (42·5 g.), 1-ethoxy-3-hydroxyiminobutan-2-one (57 g.), and 10% acetic acid (600 c.c.) were heated on the steam-bath for 1·5 hr., made alkaline with sodium hydroxide, and steam-distilled until the distillate no longer became turbid with concentrated sodium hydroxide solution. The distillate was saturated with salt and extracted with ether. Distillation of the dried (Na_2SO_4) extract gave the pale yellow *quinoxaline* (36·9 g.), b. p. 126—128°/2 mm. (Found : N, 14·5. $C_{12}H_{14}ON_2$ requires N, 13·9%).

Quinoxaline-2-aldehyde.—2-Methylquinoxaline (26 g.), freshly prepared selenium dioxide (26 g.), and ethyl acetate (300 c.c.) were stirred and refluxed for 4 hr., cooled, and filtered. The solvent was distilled off under reduced pressure and the residue was extracted with ether. The solid (23·4 g.) recovered from the ether was crystallised from light petroleum (b. p. 60—80°), giving the aldehyde (16·25 g.), m. p. 108—109°.

2-Hydroxymethylquinoline.—Quinoxaline-2-aldehyde (6·7 g.), formalin (13 c.c.), and 25% potassium hydroxide solution (50 g.) were shaken for 3 hr., cooled, and extracted with ether (4 × 100 c.c.). The extract was dried (Na_2SO_4) and evaporated, and the oily residue (4·0 g.) was rubbed with light petroleum. The crude *2-hydroxymethylquinoxaline*, m. p. 75—76°, was unstable and was best used without purification. It was crystallised from light petroleum (b. p. 60—80°), forming needles, m. p. 79—81°, which darkened rapidly on exposure to air (Found : C, 67·3; H, 5·0; N, 18·2. $C_9H_8ON_2$ requires C, 67·5; H, 5·0; N, 17·5%).

2-Acetoxymethylquinoxaline.—2-Hydroxymethylquinoxaline (1·2 g.) in dry pyridine (2·5 c.c.) was treated with acetic anhydride (1·25 c.c.). After 18 hr. the mixture was poured into water (35 c.c.), left for 1 hr. at room temperature, made faintly acid (pH 5—6) with hydrochloric acid, and extracted with ether (3 × 50 c.c.). The extract was washed successively with N-hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and evaporated, leaving *2-acetoxymethylquinoxaline* (0·9 g.; m. p. 48—50°), needles, m. p. 49—51° [from light petroleum (b. p. 40—60°)] (Found : C, 65·1; H, 4·5; N, 14·0. $C_{11}H_{10}O_2N_2$ requires C, 65·3; H, 4·95; N, 13·9%).

2-1′-Hydroxyethyl-3-methylquinoxaline.—2-Acetyl-3-methylquinoxaline (9·3 g.), aluminium *iso*propoxide (10·2 g.), and dry propan-2-ol (70 c.c.) were stirred and refluxed under a 9″ ring-packed column fitted with a Hahn condenser, about 5 drops per minute being allowed to distil. Most of the acetone distilled off in 2 hr. After 5 hr. the bulk of the solvent was distilled off under reduced pressure, and the residue was cooled, treated with 2N-hydrochloric acid (110 c.c.), and filtered. The filtrate was made alkaline with sodium hydroxide and extracted with benzene. Evaporation of the dried (Na_2SO_4) extract gave *2-1′-hydroxyethyl-3-methylquinoxaline* (6·7 g.; m. p. 76—78°), needles, m. p. 80·5—81° [from light petroleum (b. p. 60—80° and then b. p. 40—60°)] (Found : C, 70·1; H, 6·7; N, 15·6. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%).

2-1′-Acetoxyethyl-3-methylquinoxaline.—2-1′-Hydroxyethyl-3-methylquinoxaline (9·4 g.), acetylated with acetic anhydride (10 c.c.) in pyridine (20 c.c.) as described above, gave the *acetyl derivative* (9·7 g.), large prisms [from light petroleum (b. p. 40—60°)], m. p. 56—57° (Found : N, 12·4. $C_{13}H_{14}O_2N_2$ requires N, 12·2%).

2-Ethoxymethylquinoxaline 1 : 4-Dioxide.—2-Ethoxymethylquinoxaline (10 g.) and 1·2M-peracetic acid (120 c.c.) were heated overnight at 50°, evaporated to small bulk under reduced pressure, diluted with ice and water, and neutralised with sodium hydroxide solution. The precipitate was washed with water, the filtrates were extracted with chloroform, and the extract was dried and evaporated. The combined crude products were crystallised from *cyclo*hexane and then twice from methanol, yielding *2-ethoxymethylquinoxaline 1 : 4-dioxide*, m. p. 134° (Found : C, 59·9; H, 5·2; N, 12·95. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·45; N, 12·7%).

The following were made similarly :

2-*Acetoxymethylquinoxaline* 1 : 4-*dioxide* (yield 40%), m. p. 188—189° from ethanol (Found : C, 56·9; H, 5·0; N, 11·6. $C_{11}H_{10}O_4N_2$ requires C, 56·3; H, 4·3; N, 12·0%).

2 : 3-*Bisbromomethylquinoxaline* 1-*oxide*, yellow laminae, m. p. 167—168°, from ethanol (Found : C, 36·6; H, 2·5; N, 9·0; Br, 46·7. $C_{10}H_8ON_2Br_2$ requires C, 36·1; H, 2·4; N, 8·4; Br, 48·2%).

2-1′-*Acetoxyethyl*-3-*methylquinoxaline* 1(?)-*oxide*, needles, m. p. 100°, from light petroleum (b. p. 80—100°) (Found : C, 64·0; H, 5·6; N, 11·8. $C_{13}H_{14}O_3N_2$ requires C, 63·4; H, 5·7; N, 11·4%). Prolonged oxidation of 2-1′-acetoxyethyl-3-methylquinoxaline or its mono-*N*-oxide with 1·2M-peracetic acid (18 hr. at 50°, then 72 hr. at 60°) gave 2-1′-*acetoxyethyl*-3-*methylquinoxaline* 1 : 4-*dioxide*, yellow crystals, m. p. 135°, from ethyl acetate (Found : C, 59·6; H, 5·1; N, 10·2. $C_{13}H_{14}O_4N_2$ requires C, 59·5; H, 5·3; N, 10·7%).

2-*Hydroxymethylquinoxaline* 1 : 4-*Dioxide*.—2-Acetoxymethylquinoxaline 1 : 4-dioxide (3 g.) and 2N-hydrochloric acid (100 c.c.) were refluxed for 15 min., cooled in ice, neutralised with sodium hydroxide solution (to pH 7·0), and extracted with ether. The dried (Na_2SO_4) extract was evaporated and the residue crystallised from ethanol giving pale yellow needles of 2-*hydroxymethylquinoxaline* 1 : 4-*dioxide*, m. p. 191—192° (when heated rapidly) (Found : C, 56·5; H, 4·5; N, 14·1. $C_9H_8O_3N_2$ requires C, 56·2; H, 4·2; N, 14·6%).

2-1′-*Hydroxyethyl*-3-*methylquinoxaline* 1 : 4-*dioxide*, obtained similarly by hydrolysis of the acetoxy-compound (yield 80%), crystallised from methanol in yellow prisms, m. p. 161° (Found : C, 60·1; H, 5·8; N, 12·6. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·45; N, 12·7%).

2 : 3-*Bisbromomethylquinoxaline* 1 : 4-*Dioxide*.—2 : 3-Bisbromomethylquinoxaline (70 g.) was stirred with 2M-peracetic acid (320 c.c.) at 55—60° for 60 hr., more per-acid (160 c.c.) being added after 24 hr. The mixture was cooled, and the *dioxide* (61·5 g.), m. p. 191—194°, washed with acetic acid and dried at 100°. Recrystallisation from dioxan raised the m. p. to 193—194° (Found : C, 34·7; H, 2·3; N, 8·0; Br, 46·3. $C_{10}H_8O_2N_2Br_2$ requires C, 34·5; H, 2·3; N, 8·05; Br, 46·0%). This dioxide was also obtained by oxidation of the quinoxaline with performic acid.

Bromination of Quinoxaline 1 : 4-*Dioxides*.—(*a*) A solution of bromine (1·65 g.) in carbon tetrachloride (1 c.c.) was added to a solution of 2 : 3-dimethylquinoxaline 1 : 4-dioxide (1·9 g.) in chloroform (4 c.c.); the red addition compound separated. This dissolved when the mixture was refluxed for 10 min. and a yellow solid separated. Treatment with sodium hydrogen carbonate solution and extraction with chloroform gave a yellow solid (1·15 g.), m. p. 140—145°. Four crystallisations from dioxan raised the m. p. to 188—189°, not depressed by the bromo-compound (II; X = Br), prepared as described above.

(*b*) Quinoxaline 1 : 4-dioxide (4·05 g.), dissolved in chloroform (250 c.c.), was treated during 45 min. with bromine (4·0 g.) in chloroform (10 c.c.). Soon after the addition was complete platelets of the *sesquibromide* began to crystallise. The product (6·1 g.) was filtered off after several hours and washed with chloroform. The m. p. (142—143°) was not raised on crystallisation from chloroform (Found : C, 34·8; H, 2·6; N, 9·6; Br, 39·2. $2C_8H_6O_2N_2$,3Br requires C, 34·0; H, 2·1; N, 9·9; Br, 42·5%).

(*c*) 2-Methylquinoxaline 1 : 4-dioxide (4·4 g.), dissolved in chloroform (40 c.c.), was stirred and treated during 1 hr. with bromine (4·0 g.) in chloroform (10 c.c.); yellow crystals separated. Next morning, the *sesquibromide* (6·8 g.) was collected and washed with chloroform. The product melted at 126—128°, not changed on crystallisation from chloroform or benzene, but changing to m. p. 184° (decomp.) on storage for six weeks (Found : C, 36·45; H, 2·55; N, 9·8; Br, 39·5. $2C_9H_8O_2N_2$,3Br requires C, 36·5; H, 2·7; N, 9·45; Br, 40·5%). The sesquibromide (0·5 g.) was boiled for 5 min. with ethyl acetate (5 c.c.), cooled, and filtered. The solvent had become lachrymatory. The solid (0·46 g.) was dissolved in water (ionic bromine present), made alkaline with sodium carbonate, and extracted with chloroform. 2-Methylquinoxaline 1 : 4-dioxide was recovered on evaporation of the chloroform.

(*d*) 2-Methylquinoxaline 1 : 4-dioxide (3·3 g.) in chloroform (40 c.c.) was stirred and treated with bromine (3 g.) in chloroform (10 c.c.). The mixture was refluxed for 5 hr., and the initial precipitate partly redissolved. The solvent was removed by evaporation and the solid was suspended in ice–water (140 c.c.), the suspension made alkaline with sodium carbonate, and the solid filtered off and washed with water. Crystallisation from benzene gave 2-*bromomethylquinoxaline* 1 : 4-*dioxide* (0·5 g.), m. p. 163° (Found : C, 42·7; H, 2·65; N, 10·7. $C_9H_7O_2N_2Br$ requires C, 42·35; H, 2·75; N, 11·0%).

2 : 3-*Bisacetoxymethylquinoxaline* 1 : 4-*Dioxide*.—2 : 3-Bisbromomethylquinoxaline 1 : 4-dioxide (5 g.) and silver acetate (5 g.) were stirred in acetic acid (60 c.c.) at 45—50° in subdued light for 17 hr. The cooled mixture was filtered (Hyflo Supercel), and the filtrate evaporated below 40°. Crystallisation of the residue from benzene gave crude *dioxide* (1·34 g.), m. p.

160—166°, which was purified by chromatography on neutral alumina with benzene–chloroform. The pure dioxide (0·7 g.) formed yellow needles, m. p. 176—177° (Found : C, 54·6; H, 4·7; N, 8·9. $C_{14}H_{14}O_6N_2$ requires C, 54·9; H, 4·6; N, 9·15%).

2 : 3 - *Bishydroxymethylquinoxaline* 1 : 4 - *Dioxide*.—2 : 3 - Bisacetoxymethylquinoxaline 1 : 4-dioxide (2 g.) was added to 2N-hydrochloric acid (40 c.c.) at 90°, and the mixture heated at 90—95° for 4 min. The solution was cooled quickly, filtered (carbon), and its pH brought to 4 by addition of sodium hydrogen carbonate. It was then extracted continuously with chloroform for 4 hr. and the extract was dried (Na_2SO_4) and concentrated under reduced pressure. The *dioxide* crystallised from ethanol in needles (0·65 g.), m. p. 170—172° (Found : C, 54·3; H, 3·9; N, 12·4. $C_{10}H_{10}O_4N_2$ requires C, 54·1; H, 4·5; N, 12·6%).

2 : 3 - *Bisdimethylaminomethylquinoxaline* 1 : 4 - *Dioxide*.—2 : 3 - Bisbromomethylquinoxaline 1 : 4-dioxide (2 g.) was added to 20% (w/v) dimethylamine in dioxan (20 c.c.) with cooling, and the mixture was shaken for 16 hr. and then filtered. The filtrate was concentrated under diminished pressure, treated with dry ethyl acetate (40 c.c.), filtered, and diluted with *cyclo*hexane. The first and the second crop of the *dioxide* (1·15 g.) had m. p. 135—136° (decomp.) which fell on recrystallisation from *cyclo*hexane (Found : C, 61·0; H, 7·4; N, 20·2. $C_{14}H_{20}O_2N_4$ requires C, 60·85; H, 7·3; N, 20·25%). The compound cannot be prepared in aqueous or alcoholic dimethylamine.

2 : 3 - *Bispiperidinomethylquinoxaline* 1 : 4 - *Dioxide*.—2 : 3 - Bisbromomethylquinoxaline 1 : 4-dioxide (1·7 g.) and piperidine (2·5 c.c.) were shaken in methanol (15 c.c.) for 16 hr.; the yellow crystals (1·25 g.), m. p. 172° (decomp.), were washed with methanol. The *dioxide* had m. p. 175—176° (decomp.) (from methanol) (Found : C, 67·0; H, 7·5; N, 16·0. $C_{20}H_{28}O_2N_4$ requires C, 67·4; H, 7·9; N, 15·7%).

2 : 3-*Bisanilinomethylquinoxaline* 1 : 4-*Dioxide*.—The bisbromomethyl dioxide (1·05 g.) and freshly-distilled aniline (1·05 g.) were shaken in ethanol (7 c.c.) for 22 hr. The solid mixture was treated with sodium hydrogen carbonate solution and extracted with chloroform. The washed and dried (Na_2SO_4) extract was evaporated and the residue washed with methanol. The *dioxide* (0·85 g.), m. p. 152—154°, decomposed on attempted crystallisation (Found : C, 71·5; H, 5·3; N, 14·4. $C_{22}H_{20}O_2N_4$ requires C, 71·0; H, 5·4; N, 15·0%).

2 : 3-*Bis*-(p-*chloranilinomethyl*)*quinoxaline* 1 : 4-*dioxide*, prepared similarly, was also unstable to recrystallisation. The crude dioxide had m. p. 136—138° (decomp.) (Found : C, 58·1; H, 4·2; N, 12·0. $C_{22}H_{18}O_2N_4Cl_2,H_2O$ requires C, 57·6; H, 3·95; N, 12·2%).

Quinoxaline-2 : 3-*bismethyl*(*trimethylammonium*) 1 : 4-*Dioxide Dibromide*.—The bisbromomethyl dioxide (4 g.) and 20% aqueous trimethylamine (50 c.c.) were shaken for 20 hr.; the clear solution was evaporated below 40° and the residue was washed with 95% ethanol, giving the *bisquaternary salt* (3·07 g.), m. p. 208° (decomp.) (Found : C, 38·8; H, 6·0; N, 11·4. $C_{16}H_{26}O_2N_4Br_2,1·5H_2O$ requires C, 38·95; H, 5·95; N, 11·35%).

Quinoxaline-2 : 3-*bismethyl*(*pyridinium*) 1 : 4-*Dioxide Dibromide*.—The bisbromomethyl dioxide (3 g.) was stirred with pyridine (3 g.) in ethanol (35 c.c.) at 60° for 16 hr. and the fawn needles were washed with hot ethanol. The *dioxide* (3·5 g.) had m. p. 218° (decomp.) (Found : N, 11·0. $C_{20}H_{18}O_2N_4Br_2$ requires N, 11·1%).

Quinoxaline-2 : 3-*bismethyl*(*thiuronium*) 1 : 4-*Dioxide Dibromide*.—The bisbromomethyl dioxide (0·7 g.) and thiourea (0·3 g.) were refluxed in magnesium-dried ethanol (7 c.c.) for 16 hr. The yellowish brown *dioxide dibromide* (0·7 g.), m. p. 230° (decomp.), was readily soluble in water. It slowly decomposed to a tar (Found : N, 16·2. $C_{12}H_{14}O_2N_6S_2,2HBr$ requires N, 16·8%).

2 : 3-*Bisbromomethylquinoxaline* 1 : 4-*Dioxide Bishexamine Salt*.—When the bromo-dioxide (2·4 g.) was shaken with hexamine (2 g.) in pure chloroform (60 c.c.) a solid soon began to separate; it was collected after 18 hr. and dried to constant weight *in vacuo* over paraffin wax and silica gel. The yellow *bishexamine salt* (4·4 g.), m. p. 170° (decomp.), was extremely soluble in warm methanol, and formaldehyde was evolved on boiling, but no solid products were isolated. It slowly decomposed (Found : C, 38·5; H, 4·9; N, 19·1. $C_{22}H_{32}O_2N_{10}Br_2,0·5CHCl_3$ requires C, 38·4; H, 4·7; N, 20·4%).

2-*Methyl*-3-(3 : 3 : 3-*trichloro*-2-*hydroxypropyl*)*quinoxaline* 1 : 4-*Dioxide*.—2 : 3-Dimethylquinoxaline 1 : 4-dioxide (12 g.) and anhydrous chloral (9 g.) were heated in dry pyridine (45 c.c.) at 115° for 3·5 hr. After cooling, the product was collected and washed with pyridine. It was boiled with absolute ethanol (200 c.c.) and crystallised from ethanol–dioxan (1 : 3). This gave the pure *mono-derivative* (5·2 g.), m. p. 226° (decomp.) (Found : C, 43·0; H, 3·3; N, 8·8; Cl, 31·4. $C_{12}H_{11}O_3N_2Cl_3$ requires C, 42·7; H, 3·3; N, 8·3; Cl, 31·5%).

2 : 3-*Bis* 2′-*piperidinoethylquinoxaline* 1 : 4-*Dioxide*.—2 : 3-Dimethylquinoxaline 1 : 4-dioxide

(2·85 g.), piperidinium bromide (5·1 g.), and paraformaldehyde (1·2 g.) were refluxed in 95% *n*-butanol (16 c.c.) for 6 hr. The product was filtered off from the cooled mixture and washed with ethanol–acetone (1 : 2). Two recrystallisations by solution in warm 95% ethanol and dilution with acetone gave the pure *dioxide dihydrobromide hemihydrate* (dried over P_2O_5) (1·6 g.), m. p. 211° (decomp.) (Found : C, 47·6; H, 6·7; N, 10·2. $C_{22}H_{34}O_2N_4Br_2,0{\cdot}5H_2O$ requires C, 47·6; H, 6·3; N, 10·1%).

2-*Ethoxycarbonyl*-3-*methylquinoxaline* 1 : 4-*Dioxide*.—Ethyl 3-methylquinoxaline-2-carboxylate (20 g.) was dissolved in 2M-peracetic acid (150 c.c.; containing 0·3% v/v H_2SO_4), and the solution heated at 55—60°; after 24 hr. more per-acid (75 c.c.) was added, and heating continued for 60—65 hr. in all. The solution was evaporated under reduced pressure and the residue was treated with sodium hydrogen carbonate and extracted with chloroform. The dried (Na_2SO_4) extract was evaporated and the residue was extracted with boiling *cyclo*hexane to remove 2-*ethoxycarbonyl*-3-*methylquinoxaline mono*-N-*oxide* which formed needles, m. p. 93—94°, from ethanol (Found : N, 12·0. $C_{12}H_{12}O_3N_2$ requires N, 12·06%). The *dioxide* (10·6 g.) after crystallisation from aqueous ethanol had m. p. 132—134° (Found : C, 57·9; H, 5·1; N, 11·4. $C_{12}H_{12}O_4N_2$ requires C, 58·05; H, 4·85; N, 11·3%).

2-*Carboxy*-3-*methylquinoxaline* 1 : 4-*Dioxide*.—2-Ethoxycarbonyl-3-methylquinoxaline 1 : 4-dioxide (1·2 g.) was stirred with a solution of sodium hydroxide (0·25 g.) in water (8 c.c.) at 50° for 30 min. Cooling and acidification of the solution with hydrochloric acid gave the crude acid (0·5 g.) which appeared to be decarboxylated in hot water and was purified by dissolving it in sodium hydrogen carbonate solution (charcoal) and acidifying the solution. This gave the *dioxide* (0·25 g.) as golden plates, m. p. 167—169° (Found : C, 54·5; H, 4·0. $C_{10}H_8O_4N_2$ requires C, 54·5; H, 3·6%).

2-*Carbamoyl*-3-*methylquinoxaline* 1 : 4-*Dioxide*.—2-Ethoxycarbonyl-3-methylquinoxaline 1 : 4-dioxide (1·7 g.) with methanolic ammonia (20 c.c.; 6N) at room temperature for 5 days gave the *amide* (1·2 g.), m. p. 242° (decomp.), which crystallised quickly from boiling water as pale yellow plates (0·9 g.), m. p. 247° (decomp.) (Found : C, 54·5; H, 4·7. $C_{10}H_9O_3N_3$ requires C, 54·8; H, 4·2%).

2-*Hydroxyaminocarbonyl*-3-*methylquinoxaline* 1 : 4-*Dioxide*.—Hydroxylamine hydrochloride (7 g.) and sodium methoxide (from 4·5 g. of sodium) in methanol (45 c.c.) were shaken for 7 hr.; 2-ethoxycarbonyl-3-methylquinoxaline 1 : 4-dioxide (3·5 g.) was added, and shaking was continued for a further 18 hr. The solid was extracted three times with boiling ethanol (100 c.c.), and the residue from vacuum evaporation of the extracts was recrystallised from 80% ethanol. The *hydroxamic acid* had m. p. 210° (decomp.) (Found : C, 51·1; H, 3·7. $C_{10}H_9O_4N_3$ requires C, 51·0; H, 3·85%).

2-*Hydrazinocarbonyl*-3-*methylquinoxaline* 4(?)-*Oxide*.—2-Ethoxycarbonyl-3-methylquinoxaline 1 : 4-dioxide (1 g.) was ground with hydrazine hydrate (6 c.c.; 70%), and a steady effervescence set in. The product (0·3 g.) after 24 hr. was crystallised repeatedly from water, giving yellow needles, m. p. 224—225° (effervescence) of a *mono*-N-*oxide hydrazide* (Found : C, 55·2; H, 4·6; N, 26·0. $C_{10}H_{10}O_2N_4$ requires C, 55·0; H, 4·6; N, 25·7%).

2 : 3-*Bispiperidinomethylquinoxaline*.—2 : 3-Bisbromomethylquinoxaline (5 g.) added to piperidine (6 g.) in ethanol (35 c.c.) soon dissolved and the temperature rose to 60°. The solution was poured into water, which was then extracted three times with ether; the combined extracts were washed three times with water, dried (Na_2SO_4) and evaporated, and the residue was crystallised twice from 75% methanol, giving the *quinoxaline* (3·6 g.), m. p. 101—102° (Found : N, 17·1. $C_{20}H_{28}N_4$ requires N, 17·3%).

Quinoxalino[2′ : 3′-3 : 4]*pyrroline*-1-spiro-1″-*piperidinium Bromide*.—2 : 3-Bisbromomethylquinoxaline (1·8 g.) was stirred in ethanol (15 c.c.) at 50°. Piperidine (0·8 g.) was added in three equal portions at two-hourly intervals, and the mixture was stirred for a further 18 hr. at 50°. The spiro-*quaternary* salt (0·95 g.) was filtered off; after 2 crystallisations from 99% ethanol it had m. p. 265—266° (decomp.) (Found : N, 13·2. $C_{15}H_{18}N_3Br$ requires N, 13·1%). It was readily soluble in water and was not extracted from an alkaline solution by chloroform, thus proving that it was not the isomeric 2-bromomethyl-3-piperidinomethylquinoxaline.

3-*Methylquinoxaline*-2-*carboxyamide* was prepared from ethyl 3-methylquinoxaline-2-carboxylate and methanolic ammonia; it formed needles, m. p. 194—196°, from alcohol (Found : N, 22·4. $C_{10}H_9ON_3$ requires N, 22·45%).

3-Methylquinoxaline-2-hydroxamic acid was prepared by the same method as for the dioxide hydroxamic acid; it crystallised from alcohol as the *hydrate*, m. p. 178—179° (Found : C, 54·5; H, 5·1; N, 19·7. $C_{10}H_9O_2N_3,H_2O$ requires C, 54·25; H, 5·0; N, 19·0%).

3-*Methylquinoxaline*-2-*carboxyhydrazide* soon separated when the quinoxaline ester was

mixed with aqueous hydrazine; it formed stout needles (from water), m. p. 172—174° (Found: C, 59·4; H, 5·1. $C_{10}H_{10}ON_4$ requires C, 59·4; H, 4·95%).

2 : 3-*Bis*-p-*tolylthioquinoxaline*.—2 : 3-Dichloroquinoxaline (4·0 g.) and toluene-*p*-thiol (5·0 g.) were heated in an oil bath at 100° for 0·5 hr.; the bath temperature was then raised to 130—140° for 0·5 hr., and the melt was cooled, pulverised, triturated with 0·5N-sodium hydroxide (100 c.c.), filtered off, and washed with water. Crystallisation from light petroleum (b. p. 100—120°) gave the *quinoxaline* (5·6 g.) as yellow prisms, m. p. 140—142° (Found: S, 16·5. $C_{22}H_{18}N_2S_2$ requires S, 17·1%).

Oxidation.—2 : 3-Bis-*p*-tolylthioquinoxaline (1·9 g.) was dissolved in hot glacial acetic acid (100 c.c.)–98% formic acid (50 c.c.), and the solution was cooled to 50—60° and treated with 30% hydrogen peroxide (20 c.c.). The mixture was heated at 50° for 18 hr., concentrated under reduced pressure and diluted with ice–water. 2 : 3-Dihydroxyquinoxaline (0·8 g.) was filtered off and was characterised by methylation to 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline, m. p. 250°. The aqueous mother-liquor was neutralised with sodium hydroxide and treated with *S*-benzylthiuronium chloride solution to precipitate *S*-benzylthiuronium toluene-*p*-sulphonate, m. p. and mixed m. p. 180—182°.

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