108. *The Oxidation of 2-Hydroxyquinoxaline and its Derivatives with Hydrogen Peroxide.*

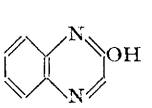
By G. T. Newbold and F. S. Spring.

Hydrogen peroxide oxidation of 2-hydroxyquinoxaline, 2-hydroxyquinoxaline-3-carboxylic acid, and quinoxaline-2 : 3-dicarboxylic acid gives 2 : 3-dihydroxyquinoxaline in each case. Similar oxidation of 2-ethoxyquinoxaline gives 3-ethoxyquinoxaline 1-oxide (XI) which on treatment with mineral acid yields 2 : 3-dihydroxyquinoxaline. Similarly, 2-ethoxy-3-methylquinoxaline is converted into 3-ethoxy-2-methylquinoxaline 1-oxide (XVII) which on treatment with hydrochloric acid gives 2-hydroxy-3-chloromethylquinoxaline (XVIII).

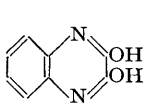
In connection with a study of the antibacterial compound aspergillic acid, which has been formulated as a cyclic hydroxamic acid related to pyrazine, model experiments were undertaken with the object of developing a synthesis of acids of this type. Since various methods are now available for the synthesis of hydroxypyrazines (see Baxter, Newbold, and Spring, *J.*, 1947, 370, where the earlier literature is reviewed), a method for the direct oxidation of a hydroxypyrazine to a pyrazinehydroxamic acid would be most attractive; because of their greater accessibility, 2-hydroxyquinoxaline derivatives rather than 2-hydroxypyrazine derivatives were chosen for preliminary examination. This paper describes the behaviour of various 2-hydroxyquinoxaline derivatives when oxidised with hydrogen peroxide.

Oxidation of quinoxaline with hydrogen peroxide gives quinoxaline di-*N*-oxide (McIlwain, *J.*, 1943, 322). Similar oxidation of 2-hydroxyquinoxaline (I) (Gowenlock, Newbold, and Spring, *J.*, 1945, 622) gives 2 : 3-dihydroxyquinoxaline (II), characterised by methylation with methyl sulphate and sodium hydroxide to 2 : 3-*diketo*-1 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (III), m. p. 256—258°. That *N*-methylation had occurred in this reaction was indicated by the high melting point of the product and was established by the preparation of the isomeric 2 : 3-dimethoxyquinoxaline (IV), m. p. 92—94°, by the action of sodium methoxide on 2 : 3-dichloroquinoxaline (V) (cf. Stevens, Pfister, and Wolf, *J. Amer. Chem. Soc.*,

1946, **68**, 1038). 2 : 3-Dihydroxyquinoxaline (which does not melt below 360°) was further characterised by its absorption spectrum in alkaline solution. The susceptibility to oxidation at the 3-position in 2-hydroxyquinoxaline derivatives was further demonstrated in attempts to obtain *N*-oxides from 2-hydroxyquinoxaline-3-carboxylic acid (VI) and quinoxaline-2 : 3-dicarboxylic acid (VII) by oxidation with hydrogen peroxide; in each case 2 : 3-dihydroxyquinoxaline was obtained as sole product. These reactions bear a formal relationship to the formation of acetic acid by the oxidation of pyruvic acid with hydrogen peroxide, the electron-attracting nuclear $-\overset{|}{C}=N-$ grouping in the quinoxaline derivatives functioning as the carbonyl group in pyruvic acid.



(I.)



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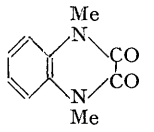

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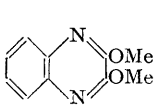

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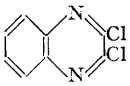

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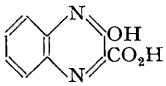

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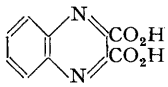
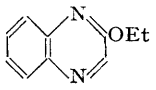


(VII.)

Oxidation of 2-ethoxyquinoxaline (VIII) (Gowenlock, Newbold, and Spring, *loc. cit.*) with hydrogen peroxide yields a compound, $C_{10}H_{10}O_2N_2$, which on hydrolysis with mineral acid yields 2 : 3-dihydroxyquinoxaline, a behaviour which appears to indicate that it is 2-hydroxy-3-ethoxyquinoxaline (IX). The latter compound was synthesised by the following route. Treatment of 2 : 3-dichloroquinoxaline (V) with one mol. of sodium ethoxide gave 2-*chloro*-3-*ethoxyquinoxaline* (X) which, when treated with potassium hydroxide, yielded 2-*hydroxy*-3-*ethoxyquinoxaline*, which proved to be different from the compound obtained by oxidation of 2-ethoxyquinoxaline. Unlike 2-hydroxy-3-ethoxyquinoxaline, the compound $C_{10}H_{10}O_2N_2$ is insoluble in alkali; the oxygen atom introduced into 2-ethoxyquinoxaline by peroxide oxidation cannot be present as a hydroxyl group and is, therefore, probably present as a *N*-oxide group, a decision confirmed by the observation that the compound $C_{10}H_{10}O_2N_2$ liberates iodine from potassium iodide solution in the presence of acetic acid by a procedure which also gives a positive reaction with quinoxaline di-*N*-oxide (McIlwain, *loc. cit.*). The compound $C_{10}H_{10}O_2N_2$ is therefore either 3-*ethoxyquinoxaline* 1-*oxide* (XI) or 2-ethoxyquinoxaline 1-oxide (XII). The fact that acid hydrolysis of the compound gave 2 : 3-dihydroxyquinoxaline and not a cyclic hydroxamic acid, together with the observation that 2 : 3-diethoxyquinoxaline is not oxidised by hydrogen peroxide, established the structure (XI). The rearrangement of an aromatic *N*-oxide to a cyclic amide by treatment with mineral acid does not appear to have been observed previously; quinoxaline di-*N*-oxide is recovered unchanged after refluxing with mineral acid under the same conditions.



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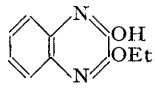
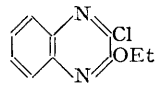
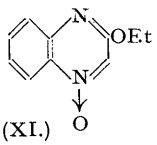


(IX.)



(X.)



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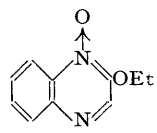

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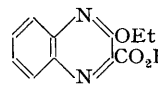
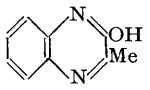


(XIII.)

Oxidation of 2-ethoxyquinoxaline-3-carboxylic acid (XIII) with hydrogen peroxide gave 2 : 3-dihydroxyquinoxaline in high yield and not the expected 2-hydroxy-3-ethoxyquinoxaline (IX). The reason for this became apparent when we treated 2-hydroxy-3-ethoxyquinoxaline with aqueous acetic acid, 2 : 3-dihydroxyquinoxaline being obtained in high yield.

2-Ethoxyquinoxaline-3-carboxylic acid was stable to aqueous acetic acid under the same conditions.



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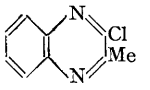

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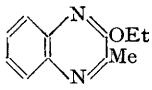

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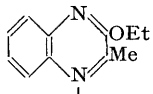
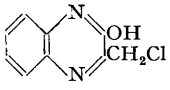
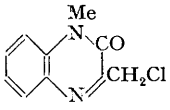


(XVII.)



(XVIII.)



(XIX.)

Treatment of 2-hydroxy-3-methylquinoxaline (XIV) (Hinsberg, *Annalen*, 1896, **292**, 245) with phosphoryl chloride gave 2-*chloro*-3-*methylquinoxaline* (XV) which was converted by the standard procedure into 2-*ethoxy*-3-*methylquinoxaline* (XVI). Hydrogen peroxide oxidation of the latter gave 3-*ethoxy*-2-*methylquinoxaline* 1-*oxide*, (XVII), which liberates iodine from acidified potassium iodide solution and on reduction with sodium dithionite (hydrosulphite) regenerates the parent 2-ethoxy-3-methylquinoxaline. Treatment of 3-ethoxy-2-methylquinoxaline 1-oxide with hydrochloric acid yields 2-*hydroxy*-3-*chloromethylquinoxaline* (XVIII) which is soluble in sodium hydroxide solution. 2-Hydroxy-3-chloromethylquinoxaline was characterised by methylation with methyl sulphate and alkali to the *monomethyl* derivative (XIX), and by its ultra-violet absorption spectrum in 0·1N-sodium hydroxide which is very similar to that of 2-hydroxy-3-methylquinoxaline :

	Max.$_1$, A.	ε.	Max.$_2$, A.	ε.
2-Hydroxy-3-methylquinoxaline	2380	23,600	3450	7450
2-Hydroxy-3-chloromethylquinoxaline	2405	26,000	3445	9000

Experimental.

2 : 3-*Dihydroxyquinoxaline*.—Meyer and Seeliger (*Ber.*, 1896, **29**, 2641) prepared 2 : 3-dihydroxyquinoxaline by treatment of *o*-phenylenediamine with ethyl oxalate; these authors do not give details of their preparation. The following method was found suitable. *o*-Phenylenediamine (10·8 g.) was heated with ethyl oxalate (60 g.) for 6 hours (bath temp. 160—170°). After cooling, the solid was collected and washed with ethanol and water. It was purified by dissolution in N-sodium hydroxide followed by filtration and acidification of the filtrate; 2 : 3-dihydroxyquinoxaline (68%) then separated as needles, m. p. > 360°. Light absorption in 0·1N-sodium hydroxide : Maxima at 3150 A. (ε = 12,000), 3260 A. (ε = 14,500), and 3400 A. (ε = 11,000). Scudi and Silber (*J. Biol. Chem.*, 1944, **156**, 343) give maxima at 3270 A. (ε = 16,800) and 3415 A. (ε = 10,600).

2 : 3-*Diketo*-1 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*.—A solution of 2 : 3-dihydroxyquinoxaline (0·7 g.) in sodium hydroxide solution (2N ; 30 c.c.) was shaken at room temperature with methyl sulphate (3 c.c.) for 2 hours. The crystalline solid was collected, washed with water, and dried (0·51 g.; 62%); m. p. 255°. Crystallisation from ethanol gave 2 : 3-*diketo*-1 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* as needles, m. p. 256—258° (Found : C, 63·1; H, 5·5; N, 14·7. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7%).

2 : 3-*Dimethoxyquinoxaline*.—A solution of 2 : 3-dichloroquinoxaline (0·7 g.) in dry methanol (30 c.c.) was treated with a methanolic solution of sodium methoxide (from 0·2 g. of sodium and 10 c.c. of dry methanol), and the mixture refluxed for 1½ hours. 2 : 3-Dimethoxyquinoxaline (0·62 g.), m. p. 92—94°, was obtained as fine needles from methanol (Found : C, 62·9; H, 5·3; N, 14·8. Calc. for $C_{10}H_{10}O_2N_2$: C, 63·2; H, 5·3; N, 14·7%).

3-*Ethoxyquinoxaline* 1-*Oxide*.—A solution of 2-ethoxyquinoxaline (1 g.) in glacial acetic acid (30 c.c.) was treated with hydrogen peroxide solution (100 vol., 10 c.c.) and heated for 18 hours at 56°. The solution was evaporated under reduced pressure to a small bulk and the residue made just alkaline by the addition of potassium hydroxide solution. The mixture was extracted with chloroform (2 × 25 c.c.), the extract dried (Na_2SO_4), and evaporated. Crystallisation of the residue from *n*-hexane gave 3-*ethoxyquinoxaline* 1-*oxide* (0·6 g.) as needles, m. p. 104—106° (Found : C, 63·4; H, 5·6. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3%). The oxide is insoluble in water, N-sodium hydroxide, and N-hydrochloric acid, but dissolves in concentrated hydrochloric acid. It liberates iodine from potassium iodide solution in the presence of acetic acid using the procedure described by McIlwain (*loc. cit.*).

Hydrolysis. A solution of the oxide (0·25 g.) in ethanol (2 c.c.) and hydrochloric acid (2·5N ; 3 c.c.) was refluxed for 3½ hours, during which time solid separated. The ethanol was removed by distillation and the residue dissolved in 3N-sodium hydroxide. Acidification with dilute hydrochloric acid gave a crystalline precipitate of 2 : 3-dihydroxyquinoxaline, m. p. > 360° (0·17 g.). The absorption spectrum of this specimen in 0·1N-sodium hydroxide showed the characteristic triplet with principal maximum at 3250 A. (ε = 13,400). Methylation gave 2 : 3-diketo-1 : 4-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline, m. p. 255—257° undepressed when mixed with an authentic specimen.

2-*Chloro*-3-*methylquinoxaline*.—2-Hydroxy-3-methylquinoxaline (Hinsberg, *Annalen*, 1896, **292**, 245)

(8 g.) was refluxed with freshly distilled phosphoryl chloride (50 c.c.) for 30 minutes. The solution was concentrated under reduced pressure and the residue treated with ice–water and the mixture extracted with ether. Removal of the ether from the dried (Na_2SO_4) extract followed by distillation gave the product as a red oil (b. p. 85°/0·5 mm.), solidifying to a crystalline mass (6·2 g., m. p. 84—86°). The colour could not be removed by crystallisation from light petroleum (b. p. 40—60°). A solution of the distillate (0·95 g.) in dry benzene (45 c.c.) was filtered through a column of activated alumina (75 × 15 mm.) and the column washed with benzene (135 c.c.). The colourless filtrate was evaporated and the residue crystallised from light petroleum (b. p. 40—60°) to yield 2-*chloro*-3-*methylquinoxaline* as colourless needles, m. p. 86—87°. The compound sublimed rapidly at 85°/0·001 mm. (Found : C, 60·9; H, 4·0; N, 15·95. $C_9H_7N_2Cl$ requires C, 60·5; H, 3·9; N, 15·7%).

2-*Ethoxy*-3-*methylquinoxaline*.—A solution of 2-chloro-3-methylquinoxaline (4·8 g.) in dry ethanol (25 c.c.) was treated with a solution of sodium ethoxide in ethanol (from 1·1 g. of sodium and 35 c.c. of ethanol). The mixture was refluxed for 1 hour, filtered, and the filtrate evaporated. The residue was treated with water and the product isolated by means of ether. Crystallisation from *n*-hexane gave 2-*ethoxy*-3-*methylquinoxaline* as needles, m. p. 55—57° (Found : C, 70·1; H, 6·5. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4%). The *picrate* separated as fine yellow needles from ethyl acetate, m. p. 116—118° (Found : C, 49·2; H, 3·5; N, 17·0. $C_{17}H_{15}O_8N_5$ requires C, 48·9; H, 3·6; N, 16·8%).

A solution of 2-ethoxy-3-methylquinoxaline (0·2 g.) in ethanol (2 c.c.) was refluxed for 1 hour with hydrochloric acid (3 c.c., 2·5N). The solution was concentrated, diluted with water, and the solid separating dissolved in N-sodium hydroxide. After filtration, the solution was acidified to litmus with hydrochloric acid and the precipitated solid collected. Crystallisation from aqueous ethanol gave 2-hydroxy-3-methylquinoxaline as needles, m. p. 245° not depressed when mixed with an authentic specimen (yield, 70%).

3-*Ethoxy*-2-*methylquinoxaline* 1-*Oxide*.—2-Ethoxy-3-methylquinoxaline (1·88 g.) in glacial acetic acid (40 c.c.) was treated with hydrogen peroxide solution (100 vol., 15 c.c.) and the mixture kept at 56° for 16 hours. The product was isolated by the method used for 3-ethoxyquinoxaline 1-oxide. Recrystallisation from light petroleum (b. p. 40—60°) gave 3-*ethoxy*-2-*methylquinoxaline* 1-*oxide* (1·7 g.) as needles from dilute solution and plates from concentrated solution, m. p. 84—86°. It liberates iodine from potassium iodide solution in the presence of acetic acid (Found : 64·6; H, 5·8; N, 13·6. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%).

A solution of 3-ethoxy-2-methylquinoxaline 1-oxide (0·2 g.) in ethanol (5 c.c.) and water (5 c.c.) was heated under reflux with sodium dithionite (hydrosulphite) (0·25 g.) for 1 hour. More sodium hydrosulphite (0·25 g.) was added and the mixture again refluxed for 1 hour. Most of the ethanol was removed by distillation, and the mixture was treated with water and cooled; the separated oil then solidified. The solid was collected, dried, and crystallised from light petroleum to give 2-ethoxy-3-methylquinoxaline as needles, m. p. 51—53° not depressed when mixed with an authentic specimen. The picrate was obtained as fine yellow needles from ethyl acetate, m. p. 115—117° either alone or when mixed with the specimen previously described.

2-*Hydroxy*-3-*chloromethylquinoxaline*.—A solution of 3-ethoxy-2-methylquinoxaline 1-oxide (0·25 g.) in ethanol (2 c.c.) and 2·5N-hydrochloric acid (3 c.c.) was heated under reflux for 3½ hours. The mixture was diluted with water, cooled, and the solid, m. p. 265°, collected. The solid readily dissolved in cold N-sodium hydroxide and was precipitated by acidification of this solution with N-sulphuric acid. Crystallisation from a large volume of boiling water (charcoal) gave 2-*hydroxy*-3-*chloromethylquinoxaline* as fine needles, m. p. 265—268° (Found : C, 55·2; H, 3·4; N, 14·2. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·6; N, 14·4%).

2-*Keto*-1-*methyl*-3-*chloromethyl*-1 : 2-*dihydroquinoxaline*.—A solution of 2-hydroxy-3-chloromethylquinoxaline (150 mg.) in N-sodium hydroxide (3 c.c.) was shaken at room temperature with methyl sulphate (0·5 c.c.). A solid (110 mg.) rapidly separated which after crystallisation from ethanol (charcoal) gave 2-*keto*-1-*methyl*-3-*chloromethyl*-1 : 2-*dihydroquinoxaline* as needles, m. p. 228—230° (Found : C, 57·1; H, 4·1; N, 13·1. $C_{10}H_9ON_2Cl$ requires C, 57·5; H, 4·3; N, 13·4%).

2-*Chloro*-3-*ethoxyquinoxaline*.—A boiling solution of 2 : 3-dichloroquinoxaline (10 g.) in dry ethanol (200 c.c.) was treated with alcoholic sodium ethoxide solution (from 1·15 g. of sodium and 100 c.c. of ethanol) added dropwise with stirring over 6 hours. The mixture was refluxed for a further 1½ hours and kept overnight at room temperature. Salt was removed by filtration and the filtrate concentrated. The crystalline solid separating was recrystallised from ethanol from which 2-*chloro*-3-*ethoxyquinoxaline* separated as fine needles, m. p. 71—73° (yield, 80%). For analysis, it was sublimed at 70°/10^{-3} mm. (Found : C, 57·5; H, 4·5. $C_{10}H_9ON_2Cl$ requires C, 57·55; H, 4·3%).

A solution of 2-chloro-3-ethoxyquinoxaline (1·0 g.) in a mixture of ethanol (20 c.c.) and hydrochloric acid (*d* 1·19; 5 c.c.) was heated on the water-bath for 1 hour. The solid separating was collected and identified as 2 : 3-dihydroxyquinoxaline by its light absorption in 0·1N-sodium hydroxide [maxima at 3140, 3270 (ε = 14,000) and 3400 A.] and by conversion into 2 : 3-diketo-1 : 4-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline which separated as needles from methanol, m. p. 255—257° either alone or when mixed with an authentic specimen.

2-*Hydroxy*-3-*ethoxyquinoxaline*.—2-Chloro-3-ethoxyquinoxaline (1·0 g.) in ethanol (5 c.c.) was treated with 20% potassium hydroxide solution (10 c.c.) and the mixture refluxed for 4½ hours. The mixture was cooled and extracted with ether which removed unchanged material (200 mg.). The aqueous solution was acidified to litmus with dilute hydrochloric acid and the precipitated solid collected (dry weight, 550 mg.). Crystallisation from aqueous ethanol gave 2-*hydroxy*-3-*ethoxyquinoxaline* as fine needles, m. p. 197—199° (Found : C, 62·85; H, 5·3; N, 14·9. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7%). 2-Hydroxy-3-ethoxyquinoxaline (200 mg.) in glacial acetic acid (5 c.c.) and water (3 c.c.) was heated at 56° for 15 hours. Evaporation of the reaction mixture gave 2 : 3-dihydroxyquinoxaline (140 mg.) characterised by its absorption spectrum in 0·1N-sodium hydroxide [maxima at 3150, 3260 (ε = 14,500) and 3410 A.] and by formation of 2 : 3-diketo-1 : 4-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline, m. p. 256—258° undepressed on admixture with an authentic specimen.

2 : 3-*Dihydroxyquinoxaline by Hydrogen Peroxide Oxidation of Quinoxaline Derivatives*.—A solution

of 2-hydroxyquinoxaline (1·46 g.) in glacial acetic acid (40 c.c.) was heated with hydrogen peroxide (100-vol., 15 c.c.) at 56° for 1½ hours, crystalline solid separating after 1 hour. The mixture was kept overnight at room temperature; the solid (dry weight 1·15 g.) was collected and dissolved in N-sodium hydroxide, acidification of the solution with N-hydrochloric acid giving 2 : 3-dihydroxyquinoxaline (1·15 g., 71%) as silky needles not melting below 340°. Light absorption in 0·1N-sodium hydroxide : Maxima at 3150 A. (ε = 12,200), 3260 A. (ε = 14,400), and 3410 A. (ε = 10,500).

Methylation of this specimen using the method described above gave 2 : 3-diketo-1 : 4-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline as needles from methanol, m. p. 256—258° either alone or when mixed with an authentic specimen.

The general procedure adopted for the oxidation of 2-ethoxyquinoxaline-3-carboxylic acid, 2-hydroxyquinoxaline-3-carboxylic acid, quinoxaline-2 : 3-dicarboxylic acid, and 2-chloro-3-ethoxyquinoxaline was as follows. A mixture of the compound (0·5—0·8 g.), glacial acetic acid (20 c.c.), and hydrogen peroxide (10 c.c., 100-vol.) was kept at 56° for 16—20 hours. 2 : 3-Dihydroxyquinoxaline was isolated and characterised in each case by the method described above (yields, 65—85%).

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