Quinoxalines and Related Compounds. Part I. The Methylation of Some 2- and 3-Hydroxyquinoxalines.

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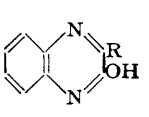
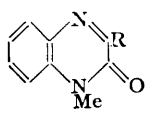
The methylation of 2-hydroxyquinoxaline and five other 2- and 3-hydroxyquinoxalines is described and discussed. Methyl sulphate gives *N*-methyl derivatives: 2-amino-3-hydroxyquinoxaline (I; R=NH_2) is converted by methyl sulphate into 3-amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = NH_2) and not, as previously reported, into the isomeric *O*-methyl derivative (III; R = NH_2). With diazomethane 2-hydroxyquinoxaline (I; R = H) forms 1 : 2-dihydro-1 : 3-dimethyl-2-oxoquinoxaline (II; R = Me) and 2-methoxyquinoxaline (III; R = H), but the other hydroxyquinoxalines studied yield mixtures of *N*- and *O*-methyl derivatives.

THE methylation of 2- and 3-hydroxyquinoxalines with a variety of reagents leads to both *N*- and *O*-methyl derivatives (Simpson, "Condensed Pyridazine and Pyrazine Rings," Interscience Publ. Ltd., London, 1953, p. 241), but the correlation between reagent and product is unpredictable. In this paper the methylation of 2-hydroxyquinoxaline (I; R = H) and five other 2- and 3-hydroxyquinoxalines is described and discussed. In each case, methyl sulphate and alkali gave the *N*-methyl derivative. Mixtures of *N*- and *O*-methyl derivatives were obtained with diazomethane, except in the case of 2-hydroxyquinoxaline where *N*-, *O*-, and *C*-methylation took place.

When 7-hydroxypteridine was treated with excess of diazomethane, a dimethyl derivative was formed (Albert, Brown, and Cheeseman, *J.*, 1952, 1620). This compound has been shown to be 7 : 8-dihydro-6 : 8-dimethyl-7-oxopteridine (Albert, Brown, and Wood, personal communication). The parallel reaction between 2-hydroxyquinoxaline (I; R = H) and diazomethane has now been investigated; it gave 1 : 2-dihydro-1 : 3-dimethyl-2-oxoquinoxaline (II; R = Me) and 2-methoxyquinoxaline (III; R = H). When 2-hydroxyquinoxaline was treated with methyl sulphate and alkali 1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = H) was formed. This compound yielded the above *CN*-dimethyl derivative (II; R = Me) on methylation with diazomethane and may therefore be an intermediate in the conversion of 2-hydroxyquinoxaline into 1 : 2-dihydro-1 : 3-dimethyl-2-oxoquinoxaline. The *N*-methylation of 2-hydroxyquinoxaline with methyl sulphate is a more convenient route to 1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = H) than the previous method involving a multi-stage synthesis from *N*-methyl-*o*-phenylenediamine (King and Clark-Lewis, *J.*, 1951, 3379; Kuhling and Kaselitz, *Ber.*, 1906, **39**, 1314).



(I)



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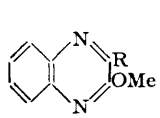

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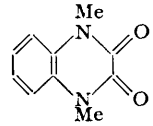

(IV)

2-Methoxyquinoxaline was readily prepared by the action of sodium methoxide on 2-chloroquinoxaline and conveniently isolated as a picrate; it did not react with diazomethane.

Ohle, Gross, and Wolter (*Ber.*, 1937, **70**, 2148) obtained 1 : 2-dihydro-1 : 3-dimethyl-2-oxoquinoxaline (II; R = Me) when 2-hydroxy-3-methylquinoxaline (I; R = Me) was treated with diazomethane. This derivative was, however, prepared in higher yield when methyl sulphate was used (Cook and Perry, *J.*, 1943, 394). A further examination of the diazomethane reaction has now shown that both the *N*-methyl derivative (II; R = Me) and the *O*-methyl derivative (III; R = Me) were formed. The latter was prepared in high yield from sodium methoxide and 2-chloro-3-methylquinoxaline.

A number of 2 : 3-dihydroxyquinoxalines have been treated with methyl sulphate and alkali and the dimethyl derivatives obtained formulated as 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxalines (Newbold and Spring, *J.*, 1948, 519; Crowther, Curd, and Stacey, *J.*, 1949, 1260; Curd, Davey, and Stacey, *J.*, 1949, 1271; see, however, Landquist, *J.*, 1953, 2816). Newbold and Spring showed that the product from 2 : 3-dihydroxyquinoxaline (I; R = OH) was not 2 : 3-dimethoxyquinoxaline (III; R = OMe) but Simpson (*op. cit.*) has pointed out that the possibility of *ON*-methylation was not excluded. *ON*-Methylation occurred when 1 : 4-dihydroxyphthalazine was treated with methyl sulphate and alkali (Rowe and Peters, *J.*, 1933, 1331). Proof that 2 : 3-dihydroxyquinoxaline was converted into 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (IV) by methyl sulphate has now been obtained by the synthesis of this compound from *NN'*-dimethyl-*o*-phenylenediamine and ethyl oxalate. When 2 : 3-dihydroxyquinoxaline was treated with diazomethane, *NN*-, *ON*-, and *OO*-methylation took place and thus (IV), 1 : 2-dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe), and 2 : 3-dimethoxyquinoxaline were formed. The *ON*-dimethyl compound (II; R = OMe) was readily synthesised by the action of sodium methoxide on 3-chloro-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = Cl), which was itself prepared from the corresponding hydroxyquinoxaline (II; R = OH) by chlorination with phosphoryl chloride. If phosphorus pentachloride is used as the chlorinating agent the hydroxy-compound is converted into 2 : 3-dichloroquinoxaline (Usherwood and Whiteley, *J.*, 1923, 1084).

1 : 2 : 3 : 4-Tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (IV) was obtained from 1 : 2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (II; R = OH) by use of methyl sulphate. Diazomethane gave also the isomeric *O*-methyl derivative (II; R = OMe). 2-Hydroxy-3-methoxyquinoxaline (I; R = OMe), prepared by the alkaline hydrolysis of 2-chloro-3-methoxyquinoxaline, was converted into 1 : 2-dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe) by methyl sulphate. Reaction with diazomethane yielded (II; R = OMe) and 2 : 3-dimethoxyquinoxaline (III; R = OMe) and thus both *N*- and *O*-methylation took place.

As methyl sulphate had proved to be an *N*-methylating agent for the above mentioned hydroxyquinoxalines, it was decided to re-investigate the report (Stevens, Pfister, and Wolf, *J. Amer. Chem. Soc.*, 1946, **68**, 1035) that *O*-methylation occurred when 2-amino-3-hydroxyquinoxaline (I; R = NH_2) was treated with dimethyl sulphate and alkali. The product had m. p. 264—270°, and was assumed to be 2-amino-3-methoxyquinoxaline (III; R = NH_2), as a compound, m. p. above 260°, and of the same carbon and hydrogen content, had been isolated in small yield from the reaction of 2-chloro-3-methoxyquinoxaline (III; R = Cl) and methanolic ammonia (*idem, loc. cit.*). It should also be possible to prepare the methoxy-amine (III; R = NH_2) by treating 2-amino-3-chloroquinoxaline with sodium methoxide, and when this reaction was carried out, a product, m. p. 151—152°, was obtained in excellent yield. This compound readily gave 2-amino-3-hydroxyquinoxaline on hydrolysis with 2·5N-hydrochloric acid at 100° and must therefore be the true 2-amino-3-methoxyquinoxaline (III; R = NH_2). The compound obtained from the methyl sulphate methylation of 2-amino-3-hydroxyquinoxaline was, however, resistant to the action of 2·5N-hydrochloric acid at 100°. It was shown to be the *N*-methyl derivative of the hydroxyquinoxaline, 3-amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = NH_2), by the synthesis of this compound in high yield by amination of 1 : 2-dihydro-1-methyl-2-oxo-3-phenoxyquinoxaline (II; R = OPh). The reaction of diazomethane and 2-amino-3-hydroxyquinoxaline yielded the expected mixture of *N*- and *O*-methyl derivatives (II and III; R = NH_2).

The preparation of 2-methoxy-3-phenoxyquinoxaline (III; R = OPh) and improved methods for obtaining several known quinoxalines are also described below.

Experimental

Aluminium oxide (Spence, type H, mesh 100—200) was used.

1 : 2-Dihydro-1 : 3-dimethyl-2-oxoquinoxaline (II; R = Me) was prepared by the method of Cook and Perry (*loc. cit.*), 1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = H) by that of

King and Clark-Lewis (*loc. cit.*), and 2 : 3-dimethoxyquinoxaline (III; R = OMe) by that of Newbold and Spring (*loc. cit.*).

2-Methoxyquinoxaline Picrate.—2-Chloroquinoxaline (2·3 g.; Gowenlock, Newbold, and Spring, *J.*, 1945, 622) in methanol (10 c.c.) was added to a solution of sodium methoxide, prepared from sodium (0·41 g.) and methanol (10 c.c.). The mixture was heated under reflux for 2 hr. and then poured into water. Extraction with ether, and evaporation of the dried (Na_2SO_4) extracts, gave 2-methoxyquinoxaline (III; R = H) (2·2 g., 98%) as an oil which crystallised as long colourless needles, m. p. *ca.* 31—33°. The *picrate*, prepared in methanol, had m. p. 141—142° (Found : C, 46·1; H, 2·75; N, 18·1. $C_{15}H_{11}O_8N_5$ requires C, 46·3; H, 2·85; N, 18·0%).

Methylation of 2-Hydroxyquinoxaline (I; R = H).—(a) *With diazomethane.* Ethereal diazomethane (from methylnitrosourea, 10·3 g.) was added to an ice-cooled suspension of 2-hydroxyquinoxaline (1·46 g., 0·01 mole; *idem, loc. cit.*) in dry methanol (20 c.c.). The mixture was left overnight at 0° and solvent and excess of diazomethane were then removed in a vacuum. The residue was dissolved in benzene (10 c.c.), and the solution filtered through a column of aluminium oxide prepared in benzene. Elution with benzene and benzene–ether (3 : 1) gave 2-methoxyquinoxaline (III; R = H) (0·42 g., 26%) as colourless needles, m. p. *ca.* 30°. The picrate had m. p. 141—142° (undepressed when mixed with an authentic specimen). Mixed crystalline solid (0·20 g.) was also removed from the column with benzene–ether (3 : 1). Elution with benzene–ether (1 : 1) and ether gave 1 : 2-dihydro-1 : 3-dimethyl-2-oxoquinoxaline (II; R = Me) (0·87 g., 50%), m. p. and mixed m. p. 85—86°. The *picrate* crystallised from methanol as yellow plates, m. p. 144—145° (Found : C, 47·7; H, 3·2; N, 17·8. $C_{16}H_{13}O_8N_5$ requires C, 47·65; H, 3·25; N, 17·4%).

(b) *With methyl sulphate.* Methyl sulphate (6 c.c.) was added to 2-hydroxyquinoxaline (1·46 g.) in 2N-sodium hydroxide (60 c.c.). The mixture was shaken until clear (about 10 min.) and then left overnight at room temperature. Extraction with chloroform, and evaporation of the dried (Na_2SO_4) extracts, gave a residue (1·1 g.), m. p. (mainly) 114—120°, which on crystallisation from light petroleum (b. p. 80—100°; 30 parts) yielded 1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = H), m. p. and mixed m. p. 120—121°.

Methylation of 1 : 2-Dihydro-1-methyl-2-oxoquinoxaline (II; R = H).—Ethereal diazomethane (from methylnitrosourea, 5·2 g.) was added to an ice-cooled suspension of the quinoxaline (1·6 g.) in dry methanol (20 c.c.). The mixture was left at 0° overnight, and solvent and excess of diazomethane were then removed in a vacuum leaving a residue, m. p. 72—81°. Crystallisation from acetone–water (2 : 1; 4 parts) gave 1 : 2-dihydro-1 : 3-dimethyl-2-oxoquinoxaline (II; R = Me) (1·2 g., 70%), m.p. and mixed m. p. 83—85°.

2-Methoxy-3-methylquinoxaline (III; R = Me).—2-Chloro-3-methylquinoxaline (1 g.; *idem, loc. cit.*) in methanol (10 c.c.) was added to a solution of sodium methoxide (1·25 equivs.), prepared from sodium (0·17 g.) and methanol (10 c.c.). The mixture was heated under reflux for 2 hr. and solvent then removed in a vacuum. Water was added to the residue, and the crystalline precipitate of *2-methoxy-3-methylquinoxaline* (0·9 g., 92%), m. p. 67—69°, collected. Crystallisation from methanol–water (2 : 1) gave colourless needles, m. p. 68—69° (Found : C, 68·9; H, 6·0; N, 15·8. $C_{10}H_{10}ON_2$ requires C, 68·95; H, 5·8; N, 16·05%).

Methylation of 2-Hydroxy-3-methylquinoxaline (I; R = Me).—The hydroxyquinoxaline (1·6 g., 0·01 mole; Hinsberg, *Annalen*, 1896, **292**, 245) was treated with diazomethane (from methylnitrosourea, 10·3 g.) similarly to 2-hydroxyquinoxaline above, and the product dissolved in benzene and fractionated on a column of aluminium oxide. Elution with benzene yielded 2-methoxy-3-methylquinoxaline (III; R = Me) (0·53 g. 30%), m. p. and mixed m. p. 69—70°, and a crystalline solid (0·14 g.), m. p. (mainly) 81—84°. 1 : 2-Dihydro-1 : 3-dimethyl-2-oxoquinoxaline (II; R = Me) (0·88 g., 51%), m. p. and mixed m. p. 85—86°, was removed from the column with benzene–ether (3 : 1 and 1 : 1).

N-*Methyl*-o-*phenylenediamine.*—The diamine was prepared by the method of Usherwood and Whiteley (*loc. cit.*) and Phillips (*J.*, 1929, 2820) except that it was found more convenient to reduce *N*-methyl-*o*-nitroaniline catalytically. The nitro-amine was hydrogenated in ethanol over 5% palladium–charcoal at room temperature and pressure. Removal of catalyst and solvent gave the diamine as a dark oil : it was used as such.

1 : 2-*Dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline* (II; R = OH).—This was prepared by Usherwood and Whiteley's method (*loc. cit.*), modified as follows. *N*-Methyl-*o*-phenylenediamine (from the reduction of 11·3 g. of *N*-methyl-*o*-nitroaniline) and ethyl oxalate (20 g.) were heated at 160—165° (bath temp.) for 2 hr. After cooling, the separated solid (12 g., 92%), m. p. 284—285°, was filtered off and washed with ethanol. Crystallisation from water (70 parts)

(charcoal) gave colourless needles of 1 : 2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline, m. p. 286—287°.

3-*Chloro*-1 : 2-*dihydro*-1-*methyl*-2-*oxoquinoxaline* (II; R = Cl).—The above hydroxy-compound (7·5 g.) and freshly distilled phosphoryl chloride (40 c.c.) were heated under reflux for 1½ hr. The resulting dark green solution was slowly poured into stirred ice-water, and the precipitated solid filtered off, washed with water, dried, and extracted with light petroleum (Soxhlet). The petroleum extract yielded pale yellow needles of 3-*chloro*-1 : 2-*dihydro*-1-*methyl*-2-*oxoquinoxaline* in two crops (total 5·5 g.), m. p. 131—133°. The original filtrate was extracted with ether, and the combined extracts were washed with sodium hydrogen carbonate solution and water, and dried (Na_2SO_4). Evaporation of solvent gave a further 1·1 g., m.p. 131—133° (total yield 80%). The m. p. was unchanged by further crystallisation from light petroleum (b. p. 60—80°) (Found: C, 55·7; H, 3·35; N, 14·5; Cl, 18·05. $C_9H_7ON_2Cl$ requires C, 55·55; H, 3·6; N, 14·4; Cl, 18·2%). 3-Chloro-1 : 2-dihydro-1-methyl-2-oxoquinoxaline was rapidly hydrolysed to the hydroxy-compound (II; R = OH) in hot aqueous methanol.

1 : 2-*Dihydro*-3-*methoxy*-1-*methyl*-2-*oxoquinoxaline* (II; R = OMe).—This compound was prepared similarly to 2-methoxy-3-methylquinoxaline. 3-Chloro-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (0·62 g.) was converted into a product (0·5 g.), m. p. (mainly) 122—123°. Crystallisation from benzene–light petroleum (1 : 1) gave colourless needles of 1 : 2-*dihydro*-3-*methoxy*-1-*methyl*-2-*oxoquinoxaline*, m. p. 122—123° (Found: C, 63·3; H, 5·4; N, 14·7. $C_{10}H_{10}O_2N_2$ requires C, 63·15; H, 5·3; N, 14·7%).

A solution of the methoxy-compound (0·38 g.) in ethanol (8 c.c.) and hydrochloric acid (*d* 1·18; 2 c.c.) was heated under reflux for 1 hr. On cooling to 0°, the mixture deposited needles of 1 : 2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (II; R = OH) (0·31 g., 88%), m. p. and mixed m. p. 285—286°.

1 : 2 : 3 : 4-*Tetrahydro*-1 : 4-*dimethyl*-2 : 3-*dioxoquinoxaline* (IV).—A mixture of *NN'*-dimethyl-*o*-phenylenediamine (1·36 g.; Elderfield and Meyer, *J. Amer. Chem. Soc.*, 1954, **76**, 1887) and ethyl oxalate (4 g.) was heated under reflux for 1 hr. After cooling, the crystalline precipitate (0·7 g; m.p. 250—253°) was filtered off and washed with ethanol. A further crop (0·3 g.; m. p. 246—248°) was obtained by vacuum-concentration of the mother-liquor. Crystallisation from ethanol (50 parts) (charcoal) gave colourless needles of 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (0·7 g., 37%), m. p. 252—253°. The m. p. was not raised by further crystallisation.

Methylation of 2 : 3-*Dihydroxyquinoxaline* (I; R = OH).—(a) *With diazomethane.* The dihydroxyquinoxaline (1·62 g., 0·01 mole; Newbold and Spring, *loc. cit.*) was treated with diazomethane (from methylnitrosourea, 10·3 g.) similarly to 2-hydroxyquinoxaline above, except that the mixture was stirred initially for 2 hr. The product was heated under reflux with benzene (15 c.c.) and, after cooling, the crystalline precipitate of 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (IV) (0·24 g.; m. p. and mixed m. p. 252—253°) was filtered off. The filtrate was then passed through a column of aluminium oxide prepared in benzene. Elution with benzene gave 2 : 3-dimethoxyquinoxaline (III; R = OMe) (0·42 g., 22%), m. p. and mixed m. p. 92—93°. 1 : 2-Dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe) (0·99 g., 52%), m. p. and mixed m. p. (mainly) 121—123°, was removed from the column with ether and ether–methanol (9 : 1). Elution with ether–methanol (9 : 1) also yielded a further quantity of the dimethyl derivative (IV) (0·15 g.), m. p. (mainly) 245—251° (total yield 21%).

(b) *With methyl sulphate.* The dihydroxy-compound was treated with methyl sulphate and alkali as described by Newbold and Spring (*loc. cit.*). Colourless needles of 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (IV) were obtained, m. p. 252—253° (undepressed when mixed with a specimen prepared as described above). Newbold and Spring give m. p. 256—258°.

Methylation of 1 : 2-*Dihydro*-3-*hydroxy*-1-*methyl*-2-*oxoquinoxaline* (II; R = OH).—(a) *With diazomethane.* The hydroxyquinoxaline (1·76 g., 0·01 mole) was caused to react with diazomethane (from methylnitrosourea, 10·3 g.) similarly to 2-hydroxyquinoxaline above, except that the mixture was stirred initially for 3 hr. The product was heated under reflux with benzene (25 c.c.) and, after cooling, the crystalline precipitate of 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (IV) (0·82 g., 43%), m. p. and mixed m. p. 248—252°, was filtered off. The filtrate was then passed through a column of aluminium oxide prepared in benzene. Elution with benzene–ether (3 : 1) gave 1 : 2-dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe) (1 g., 53%), m. p. and mixed m. p. 122—123°.

(b) *With methyl sulphate.* Methyl sulphate (1·26 c.c.) was shaken with a solution of the hydroxyquinoxaline (1·76 g.) in 5% aqueous potassium hydroxide (20 c.c.) (about 5 min.).

Colourless needles of 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline (IV) (1·4 g.; m. p. 250—252°) were soon deposited; these were collected after cooling to 0°. The mother-liquor was extracted with chloroform and evaporation of the dried (Na_2SO_4) extracts gave a further 0·35 g., m. p. (mainly) 246—248° (total yield 92%).

2 : 3-*Dichloroquinoxaline*.—2 : 3-Dihydroxyquinoxaline (I; R = OH) (15 g.) was heated under reflux with freshly distilled phosphoryl chloride (45 c.c.) and diethylaniline (15 g.) for 2½ hr. The cooled mixture was slowly poured into stirred ice-water, and the precipitated 2 : 3-dichloroquinoxaline (18 g., 98%), m. p. (mainly) 152—155°, filtered off and washed with water. Crystallisation from benzene gave pale yellow needles, m. p. 151—153°.

2-*Chloro*-3-*methoxyquinoxaline*.—This was prepared by the method of Stevens *et al.* (*loc. cit.*), modified as follows. A solution of sodium methoxide, prepared from sodium (1·73 g.) and methanol (100 c.c.), was added dropwise in 3 hr. to a stirred suspension of 2 : 3-dichloroquinoxaline (15 g.) in boiling methanol (250 c.c.). The undissolved solid gradually went into solution. The mixture was heated under reflux for a further 3 hr., and then concentrated to 100 c.c. After cooling to 0°, the precipitate of mixed crystalline solid was collected and ground with water (to remove salt). 2-Chloro-3-methoxyquinoxaline (11·6 g., 79%), m. p. 74—77°, was obtained by filtration. Crystallisation from methanol gave needles, m. p. 79—80° (Found: C, 56·05; H, 3·9; N, 14·3; Cl, 17·9%). Stevens *et al.* give m. p. 74—75°.

2-*Hydroxy*-3-*methoxyquinoxaline* (I; R = OMe).—2-Chloro-3-methoxyquinoxaline (5 g.) was heated with potassium hydroxide (10 g.) in water (50 c.c.) and methanol (100 c.c.) under reflux for 17 hr. After cooling and dilution with water (200 c.c.), the pale yellow solution was thoroughly extracted with ether to remove any unchanged starting material. The aqueous layer was warmed to remove dissolved ether and then acidified with acetic acid. The precipitated *hydroxy-compound* (3·9 g., 86%), m. p. 238—241° (decomp.), crystallised from methanol as pale yellow needles, m. p. 243—244° (decomp.) (Found: C, 61·5; H, 4·65; N, 16·1. $C_9H_8O_2N_2$ requires C, 61·35; H, 4·6; N, 15·9%).

Methylation of 2-*Hydroxy*-3-*methoxyquinoxaline* (I; R = OMe).—(a) *With diazomethane*. The hydroxyquinoxaline (1·76 g., 0·01 mole) was treated with diazomethane (from methyl-nitrosourea, 10·3 g.) similarly to 2-hydroxyquinoxaline above, except that the mixture was stirred initially for 3 hr. The product was dissolved in benzene and fractionated on a column of aluminium oxide. Elution with benzene gave 2 : 3-dimethoxyquinoxaline (III; R = OMe) (0·77 g., 41%), m. p. and mixed m. p. 92—93°. 1 : 2-Dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe) (1·06 g., 56%), m. p. and mixed m. p. 122—123°, was eluted from the column with benzene–ether (1 : 1) and ether.

(b) *With methyl sulphate*. Methyl sulphate (1·26 c.c.) was shaken with a solution of the hydroxyquinoxaline (1·76 g.) in 5% aqueous potassium hydroxide (20 c.c.) (about 15 min.). Colourless crystals of 1 : 2-dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe) (1·67 g., 88%; m. p. 118—122°) were soon deposited; these were collected after cooling to 0°.

1 : 2-*Dihydro*-1-*methyl*-2-*oxo*-3-*phenoxyquinoxaline* (II; R = OPh).—3-Chloro-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = Cl) (1·95 g.) was heated with phenol (10 g.) containing potassium hydroxide (0·67 g.) at 95° for 3 hr. The mixture was poured into excess of 2N-sodium hydroxide, and the precipitated solid filtered off and washed with water. Crystallisation from methanol (25 parts) gave 1 : 2-*dihydro*-1-*methyl*-2-*oxo*-3-*phenoxyquinoxaline* (2·0 g., 79%) as colourless needles or plates, m. p. 170—172° (Found: C, 71·2; H, 5·0; N, 11·2. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8; N, 11·1%).

A solution of the phenoxy-compound (0·4 g.) in ethanol (8 c.c.) and hydrochloric acid (*d* 1·18; 2 c.c.) was heated under reflux for 1 hr. On cooling to 0°, the mixture deposited needles of 1 : 2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (II; R = OH) (0·25 g., 89%), m. p. and mixed m. p. 285—286°.

3-*Amino*-1 : 2-*dihydro*-1-*methyl*-2-*oxoquinoxaline* (II; R = NH_2).—(*a*) The above phenoxy-compound (1·5 g.) was heated with ammonium acetate (9 g.) which had been previously heated to 180° and allowed to cool to 160°. The temperature was raised during 5 min. to 200° and maintained at 200—215° for 15 min. (cf. Keneford, Morley, Simpson, and Wright, *J.*, 1950, 1104). When cold, the melt was diluted with water and the crystalline precipitate of 3-amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (0·87 g., 84%), m. p. 273—275°, filtered off (Found: C, 62·0; H, 5·1; N, 24·0. Calc. for $C_9H_9ON_3$: C, 61·7; H, 5·2; N, 24·0%).

(*b*) A solution of 1 : 2-dihydro-3-methoxy-1-methyl-2-oxoquinoxaline (II; R = OMe) (0·95 g.) in methanol (20 c.c.; saturated at room temperature with ammonia) was heated in a sealed tube at 140—145° for 8 hr. The separated solid (0·25 g.) was collected by filtration;

it gave colourless needles of 3-amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline, m. p. and mixed m. p. 273—274°, after successive crystallisation (charcoal) from methanol (500 parts) and water (1500 parts). Evaporation of the original methanolic mother-liquor gave a residue (0·7 g.) consisting mainly of unchanged starting material.

3-Amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (0·5 g.) and 2·5N-hydrochloric acid (20 c.c.) were heated on the water-bath for 1 hr. The mixture was made strongly alkaline with 10% aqueous sodium hydroxide, and the precipitated unchanged amino-compound (0·45 g.) was collected.

2-*Amino*-3-*methoxyquinoxaline* (III; R = NH_2).—This compound was prepared similarly to 2-methoxy-3-methylquinoxaline above, except that the mixture was heated under reflux for 1 hr. 2-Amino-3-chloroquinoxaline (7·2 g.; Haworth and Robinson, *J.*, 1948, 777) was converted into a product (6·95 g.), m. p. 148—152°. Crystallisation from benzene (5 parts) gave yellow prisms of 2-*amino*-3-*methoxyquinoxaline*, m. p. 151—152° (Found: C, 62·1; H, 5·25; N, 24·0; OMe, 18·25. $C_9H_9ON_3$ requires C, 61·7; H, 5·2; N, 24·0; OMe, 17·7%).

A mixture of 2-amino-3-methoxyquinoxaline (1·75 g.) and 2·5N-hydrochloric acid (25 c.c.) was heated on the water-bath for 1 hr., then basified with 6N-ammonia, and the precipitated 2-amino-3-hydroxyquinoxaline (I; R = NH_2) (1·6 g.; m. p. above 360°) was filtered off and washed with water. A portion was converted into 3-amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = NH_2), m. p. and mixed m. p. 273—274°, as described below.

Methylation of 2-*Amino*-3-*hydroxyquinoxaline* (I; R = NH_2).—(a) *With diazomethane.* The hydroxyquinoxaline (1·61 g., 0·01 mole; Stevens *et al.*, *loc. cit.*) was treated with diazomethane (from methylnitrosourea, 10·3 g.) similarly to 2-hydroxyquinoxaline above, except that the mixture was stirred initially for 4 hr. and then left at 0° for 3 days. The product was extracted with cold 5% aqueous sodium hydroxide (30 c.c.), and the solid (0·97 g.), obtained by filtration, washed with 5% aqueous sodium hydroxide and water, dried, and then heated under reflux with light petroleum (b. p. 60—80°; 150 c.c.). 3-Amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline (II; R = NH_2) (0·65 g., 37%), m. p. 268—271°, was filtered off; the filtrate was concentrated to *ca.* 10 c.c. and on cooling deposited yellow prisms of 2-amino-3-methoxyquinoxaline (III; R = NH_2) (0·22 g., 13%), m. p. 149—152°. The initial alkaline filtrate gave unchanged 2-amino-3-hydroxyquinoxaline (0·48 g.) on acidification with acetic acid.

(b) *With methyl sulphate.* The hydroxyquinoxaline was treated with methyl sulphate and alkali as described by Stevens *et al.* (*loc. cit.*) and the m. p. of the crude product raised to 274—275° by successive crystallisation from methanol and water (charcoal). The m. p. was not depressed on admixture with an authentic specimen of 3-amino-1 : 2-dihydro-1-methyl-2-oxoquinoxaline. Stevens *et al.* give m. p. 264—270°.

2-*Methoxy*-3-*phenoxyquinoxaline* (III; R = OPh).—2-Chloro-3-methoxyquinoxaline (1·75 g.) was added to a solution of sodium phenoxide, prepared from phenol (15 g.) and sodium (0·46 g.). The mixture was heated at 95° for 17 hr. and then poured into excess of 2N-sodium hydroxide. The precipitated solid was filtered off and washed with water. Crystallisation from methanol (45 parts) gave 2-*methoxy*-3-*phenoxyquinoxaline* (1·7 g., 75%) as very pale yellow needles, m. p. 134—135·5° (Found: C, 71·4; H, 4·5; N, 11·3%).

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