

**543.** *Quinoxaline Oxides. Part II.\* The Action of Hydrochloric Acid on 3-Ethoxy-2-methylquinoxaline 1-Oxide.*

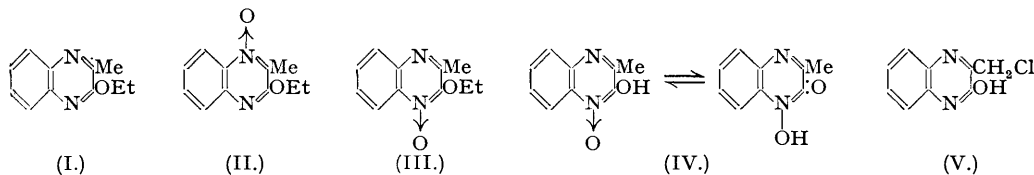
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A synthesis of 2-hydroxy-3-chloromethylquinoxaline (V) is described; the product is different from the isomeric compound, m. p. 265—268°, obtained by treatment of 3-ethoxy-2-methylquinoxaline 1-oxide (II) with hydrochloric acid. A synthesis of 6-chloro-3-hydroxy-2-methylquinoxaline (VIII) is described; it is identical with the compound, m. p. 265—268°.

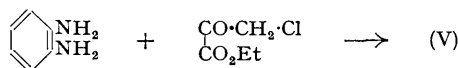
OXIDATION of 2-ethoxy-3-methylquinoxaline (I) with hydrogen peroxide gives a monoxide formulated as 3-ethoxy-2-methylquinoxaline 1-oxide (II), the alternative structure 2-ethoxy-3-

\* Part I is "The Oxidation of 2-Hydroxyquinoxaline and its Derivatives with Hydrogen Peroxide," *J.*, 1948, 519.

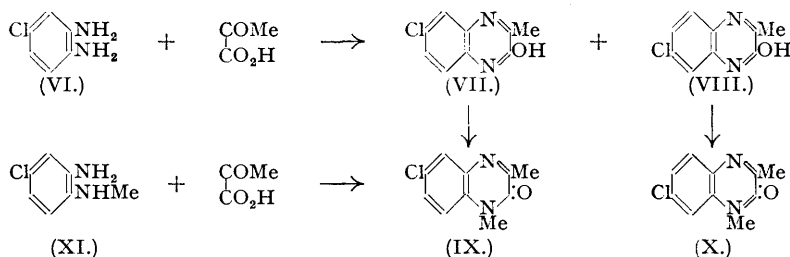
methylquinoxaline 1-oxide (III) being excluded since treatment of the oxide with dilute hydrochloric acid did not yield the cyclic hydroxamic acid (IV) (Newbold and Spring, *J.*, 1948, 519). The product from the latter reaction was a compound  $C_9H_7ON_2Cl$ , m. p. 265—268°, the ultra-violet absorption spectrum of which was very similar to that of 2-hydroxy-3-methylquinoxaline; it was described by Newbold and Spring as 2-hydroxy-3-chloromethylquinoxaline (V).



2-Hydroxy-3-chloromethylquinoxaline (V) has been synthesised by an unambiguous route; the product differs from the compound, m. p. 265—268°, obtained by the action of hydrochloric acid upon 3-ethoxy-2-methylquinoxaline 1-oxide. The synthesis was effected by condensation of ethyl chloropyruvate with *o*-phenylenediamine:



The compound  $C_9H_7ON_2Cl$ , m. p. 265—268°, is soluble in dilute sodium hydroxide and is precipitated from this solution on acidification. It would thus appear to be a chloro-substituted 2-hydroxy-3-methylquinoxaline, and the side chain, since it does not carry the halogen substituent must be at position 5, 6, 7, or 8 (*i.e.*, the compound is 5- or 6-chloro-2-hydroxy-3-methylquinoxaline or 6- or 5-chloro-3-hydroxy-2-methylquinoxaline). A synthesis



of 6-chloro-2-hydroxy-3-methyl- (VII) and/or 6-chloro-3-hydroxy-2-methylquinoxaline (VIII) was attempted by condensation of 4-chloro-*o*-phenylenediamine (VI) with pyruvic acid. The product was a mixture from which a compound  $C_9H_7ON_2Cl$ , m. p. 265—267°, was isolated. Its identity with that obtained from 3-ethoxy-2-methylquinoxaline 1-oxide was established by the preparation and comparison of the *N*-methyl derivatives.

Treatment of the crude reaction product from 4-chloro-*o*-phenylenediamine and pyruvic acid with methyl sulphate and alkali gave the expected two *N*-methyl derivatives, m. p. 144—145° and 227—229°. The latter is identical with the *N*-methyl derivative obtained from the previously described chloro-2-hydroxy-3-methylquinoxaline, m. p. 265—267°. The *N*-methyl derivative, m. p. 144—145°, was identified as 6-chloro-2-keto-1:3-dimethyl-1:2-dihydroquinoxaline (IX) by its synthesis from 4-chloro-2-amino-*N*-methylaniline (XI) and pyruvic acid. It follows that the *N*-methyl derivative, m. p. 227—229°, is 7-chloro-2-keto-1:3-dimethyl-1:2-dihydroquinoxaline (X) and that its parent compound,  $C_9H_7ON_2Cl$ , m. p. 265—267°, is 6-chloro-3-hydroxy-2-methylquinoxaline (VIII).

#### EXPERIMENTAL.

**2-Hydroxy-3-chloromethylquinoxaline.**—Ethyl chloropyruvate (b. p. 79—80°/10 mm.; 0.9 g.) in ethanol (2 c.c.) was added to a solution of *o*-phenylenediamine (0.55 g.) in ethanol (5 c.c.) at 55°. The solid product which separated was collected and crystallised from ethanol (charcoal) from which 2-hydroxy-3-chloromethylquinoxaline separated as felted needles, m. p. 221—222° (decomp.) (Found: C, 55.6; H, 3.6; N, 14.5.  $C_9H_7ON_2Cl$  requires C, 55.5; H, 3.6; N, 14.4%). 2-Hydroxy-3-chloromethylquinoxaline is sparingly soluble in water, soluble in dilute sodium hydroxide, and precipitated from alkaline solutions by dilute mineral acids. Light absorption in 0.1*N*-sodium hydroxide: Maxima, 2380 Å.,  $\epsilon = 23,600$ ; and 2540 Å.,  $\epsilon = 7400$ .

6-Chloro-3-hydroxy-2-methylquinoxaline.—A solution of 4-chloro-*o*-phenylenediamine (1.43 g.; Haworth and Robinson, *J.*, 1948, 777) in water (50 c.c.) was treated at 70° with a solution of pyruvic acid (1.5 g.) in water (10 c.c.) with shaking. The mixture was cooled and the solid collected, washed with ice-water, and dried (1.87 g.; m. p. 235–240° with sintering at 220°). The mixture was crystallised five times from aqueous acetic acid giving needles (0.56 g.), m. p. 251–254°. A solution of this solid in warm chloroform (200 c.c.) was filtered through a column of alumina (Spence H, 12 × 3 cm.). This column was washed with chloroform and the following fractions were collected:

Fraction.	Eluate (c.c.)	Solute (mg.)	M. p.	Fraction.	Eluate (c.c.)	Solute (mg.)	M. p.
1	300	15	} oily	6	380	110	249–252°
2	260	15		7	380	80	240–243
3	400	30	260–262°	8	400	30	240 approx.
4	280	60	260–262	9	500	20	240 approx.
5	400	190	250–255				

Fractions 3 and 4 were combined, crystallised from ethanol, and then sublimed at 180°/10<sup>-3</sup> mm., giving 6-chloro-3-hydroxy-2-methylquinoxaline as needles, m. p. 265–267° (Found: C, 55.5; H, 3.7. C<sub>9</sub>H<sub>7</sub>ON<sub>2</sub>Cl requires C, 55.5; H, 3.6%). Light absorption in 0.1N-sodium hydroxide: Maxima, 2400 Å.,  $\epsilon = 27000$ ; and 3450 Å.,  $\epsilon = 9100$ . 6-Chloro-3-hydroxy-2-methylquinoxaline is sparingly soluble in water; it is soluble in dilute sodium hydroxide and precipitated from this solution on acidification. A mixture with the compound, m. p. 265–268°, obtained by the action of hydrochloric acid on 3-ethoxy-2-methylquinoxaline 1-oxide (Newbold and Spring, *loc. cit.*) had the same m. p.

7-Chloro-2-keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline.—(a) Treatment of 6-chloro-3-hydroxy-2-methylquinoxaline in alkaline solution with methyl sulphate gave the alkali-insoluble 7-chloro-2-keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline which separated from ethanol as needles, m. p. 227–229° (Found: C, 57.3; H, 4.5. C<sub>10</sub>H<sub>9</sub>ON<sub>2</sub>Cl requires C, 57.55; H, 4.3%). A mixture with the compound, described as 2-keto-1-methyl-3-chloromethyl-1 : 2-dihydroquinoxaline by Newbold and Spring (*loc. cit.*), had the same m. p.

(b) A solution of the crude solid (m. p. 235–240°, with sintering at about 220°) (0.9 g.) obtained by the condensation of 4-chloro-*o*-phenylenediamine (0.72 g.) and pyruvic acid (0.75 g.) as described above, in N-sodium hydroxide (18 c.c.) was shaken at room temperature with methyl sulphate (3 c.c.). After 30 minutes the separated solid was collected, washed with water, and dried (0.62 g.; m. p. 130–180°). A solution of the solid in warm benzene (100 c.c.) was filtered through a column (20 × 3 cm.) of alumina (Spence H). The column was washed with benzene (fractions 1–9) and finally with benzene-ethanol (2 : 1, fraction 10; 1 : 1, fraction 11) to give the following fractions:

Fraction.	Eluate (c.c.)	Solute (mg.)	M. p.*	Fraction.	Eluate (c.c.)	Solute (mg.)	M. p.*
1	200	} nil	—	7	200	50	221–223°
2	300		—	8	600	60	218–220
3	150		—	9	500	80	170–205
4	330		—	10	450	280	137–139
5	250		30	223–226°	11	300	nil
6	200	50	222–224				

\* After one crystallisation from ethanol.

Fractions 5 and 6 were combined and recrystallised from ethanol to give 7-chloro-2-keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline as needles, m. p. 227–229°, not depressed when mixed with the specimen prepared as described under (a).

6-Chloro-2-keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline.—(a) 4-Chloro-2-nitro-*N*-methylaniline was obtained in 60% yield from 2 : 5-dichloronitrobenzene and methylamine as described by Blanksma (*Rec. Trav. chim.*, 1902, **21**, 273) with the important modification that the reaction temperature was maintained at 143°. When the temperature used was that given by Blanksma (160°) an intractable tar was obtained. 4-Chloro-2-nitro-*N*-methylaniline separates from ethanol in small orange needles, m. p. 106° (Blanksma gives m. p. 108°). 4-Chloro-2-nitro-*N*-methylaniline (2.8 g.) was added in small portions to a solution of stannous chloride (14 g.) in hydrochloric acid (30 c.c.; *d* 1.19) at 90° and the mixture kept at this temperature for 15 minutes. The cooled mixture was poured into ice-cold sodium hydroxide solution (60 c.c.; 30%) and extracted with ether (4 × 40 c.c.). The solvent was evaporated from the dried (Na<sub>2</sub>SO<sub>4</sub>) extract, the residual brown oil dissolved in dry ether (20 c.c.), and the solution treated with a stream of dry hydrogen chloride until the separation of hydrochloride was complete. The hydrochloride (1.7 g.) was collected and added to a solution of pyruvic acid (5 g.) in water (5 c.c.), and the mixture neutralised with ammonia, a pale yellow solid (0.5 g.) separating. Crystallisation of the solid from ethanol gave 6-chloro-2-keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline as fine needles, m. p. 144–145° (Found: C, 58.0; H, 4.4. C<sub>10</sub>H<sub>9</sub>ON<sub>2</sub>Cl requires C, 57.55; H, 4.3%).

Light absorption in ethanol.

	Max., Å.	$\epsilon$ .
2-Keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline (prepared as described by Cock and Perry, <i>J.</i> , 1943, 394)	2290	21,200
	2805	5,600
	3365	6,700
7-Chloro-2-keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline	2320	24,800
	2810	6,200
	3350	6,600
6-Chloro-2-keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline	2360	31,000
	2780	5,200
	3420	5,200

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(b) Fraction 10 from the alumina column used in the preparation of 7-chloro-2-keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline, described above, was crystallised thrice from ethanol and gave 6-chloro-2-keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline as needles, m. p. 144—145°, undepressed when mixed with the specimen obtained by method (a).

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[Received, May 19th, 1949.]

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