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

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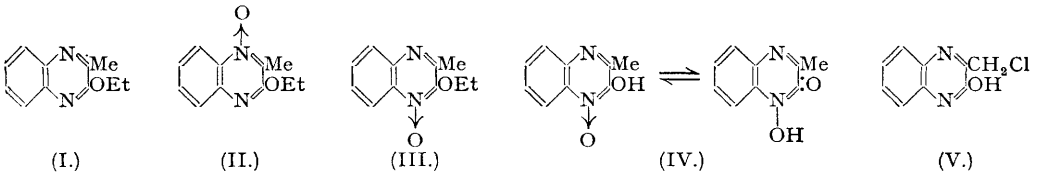
A synthesis of 2-hydroxy-3-chloromethylquinoxaline (V) is described; the product is different from the isomeric compound, m. p. 265—268°, obtained by treatment of 3-ethoxy-2-methylquinoxaline 1-oxide (II) with hydrochloric acid. A synthesis of 6-chloro-3-hydroxy-2-methylquinoxaline (VIII) is described;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

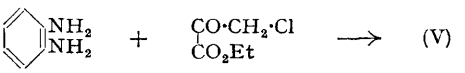
* Part I is "The Oxidation of 2-Hydroxyquinoxaline and its Derivatives with Hydrogen Peroxide," *J.*, 1948, 519.

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).

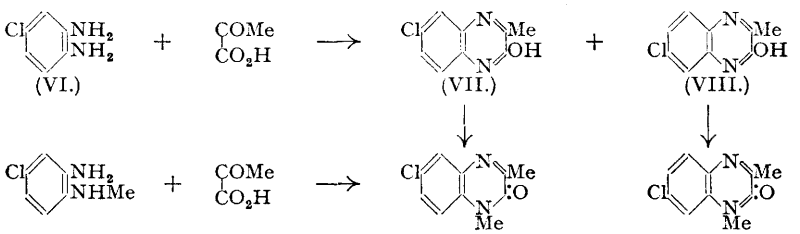


(I.) (II.) (III.) (IV.) (V.)

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



(VI.) (VII.) (VIII.) (XI.) (IX.) (X.)

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 0·1N-sodium hydroxide: Maxima, 2380 A., $\varepsilon = 23{,}600$; and 2540 A., $\varepsilon = 7400$.

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^{-3} mm., giving 6-*chloro*-3-*hydroxy*-2-*methylquinoxaline* as needles, m. p. 265—267° (Found : C, 55·5; H, 3·7. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·6%). Light absorption in 0·1N-sodium hydroxide : Maxima, 2400 A., $\varepsilon = 27000$; and 3450 A., $\varepsilon = 9100$. 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. $C_{10}H_9ON_2Cl$ 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_2SO_4) 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. $C_{10}H_9ON_2Cl$ requires C, 57·55; H, 4·3%).

Light absorption in ethanol.	Max., A.	ε.
2-Keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline (prepared as described by Cock and Perry, *J.*, 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

(*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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