260. 2-*Hydroxy-* and 2-*Amino-derivatives of* 6- *and* 7-*Methylquinoxaline.*

By Bertie C. Platt.

A compound of m. p. 241° which has hitherto been known as 2-hydroxy-6-methylquinoxaline has been shown to be a mixture of the 6-*methyl* compound (IV) (m. p. 274°) and the 7-methyl isomer (III) (m. p. 270—272°).

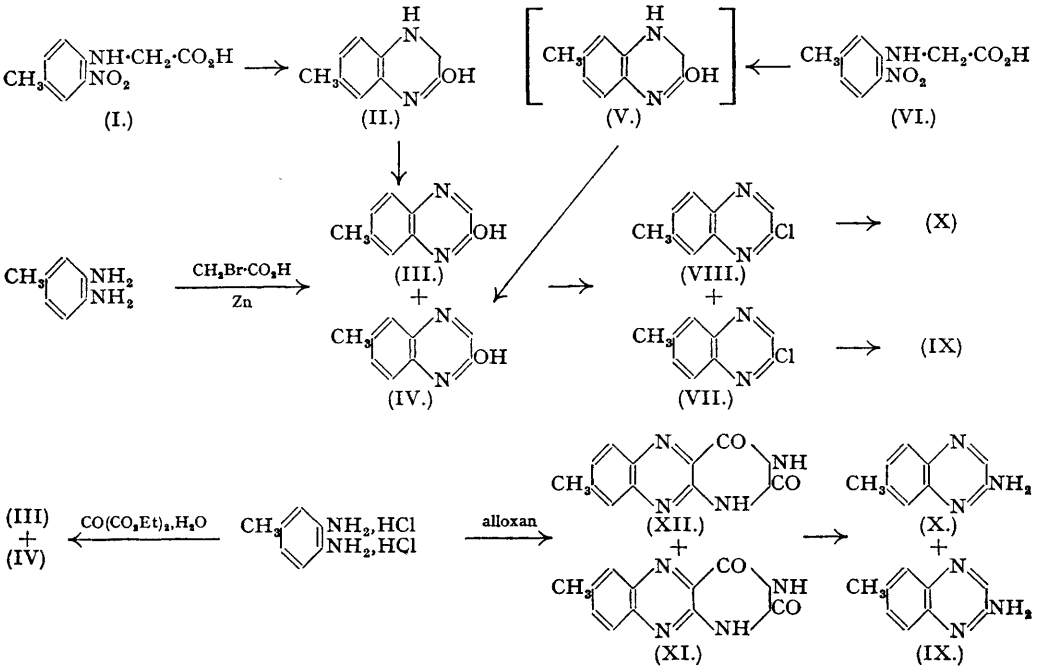
2-*Amino*-6-*methylquinoxaline* (IX) and 2-*amino*-7-*methylquinoxaline* (X) have both been prepared, and it has been shown that the reaction of 3 : 4-diaminotoluene dihydrochloride with either ethyl mesoxalate or alloxan and of the diamine base with bromoacetic acid gives in all three cases a mixture of isomerides.

Hinsberg (*Annalen*, 1888, **248**, 71) prepared 2-hydroxy-7-methylquinoxaline (III) unambiguously by the reduction of 3-nitro-*p*-tolylglycine (I) followed by air oxidation of the resultant 2-hydroxy-7-methyl-3 : 4-dihydroquinoxaline (II). This corrected earlier work by Plöchl (*Ber.*, 1886, **19**, 9) and Leuckart (*ibid.*, p. 174) who had mistaken (III) for (II). 2-Hydroxy-7-methylquinoxaline was also obtained from the interaction of 3 : 4-diaminotoluene with chloroacetic ester (Hinsberg, *Ber.*, 1886, **19**, 483; *Annalen*, 1887, **237**, 327).

A second substance (m. p. 241°) which gave analyses in agreement with a hydroxymethylquinoxaline was obtained (Hinsberg, *Ber.*, 1885, **18**, 1230) by treating 3 : 4-diaminotoluene with alloxan, followed by hydrolysis and decarboxylation of the resulting ureide. This compound was assumed (*idem*, *Annalen*, 1887, **237**, 363; 1888, **248**, 76) to be 2-hydroxy-6-methylquinoxaline although in the later communication Hinsberg refers to the possibility that this compound of m. p. 241° might be a mixture of the 6- and the 7-methyl isomers. Nevertheless, it has been incorporated into the literature as 2-hydroxy-6-methylquinoxaline (Beilstein, 4th edn., **24**, 166).

2-*Hydroxy*-6-*methylquinoxaline* (IV) has now been synthesised unambiguously from 4-*nitro*-m-*tolylglycine* (VI) and has m. p. 274°. A mixture of approximately equal parts of authentic 2-hydroxy-6- and -7-methylquinoxalines prepared from the appropriate *N*-substituted glycines has m. p. 242—246°. It is obvious that the above reactions used by Hinsberg, namely, interaction of 3 : 4-diaminotoluene with either chloroacetic ester or alloxan, could have given rise to the two isomers.

The reactions between 3 : 4-diaminotoluene and bromoacetic acid in the presence of zinc and between 3 : 4-diaminotoluene dihydrochloride and ethyl mesoxalate have also both led to a mixture of 2-hydroxy-6- and -7-methylquinoxalines with m. p. 241°. By fractional recrystallisation from water, pure 2-hydroxy-6-methylquinoxaline (m. p. 274°) has been isolated from the mixture. (Hinsberg, *Ber.*, 1886, **19**, 485, was unable to raise the m. p. above 241° by this means.)



The synthesis of 2-hydroxy-6-methylquinoxaline *via* 4-nitro-*m*-tolylglycine required 4-nitro-*m*-toluidine as starting material. This was prepared from 3-nitro-*p*-toluidine by conversion into 3 : 4-dinitrotoluene (Page and Heasman, *J.*, 1923, **123**, 3241; Geerling and Wibaut, *Rec. Trav. chim.*, 1934, **53**, 1014), followed by treatment with methyl-alcoholic ammonia (Kenner and Parkin, *J.*, 1920, **117**, 858; Elson, Gibson, and Johnson, *J.*, 1929, 2739; Geerling and Wibaut, *loc. cit.*). This last step may have given rise to some 3-nitro-*p*-toluidine which would, in its turn, have led to contamination of the required 2-hydroxy-6-methylquinoxaline with 2-hydroxy-7-methylquinoxaline. This contamination was avoided by purifying the 4-nitro-*m*-toluidine *via* its mono- and *bis-benzenesulphonyl* derivatives, since the m. p.s of each of these derivatives of the two isomers differ widely.

The mixed 2-hydroxy-6- and -7-methylquinoxalines obtained from the ethyl mesoxalate reaction were converted into the mixed chloro-derivatives with phosphorus oxychloride. The product was separated by fractional crystallisation from light petroleum and treatment with hydrochloric acid into 2-*chloro*-6-*methylquinoxaline* (VII) (m. p. 105—107°) and the 7-methyl isomer (VIII) (m. p. 76°).

These two chloro-derivatives were converted by means of an alcoholic solution of ammonia into 2-*amino*-6-*methylquinoxaline* (IX) (m. p. 181—182°) and its 7-*methyl* analogue (X) (m. p. 178—180°). Interaction of 3 : 4-diaminotoluene dihydrochloride with alloxan gave a mixture of 6- and 7-methylalloxazine (XI and XII) since the product, after treatment with concentrated sulphuric acid followed by decarboxylation, yielded a mixture of 2-amino-6- and -7-methylquinoxaline.

Attempts to separate the mixed 6- and 7-methylalloxazines, the mixed 2-amino-6- and -7-methylquinoxaline-3-carboxylic acids, or the mixed 2-amino-6- and -7-methylquinoxalines were unsuccessful. (Kuhn, Vetter, and Rzeppa, *Ber.*, 1937, **70**, 1313, obtained 6- and 7-methylalloxazines as a by-product and were unable to separate them by chromatographic adsorption on alumina.)

For the preparation of 6- and 7-methylalloxazines it was found unnecessary first to isolate

3 : 4-diaminotoluene or its hydrochloride (produced by reduction of 3-nitro-*p*-toluidine) before treatment with alloxan. The yield of 6- and 7-methylalloxazines was raised from 37 to 81% by the addition of boric acid during the condensation.

Experimental.

Mono- and Bis-benzenesulphonyl Derivatives of 3-*Nitro*-p-*toluidine.*—A solution of 3-nitro-*p*-toluidine (4·5 g.; McGookin and Swift, *J. Soc. Chem. Ind.*, 1939, **58**, 152) and benzenesulphonyl chloride (13 g.) in dry pyridine (25 c.c.) was refluxed for 2 hrs., cooled, poured into water, and acidified to give a precipitate which was treated with 2% sodium hydroxide solution. The soluble portion yielded, on acidification, the monobenzenesulphonyl derivative (4·7 g.), m. p. 99—100° (Morgan and Scharff, *J.*, 1914, **105**, 119, give m. p. 101—102°); the insoluble portion, after recrystallisation from alcohol, yielded colourless needles of the *bisbenzenesulphonyl* derivative (1·6 g.), m. p. 199—200° (Found: C, 52·3; H, 3·6; N, 6·5; S, 14·6. $C_{19}H_{16}O_6N_2S_2$ requires C, 52·8; H, 3·7; N, 6·5; S, 14·8%).

Mono- and Bis-benzenesulphonyl Derivatives of 4-*Nitro*-m-*toluidine.*—4-Nitro-*m*-toluidine (0·7 g., prepared from 3-nitro-*p*-toluidine as described, m. p. 111°) was added to a solution of benzenesulphonyl chloride (0·9 g.) in dry pyridine (5 c.c.) and heated under reflux for 1½ hours. Cooling and addition of water gave a yellow precipitate which was extracted with 2% sodium hydroxide solution; acidification and recrystallisation from light petroleum gave the monobenzenesulphonyl derivative (1·0 g., 74%), m. p. 136—138°. (Morgan and Scharff, *loc. cit.*, p. 122, give m. p. 137—138°; their more drastic conditions for its preparation are unnecessary.)

Use of excess of benzenesulphonyl chloride gave the *bisbenzenesulphonyl* derivative, insoluble in 2% sodium hydroxide solution and recrystallisable from alcohol in very pale yellow platelets, m. p. 155° (Found: C, 52·8; H, 3·7; N, 6·3; S, 15·5%).

4-*Nitro*-m-*toluidine.*—Both the mono- and the bis-benzenesulphonyl derivatives of this base were hydrolysed by concentrated sulphuric acid on the water-bath in 1 hour. The base, after recrystallisation from light petroleum, had m. p. 110—111° (lit., m. p. 111°).

4-*Nitro*-m-*tolylglycine.*—4-Nitro-*m*-toluidine (1·0 g.) and iodoacetic acid (0·7 g.) were heated together on the water-bath for 5 hrs. The product was ground under sodium carbonate solution, 0·7 g. of unreacted base remaining undissolved; acidification of the solution gave the *glycine* (0·2 g.), yellow crystals from benzene, m. p. 208° (efferv.) (Found: C, 51·8; H, 4·8; N, 12·7. $C_9H_{10}O_4N_2$ requires C, 51·4; H, 4·8; N, 13·3%).

2-*Hydroxy*-6-*methylquinoxaline.*—The foregoing glycine (0·9 g.) was reduced with tin (1·2 g.) and concentrated hydrochloric acid (20 c.c.). Addition of water and removal of tin as sulphide left a clear pale yellow solution; this was concentrated (100 c.c.), made just alkaline with sodium carbonate solution, and allowed to crystallise (0·41 g., 60%). Some indication of the formation of the 3 : 4-dihydro-derivative (V) was obtained since the product began to soften *ca.* 85°, but on exposure to air the m. p. rose to 270—273°. Sublimation in a vacuum at 200° yielded thin, very pale yellow plates of 2-*hydroxy*-6-*methylquinoxaline*, m. p. 274° (Found: C, 67·8; H, 5·05; N, 17·6. $C_9H_8ON_2$ requires C, 67·5; H, 5·0; N, 17·5%).

2-Hydroxy-7-methylquinoxaline (Plöchl, *Ber.*, 1886, **19**, 9) was obtained in 63% yield by reduction (tin and hydrochloric acid) of 3-nitro-*p*-tolylglycine, obtained by heating 3-nitro-*p*-toluidine (2 mols.) with bromoacetic acid (1 mol.) for 1 hour at 120—140°. After recrystallisation from water, it had m. p. 270—272° (Found: C, 67·7; H, 5·1; N, 18·0%) (Plöchl, *loc. cit.*, gives m. p. 265°; Hinsberg, *Annalen*, 1888, **248**, 76, gives m. p. 266—267°). A mixture of approximately equal portions of authentic 2-hydroxy-6- and -7-methylquinoxaline melted at 242—246°.

Reaction between 3 : 4-*Diaminotoluene, Bromoacetic Acid, and Zinc.*—3 : 4-Diaminotoluene (3·6 g., 1·5 mols.), bromoacetic acid (2·8 g., 1 mol.), and zinc dust (1·2 g.) were heated for 50 minutes on the water-bath. A short but vigorous reaction occurred within a few minutes. The product was extracted with hot water, decanted from the gum which separated on cooling, and the solution heated on the water-bath with a few c.c. of hydrogen peroxide (10-vol.). On cooling, the mixed 2-hydroxy-6- and -7-methylquinoxalines (0·3 g.) were precipitated. Sublimation in a vacuum gave needles, m. p. 240—243°.

2-*Hydroxy*-3-*carbethoxy*-6- *and* -7-*methylquinoxalines.*—Finely ground 3-nitro-*p*-toluidine (45 g.) was suspended in concentrated hydrochloric acid (270 c.c.), and iron filings (81 g.) added in portions. At the end of the reaction, water (300 c.c.) was added, unreacted iron removed, and a solution of ethyl mesoxalate monohydrate (47 g., *Org. Synth.*, Coll. Vol. I, p. 266) in water (300 c.c.) was added. A yellow precipitate began to separate almost at once and the reaction was completed by heating on the water-bath for 1½ hours. After cooling, the yellow precipitate of the mixed quinoxalines was filtered off, washed, and dried (59 g., 86%; decomp. 195°).

2-*Hydroxy*-3-*carboxy*-6- *and* -7-*methylquinoxalines* (Hinsberg, *Ber.*, 1885, **18**, 1230; Kuhling, *Ber.*, 1891, **24**, 2368).—The foregoing crude mixture of esters (49 g.) was hydrolysed with sodium hydroxide solution (10%, 500 c.c.) on the water-bath for 1 hour. Acidification gave the mixed carboxylic acids (35 g., 81%; decomp. 219°).

2-*Hydroxy*-6- *and* -7-*methylquinoxalines.*—The above crude mixed acids (35 g.) were decarboxylated by heating at 240° for ½ hour to give the mixed quinoxalines (18 g., 66%; m. p. 237—241°). Repeated fractional recrystallisation from water yielded 2-hydroxy-6-methylquinoxaline, identical with that obtained by reduction of 4-nitro-*m*-tolylglycine.

2-*Chloro*-6- *and* -7-*methylquinoxalines.*—The crude mixed hydroxyquinoxalines (5·6 g.) were refluxed with phosphorus oxychloride (56 c.c.) for ½ hour. The cooled solution was poured slowly into ice-water, made alkaline with sodium hydroxide (ice cooling), and the precipitated 2-chloro-6- and -7-methylquinoxalines filtered off, washed, and dried (6·1 g., 97%; m. p. 70—104°). Fractional recrystallisation from light petroleum yielded 2-*chloro*-6-*methylquinoxaline* as colourless thin plates, m. p. 105—107° (Found: C, 60·1; H, 4·0; N, 15·8; Cl, 20·4. $C_9H_7N_2Cl$ requires C, 60·5; H, 3·95; N, 15·7; Cl, 19·9%). Treatment of the solid from the more soluble light petroleum fractions with cold concentrated

hydrochloric acid yielded a precipitate of pure 2-chloro-7-methylquinoxaline, m. p. 76°, unaltered by recrystallisation. Leuckart and Hermann (*Ber.*, 1887, **20**, 29) give m. p. 77°.

2-*Amino*-6-*methylquinoxaline*.—2-Chloro-6-methylquinoxaline (0·95 g.) was heated in an autoclave at 155—165° for 5½ hours with a saturated solution of dry ammonia in absolute alcohol (40 c.c.). The resulting solution was evaporated to dryness, and unchanged 2-chloro-6-methylquinoxaline (0·35 g.) removed with light petroleum; the residue after recrystallisation from water gave very pale yellow crystals of 2-*amino*-6-*methylquinoxaline* (0·2 g., m. p. 181—182°) (Found: C, 67·8; H, 5·7; N, 26·5. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%). The *picrate* was obtained from alcohol as yellow crystals, m. p. 278—280° (decomp.) (Found: N, 21·2. $C_{15}H_{13}O_7N_6$ requires N, 21·6%).

2-*Amino*-7-*methylquinoxaline*.—2-Chloro-7-methylquinoxaline (1·1 g., from 2-hydroxy-7-methylquinoxaline and phosphorus oxychloride; Leuckart and Hermann, *Ber.*, 1887, **20**, 29, used phosphorus pentachloride), copper powder (0·1 g.), and an absolute alcoholic solution (40 c.c.) saturated with dry ammonia were heated in an autoclave at 165—180° for 18 hours. After cooling, the copper was filtered off, the solution taken to dryness, and the residue extracted successively with water and with light petroleum. The residue was sublimed in a vacuum to give very pale yellow crystals of 2-*amino*-7-*methylquinoxaline*, m. p. 178—180° (Found: C, 67·6; H, 5·5; N, 26·4%). The picrate crystallised from alcohol, m. p. 259—262° (decomp.).

A mixed m. p. of authentic 2-amino-6- and -7-methylquinoxalines was 172—175°, and that of the corresponding picrates was 239—244°. Both these sets of figures agree with those for the mixed derivatives obtained from 6- and 7-methylalloxazines (see below).

6- *and* 7-*Methylalloxazines* (Kühling, *Ber.*, 1891, **24**, 2365).—Iron filings (75 g.) were added portionwise to a suspension of 3-nitro-*p*-toluidine (45 g.) in concentrated hydrochloric acid (300 c.c.); after removal of unreacted iron the hot yellow solution was mixed with a hot solution of alloxan (48 g.) and boric acid (40 g.) in water (350 c.c.). A yellow precipitate began to separate almost at once. After 1 hour on the water-bath, water (1 l.) was added, and the mixture of 6- and 7-methylalloxazines (decomp. 360°; 55 g., 81%) filtered off, washed, and dried. The solid was purified by addition of water to its solution in cold concentrated hydrochloric acid (Found: N, 24·2. Calc. for $C_{11}H_8O_2N_4$: N, 24·5%).

2-*Amino*-6- *and* -7-*methylquinoxaline*-3-*carboxylic Acids*.—The above mixture of 6- and 7-methylalloxazines (4·0 g.) was heated with ammonia (*d* 0·88; 20 c.c.) in an autoclave at 170—178° for 5½ hours. The yellow mass was treated with water, excess of ammonia was boiled off, and the solution just acidified (Congo-red) to precipitate the mixed *acids* (2·7 g., 76%) on cooling. Recrystallisation from water gave yellow crystals, decomp. 204° (Found: N, 20·4. $C_{10}H_9O_2N_3$ requires N, 20·6%).

2-*Amino*-6- *and* -7-*methylquinoxalines*.—The *dry* ammonium salt from the above mixed acids (5·3 g.) was refluxed in suspension in ethyl benzoate (30 c.c.) for ½ hour. Addition of light petroleum to the cooled solution precipitated the mixed 2-amino-6- and -7-methylquinoxalines (3·6 g., 87%) with m. p. 172—174° after sublimation in a vacuum (Found: C, 67·6; H, 5·6; N, 26·6. Calc. for $C_9H_9N_3$: C, 67·9; H, 5·7; N, 26·4%). It is essential first to isolate the mixed acids, since no 2-amino-6- or -7-methylquinoxaline was obtained when the yellow solution resulting from the action of ammonia on 6- and 7-methylalloxazines was taken to dryness and the residue refluxed with ethyl benzoate.

The picrate formed from this mixture of 2-amino-6- and -7-methylquinoxalines had m. p. 239—244°.

Reaction of nitrous acid with the 2-amino-6- and -7-methylquinoxalines obtained from 6- and 7-methylalloxazines gave a mixture of 2-hydroxy-6- and -7-methylquinoxalines, m. p. 239—250°.

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