

167. Syntheses of 2-Monosubstituted and 2:3-Disubstituted Quinoxalines.

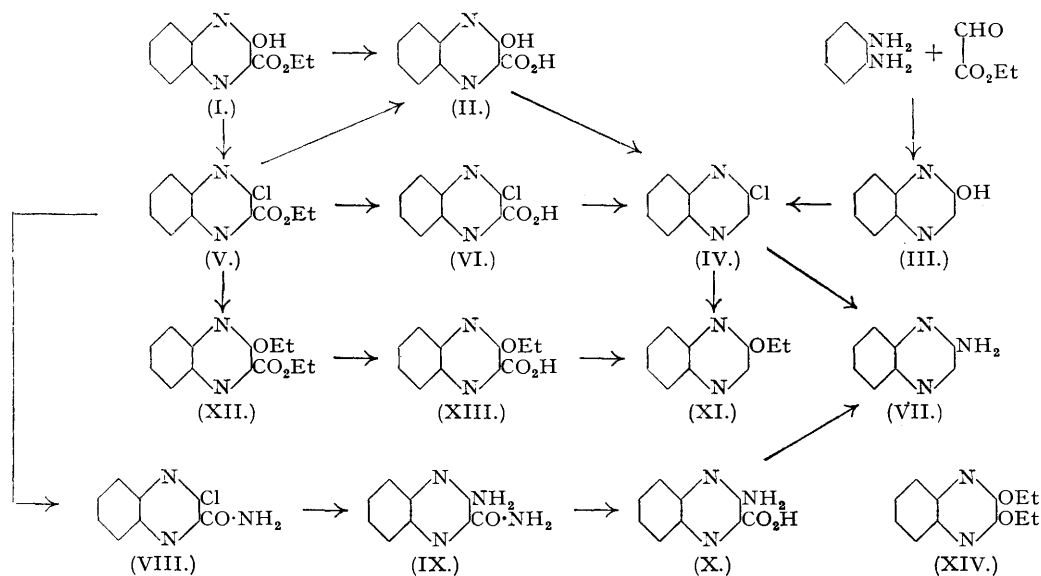
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With the object of preparing pyrazine-2:3-dicarboxylic acids carrying certain substituents at the 5- and 5:6-positions, some 2-monosubstituted and 2:3-disubstituted quinoxalines have been synthesised. Most of these syntheses depend upon transformations of the readily available *ethyl 2-hydroxyquinoxaline-3-carboxylate* (I) which is converted into 2-hydroxyquinoxaline (III), 2-chloroquinoxaline (IV), 2-ethoxyquinoxaline (XI) and 2-aminoquinoxaline (VII). At least one alternative synthesis of each of the 2-substituted quinoxalines has been accomplished. 2:3-Diethoxyquinoxaline and 2:3-diaminoquinoxaline have been prepared from 2:3-dichloroquinoxaline; 2:3-diethoxyquinoxaline is hydrolysed to 2:3-dihydroxyquinoxaline by mineral acid but is stable to aqueous alkali.

2:6-DIHYDROXYPTERIDINE is obtained by the action of alkaline potassium hypobromite solution upon pyrazine-2:3-dicarboxamide (Gabriel and Sonn, *Ber.*, 1907, 40, 4857; Baxter and Spring, *J.*, 1945, 229). In order to apply this method to the synthesis of 8- or 9-monosubstituted and 8:9-disubstituted 2:6-dihydroxypteridines it became necessary to prepare 5-monosubstituted and 5:6-disubstituted pyrazine-2:3-dicarboxylic acids. A possible route to such pyrazine derivatives is by the oxidation of 2-monosubstituted and 2:3-disubstituted quinoxalines. This paper records syntheses of some of the required quinoxaline intermediates including 2-hydroxy-, 2-chloro-, 2-ethoxy- and 2-aminoquinoxaline and 2:3-diamino- and 2:3-diethoxyquinoxaline.

Condensation of *o*-phenylenediamine with ethyl glyoxylate gives 2-hydroxyquinoxaline (III) identical with the product obtained by decarboxylation of 2-hydroxyquinoxaline-3-carboxylic acid (II) (Kuhling, *Ber.*,

1891, 24, 2368; Hinsberg, *Annalen*, 1896, 292, 245; Motylewski, *Ber.*, 1908, 41, 800; Hinsberg, *ibid.*, p. 2033; Kuhn and Bar, *Ber.*, 1934, 67, 898; Ohle and Gross, *Ber.*, 1935, 68, 2262).



2-Chloroquinoxaline (IV) has been prepared by three methods. In the first, ethyl 2-hydroxyquinoxaline-3-carboxylate (I) (Ohle and Gross, *loc. cit.*) is converted into ethyl 2-chloroquinoxaline-3-carboxylate (V) by treatment with phosphorus oxychloride; hydrolysis of (V) by means of sodium carbonate gives 2-chloroquinoxaline-3-carboxylic acid (VI) which when maintained at its melting point for a short time gave 2-chloroquinoxaline. Hydrolysis of ethyl 2-chloroquinoxaline-3-carboxylate by means of sodium hydroxide solution gives 2-hydroxyquinoxaline-3-carboxylic acid (II). In the second method, 2-chloroquinoxaline was obtained directly from 2-hydroxyquinoxaline. Motylewski (*loc. cit.*) found that treatment of 2-hydroxyquinoxaline with phosphorus pentachloride gave 2:3-dichloroquinoxaline. 2-Hydroxyquinoxaline is almost quantitatively converted into 2-chloroquinoxaline by means of phosphorus oxychloride. Finally, 2-chloroquinoxaline is also obtained in small yield by refluxing 2-hydroxyquinoxaline-3-carboxylic acid (II) with phosphorus oxychloride.

Treatment of ethyl 2-chloroquinoxaline-3-carboxylate (V) with alcoholic sodium ethoxide gives ethyl 2-ethoxyquinoxaline-3-carboxylate (XII) alkaline hydrolysis of which yielded 2-ethoxyquinoxaline-3-carboxylic acid (XIII). When heated for a short time at 180° this acid loses carbon dioxide and gives 2-ethoxyquinoxaline (XI). 2-Ethoxyquinoxaline was also obtained by treatment of 2-chloroquinoxaline (IV) with alcoholic sodium ethoxide. 2:3-Diethoxyquinoxaline (XIV) was obtained readily by treatment of 2:3-dichloroquinoxaline with alcoholic sodium ethoxide. It is readily hydrolysed to 2:3-dihydroxyquinoxaline by mineral acid but it is stable to alkali.

When heated with alcoholic ammonia, 2-chloroquinoxaline (IV) readily yields 2-aminoquinoxaline (VII), characterised by its acetyl derivative. A second synthesis of 2-aminoquinoxaline was accomplished starting from ethyl 2-chloroquinoxaline-3-carboxylate (V). Treatment of (V) with alcoholic ammonia at 0° gives 2-chloroquinoxaline-3-carboxamide (VIII) whereas treatment of the chloro-ester (V) with alcoholic ammonia at 150—160° gives 2-aminoquinoxaline-3-carboxamide (IX) which is also obtained by treatment of (VIII) with ammonia at 160°. Hydrolysis of 2-aminoquinoxaline-3-carboxamide gives 2-aminoquinoxaline-3-carboxylic acid (X) identical with the acid obtained by Baxter and Spring (*loc. cit.*) from quinoxaline-2:3-dicarboxamide, and further characterised by the preparation of its methyl ester. When heated for a short time at 250°, 2-aminoquinoxaline-3-carboxylic acid gives 2-aminoquinoxaline. After this section of our study of quinoxaline derivatives was completed, Weijlard, Tishler and Erickson (*J. Amer. Chem. Soc.*, 1944, 66, 1957) described 2-aminoquinoxaline which they obtained by using two methods starting in each case from alloxazine. The properties of the base and its acetyl derivative prepared in this way are in close agreement with those observed by us with the exception that we obtain the acetyl derivative as colourless needles whereas the American authors describe it as yellow crystals.

2:3-Diaminoquinoxaline, which has previously been obtained by the action of cyanogen on *o*-phenylenediamine (Bladin, *Ber.*, 1885, 18, 672; Hinsberg and Schwartes, *Ber.*, 1903, 36, 4040) is readily obtained by the action of alcoholic ammonia upon 2:3-dichloroquinoxaline.

EXPERIMENTAL.

Ethyl 2-Hydroxyquinoxaline-3-carboxylate (cf. Ohle and Gross, *loc. cit.*).—A solution of *o*-phenylenediamine (10.8 g.; 0.1 mol.) and ethyl ketomalonnate (17.4 g.; 0.1 mol.) in absolute alcohol (200 c.c.) was refluxed for 1 hour. After filtering, the hot solution was diluted with water (400 c.c.), and boiled for 15 minutes with charcoal. On cooling, the filtered

solution deposited ethyl 2-hydroxyquinoxaline-3-carboxylate (*ca.* 18 g.) in long pale yellow needles which, after recrystallisation from 95% alcohol, had m. p. 175.5–176.5° (Found: C, 60.4; H, 4.8; N, 13.0. $C_{11}H_{10}O_3N_2$ requires C, 60.55; H, 4.6; N, 12.9%). This ester (11.0 g.) was hydrolysed by heating with 3*N* sodium hydroxide solution (100 c.c.) for 30 minutes on a steam bath. The solution was made acid (Congo-red) and the acid precipitated in yellow-brown needles (95%), m. p. 263–265° (decomp.). Hinsberg (*loc. cit.*) gives m. p. 265° (Found: N, 14.7. Calc. for $C_9H_8O_3N_2$: N, 14.7%). The acid was heated at 265° until evolution of carbon dioxide ceased and the cooled mass sublimed at 200°/10 mm. giving 2-hydroxyquinoxaline (72%), m. p. 266°, identical with the specimen prepared by the method described below.

Ethyl 2-Chloroquinoxaline-3-carboxylate.—A mixture of ethyl 2-hydroxyquinoxaline-3-carboxylate (10.9 g.) and phosphorus oxychloride (50 c.c.) was heated at 110–120° for 10 minutes and the excess phosphorus oxychloride removed in a vacuum. The dark green coloured viscous residue was poured on to crushed ice (600 g.), the mixture neutralised by the addition of ammonia and extracted with ether. The dried (alkali-free sodium sulphate) extract was evaporated and the residue distilled at 10⁻² mm. (bath temperature 170–180°). The chloro-ester distilled as a slightly pink oil and solidified to a mass of nearly white needles (10.65 g., 90%), m. p. 42°. If the crude product obtained by pouring the reaction mixture on to ice is directly crystallised from aqueous methanol (charcoal) the ester is obtained in pink coloured needles m. p. 42° not altered either in colour or m. p. by subsequent recrystallisation. A specimen was sublimed at 60°/6 × 10⁻³ mm. and *ethyl 2-chloroquinoxaline-3-carboxylate* was obtained as a colourless solid, m. p. 42.5° (Found: C, 55.9; H, 4.1; N, 11.9. $C_{11}H_9O_3N_2Cl$ requires C, 55.8; H, 3.8; N, 11.8%). The chloro-ester is very soluble in the common organic solvents at the ordinary temperature. It is sparingly soluble in cold water and moderately soluble in hot water. When stored in air it gradually becomes pink in colour; it is best stored in alcoholic solution at 0°.

Hydrolysis of Ethyl 2-Chloroquinoxaline-3-carboxylate.—(a) *2-Hydroxyquinoxaline-3-carboxylic acid.* The ester (1.0 g.) was refluxed with 3*N* sodium hydroxide solution (20 c.c.) for 30 minutes. The solution was acidified with dilute hydrochloric acid, and made alkaline by the addition of dilute ammonia solution. Addition of an excess of barium chloride solution precipitated a granular barium salt which was collected and decomposed by the addition of a slight excess of *N*-sulphuric acid. Removal of the barium sulphate followed by concentration of the filtrate gave 2-hydroxyquinoxaline-3-carboxylic acid as yellow needles, m. p. 265° (decomp.), undepressed when mixed with an authentic specimen. (b) *2-Chloroquinoxaline-3-carboxylic acid.* A solution of ethyl 2-chloroquinoxaline-3-carboxylate (2.0 g.) and sodium carbonate (0.5 g.) in methanol (80%; 50 c.c.) was refluxed for 4 hours and then evaporated to dryness under reduced pressure. The residue was dissolved in water (20 c.c.) and the solution acidified to Congo-red by the addition of hydrochloric acid. The precipitated acid was collected (1.8 g.) and crystallised from water to give *2-chloroquinoxaline-3-carboxylic acid* as pale yellow prisms, m. p. 146–147° (decomp.). The chloro-acid is also obtained by hydrolysis of the chloro-ester with an aqueous-methanolic solution of sodium cyanide. It is soluble in most organic solvents; it is slightly soluble in concentrated hydrochloric acid the solution having a deep yellow colour, discharged by the addition of water (Found: C, 51.8; H, 2.1; N, 13.6; equiv., 207. $C_9H_7O_3N_2Cl$ requires C, 51.8; H, 2.4; N, 13.4%; equiv., 208.5).

2-Chloroquinoxaline-3-carboxamide.—A solution of ethyl 2-chloroquinoxaline-3-carboxylate (1.0 g.) in anhydrous ethanol (20 c.c.) was treated at 0° for 4 hours with a stream of dry ammonia. After standing at 0° for a further 20 hours the solid (0.55 g.) was collected and crystallised from methanol giving *2-chloroquinoxaline-3-carboxamide* in long white needles, m. p. 214–215°. A further quantity of the amide was recovered from the ethanol mother liquor (total yield, 85%). The amide can also be prepared in rather smaller yield by the addition of aqueous ammonia (*d.* 0.88) to a solution of ethyl 2-chloroquinoxaline-3-carboxylate in 80% methanol at room temperature. It is only slightly soluble in boiling ether and boiling ligroin and freely soluble in boiling methanol, ethanol, chloroform, benzene, acetone, and water (Found: C, 52.0; H, 2.9; N, 20.2. $C_9H_8ON_2Cl$ requires C, 52.0; H, 2.9; N, 20.2%).

2-Aminoquinoxaline-3-carboxamide.—A mixture of ethyl 2-chloroquinoxaline-3-carboxylate (4.0 g.) and alcohol (120 c.c.) saturated at 0° with dry ammonia was heated with stirring in an autoclave at 150–160° for 5 hours. When the reaction mixture had cooled the separated bright yellow needles (1.5 g.) were collected and recrystallised from 70% acetic acid or from aqueous pyridine to give *2-aminoquinoxaline-3-carboxamide* as fine, bright yellow needles m. p. 263–264° (Found: C, 57.5; H, 4.3; N, 29.7. $C_9H_8ON_3$ requires C, 57.4; H, 4.3; N, 29.8%). The original alcohol mother-liquor was evaporated to dryness and the residual solid extracted with hot glacial acetic acid. When diluted with water, this extract gave a further crop (0.94 g.) of the amino-amide (total yield, 77%). The m. p. of the amino-amide varies slightly with the rate of heating. It is soluble in cold dilute hydrochloric acid but not in cold dilute sodium hydroxide solution.

2-Aminoquinoxaline-3-carboxylic Acid.—*2-Aminoquinoxaline-3-carboxamide* (1.0 g.) was refluxed for 3 hours with 10% sodium hydroxide solution (50 c.c.); ammonia was evolved. The cold solution was acidified to Congo-red by the addition of concentrated hydrochloric acid. After standing, the yellow precipitate was collected (0.9 g.) and crystallised from glacial acetic acid to give *2-aminoquinoxaline-3-carboxylic acid* in small yellow needles, m. p. 212–213° (decomp.) undepressed when mixed with the specimen described by Baxter and Spring (*loc. cit.*) (Found: N, 22.4. Calc. for $C_9H_7O_3N_3$: N, 22.2%).

Methyl 2-Aminoquinoxaline-3-carboxylate.—*2-Aminoquinoxaline-3-carboxylic acid* (0.7 g.) suspended in dry boiling methanol (30 c.c.) was treated with dry hydrogen chloride until solution was complete. The brown coloured solution was refluxed for 2 hours and then concentrated (vacuum). The dark yellow crystalline solid was collected, washed with methanol and recrystallised from dry methanol-ether mixture. *Methyl 2-aminoquinoxaline-3-carboxylate hydrochloride* (76%) crystallised in light yellow needles, m. p. 188–189° (decomp.) (Found: C, 50.4; H, 4.5; N, 17.9. $C_{10}H_{10}O_3N_3Cl$ requires C, 50.1; H, 4.2; N, 17.5%). The hydrochloride is soluble in methanol but insoluble in ether. A solution of the hydrochloride (0.2 g.) in hot methanol (25 c.c.) was treated with hot water (50 c.c.). The solution was heated on the steam bath for 45 minutes. On cooling, the solution deposited long yellow needles (60%) of *methyl 2-aminoquinoxaline-3-carboxylate* which, after recrystallisation from methanol, had m. p. 218–219°; it contained no halogen (Found: C, 58.8; H, 4.4. $C_{10}H_9O_3N_3$ requires C, 59.1; H, 4.4%). This ester (30 mg.) was hydrolysed by refluxing with methanol (3 c.c.) and aqueous 10% potassium hydroxide (2 c.c.) for 1 hour. The concentrated solution was acidified (Congo-red) and the *2-aminoquinoxaline-3-carboxylic acid* collected and crystallised from aqueous acetic acid; it had m. p. 211° (decomp.), unaffected when mixed with the specimen described above.

2-Hydroxyquinoxaline.—Ethyl glyoxylate (3.8 g.) (Oroshnik and Spoerri, *J. Amer. Chem. Soc.*, 1941, **63**, 3338) was added to a solution of *o*-phenylenediamine (2.7 g.) in ethanol (50 c.c.). The reaction mixture became hot and deposited solid. When the initial vigorous reaction had abated, the mixture was heated under reflux for 30 minutes, cooled and the solid collected and washed with a little alcohol. Sublimation of this solid at 200°/0.5 mm. gave 2-hydroxyquinoxaline (57%) as needles, m. p. 271° (Hinsberg, *loc. cit.* gives m. p. 265° and Motylewski, *loc. cit.*, m. p. 269°) (Found: C, 65.5; H, 4.6; N, 19.2. Calc. for $C_8H_8ON_2$: C, 65.75; H, 4.1; N, 19.2%).

2-Chloroquinoxaline.—(a) *2-Chloroquinoxaline-3-carboxylic acid* (1.8 g.) was mixed with glass wool and heated at 0.1 mm. When the bath temperature attained 160°, a yellow oil distilled and solidified on cooling (0.85 g.), a black amorphous mass remaining in the flask. Crystallisation of the distillate from *n*-pentane gave *2-chloroquinoxaline* in slightly yellow coloured clusters of prismatic needles, m. p. 46–47° (Found: C, 58.2; H, 2.9; N, 16.8. $C_8H_7N_2Cl$

requires C, 58.4; H, 3.0; N, 17.0%). (b) 2-Hydroxyquinoxaline (0.7 g.) was heated under reflux with freshly distilled phosphorus oxychloride (20 c.c.) for 20 minutes. The solution was concentrated (reduced pressure) and the residual oil poured into ice-water. The solid was collected by means of ether, the ethereal solution washed with water, dried (sodium sulphate) and the ether removed. Distillation of the residue gave a colourless oil (b. p. 80°/0.5 mm.) setting to a mass of needles which after one crystallisation from *n*-pentane gave 2-chloroquinoxaline in colourless needles (85%), m. p. 46–47°, unchanged when mixed with a specimen prepared by method (a) (Found: C, 58.8; H, 2.8%). (c) 2-Hydroxyquinoxaline-3-carboxylic acid (2 g.) was refluxed with phosphorus oxychloride (30 c.c.) for 30 minutes and the reaction mixture treated as described above. 2-Chloroquinoxaline (18%) was obtained in long colourless needles from *n*-pentane, m. p. 46–47°, unchanged when mixed with a specimen prepared by method (a). 2-Chloroquinoxaline is insoluble in water and soluble in common organic solvents. It dissolves readily in 5*N* hydrochloric acid and in 10*N* hydrochloric acid, but in the latter case solution is immediately followed by the separation of a hydrochloride.

2-Aminoquinoxaline.—(a) 2-Chloroquinoxaline (1.0 g.) was heated in an autoclave for 7 hours at 150° with a dry ethanolic solution of ammonia (20 c.c., saturated at 0°). The solution was evaporated to dryness (reduced pressure) and the residual solid twice crystallised (charcoal) from water from which the 2-aminoquinoxaline (86%) separated in faintly yellow coloured needles, m. p. 155–157°. 2-Aminoquinoxaline is very soluble in methanol and ethanol, but only sparingly soluble in ether. It sublimes rapidly at 130–140°/10⁻³ mm. (Found: C, 66.5; H, 5.0. Calc. for C₈H₆N₂: C, 66.2; H, 4.8%). (b) 2-Aminoquinoxaline-3-carboxylic acid (1.0 g.) was heated at 250° for 3 minutes. The acid melted with evolution of carbon dioxide. The cooled mass was extracted with boiling water (25 c.c.) and the extract concentrated (charcoal). This deposited 2-aminoquinoxaline (38%) in yellow felted needles, m. p. 155–157° undepressed when mixed with the specimen prepared by method (a). 2-Aminoquinoxaline (0.2 g.) was refluxed with acetic anhydride (3 c.c.) for 45 minutes. Methanol (5 c.c.) was added and the solution evaporated to dryness. The residual brown crystalline mass was twice crystallised from methanol and 2-acetamidoquinoxaline obtained in small colourless needles, m. p. 193–194° (Found: C, 64.0; H, 4.9. Calc. for C₁₀H₉ON₃: C, 64.2; H, 4.8%).

Ethyl 2-Ethoxyquinoxaline-3-carboxylate.—A solution of ethyl 2-chloroquinoxaline-3-carboxylate (2 g.) in dry ethanol (11 c.c.) was added to a hot solution of sodium ethoxide in ethanol (from 0.2 g. sodium and 25 c.c. ethanol). The mixture was refluxed for two hours, cooled and filtered. The filtrate was evaporated to a small bulk, diluted with water and extracted with ether. The dried extract was evaporated and the residue distilled at 0.01 mm. (bath temp. 180°) yielding ethyl 2-ethoxyquinoxaline-3-carboxylate (80%) as a white solid, m. p. 25°. The ester is very soluble in the common organic solvents (Found: N, 11.5. C₁₃H₁₄O₃N₂ requires N, 11.4%).

2-Ethoxyquinoxaline-3-carboxylic Acid.—(a) A solution of ethyl 2-ethoxyquinoxaline-3-carboxylate (1.0 g.) in ethanol (20 c.c.) and aqueous potassium hydroxide (10%; 2 c.c.) was refluxed for 1 hour. The solution was concentrated, diluted with water and acidified (Congo-red) with dilute hydrochloric acid. The crystalline acid separating at 0° was collected and recrystallised from aqueous methanol to give 2-ethoxyquinoxaline-3-carboxylic acid (70%) in colourless needles, m. p. 120–121° (Found: C, 60.5; H, 4.7; N, 12.4%; equiv., 219. C₁₁H₁₀O₃N₂ requires C, 60.55; H, 4.6; N, 12.8%; equiv., 218).

2-Ethoxyquinoxaline.—(a) 2-Ethoxyquinoxaline-3-carboxylic acid (1.0 g.) was heated to 180° until evolution of carbon dioxide ceased. The resulting solid was dissolved in ether, the solution washed with 3*N* sodium hydroxide and dried (sodium sulphate). Removal of the ether followed by crystallisation from *n*-pentane gave 2-ethoxyquinoxaline (94%) in colourless needles, m. p. 56–58° undepressed when mixed with the specimen described below. (b) A solution of 2-chloroquinoxaline (1.64 g.) in dry ethanol (25 c.c.) added to a solution of sodium ethoxide in ethanol (from 0.3 g. sodium and 25 c.c. ethanol) was heated under reflux for one hour, cooled, and the separated salt removed by filtration. The filtrate was evaporated to remove alcohol, diluted with water and the precipitated solid isolated by means of ether. One crystallisation of the product from *n*-pentane gave pure 2-ethoxyquinoxaline (81%) as rosettes of colourless needles, m. p. 56–58°. It is very soluble in the common organic solvents (Found: C, 69.2; H, 5.7; N, 15.9. C₁₀H₁₀ON₂ requires C, 69.0; H, 5.7; N, 16.1%).

2 : 3-Diethoxyquinoxaline.—A solution of 2 : 3-dichloroquinoxaline (1.99 g.) (Hinsberg and Pollak, *Ber.*, 1896, 29, 784) in dry ethanol (30 c.c.) was mixed with a solution of sodium ethoxide in ethanol (from 0.5 g. sodium and 30 c.c. ethanol). The mixture was refluxed for 3½ hours, cooled and the salt removed by filtration. The filtrate was concentrated, pure 2 : 3-diethoxyquinoxaline (80%) separating as long colourless needles, m. p. 78° (Found: C, 66.0; H, 6.4; N, 12.9. C₁₂H₁₄O₂N₂ requires C, 66.1; H, 6.4; N, 12.8%). 2 : 3-Diethoxyquinoxaline was recovered unchanged after refluxing for 1 hour with 0.2*N* aqueous-ethanolic potassium hydroxide solution. 2 : 3-Diethoxyquinoxaline (0.2 g.) in ethanol (15 c.c.) was refluxed for 1 hour with hydrochloric acid (*d* 1.19, 5 c.c.). The solution was concentrated to a bulk of 5 c.c., diluted with water (10 c.c.) and cooled; 2 : 3-dihydroxyquinoxaline, not melting below 350°, separated. It is freely soluble in sodium hydroxide solution and is precipitated from this solution on acidification. In 0.1*N* sodium hydroxide it exhibits maxima at 3160 Å. ($\epsilon = 12,200$), 3260 Å. ($\epsilon = 14,400$) and 3410 Å. ($\epsilon = 10,500$). Scudi and Silber (*J. Biol. Chem.*, 1944, 156, 343) give maxima at 3270 Å. ($\epsilon = 16,800$) and 3415 Å. ($\epsilon = 10,600$) for 2 : 3-dihydroxyquinoxaline.

2 : 3-Diaminoquinoxaline.—2 : 3-Dichloroquinoxaline (2 g.) was heated for 6 hours at 150° with a solution of ammonia in ethanol (30 c.c. saturated at 0°). The solution was evaporated to dryness (reduced pressure) and the residue extracted with boiling pyridine (2 × 25 c.c.). After concentration, the extract yielded the diamino-compound (47%) in yellow needles, m. p. 328–330° (decomp.) after three recrystallisations from the same solvent (Found: C, 60.2; H, 5.2; N, 34.5. Calc. for C₈H₈N₄: C, 60.0; H, 5.0; N, 35.0%).