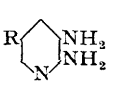
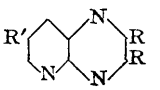
282. *Some 5-Azaquinoxalines and 4-Azabenziminazoles.*

By V. Petrow and J. Saper.

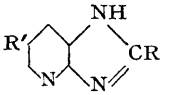
5-Aza- and *7-bromo-5-aza-quinoxalines* have been prepared by condensation of 2 : 3-diaminopyridine (I) and *5-bromo-2 : 3-diaminopyridine* (I*a*) with certain *α*-diketones. *6-Amino-2 : 3-diphenyl-5-azaquinoxaline* has been obtained by reaction of benzil with 2 : 3 : 6-triaminopyridine. The conversion of the diaminopyridines (I) and (I*a*) into certain 4-azabenziminazoles is described.



(I; R = H. I*a*; R = Br.)



(II; R′ = H. II*a*; R′ = Br.)



(III.)

THE study of heavily basic ring systems of potential biological interest, in progress in these laboratories, has now been extended to some derivatives of 5-azaquinoxaline (II) and 4-azabenziminazole (III).

5-Azaquinoxaline (II; R = H) and its 2 : 3-*dimethyl* (II; R = Me) and 2 : 3-diphenyl (II; R = Ph; see Tschitschibabin and Kirsanow, *Ber.*, 1927, **60**, 773) derivatives were severally prepared by condensation of glyoxal sodium bisulphite, diacetyl, and benzil with 2 : 3-diaminopyridine (I). 3-Nitro-2-aminopyridine, required for reduction to the latter compound (I), was prepared by the method of Caldwell and Kornfeld (*J. Amer. Chem. Soc.*, 1942, **64**, 1696), although in only 1—2% yield. Small-scale experiments using Tschitschibabin's method (*J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1236) occasionally gave 5% yields which could not be reproduced on a larger scale. Reduction of the 3-nitro-2-aminopyridine to (I) has been described by Tschitschibabin and Kirsanow (*loc. cit.*), who used tin and concentrated hydrochloric acid. This method of reduction is both long and unsuitable, yielding a mixture of (I) and 4(or 6)-chloro-2 : 3-diaminopyridine, separated by fractionation from water in which (I) is the more soluble component. The 51% yield of (I) claimed by the Russian authors was unfortunately never reached in our hands, only 10—15% yields being in general obtained. It was ultimately found that (I) was formed in yields exceeding 75% by reduction of 3-nitro-2-aminopyridine with reduced iron in acidulated aqueous ethanol to give a product of substantially higher melting point (119·5°) than that recorded in the literature (113°). The 2 : 3-diphenyl-5-azaquinoxaline (II; R = Ph), referred to above, prepared from this diamino-base, also had a melting point higher than that previously reported.

7-Bromo-5-azaquinoxaline (IIa; R = H), and its 2 : 3-*dimethyl* (IIa; R = Me) and 2 : 3-*diphenyl* (IIa; R = Ph) derivatives were prepared by condensation of *5-bromo-2 : 3-diaminopyridine* (Ia) with glyoxal sodium bisulphite, diacetyl, and benzil. Condensation with phenanthraquinone gave *7-bromophenanthro*(9′ : 10′ : 2 : 3)-*5-azaquinoxaline*. An improved method for obtaining 5-bromo-3-nitro-2-aminopyridine, required for conversion into (Ia), had perforce to be developed. The procedure used by Tschitschibabin and Tjashelowa (*J. Russ. Phys. Chem. Soc.*, 1918, **50**, 483), involving the isolation and rearrangement of 5-bromo-2-nitroaminopyridine, broke down when applied to substantial quantities of materials. The method finally adopted (see Experimental) gave 40% yields of 5-bromo-3-nitro-2-aminopyridine calculated on 2-aminopyridine. Its reduction with reduced iron in acidulated aqueous ethanol gave (Ia) in excellent yield, characterised by conversion into the *diformyl* and the *diacetyl* derivative.

6-Amino-2 : 3-diphenyl-5-azaquinoxaline was prepared by reaction between benzil and 2 : 3 : 6-triaminopyridine. The preparation of the latter compound was attended by some difficulty. Its isolation as a dihydrochloride following catalytic reduction of 2 : 6-diamino-3-benzeneazopyridine has been recorded by Tschitschibabin and Hoffmann (*Compt. rend.*, 1937, **205**, 153), whilst the preparation of 3-amino-2 : 6-diacetamidopyridine by catalytic reduction of 3-nitro-2 : 6-diaminopyridine is claimed in Swiss Patent, 212,197. Free triaminopyridine is oxidised by air to a blue dye with extreme rapidity, and its isolation before condensation with benzil proved a failure. The above quinoxaline was finally obtained by reduction of (*a*) 3-nitro-2 : 6-diaminopyridine with reduced iron in acidulated aqueous ethanol, or (*b*) 3-nitroso-2 : 6-diaminopyridine (Tschitschibabin and Seide, *J. Gen. Chem. Russia*, 1918, **50**, 536) with sodium sulphide or ammonium sulphide, followed in both cases by direct addition of benzil. The identity of the products obtained by the two methods was confirmed by a comparison of their *acetyl* derivatives. The formation of 2 : 3 : 6-triaminopyridine under the above conditions of reduction was independently confirmed by conversion of the reduction product obtained by method (*b*) into the known 2 : 3 : 6-triacetamidopyridine (Tschitschibabin and Hoffmann, *loc. cit.*).

Bernstein, Stearns, Shaw, and Lott (*J. Amer. Chem. Soc.*, 1947, **69**, 115) have since described the preparation of some 6-amino-5-azaquinoxalines by an essentially similar method.

Attempts to convert some of the above azaquinoxalines into their *N*-oxides for examination as bacteriostatic agents (see McIlwain, *J.*, 1943, 332) did not give encouraging results. 2 : 3-Dimethyl-5-azaquinoxaline (II; R = Me) was unaffected by hydrogen peroxide in glacial acetic acid at 70°, and the product obtained from 2 : 3-diphenyl-5-azaquinoxaline (II; R = Ph) could not be purified satisfactorily. 7-Bromo-5-azaquinoxaline (IIa; R = H), however, gave a *mono*-N-*oxide* under these conditions.

Some interesting biological results have recently been reported for benziminazole derivatives in the fields of bacterial growth-inhibitors (Woolley, *J. Biol. Chem.*, 1944, **152**, 225) and thyroid hyperfunction (McGinty *et al.*, *J. Pharm. Exp. Thor.*, 1945, **84**, 342; **85**, 14). The 4-azabenz-

iminazoles (III) are structurally related both to these compounds and to the purines. We have consequently synthesised a few members of this group.

4-Azabenziminazole (III; R = R′ = H) was obtained by the action of boiling formic acid on (I). *6-Bromo-2-methyl-4-azabenziminazole* (III; R = Me; R′ = Br) was formed by heating 5-bromo-2 : 3-diacetamidopyridine above its melting point. *2-Hydroxy-4-azabenzimidazole* (III; R = OH, R′ = H) and its *6-bromo*-derivative (III; R = OH, R′ = Br) were prepared by fusion of (I) and (I*a*) with urea. The corresponding *thiols* (III; R = SH, R′ = H, and R = SH, R′ = Br) were obtained by the action of alcoholic carbon disulphide on the diamino-bases and, in the case of the bromo-thiol, by fusion of (I*a*) with thiourea.

Experimental.

M. p.s are corrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.

2 : 3-*Diaminopyridine* (I).—3-Nitro-2-aminopyridine (2·5 g.), reduced iron (7·5 g.), spirit (15 ml.), water (8 ml.), and concentrated hydrochloric acid (0·5 ml.) were heated under reflux for 1 hour. The filtrate and washings were evaporated to very small volume, made alkaline with sodium hydroxide, and the precipitated black solids dried and extracted with boiling benzene (charcoal). 2 : 3-Diaminopyridine separated in white needles (1·5 g., 75%), m. p. 118·5—119·5° (Found : C, 54·9; H, 6·4. Calc. for $C_5H_7N_3$: C, 55·0; H, 6·4%). Tschitschibabin and Kirsanow (*Ber.*, 1927, **60**, 771) give m. p. 112—113°. 2 : 3-Diphenyl-5-azaquinoxaline prepared from this compound had m. p. 146—148° (Tschitschibabin and Kirsanow, *ibid.*, p. 773, give m. p. 136—138°).

5-Azaquinoxaline (II; R = H).—A suspension of 2 : 3-diaminopyridine (1·5 g.) and glyoxal sodium bisulphite (4 g.) in aqueous spirit (20 ml.) was heated on the water-bath for 1 hour. The solution was evaporated to very small volume, sodium hydroxide solution (3 ml. of 33%) added, and the dark green product taken to dryness. Extraction of the residue with light petroleum (b. p. 60—80°) gave small needles (300 mg., 17%) of *5-azaquinoxaline*, m. p. 147—148° (Found : N, 32·4. $C_7H_5N_3$ requires N, 32·1%).

2 : 3-*Dimethyl-5-azaquinoxaline* (II; R = Me).—Diacetyl (900 mg.) and 2 : 3-diaminopyridine (1·1 g.) in benzene (20 ml.) were heated under reflux for 1½ hours. Evaporation of the solution gave 2 : 3-*dimethyl-5-azaquinoxaline* (700 mg., 40%), straw-coloured needles from benzene; m. p. 148—149° (Found : C, 68·2; H, 5·6; N, 27·0. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%).

5-Bromo-3-nitro-2-aminopyridine.—The following improved method of preparation was used (cf. Tschitschibabin and Tjashelowa, *loc. cit.*) : 5-Bromo-2-aminopyridine (20 g.) was slowly added with mechanical stirring to sulphuric acid (*d* 1·4) (120 ml.) at 0°. Fuming nitric acid (3·4 ml.) was then added dropwise to the stirred solution. The mixture was kept for a further hour at 0°, then for 1 hour at room temperature, and finally for 1 hour at 50—60°. The product was poured on crushed ice (*ca.* 2 l.), basified with sodium hydroxide, and the precipitated yellow solids crystallised from spirit, yielding 5-bromo-3-nitro-2-aminopyridine (10 g., 40%) in long yellow needles, m. p. 211—212°.

5-Bromo-2 : 3-diaminopyridine (I*a*).—5-Bromo-3-nitro-2-aminopyridine (10 g.), reduced iron (30 g.), spirit (40 ml.), water (10 ml.), and concentrated hydrochloric acid (0·5 ml.) were heated under reflux for 1 hour. Evaporation of the filtrate and washings followed by crystallisation from benzene (charcoal) gave white plates of *5-bromo-2 : 3-diaminopyridine* (6 g., 70%), m. p. 164—165° (Found : C, 32·4; H, 3·2; Br, 42·0. $C_5H_6N_3Br$ requires C, 31·9; H, 3·2; Br, 42·5%).

5-Bromo-2 : 3-diformamidopyridine, white needles from ethanol–light petroleum (b. p. 80—100°), m. p. 230—231° (softening at 179°) (Found : C, 34·3; H, 2·7. $C_7H_6O_2N_3Br$ requires C, 34·4; H, 2·5%), was obtained when 5-bromo-2 : 3-diaminopyridine (1 g.) was treated with formic acid (1 ml., 98%) under reflux for 15 minutes, followed by precipitation with aqueous ammonia.

5-Bromo-2 : 3-diacetamidopyridine, felted white needles from benzene, m. p. 214—215° (decomp. at 255°) (Found : C, 39·9; H, 3·8; N, 15·6. $C_9H_{10}O_2N_3Br$ requires C, 39·7; H, 3·7; N, 15·4%), was prepared by heating the amino-compound (2 g.) with acetic anhydride (5 ml.) under reflux for 30 minutes.

7-Bromo-5-azaquinoxaline (II*a*; R = H).—A suspension of 5-bromo-2 : 3-diaminopyridine (1·9 g.) and glyoxal sodium bisulphite (2·6 g.) in aqueous ethanol (20 ml.) was heated on the water-bath for 1 hour. The cooled solution was basified with 5N-sodium hydroxide solution. The precipitated solids gave *7-bromo-5-azaquinoxaline*, small needles (800 mg., 36%) from light petroleum (b. p. 80—100°), m. p. 167° (Found : C, 40·2; H, 2·0; Br, 37·6. $C_7H_4N_3Br$ requires C, 40·0; H, 1·9; Br, 38·1%).

7-Bromo-2 : 3-dimethyl-5-azaquinoxaline (II*a*; R = Me).—The following experimental conditions must be strictly followed : A solution of diacetyl (1 g.) and 5-bromo-2 : 3-diaminopyridine (1·9 g.) in spirit (40 ml.) was heated under reflux for 30 minutes. The solution was evaporated, and the product which separated on cooling collected. *7-Bromo-2 : 3-dimethyl-5-azaquinoxaline* formed thin, light grey needles (1·6 g., 66%) from light petroleum (b. p. 80—100°), m. p. 150° (decomp.) (Found : C, 45·6; H, 3·7; Br, 33·3. $C_9H_8N_3Br$ requires C, 45·4; H, 3·4; Br, 33·6%).

7-Bromo-2 : 3-diphenyl-5-azaquinoxaline (II*a*; R = Ph).—A mixture of benzil (2·2 g.) and 5-bromo-2 : 3-diaminopyridine (2 g.) in benzene (60 ml.) was heated under reflux for 1½ hours. The solution was evaporated, and *7-bromo-2 : 3-diphenyl-5-azaquinoxaline* crystallised on cooling. It formed clusters of yellow needles (2·5 g., 65%) from light petroleum (b. p. 80—100°), m. p. 156—158° (Found : C, 62·8; H, 3·6; Br, 22·1. $C_{19}H_{12}N_3Br$ requires C, 63·0; H, 3·3; Br, 22·1%). The *trimethiodide* was prepared from the methosulphate, obtained by adding methyl sulphate (3 g.) to a hot solution of the base (3 g.) in nitrobenzene (15 ml.). It formed short red needles from ethanol, m. p. 192° (decomp.) (Found : N, 5·0; $C_{22}H_{22}N_3BrI_3$ requires N, 5·3%).

7-Bromo-phenanthro(9′ : 10′ : 2 : 3)*-5-azaquinoxaline.*—5-Bromo-2 : 3-diaminopyridine (1 g.) and phenanthraquinone (1·1 g.) in glacial acetic acid (10 ml.) were heated under reflux for 1½ hours. The

golden solid which separated on addition of water was collected, and crystallised first from benzene and finally from aqueous acetic acid. The *azaquinoxaline* separated in felted golden needles, m. p. 222° (Found : C, 63·5; H, 3·0. $C_{19}H_{10}N_3Br$ requires C, 63·3; H, 2·8%).

2 : 3 : 6-*Triacetamidopyridine.*—Hydrogen sulphide was passed into a suspension of 3-nitroso-2 : 6-diaminopyridine (1·5 g.) in ethanolic ammonia (50 ml.) until a clear yellow solution was obtained. The product was evaporated to dryness under reduced pressure, acetic anhydride (20 ml.) added to the yellow residue, and the mixture heated under reflux for 15 minutes. Excess of acetic anhydride was removed under reduced pressure. Extraction of the residue with ethanol followed by evaporation of the filtrate to small volume and addition of light petroleum (b. p. 80—100°) gave 2 : 3 : 6-triacetamidopyridine, small white prisms from ethanol–light petroleum (b. p. 80—100°) (1 g., 37%), m. p. 251—252° (Found : C, 52·6; H, 5·3; N, 22·5. Calc. for $C_{11}H_{14}O_3N_4$: C, 52·8; H, 5·6; N, 22·4%).

6-*Amino*-2 : 3-*diphenyl*-5-*azaquinoxaline.*—(a) 3-Nitro-2 : 6-diaminopyridine (1·5 g.), reduced iron (4 g.), spirit (10 ml.), water (5 ml.), and concentrated hydrochloric acid (0·5 ml.) were heated under reflux for 10 minutes. A solution of benzil (2 g.) in spirit was added, and the mixture heated for a further hour. The filtered mixture gave 6-*amino*-2 : 3-*diphenyl*-5-*azaquinoxaline*, light-yellow felted needles (1 g., 26%) from benzene, m. p. 273° (Found : C, 75·7; H, 4·9; N, 19·6. $C_{19}H_{14}N_4$ requires C, 76·5; H, 4·7; N, 18·8%).

(b) 3-Nitroso-2 : 6-diaminopyridine (1 g.) was reduced with hydrogen sulphide (see above). A solution of benzil (1 g.) in spirit was added to the yellow residue, and the mixture heated under reflux for 30 minutes. Evaporation of the filtrate gave 6-amino-2 : 3-diphenyl-5-azaquinoxaline, m. p. 273°, alone or mixed with an authentic specimen.

6-*Acetamido*-2 : 3-*diphenyl*-5-*azaquinoxaline*, white felted needles from aqueous ethanol, m. p. 268—269° (Found : C, 73·6; H, 4·9; N, 16·5. $C_{21}H_{16}ON_4$ requires C, 74·1; H, 4·7; N, 16·5%), was obtained when the amino-compound (1 g.) was heated under reflux with acetic anhydride (10 ml.) for 15 minutes followed by precipitation with dilute ammonium hydroxide.

7-*Bromo*-5-*azaquinoxaline mono*-N-*oxide*, small cream needles (1·1 g., 73%) from spirit, m. p. 286° (decomp.) (Found : C, 37·5; H, 1·9. $C_7H_4ON_3Br$ requires C, 37·2; H, 1·8%), separated when a mixture of hydrogen peroxide (100-vol.) (2 ml.) and 7-bromo-5-azaquinoxaline (1·4 g.) in glacial acetic acid (6 ml.) was warmed to 70° for 1 hour.

4-*Azabenziminazole* (III; R = R′ = H).—2 : 3-Diaminopyridine (700 mg.) in formic acid (98%) (1 ml.) was heated under reflux for 1 hour. Excess of formic acid was removed under reduced pressure, and the brown glassy residue crystallised from ethanol–light petroleum (b. p. 80—100°). 4-*Azabenziminazole* separated in small spangles of white needles (400 mg., 52%), m. p. 153—154° (Found : C, 60·4; H, 4·8; $C_6H_5N_3$ requires C, 60·5; H, 4·2%).

6-*Bromo*-2-*methyl*-4-*azabenziminazole* (III; R = Me, R′ = Br).—Obtained when 5-bromo-2 : 3-diacetamidopyridine (1·3 g.) was heated at 315° for *ca.* two minutes, this *compound* formed clusters of small white needles (500 mg., 50%) from spirit, m. p. 299° (Found : C, 39·8; H, 3·3; N, 19·7. $C_7H_6N_3Br$ requires C, 39·6; H, 2·8; N, 19·8%).

2-*Hydroxy*-4-*azabenziminazole* (III; R = OH, R′ = H), small white needles from spirit, m. p. 274° (Found : C, 52·7; H, 3·9. $C_6H_5ON_3$ requires C, 53·3; H, 3·7%), was obtained when an intimate mixture of 2 : 3-diaminopyridine (1·1 g.) and urea (600 mg.) was fused at 130—140° for 30 minutes.

6-*Bromo*-2-*hydroxy*-4-*azabenziminazole* (III; R = OH, R′ = Br), small crystals from glacial acetic acid, m. p. > 300° (Found : C, 34·4; H, 2·2. $C_6H_4ON_3Br,\frac{1}{2}CH_3{\cdot}CO_2H$ requires C, 34·4; H, 2·5%), was obtained when a finely powdered mixture of 5-bromo-2 : 3-diaminopyridine (900 mg.) and urea (300 mg.) was fused at 160—170° for 45 minutes.

4-*Azabenziminazole*-2-*thiol* (III; R = SH, R′ = H), short cream needles (800 mg., 58%), m. p. > 300° (Found : C, 47·8; H, 3·5; S, 21·6. $C_6H_5N_3S$ requires C, 47·7; H, 3·3; S, 21·2%), from spirit, was obtained when carbon disulphide (800 mg.) was added to a solution of 2 : 3-diaminopyridine (1 g.) in ethanol (20 ml.) and the mixture boiled under reflux for 5 hours.

6-*Bromo*-4-*azabenziminazole*-2-*thiol* (III; R = SH, R′ = Br).—(a) A mixture of carbon disulphide (800 mg.), 5-bromo-2 : 3-diaminopyridine (1·9 g.), and potassium hydroxide (100 mg.) in ethanol was heated under reflux for 2 hours. The product which separated on cooling was collected and crystallised from ethanol, affording light yellow needles of 6-*bromo*-4-*azabenziminazole*-2-*thiol*, m. p. > 300° (Found : C, 31·3; H, 1·7; S, 13·7. $C_6H_4N_3BrS$ requires C, 31·3; H, 1·7; S, 13·9%).

(b) 5-Bromo-2 : 3-diaminopyridine (1·9 g.) and thiourea (800 mg.) were fused together at 180° for 45 minutes. The dark brown solid was crystallised from ethanol (charcoal), yielding the thiol, m. p. > 300° (Found : C, 31·8; H, 1·8%).

The authors thank the Therapeutic Research Corporation of Great Britain Limited for grants and for certain facilities.

QUEEN MARY COLLEGE (UNIVERSITY OF LONDON), E.1. [*Received, October 28th,* 1947.]