275. *Synthetic Antimalarials. Part XL. The Effect of Variation of Substituents in 2-Chloro-3-β-diethylaminoethylaminoquinoxaline.*

By (the late) F. H. S. Curd, D. G. Davey, and G. J. Stacey.

The novel lead provided by the observation that 2 : 6-dichloro-3-β-diethylaminoethylaminoquinoxaline (Haworth and Robinson, *J.*, 1948, 777) possessed marked antimalarial activity has been followed up by the preparation of a number of analogous compounds containing different substituents in the 6-position. The synthetic method utilised in the original work and extended in the previous paper has been successfully applied in the case of the substances now described. The various compounds have been tested for antimalarial activity against *P. gallinaceum* in chicks, and it has been found that none of the 6-substituents investigated promoted antimalarial activity as high as that of the original 6-chloro-compound. Of the individual compounds, highest activity was shown by 2 : x-*dichloro*-3-β-*diethylaminoethylamino*-6(or 7)-*methoxyquinoxaline* which was derived from 2 : 3 : x-*trichloro*-6-*methoxyquinoxaline*, the product of interaction of 2 : 3-dihydroxy-6-methoxyquinoxaline with phosphorus pentachloride. Nuclear chlorination was avoided by the use of phosphoryl chloride which gave 2 : 3-*dichloro*-6-*methoxyquinoxaline*.

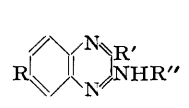
Although the antimalarial activity of 4-dialkylaminoalkylaminoquinolines is well known, and has been made the subject of much study by German and American workers, correspondingly

substituted 2-dialkylaminoalkylaminoquinolines are apparently without such activity (see, *e.g.*, Lutz, Ashburn, and Rowlett, *J. Amer. Chem. Soc.*, 1946, **68**, 1322; Wiselogle, "Survey of Antimalarial Drugs," 1941—45, pp. 1135, 1144, 1187, and confirmed by our own unpublished work). It was therefore of more than usual interest that 2 : 6-dichloro-3-β-diethylaminoethylaminoquinoxaline (I; R = R′ = Cl, R″ = $[CH_2]_2$·NEt_2) (Haworth and Robinson, Part XXVII, *J.*, 1948, 777) should possess marked antimalarial activity (*P. gallinaceum* in chicks) in view of its α-dialkylaminoalkylamino-heterocyclic structure, and a thorough investigation of this novel type appeared to provide an excellent opportunity for the further study of the relationship between chemical constitution and antimalarial activity.

In the preceding paper it has been shown that both chlorine atoms have a profound influence on the antimalarial activity of this type of compound : removal of the 2-chlorine atom or its replacement by other groups in 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline led to a complete loss of activity while 2-chloro-3-β-diethylaminoethylaminoquinoxaline (I; R = H, R′ = Cl, R″ = $[CH_2]_2$·NEt_2) exhibited only a fraction of the activity of its 6-chloro-derivative.

In the present paper, the investigation has been extended, and the effect on antimalarial activity of substituents other than chlorine in the benz-nucleus of 2-chloro-3-dialkylaminoalkylaminoquinoxalines has been studied. On account of the importance of the methoxyl group in other types of antimalarials, this substituent was the obvious first choice for investigation. Without purification, 4-methoxy-1 : 2-phenylenediamine, prepared by reduction of 2-nitro-4-methoxyaniline, was treated with ethyl oxalate to give 2 : 3-dihydroxy-6-methoxyquinoxaline (II; R = OMe) which was characterised as its methylation product, 2 : 3-*diketo*-6-*methoxy*-1 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (III; R = OMe). There seemed little doubt as to the constitution of this compound in view of its non-identity with 2 : 3 : 6-*trimethoxyquinoxaline* (V; R = OMe), which was prepared by the action of methanolic sodium methoxide on 2 : 3-*dichloro*-6-*methoxyquinoxaline* (IV; R = OMe). This was satisfactorily prepared by the action of phosphoryl chloride on (II; R = OMe), whereas phosphorus pentachloride, which is usually necessary for such conversions, led to nuclear chlorination. Condensation of 2 : 3-dichloro-6-methoxyquinoxaline with β-diethylaminoethylamine, γ-diethylaminopropylamine and γ-piperidinopropylamine gave respectively 2-*chloro*-3-β-*diethylaminoethylamino*-, 2-*chloro*-3-γ-*diethylaminopropylamino*-, and 2-*chloro*-3-γ-*piperidinopropylamino*-6-*methoxyquinoxalines* (I; R = OMe, R′ = Cl, R″ = $[CH_2]_2$·NEt_2, $[CH_2]_3$·NEt_2, $[CH_2]_3$·N<$[CH_2]_4$>CH_2, respectively), and mild acid hydrolysis of the first afforded 3-β-*diethylaminoethylamino*-2-*hydroxy*-6-*methoxyquinoxaline* (I; R = OMe, R′ = OH, R″ = $[CH_2]_2$·NEt_2).

The constitution of (I; R = OMe, R′ = Cl, R″ = $[CH_2]_3$·N<$[CH_2]_4$>CH_2) was proved (and those of the related compounds followed by analogy) by a method similar to that employed in Part XXXIX (preceding paper) to demonstrate that the 3-chlorine atom is more reactive than the 2-chlorine atom in the interaction of 2 : 3 : 6-trichloroquinoxaline with aminoalkylamines. Subjected to reductive dehalogenation, using hydrogen and Raney nickel in alcoholic solution in presence of one equivalent of sodium hydroxide, it gave a product which was demonstrated to be 2-γ-*piperidinopropylamino*-7-*methoxyquinoxaline* (I; R = OMe, R′ = H, R″ = $[CH_2]_3$·N<$[CH_2]_4$>CH_2), and not 3-γ-*piperidinopropylamino*-6-*methoxy*-2-*ethoxyquinoxaline* (I; R = OMe, R′ = OEt, R″ = $[CH_2]_3$·N<$[CH_2]_4$>CH_2) (cf. preceding paper), by synthesis of the former by a method which left no doubt as to its constitution. Interaction of 4-nitro-2-methoxyaniline with bromoacetic acid gave 2-*nitro*-4-*methoxyphenylglycine* (VI) which on treatment with hydrogen in presence of Raney nickel was reduced and cyclised in one operation to give 2-*hydroxy*-7-*methoxy*-3 : 4-*dihydroquinoxaline* (VII); oxidation of this with ammoniacal silver nitrate afforded 2-*hydroxy*-7-*methoxyquinoxaline* (VIII; R = OH) from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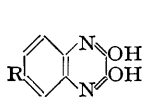
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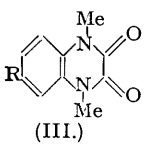
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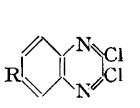
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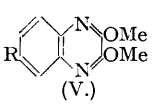
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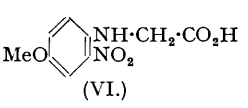
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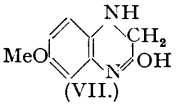
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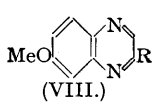
(VIII.)

which 2-*chloro*-7-*methoxyquinoxaline* (VIII; R = Cl) was obtained, by the action of phosphoryl chloride, and condensed with γ-piperidinopropylamine to give (I; R = OMe, R′ = H,

R″ = $[CH_2]_3$·N<$[CH_2]_4$>CH_2). The above-mentioned 3-γ-piperidinopropylamino-6-methoxy-2-ethoxyquinoxaline was prepared by the action of alcoholic sodium ethoxide on 2-chloro-3-γ-piperidinopropylamino-6-methoxyquinoxaline.

Having demonstrated in two cases that condensation between a 6-substituted-2 : 3-dichloroquinoxaline and an aminoalkylamine occurred preferentially in the 3-position, it was concluded that 2 : 3-*dichloro*-6-*bromoquinoxaline* (IV; R = Br) and 2 : 3-*dichloro*-6-*methylquinoxaline* (IV; R = Me) behaved similarly and that their respective condensation products with β-diethylaminoethylamine were 2-*chloro*-6-*bromo*-3-β-*diethylaminoethylaminoquinoxaline* (I; R = Br, R′ = Cl, R″ = $[CH_2]_2$·NEt_2) and 2-*chloro*-3-β-*diethylaminoethylamino*-6-*methylquinoxaline* (I; R = Me, R′ = Cl, R″ = $[CH_2]_2$·NEt_2).

Finally, 4-nitro-1 : 2-phenylenediamine was condensed with ethyl oxalate to give 6-nitro-2 : 3-dihydroxyquinoxaline (II; R = NO_2) which, without being characterised, was treated with phosphorus pentachloride to yield 2 : 3-*dichloro*-6-*nitroquinoxaline* (IV; R = NO_2). On treatment of this with β-diethylaminoethylamine in boiling alcoholic solution it yielded a mono-condensation product, 2-*chloro*-6(or 7)-*nitro*-3-β-*diethylaminoethylaminoquinoxaline*. The constitution of this compound has not been definitely proved, and since the nitro-group may have a different effect on the relative reactivities of the chlorine atoms in 2 : 3-dichloro-6-nitroquinoxaline from that of the other substituents studied, we do not feel justified in assuming that the 3-chlorine atom has reacted preferentially.

Comparison of the antimalarial activities given in the Table with those given in the preceding paper for 2 : 6-dichloro-3-β-diethylaminoethylaminoquinoxaline shows that the 6-chlorine atom is the most potent for antimalarial activity. The corresponding 6-bromo-compound (7284) is somewhat less active and the methoxy-analogue (6731) has a significantly low activity. The inferiority of 2-chloro-3-β-diethylaminoethylamino-6-methoxyquinoxaline, which is reflected in the more rapid fall-off of activity with increase in size of the dialkylaminoalkylamino-group than that which occurs in the 2 : 6-dichloro-3-dialkylaminoalkylaminoquinoxaline series, is similar to that which obtains in 7-substituted 4-dialkylaminoalkylaminoquinolines (Wiselogle, *op. cit.*, pp. 1145, 1187) and -quinazolines (Chapman, Gibson, and Mann, *J.*, 1947, 890). The inactivation of 2-chloro-3-β-diethylaminoethylamino-6-methoxyquinoxaline (6731) which occurs on replacing the 2-chlorine atom by a hydroxyl group (7397) is similar to that noted in the previous paper in the case of analogous compounds.

Antimalarial Activities.

The activity of the various compounds was estimated against the blood forms of *P. gallinaceum* in chicks by the method described by one of us (D.G.D.) (*Ann. Trop. Med. Parasit.*, 1946, **40**, 52). The results given below are expressed in the same way as in previous papers of this series.

Ref. no.	Quinoxaline.	Dose, mg./kg.	Activity.
6731	2-Chloro-3-β-diethylaminoethylamino-6-methoxy-	160	++
		80	++
		40	−
6830	2-Chloro-3-γ-diethylaminopropylamino-6-methoxy-	160	−
7415	2-Chloro-3-γ-piperidinopropylamino-6-methoxy-	80	−
7284	2-Chloro-6-bromo-3-β-diethylaminoethylamino-	40	++
		20	+
		10	−
7172	2-Chloro-3-β-diethylaminoethylamino-6-methyl-	160	++
		80	±
7176	2-Chloro-6(or 7)-nitro-3-β-diethylaminoethylamino-	160	+
		80	−
7220	2 : *x*-Dichloro-3-β-diethylaminoethylamino-6(or 7)-methoxy-	40	++
		20	++
7397	3-β-Diethylaminoethylamino-2-hydroxy-6-methoxy-	160	−
7535	2-γ-Piperidinopropylamino-7-methoxy-	80	−
7621	3-γ-Piperidinopropylamino-6-methoxy-2-ethoxy-	40	−

In addition, some of the compounds were tested for prophylactic activity against *P. gallinaceum* in chicks by the method previously described (Davey, *ibid.*, p. 453), Nos. 6731 and 6830 at 160 mg./kg., No. 7220 at 40 mg./kg., and No. 7397 at 80 mg./kg., but none was active.

EXPERIMENTAL.

2 : 3-*Dihydroxy*-6-*methoxyquinoxaline* (II; R = OMe).—2-Nitro-4-methoxyaniline (84·1 g.) (Reverdin, *Ber.*, 1896, **29**, 2595) was added gradually with stirring to a solution of stannous chloride (450 g.) in hydrochloric acid (900 c.c.), the temperature being kept at or below 20°. When the addition was

complete, the mixture was stirred for 2 hours and then slowly added to 30% aqueous sodium hydroxide (2 l.), the temperature being kept below 40°. The alkaline mixture was extracted with benzene, and the benzene extract washed once with water and evaporated. Ethyl oxalate (500 c.c.) was added to the residual crude 4-methoxy-1 : 2-phenylenediamine, and the mixture heated under reflux in an oil-bath at 175—185° for 3½ hours. The finely divided solid which had separated was filtered off, after cooling, washed with light petroleum, and dried. The only satisfactory method of purification discovered was by dissolution in aqueous sodium hydroxide and reprecipitation with hydrochloric acid (yield, 76%). For characterisation, the 2 : 3-dihydroxy-6-methoxyquinoxaline (2·9 g.) was dissolved in N-sodium hydroxide (70 c.c.) and methylated with methyl sulphate (7·6 g.) to give 2 : 3-*diketo*-6-*methoxy*-1 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (III; R = OMe), which crystallised from alcohol as colourless needles, m. p. 182—183° (Found: C, 59·9; H, 5·2; N, 12·7. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·5; N, 12·7%).

2 : 3-*Dichloro*-6-*methoxyquinoxaline* (IV; R = OMe).—2 : 3-Dihydroxy-6-methoxyquinoxaline (72 g.) and phosphoryl chloride (150 c.c.) were heated together at 120—125° for 1 hour, and the excess of the latter then removed by distillation under reduced pressure. The residue was treated with ice-cold water, and the solid product collected and washed well with water. After drying, it was extracted with boiling benzene, and the extract carbon-treated and filtered. Concentration of the benzene filtrate gave pale cream flakes of 2 : 3-*dichloro*-6-*methoxyquinoxaline* (yield, 81%), m. p. 160° (Found: C, 47·3; H, 2·7; N, 11·7. $C_9H_6ON_2Cl_2$ requires C, 47·2; H, 2·6; N, 12·2%).

2 : 3 : x-*Trichloro*-6-*methoxyquinoxaline*.—An intimate mixture of 2 : 3-dihydroxy-6-methoxyquinoxaline (57·6 g.) and phosphorus pentachloride (135 g.) was heated at 170—180° for 1 hour, obvious reaction occurring when the temperature reached 160°. The reaction mixture was then distilled under diminished pressure to remove phosphoryl chloride, and the residue triturated, and finally ground, with water. The product was then collected, washed with water, and dried. Two extractions with boiling benzene (600 c.c., 400 c.c.) and evaporation of the combined extracts to dryness gave the *trichloro*-compound (29 g.), which was recrystallised from benzene; pale cream plates, m. p. 188° (Found: C, 41·0; H, 2·2; N, 10·3; Cl, 40·3. $C_9H_5ON_2Cl_3$ requires C, 41·0; H, 1·9; N, 10·6; Cl, 40·4%).

2 : 3 : 6-*Trimethoxyquinoxaline* (V; R = OMe).—2 : 3-Dichloro-6-methoxyquinoxaline (2·3 g.) was added to a solution of sodium (0·6 g.) in methanol (70 c.c.), and the whole heated under reflux for 1½ hours. The reaction mixture was then filtered and set aside to crystallise. The *quinoxaline* recrystallised from methanol in colourless needles, m. p. 125—126° (Found: C, 60·2; H, 5·6; N, 12·4. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·5; N, 12·7%).

2 : x-*Dichloro*-3-β-*diethylaminoethylamino*-6(*or* 7)-*methoxyquinoxaline*.—β-Diethylaminoethylamine (3·5 g.) was gradually added to a suspension of 2 : 3 : *x*-trichloro-6-methoxyquinoxaline (7·9 g.) in boiling alcohol (120 c.c.), and the mixture boiled under reflux for 16 hours. The solvent was then distilled off, the residue extracted with dilute acetic acid, and the filtered extract made alkaline with sodium hydroxide. The precipitated oil solidified on standing and was collected, washed, and dried. Crystallisation from light petroleum (b. p. 40—60°) gave the *dichloro*-compound as pale yellow prisms, m. p. 70° (Found: C, 52·7; H, 5·7; N, 16·3. $C_{15}H_{20}ON_4Cl_2$ requires C, 52·4; H, 5·9; N, 16·3%) (7220). With alcoholic picric acid it gave a *picrate*, which separated from 2-ethoxyethanol as minute yellow rods, m. p. 150° (Found: C, 44·3; H, 4·2; N, 16·7. $C_{15}H_{20}ON_4Cl_2,C_6H_3O_7N_3$ requires C, 44·1; H, 4·05; N, 17·1%).

2-*Chloro*-3-β-*diethylaminoethylamino*-6-*methoxyquinoxaline* (I; R = OMe, R′ = Cl, R″ = $[CH_2]_2{\cdot}NEt_2$).—To a boiling mixture of alcohol (120 c.c.) and 2 : 3-dichloro-6-methoxyquinoxaline (9·2 g.), β-diethylaminoethylamine (4·7 g.) was gradually added. Complete solution was obtained after a few minutes' refluxing, which was continued altogether for 20 hours. The alcohol was then removed by evaporation, and the residue extracted with hot dilute hydrochloric acid. The filtered extract was cooled and made alkaline with sodium hydroxide. The precipitated product was collected, dried, and crystallised from light petroleum (b. p. 60—80°), giving 2-*chloro*-3-β-*diethylaminoethylamino*-6-*methoxyquinoxaline* (6731) as fine colourless needles (yield, 5·9 g.), m. p. 73—74° (Found: C, 58·5; H, 6·5; N, 18·4. $C_{15}H_{21}ON_4Cl$ requires C, 58·3; H, 6·85; N, 18·1%). The corresponding *picrate* crystallised from 2-ethoxyethanol as tufts of pale yellow needles, m. p. 158° (Found: C, 47·2; H, 4·5; N, 18·1. $C_{15}H_{21}ON_4Cl,C_6H_3O_7N_3$ requires C, 46·9; H, 4·5; N, 18·2%).

2-*Chloro*-3-γ-*diethylaminopropylamino*-6-*methoxyquinoxaline* (I; R = OMe, R′ = Cl, R″ = $[CH_2]_3{\cdot}NEt_2$) (6830), prepared in a similar manner but with γ-diethylaminopropylamine in place of β-diethylaminoethylamine, crystallised from light petroleum (b. p. 40—60°) as pale cream prisms (yield, 67%), m. p. 66° (Found: C, 59·6; H, 6·9; N, 17·3. $C_{16}H_{23}ON_4Cl$ requires C, 59·5; H, 7·2; N, 17·4%). It formed a *picrate* which crystallised from 2-ethoxyethanol as yellow needles, m. p. 170° (Found: C, 47·9; H, 5·0; N, 17·5. $C_{16}H_{23}ON_4Cl,C_6H_3O_7N_3$ requires C, 47·9; H, 4·7; N, 17·8%).

2-*Chloro*-3-γ-*piperidinopropylamino*-6-*methoxyquinoxaline* (I; R = OMe, R′ = Cl, R″ = $[CH_2]_3{\cdot}N < [CH_2]_4 > CH_2$).—2 : 3-Dichloro-6-methoxyquinoxaline (11·5 g.) and γ-piperidinopropylamine (7·2 g.) were caused to react together in boiling alcohol (120 c.c.), and the crude product isolated in the above-described manner. Crystallisation from light petroleum (b. p. 60—80°) gave 2-*chloro*-3-γ-*piperidinopropylamino*-6-*methoxyquinoxaline* (7415) as practically colourless prisms (yield, 59%), m. p. 118—119° (Found: C, 61·0; H, 6·8; N, 16·6. $C_{17}H_{23}ON_4Cl$ requires C, 61·0; H, 6·9; N, 16·7%), which afforded a *picrate*, minute lemon-yellow plates from 2-ethoxyethanol, m. p. 206—208° (decomp.) (Found: C, 48·9; H, 4·4; N, 17·9. $C_{17}H_{23}ON_4Cl,C_6H_3O_7N_3$ requires C, 49·0; H, 4·6; N, 17·4%). On concentration of the light petroleum mother-liquors from the above main product a mixture of prisms and silky needles was obtained. Separated by hand and recrystallised from light petroleum (b. p. 60—80°), the latter gave, in very small quantity, an isomer of (I; R = OMe, R′ = Cl, R″ = $[CH_2]_3{\cdot}N < [CH_2]_4 > CH_2$) which was presumed to be 2-*chloro*-3-γ-*piperidinopropylamino*-7-*methoxyquinoxaline*; recrystallised from light petroleum (b. p. 60—80°), it formed colourless needles, m. p. 130—131° (Found: C, 60·6; H, 6·7; N, 16·9. $C_{17}H_{23}ON_4Cl$ requires C, 61·0; H, 6·9; N, 16·7%). Mixed with 2-chloro-3-γ-piperidinopropylamino-6-methoxyquinoxaline it melted at 105—112°.

3-β-*Diethylaminoethylamino*-2-*hydroxy*-6-*methoxyquinoxaline* (I; R = OMe, R′ = OH, R″ = $[CH_2]_2{\cdot}NEt_2$).—2-Chloro-3-β-diethylaminoethylamino-6-methoxyquinoxaline (4·6 g.) and 2N-hydrochloric

acid (120 c.c.) were heated under reflux together for 1½ hours. After cooling, the reaction mixture was filtered, and the filtrate neutralised with sodium hydroxide. The precipitated *base* was collected and purified by crystallisation from aqueous methanol; colourless needles, m. p. 112° (Found: C, 62·4; H, 7·3; N, 19·0. $C_{15}H_{22}O_2N_4$ requires C, 62·05; H, 7·6; N, 19·3%) (7397).

N-(2-*Nitro*-4-*methoxyphenyl*)*glycine* (VI).—Bromoacetic acid (34·8 g.) was added gradually during 2 hours with stirring to melted 2-nitro-4-methoxyaniline (84 g.) at 120—125°. Towards the end of the addition the mixture became very thick, and xylene (50 c.c.) was added to render it more fluid. After being heated at 125—130° for a further ¾ hour, the reaction mixture was made alkaline to brilliant-yellow with aqueous ammonia and steam-distilled to remove the xylene. After dilution to 500 c.c. with water, the residue was filtered at 60°. The insoluble residue and the solid which separated on cooling were combined and re-extracted with dilute aqueous ammonia at 60°, the insoluble residue being given a third extraction with aqueous ammonia. The combined extracts were acidified with hydrochloric acid, the precipitated product collected, washed with water, and dried (yield, 32·7 g.). Recrystallisation from alcohol gave N-(2-*nitro*-4-*methoxyphenyl*)*glycine* as clusters of orange-red needles, m. p. 172° (decomp.) (Found: C, 48·1; H, 4·9; N, 12·6. $C_9H_{10}O_5N_2$ requires C, 47·8; H, 4·45; N, 12·4%). The corresponding *ethyl* ester, formed from the acid by heating it in alcohol solution in presence of a little hydrochloric acid, crystallised from light petroleum (b. p. 60—80°) as bright reddish-orange needles, m. p. 75° (Found: C, 52·3; H, 6·0; N, 11·2. $C_{11}H_{14}O_5N_2$ requires C, 52·0; H, 5·55; N, 11·0%).

2-*Hydroxy*-7-*methoxy*-3 : 4-*dihydroquinoxaline* (VII).—*N*-(2-Nitro-4-methoxyphenyl)glycine (4·5 g.) in alcohol (100 c.c.) and Raney nickel were shaken with hydrogen at 60° and a pressure of 60 atm. After cooling, the reaction mixture was filtered, and the filtrate evaporated to dryness under diminished pressure. Crystallisation of the residue from water (decolorising carbon) gave the *hydroxy*-compound as practically colourless plates, m. p. 169—171° (Found: C, 60·0; H, 5·4; N, 16·3. $C_9H_{10}O_2N_2$ requires C, 60·7; H, 5·65; N, 15·7%). It was difficult to avoid some oxidation to the corresponding quinoxaline derivative during crystallisation.

2-*Hydroxy*-7-*methoxyquinoxaline* (VIII; R = OH).—To the preceding compound (1·6 g.), suspended in boiling water (30 c.c.), was added a solution of ammoniacal silver nitrate [prepared by adding ammonia to a solution of silver nitrate (3·4 g.) in water (12 c.c.) so as just to dissolve the initial precipitate]. The mixture was boiled under reflux with stirring for ½ hour, cooled, and filtered. Repeated extraction of the dried residue with boiling 2-ethoxyethanol, followed by concentration of the combined extracts, yielded 2-*hydroxy*-7-*methoxyquinoxaline* (0·9 g.). Recrystallised from 2-ethoxyethanol, it formed practically colourless plates, m. p. 235—236° (Found: C, 61·0; H, 4·7; N, 15·9. $C_9H_8O_2N_2$ requires C, 61·4; H, 4·6; N, 15·9%).

2-*Chloro*-7-*methoxyquinoxaline* (VIII; R = Cl).—2-Hydroxy-7-methoxyquinoxaline (3·5 g.) and phosphoryl chloride (30 c.c.) were boiled together gently under reflux for ½ hour. Excess phosphoryl chloride was then distilled off under diminished pressure, and the residue treated with ice and water. The product so obtained was collected, washed acid free with water, and dried. Recrystallised from light petroleum (b. p. 80—100°), 2-*chloro*-7-*methoxyquinoxaline* formed colourless rods (3·1 g.), m. p. 102° (Found: C, 55·5; H, 3·5; N, 14·0. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·6; N, 14·4%).

2 - γ - *Piperidinopropylamino* - 7 - *methoxyquinoxaline* (I; R = OMe, R′ = H, R″ = $[CH_2]_3{\cdot}N < [CH_2]_4 > CH_2$).—2-Chloro-7-methoxyquinoxaline (1·2 g.) and γ-piperidinopropylamine (6 c.c.) were heated gently under reflux together for 2 hours. After cooling, the reaction mixture was dissolved in 5N-acetic acid, and the solution made alkaline with sodium hydroxide to precipitate an oil, which solidified on standing. The product was collected, washed with water, and purified by crystallisation from aqueous methanol (carbon), giving 2-γ-*piperidinopropylamino*-7-*methoxyquinoxaline* (7535) as a colourless microcrystalline powder (yield, 89%), m. p. 80—81° (Found: C, 60·7; H, 8·2; N, 16·6. $C_{17}H_{24}ON_4,2H_2O$ requires C, 60·7; H, 8·4; N, 16·7%). With alcoholic picric acid it gave a *dipicrate*, which crystallised from 2-ethoxyethanol as minute yellow prisms, m. p. 219—220° (decomp.) (Found: C, 45·9; H, 4·1; N, 18·5. $C_{17}H_{24}ON_4,2C_6H_3O_7N_3$ requires C, 45·9; H, 4·0; N, 18·5%).

Reductive Dehalogenation of 2-*Chloro*-3-γ-*piperidinopropylamino*-6-*methoxyquinoxaline*.—A mixture of 2-chloro-3-γ-piperidinopropylamino-6-methoxyquinoxaline (3·4 g.), finely ground sodium hydroxide (0·4 g.), and alcohol (100 c.c.) was treated with hydrogen and Raney nickel at N.T.P. When hydrogen uptake had ceased (after 4 hours) the reaction mixture was filtered and evaporated to dryness under reduced pressure. The semi-solid residue crystallised from aqueous methanol to give a product, m. p. 80—81° undepressed in admixture with authentic 2-γ-piperidinopropylamino-7-methoxyquinoxaline prepared as described above (Found: C, 60·8; H, 8·3; N, 16·3%). It formed a dipicrate which, after crystallisation from 2-ethoxyethanol, had m. p. 219—221° either alone or in admixture with the dipicrate of 2-γ-piperidinopropylamino-7-methoxyquinoxaline (Found: C, 45·9; H, 4·0; N, 18·9%). Omission of the sodium hydroxide made dehalogenation inconveniently slow.

3-γ-*Piperidinopropylamino*-6-*methoxy*-2-*ethoxyquinoxaline* (I; R = OMe, R′ = OEt, R″ = $[CH_2]_3{\cdot}N < [CH_2]_4 > CH_2$).—2-Chloro-3-γ-piperidinopropylamino-6-methoxyquinoxaline (5 g.) was added to a solution of sodium (0·35 g.) in alcohol (30 c.c.), the mixture heated under reflux for 5 hours, and then filtered. Dilution with water precipitated the *base* which, after drying, crystallised from light petroleum (b. p. 60—80°) as small colourless rods (yield, 85%), m. p. 93—94° (Found: C, 66·0; H, 7·8; N, 15·8. $C_{19}H_{28}O_2N_4$ requires C, 66·25; H, 8·2; N, 16·3%) (7621). The *dipicrate* separated from 2-ethoxyethanol as small lemon-yellow plates, m. p. 164—168° (Found: C, 46·9; H, 4·7; N, 17·3. $C_{19}H_{28}O_2N_4,2C_6H_3O_7N_3$ requires C, 46·4; H, 4·3; N, 17·45%).

6-*Bromo*-2 : 3-*dihydroxyquinoxaline* (II; R = Br).—4-Bromo-2-nitroaniline was prepared by the following sequence of reactions: acetanilide ⟶ *p*-bromoacetanilide ⟶ 4-bromo-2-nitroacetanilide ⟶ 4-bromo-2-nitroaniline. The procedures used in the first and the second stage were respectively those of Remmeres (*Ber.*, 1874, **7**, 346) and Hubner (*Annalen*, 1881, **209**, 356). For the hydrolysis in the third stage, we preferred to employ acid hydrolysis using equal parts of water and concentrated hydrochloric acid rather than alkaline hydrolysis as described by Hubner (*loc. cit.*).

4-Bromo-2-nitroaniline (108·5 g.) was reduced with stannous chloride (450 g.) and hydrochloric acid (900 c.c.), and the reaction mixture worked up as described above to give crude 4-bromo-1 : 2-phenylene-

diamine (cf. Hubner, *loc. cit.*). Without purification this was heated with ethyl oxalate (400 c.c.) at 175—185° for 3½ hours and then cooled. The solid which had separated was collected, washed with light petroleum, and dried, giving 6-bromo-2 : 3-dihydroxyquinoxaline as a brownish powder (yield, 80%). For characterisation, a solution of a sample (2·4 g.) in warm N-sodium hydroxide (60 c.c.) was methylated at the boil with methyl sulphate (7·55 g.) for 4½ hours to give 6-*bromo*-2 : 3-*diketo*-1 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (III; R = Br), which crystallised from alcohol as colourless needles, m. p. 205—206° (Found : C, 44·6; H, 3·4; N, 10·1. $C_{10}H_9O_2N_2Br$ requires C, 44·6; H, 3·4; N, 10·4%).

2 : 3-*Dichloro*-6-*bromoquinoxaline* (IV; R = Br).—6-Bromo-2 : 3-dihydroxyquinoxaline (60 g.) and phosphorus pentachloride (45·9 g.) were intimately mixed and heated together at 165—175° under reflux for ½ hour. Phosphoryl chloride was then removed by distillation under diminished pressure, the residue ground with ice-water, and the product collected, dried, and extracted with benzene. Concentration of the dried, carbon-treated extract gave the *dichloro*-compound, which crystallised from light petroleum (b. p. 80—100°) as practically colourless irregular plates (yield, 56%), m. p. 132° (Found : C, 34·6; H, 1·2; N, 10·0. $C_8H_3N_2Cl_2Br$ requires C, 34·5; H, 1·1; N, 10·1%).

6-*Bromo*-2 : 3-*dimethoxyquinoxaline* (V; R = Br).—Prepared by interaction of 2 : 3-dichloro-6-bromoquinoxaline with sodium methoxide as described above in the case of the 2 : 3 : 6-trimethoxyquinoxaline, this *bromo*-compound separated from methanol as colourless needles, m. p. 114—115° (Found : C, 44·9; H, 3·5; N, 10·0. $C_{10}H_9O_2N_2Br$ requires C, 44·6; H, 3·4; N, 10·4%).

2-*Chloro*-6-*bromo*-3-*β*-*diethylaminoethylaminoquinoxaline* (I; R = Br, R′ = Cl, R″ = $[CH_2]_2{\cdot}NEt_2$).—Prepared as described above for similar cases, but from 2 : 3-dichloro-6-bromoquinoxaline and β-diethylaminoethylamine, this *compound* crystallised from light petroleum (b. p. 40—60°) as pale cream prisms, m. p. 87° (Found : C, 46·8; H, 4·7; N, 15·3. $C_{14}H_{18}N_4ClBr$ requires C, 47·0; H, 5·1; N, 15·7%) (7284). The corresponding *picrate* crystallised from 2-ethoxyethanol as small yellow needles, m. p. 153—154° (Found : C, 40·5; H, 3·9; N, 16·5. $C_{14}H_{18}N_4ClBr,C_6H_3O_7N_3$ requires C, 40·95; H, 3·6; N, 16·7%).

2 : 3-*Dihydroxy*-6-*methylquinoxaline* (II; R = Me).—3-Nitro-4-toluidine (76 g.) (Gattermann, *Ber.*, 1885, **18**, 1483) was reduced at 50° with stannous chloride (450 g.) and hydrochloric acid (900 c.c.), and the product isolated as in similar reductions described above. The resulting crude 4-methyl-1 : 2-phenylenediamine (cf. Beilstein and Kuhlberg, *Annalen*, 1871, **158**, 351) was heated for 3 hours at 170—180° with ethyl oxalate (400 c.c.), and the reaction mixture cooled and filtered. The crude 2 : 3-dihydroxy-6-methylquinoxaline (yield, 94%) thus obtained as a pale yellow powder was converted into 2 : 3-*diketo*-1 : 4 : 6-*trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (III; R = Me), by methylation with methyl sulphate and sodium hydroxide, for the purposes of characterisation. This crystallised from alcohol as colourless needles, m. p. 196—197° (Found : C, 64·6; H, 5·6; N, 13·8. $C_{11}H_{12}O_2N_2$ requires C, 64·6; H, 5·9; N, 13·7%).

2 : 3-*Dichloro*-6-*methylquinoxaline* (IV; R = Me).—2 : 3-Dihydroxy-6-methylquinoxaline (88 g.) and phosphoryl chloride (200 c.c.) were heated together at 120—130° under reflux for 1 hour. Excess of phosphoryl chloride was removed by distillation under diminished pressure, and the residue triturated with ice-cold water. The resulting product was dried, extracted with boiling benzene (350 c.c.), and the benzene extract carbon-treated and evaporated to dryness. Crystallisation of the residue from light petroleum (b. p. 80—100°) gave 2 : 3-*dichloro*-6-*methylquinoxaline* as colourless feathery plates (yield, 51%), m. p. 114° (Found : C, 50·5; H, 2·6; N, 13·3. $C_9H_6N_2Cl_2$ requires C, 50·75; H, 2·8; N, 13·1%). The use of phosphorus pentachloride led to some nuclear chlorination and the isolation of a mixed product.

2 : 3-*Dimethoxy*-6-*methylquinoxaline* (V; R = Me).—Prepared from 2 : 3-dichloro-6-methylquinoxaline and methanolic sodium methoxide, the *dimethoxy*-compound crystallised from aqueous methanol as colourless needles, m. p. 82—83° (Found : C, 64·8; H, 6·1; N, 13·3. $C_{11}H_{12}O_2N_2$ requires C, 64·6; H, 5·9; N, 13·7%).

2-*Chloro*-3-*β*-*diethylaminoethylamino*-6-*methylquinoxaline* (I; R = Me, R′ = Cl, R″ = $[CH_2]_2{\cdot}NEt_2$).—2 : 3-Dichloro-6-methylquinoxaline (16 g.) was dissolved in boiling alcohol (120 c.c.), and β-diethylaminoethylamine (8·7 g.) gradually added. The mixture was then heated under reflux for 18 hours, the solvent distilled off, and the residue extracted with cold 5N-acetic acid (50 c.c.). The filtered extract was made alkaline with sodium hydroxide, and the precipitated oil extracted with ether. Evaporation of the dried (K_2CO_3) ether extract and vacuum distillation of the residual oil gave the *base* as a pale yellow oil, b. p. 158—160°/5 × 10^{-3} mm. (yield, 43%) (Found : C, 61·5; H, 7·1; N, 19·2. $C_{15}H_{21}N_4Cl$ requires C, 61·5; H, 7·2; N, 19·1%) (7172). With alcoholic picric acid it gave a *picrate*, which crystallised from 2-ethoxyethanol as minute yellow rods, m. p. 150—151° (Found : C, 48·2; H, 4·6; N, 18·5. $C_{15}H_{21}N_4Cl$, $C_6H_3O_7N_3$ requires C, 48·3; H, 4·6; N, 18·8%).

3-*β*-*Diethylaminoethylamino*-2-*hydroxy*-6-*methylquinoxaline* (I; R = Me, R′ = OH, R″ = $[CH_2]_2{\cdot}NEt_2$) was obtained in a similar experiment in which the product was extracted with hot N-hydrochloric acid instead of cold 5N-acetic acid. It crystallised from light petroleum (b. p. 60—80°) as short colourless needles, m. p. 103—104° (Found : C, 65·1; H, 7·9; N, 20·2. $C_{15}H_{22}ON_4$ requires C, 65·7; H, 8·1; N, 20·4%). The *dipicrate* crystallised from 2-ethoxyethanol as small yellow prisms containing solvent of crystallisation, m. p. 106—107° (Found : C, 45·3; H, 4·8; N, 16·6. $C_{15}H_{22}ON_4,2C_6H_3O_7N_3,C_4H_{10}O_2$ requires C, 45·2; H, 4·65; N, 17·0%).

2 : 3-*Dichloro*-6-*nitroquinoxaline* (IV; R = NO_2).—4-Nitro-1 : 2-phenylenediamine (107 g.) (Brand, *J. pr. Chem.*, 1906, **74**, 470) and ethyl oxalate (600 c.c.) were heated together at 175—185° under reflux for 4 hours with stirring. After cooling, the solid product was collected and purified by dissolution in hot aqueous sodium hydroxide followed by reprecipitation with hydrochloric acid. 6-Nitro-2 : 3-dihydroxyquinoxaline (yield 66%) was thus obtained as buff-coloured crystals, m. p. 344—346° (decomp.) (not analysed). It could not be methylated satisfactorily to give a 1 : 4-dimethyl derivative.

6-Nitro-2 : 3-dihydroxyquinoxaline (83 g.) and phosphorus pentachloride (185 g.) were heated together under reflux at 170—180° for 1 hour, and the reaction mixture then distilled under reduced pressure to remove phosphoryl chloride. The residue was ground with ice-water, collected, and extracted with benzene. Evaporation of the benzene extract gave 2 : 3-*dichloro*-6-*nitroquinoxaline*, which crystallised from light petroleum (b. p. 80—100°) as small, pale cream, irregular plates

(yield, 75%), m. p. 152° (Found: C, 39·1; H, 1·5; N. 17·1. $C_8H_3O_2N_3Cl_2$ requires C, 39·3; H, 1·2; N, 17·2%).

2-*Chloro*-6(or 7)-*nitro*-3-*β*-*diethylaminoethylaminoquinoxaline*, prepared from 2 : 3-dichloro-6-nitroquinoxaline and *β*-diethylaminoethylamine as in the case of similar compounds, crystallised from methanol as tufts of yellow needles (yield, 42%), m. p. 102° (Found: C, 52·0; H, 5·5; N, 21·2. $C_{14}H_{18}O_2N_5Cl$ requires C, 51·9; H, 5·6; N, 21·6%) (7176). The corresponding *picrate* crystallised from 2-ethoxyethanol as clusters of yellow needles, m. p. 154° (Found: C, 43·6; H, 3·8; N, 20·2. $C_{14}H_{18}O_2N_5Cl,C_6H_3O_7N_3$ requires C, 43·5; H, 3·8; N, 20·3%).

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