274. *Synthetic Antimalarials. Part XXXIX. Dialkylaminoalkylaminoquinoxalines.*

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Following the observation that 2 : 6-dichloro-3-β-diethylaminoethylaminoquinoxaline (Part XXVII, *J.*, 1948, 777) possessed marked activity against avian malaria (*P. gallinaceum* in chicks), it is shown that increasing the complexity of the side-chain has a dystherapeutic effect, whilst removing the 2-chlorine atom, or replacing it by other groups such as hydroxyl, ethoxyl, or thiol, leads to a loss of activity. In the simple 2-chloro-3-dialkylaminoalkylaminoquinoxalines, replacing the chlorine by methyl has a similar effect.

Although in the majority of cases only one product appears to be formed from 2 : 3 : 6-trichloroquinoxaline and a dialkylaminoalkylamine, with γ-piperidinopropylamine 2 : 7-*dichloro*-3-γ-*piperidinopropylaminoquinoxaline* was also isolated. Parallel proof that the main product was the 2 : 6-*dichloro*-analogue validates the assumption made in Part XXVII that in 2 : 3 : 6-trichloroquinoxaline the chlorine atom in the 3-position is more reactive than that in the 2-position, and provides evidence for the structure of all the compounds of type (I) described in this paper. An indication of initial reaction at both the 2- and the 3-position was also obtained in the condensation of (VII; R = H, R′ = R″ = Cl) with β-dimethylaminoethylamine. Reaction in the cold led to the isolation of 2 : 6-*dichloro*-3-β-*dimethylaminoethylaminoquinoxaline* which was readily cyclised by heat to give 6-*chloro*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra-aza-anthracene*, whilst in boiling alcohol the 7-*chloro*-isomer of the latter was also formed.

2 : 6-Dichloro-3-γ-piperidinopropylaminoquinoxaline was hydrolysed to give 6-*chloro*-3-γ-*piperidinopropylamino*-2-*hydroxyquinoxaline*, but attempts to synthesis the hydroxy-compound from N-(4-*chloro*-2-*aminophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide* failed. Cyclisation to a quinoxaline derivative could be accomplished only with simultaneous loss of the γ-piperidinopropylamino-side-chain; cyclisation by heat gave 5(or 6)-*chlorobenziminazole*-2-*carboxy*-γ-*piperidinopropylamide*.

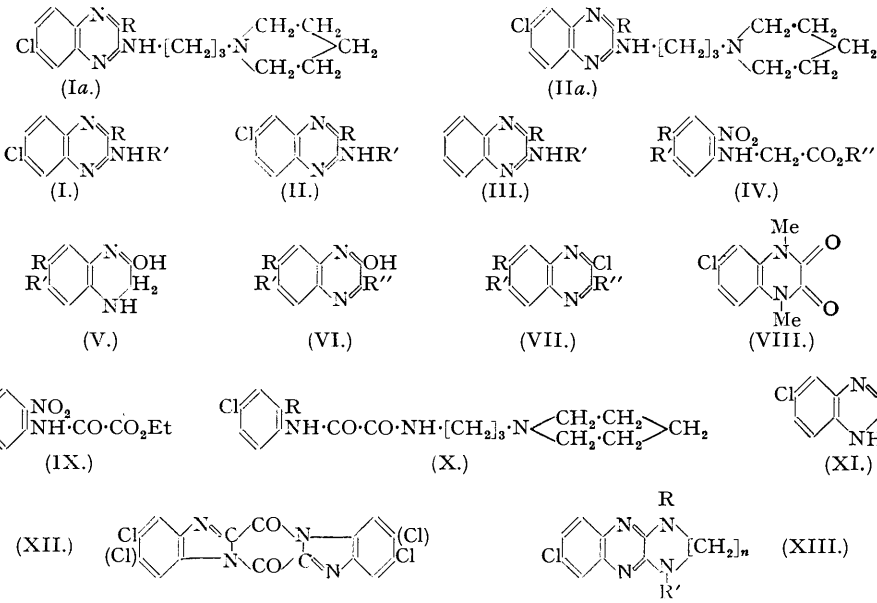
In Part XXVII (Haworth and Robinson, *J.*, 1948, 777) the preparation of a number of dialkylaminoalkylaminoquinoxalines was reported. The observation that 2 : 6-dichloro-3-β-diethylaminoethylaminoquinoxaline (I; R = Cl, R′ = $[CH_2]_2$·NEt_2) was active against the blood forms of *P. gallinaceum* in chicks at a dose of 10 mg./kg. made it of interest to examine further compounds of this type and also strictly to establish the constitution of the products. For the latter purpose it was decided to employ compounds containing the γ-piperidinopropylamino-side-chain since other work suggested that these were likely to be the most readily crystallised.

When equimolecular proportions of 2 : 3 : 6-trichloroquinoxaline and γ-piperidinopropylamine reacted in boiling alcoholic solution, formation of two products, 2 : 6- (I*a*; R = Cl), m. p. 108°, and 2 : 7-*dichloro*-3-γ-*piperidinopropylaminoquinoxaline* (II*a*; R = Cl), m. p. 76—77°, in the approximate ratio of 3 : 1, was observed. The orientations of these two isomers were proved by reductive partial dehalogenation, using hydrogen and Raney nickel, to give, respectively, 7- (I*a*; R = H) and 6-*chloro*-2-γ-*piperidinopropylaminoquinoxaline* (II*a*; R = H), both of which were prepared by the independent unambiguous syntheses described below, in which the earlier stages were analogous to methods previously reported in the literature for related compounds (cf. Plöchl, *Ber.*, 1886, **19**, 7; Hinsberg, *Annalen*, 1888, **248**, 73; *Ber.*, 1892, **25**, 2417; *ibid.*, 1908, **41**, 2032; F.P. 824,531, *Chem. Zentr.*, 1938, II, 178; Motylewski, *Ber.*, 1908, **41**, 802).

4-Chloro-2-nitroaniline was heated with bromoacetic acid to give N-(4-*chloro*-2-*nitrophenyl*)-*glycine* (IV; R = Cl, R′ = R″ = H), which on reduction with hydrogen and Raney nickel afforded 7-*chloro*-2-*hydroxy*-3 : 4-*dihydroquinoxaline* (V; R = Cl, R′ = H). Oxidation of this compound with ammoniacal silver nitrate gave 7-*chloro*-2-*hydroxyquinoxaline* (VI; R = Cl, R′ = R″ = H), converted by phosphoryl chloride into 2 : 7-*dichloroquinoxaline* (VII; R = Cl, R′ = R″ = H) and thence by γ-piperidinopropylamine into (I*a*; R = H). The identity of the 7-chloro-2-γ-piperidinopropylaminoquinoxaline prepared in this way with the material obtained from 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline was established by comparison not only of the bases, but also of the *picrates*.

The starting material for the synthesis of the isomeric 6-chloro-2-γ-piperidinopropylaminoquinoxaline was 4-chloro-1 : 2-dinitrobenzene. This reacted smoothly in benzene solution with ethyl aminoacetate to give *ethyl* 5-*chloro*-2-*nitroanilinoacetate* (IV; R = H, R′ = Cl, R″ = Et) (cf. the reaction with ammonia to give 5-chloro-2-nitroaniline, Laubenheimer, *Ber.*, 1876, **9**, 1826) which, on catalytic reduction and simultaneous ring-closure, gave 6-*chloro*-2-*hydroxy*-3 : 4-*dihydroquinoxaline* (V; R = H, R′ = Cl). This was then successively converted into the analogous *compounds* (VI) and (VII), and thence into 6-chloro-2-γ-piperidinopropylamino-

quinoxaline (II*a*; R = H), identical in every way with the partial-dehalogenation product of 2 : 7-dichloro-3-γ-piperidinopropylaminoquinoxaline.



The degradation of (I*a*; R = Cl) to 7-chloro-2-γ-piperidinopropylaminoquinoxaline was also effected by a two-step process in which it was first treated with sodium hydrogen sulphide in alcohol, to give 6-*chloro*-3-γ-*piperidinopropylamino*-2-*mercaptoquinoxaline* (I*a*; R = SH), and this was then desulphurised by means of Raney nickel. However, application of this method to 2 : 7-dichloro-3-γ-piperidinopropylaminoquinoxaline failed, for, although conversion into 7-*chloro*-3-γ-*piperidinopropylamino*-2-*mercaptoquinoxaline* (II*a*; R = SH) was successful, subsequent treatment with Raney nickel gave only intractable material. Early attempts to reduce 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline catalytically to (I*a*; R = H) with the addition of one equivalent of sodium hydroxide as acid-binding agent (cf. Whitmore and Revukas, *J. Amer. Chem. Soc.*, 1940, **62**, 1691; Krahler and Burger, *ibid.*, 1941, **63**, 2370) led to mixtures, from which the only isolable product was 6-*chloro*-3-γ-*piperidinopropylamino*-2-*ethoxyquinoxaline* (I*a*; R = OEt) identical with material made by the action of alcoholic sodium ethoxide on (I*a*; R = Cl) (cf. the observations of Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405, in the quinazoline series).

Earlier, an abortive attempt was made to establish the orientation of the major product of interaction of 2 : 3 : 6-trichloroquinoxaline and γ-piperidinopropylamine (2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline) by an independent synthesis of 6-*chloro*-3-γ-*piperidinopropylamino*-2-*hydroxyquinoxaline* (I*a*; R = OH) obtained from it by short acid hydrolysis; prolonged hydrolysis led to 6-chloro-2 : 3-dihydroxyquinoxaline (VI; R = Cl, R′ = H, R″ = OH), characterised by conversion into 6-*chloro*-2 : 3-*diketo*-1 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (VIII) identical with material made from authentic (VI; R = Cl, R′ = H, R″ = OH), and distinct from 6-*chloro*-2 : 3-*dimethoxyquinoxaline*.

4-Chloro-2-nitroaniline was caused to interact with a large excess of ethyl oxalate to give *ethyl* 4-*chloro*-2-*nitro-oxanilate* (IX) together with a smaller proportion of NN′-*di*-(4-*chloro*-2-*nitrophenyl*)*oxamide*. (IX) was readily hydrolysed to 4-chloro-2-nitroaniline by cold, dilute, aqueous sodium hydroxide, and this ease of hydrolysis was reflected in the difficulties at first encountered in the preparation of N-(4-*chloro*-2-*nitrophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide* (X; R = NO_2) from (IX) and γ-piperidinopropylamine. For example, treatment of (IX) with excess of γ-piperidinopropylamine alone, with or without external heating, gave exclusively 4-chloro-2-nitroaniline and NN′-*di*-(γ-*piperidinopropyl*)*oxamide*, independently prepared from γ-piperidinopropylamine and ethyl oxalate. In this connexion it is also noteworthy that *NN′*-di-(4-chloro-2-nitrophenyl)oxamide, when stirred with excess of γ-piperidinopropylamine in the cold, was converted almost quantitatively into 4-chloro-2-

nitroaniline and *NN'*-di-(γ-piperidinopropyl)oxamide. The desired mixed oxamide (X; R = NO_2) was ultimately obtained by causing equimolecular quantities of γ-piperidinopropylamine and ethyl 4-chloro-2-nitro-oxanilate to react in cold benzene solution, and its reduction to N-(4-*chloro*-2-*aminophenyl*)-N'-(γ-*piperidinopropyl*)*oxamide* (X; R = NH_2) was accomplished with hydrogen and Raney-nickel catalyst. The projected synthesis was arrested at this stage since (X; R = NH_2) could not be cyclised to give (I*a*; R = OH). Various cyclising agents were tried: either the starting material was recovered unchanged (as with concentrated sulphuric acid and phosphorus pentoxide), or the products were unrecognisable (phosphorus pentachloride, phosphoryl chloride, phosphorus trichloride) or, if cyclisation to a quinoxaline derivative did occur, this involved loss of the γ-piperidinopropylamino-side-chain and the formation of 6-chloro-2 : 3-dihydroxyquinoxaline (aqueous alcoholic hydrogen chloride). When (X; R = NH_2) was heated at 190—200°, cyclisation with loss of water occurred, but to give the benziminazole derivative (XI; R = $CO{\cdot}NH{\cdot}[CH_2]_3{\cdot}N < [CH_2]_4 > CH_2$). The constitution of this substance was first indicated by its degradation to 5(or 6)-*chlorobenziminazole*-2-*carboxylic acid* (XI; R = CO_2H) and thence to 5(or 6)-chlorobenziminazole (XI; R = H) identical with material made by the method of Fischer (*Ber.*, 1904, **37**, 556); substantiating proof was provided by its synthesis by a method analogous to that described by Copeland and Day (*J. Amer. Chem Soc.*, 1943, **65**, 1072) for a series of benziminazole-2-carboxyamides. 5(or 6)-*Chloro*-2-*hydroxymethylbenziminazole* (XI; R = $CH_2{\cdot}OH$), prepared by treating 4-chloro-1 : 2-phenylenediamine with glycollic acid under the conditions used by Phillips (*J.*, 1928, 2395) for similar condensations, was oxidised to give 5(or 6)-chlorobenziminazole-2-carboxylic acid (cf. the synthesis of benziminazole-2-carboxylic acid by Bistrzycki and Przeworski, *Ber.*, 1912, **45**, 3489). With thionyl chloride this was converted into 5'(or 6') : 5''(or 6'')-*dichloro*-3 : 6-*diketodibenziminazolo*(1' : 2' : 1 : 2)(1'' : 2'' : 4 : 5)*piperazine* (XII), which with γ-piperidinopropylamine yielded 5(or 6)-*chlorobenziminazole*-2-*carboxy*-γ-*piperidinopropylamide*.

Having confirmed the deduction made in Part XXVII (*loc. cit.*) that the chlorine atom in the 3-position of 2 : 3 : 6-trichloroquinoxaline was more reactive than that in the 2-position, we prepared further compounds of type (I; R = Cl, R' = dialkylaminoalkyl). Originally the reaction between 2 : 3 : 6-trichloroquinoxaline and β-diethylaminoethylamine (2 mols.) was carried out by mixing them at 0°, and evidence was adduced to show that an uncontrolled reaction led to the production of some 6-chloro-2 : 3-bis-(β-diethylaminoethylamino)quinoxaline. When this method was tried with γ-diethylaminopropylamine and more complex aminoalkylamines, very little reaction occurred, and after considerable experimentation it was found that the use of equimolecular proportions of the reactants in boiling alcohol gave the best results. In this way 2 : 6-dichloroquinoxaline *derivatives* (I; R = Cl) were made in which R' was 3-γ-*diethylaminopropyl*, 3-δ-*diethylamino*-α-*methylbutyl* and 3-γ-di-*n*-butylaminopropyl. In the last case the *hydrochloride* was separated directly from the reaction mixture, and no isomeric product was sought. In the other two cases failure to detect any of the second isomer was possibly due to its loss during crystallisation; alternatively, it may have been attributable to hydrolysis during the working-up process, in the course of which the product was extracted with hydrochloric acid. In support of the latter hypothesis, it can be said that in preliminary condensations of 2 : 3 : 6-trichloroquinoxaline with γ-piperidinopropylamine, involving extraction with hydrochloric acid, only 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline was isolated, and that the second isomer was detected only when acetic acid was used in place of hydrochloric acid.

In order to obtain 2 : 6-*dichloro*-3-β-*dimethylaminoethylaminoquinoxaline* (I; R = Cl, R' = $[CH_2]_2{\cdot}NMe_2$) it was essential to carry out the reaction between 2 : 3 : 6-trichloroquinoxaline and β-dimethylaminoethylamine in the cold. In boiling alcoholic solution loss of methyl chloride occurred in addition to condensation, and the formation of two isomeric tricyclic compounds, 6-*chloro*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra-aza-anthracene* (XIII; R = Me, R' = H, *n* = 2) and 7-*chloro*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra-aza-anthracene* (XIII; R = H, R' = Me, *n* = 2) was observed. As expected, the former was formed in greater quantity, but it was not possible completely to free it from the latter although a pure specimen was obtained by heat-cyclisation of 2 : 6-dichloro-3-β-dimethylaminoethylaminoquinoxaline, and the substantial identity of the two products was demonstrated by the formation of identical *acetyl* and *benzoyl* derivatives. Heating (I; R = Cl, R' = $[CH_2]_2{\cdot}NMe_2$) at 135—145° gave not only 6-chloro-1-methyl-1 : 2 : 3 : 4-tetrahydro-1 : 4 : 9 : 10-tetra-aza-anthracene itself, but also a derived *dimethochloride*, approximately 56% of the methyl chloride being retained in this manner.

2 : 3 : 6-Trichloroquinoxaline and *NN'*-dimethylethylenediamine in boiling alcohol gave

rise to 6-*chloro*-1 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra-aza-anthracene* (XIII; R = R′ = Me, *n* = 2), but the only product isolated from the reaction of (VII; R = H, R′ = R″ = Cl) and ethylenediamine under similar conditions was NN′-*bis*-(2 : 6-*dichloro*-3-*quinoxalyl*)*ethylenediamine* [cf. the condensation of 2 : 3-dichloroquinoxaline with ethylenediamine to give 1 : 2 : 3 : 4-tetrahydro-1 : 4 : 9 : 10-tetra-aza-anthracene (Ogg and Bergström, *J. Amer. Chem. Soc.*, 1931, **53**, 1847)].

Antimalarial Activities.

The compounds were tested for antimalarial activity against the blood forms of *P. gallinaceum* in chicks, by the method previously described (Davey, *Ann. Trop. Med. Parasit.*, 1946, **40**, 52). The results given below are expressed in the same way as in previous papers in this series (*J.*, 1946, 343).

Ref. no.	Compound	Dose, mg./kg.	Activity
6971	2 : 6-Dichloro-3-β-dimethylaminoethylaminoquinoxaline	80	++
		40	+
		20	−
5587	2 : 6-Dichloro-3-β-diethylaminoethylaminoquinoxaline *	20	++
		10	+
		5	−
6231	2 : 6-Dichloro-3-γ-diethylaminopropylaminoquinoxaline	40	++
		20	+
6219	2 : 6-Dichloro-3-γ-piperidinopropylaminoquinoxaline	80	++
		40	+
		20	−
6396	2 : 6-Dichloro-3-γ-di-*n*-butylaminopropylaminoquinoxaline hydrochloride	160	+ to ++
		80	+
		40	−
6480	2 : 6-Dichloro-3-δ-diethylamino-α-methylbutylaminoquinoxaline	160	++
		80	+
		40	±
		20	−
6991	2 : 7-Dichloro-3-γ-piperidinopropylaminoquinoxaline	160	+
		80	−
7219	6-Chloro-3-γ-piperidinopropylamino-2-hydroxyquinoxaline	80	−
6946	6-Chloro-3-γ-piperidinopropylamino-2-ethoxyquinoxaline	160	−
7175	6-Chloro-3-γ-piperidinopropylamino-2-thiolquinoxaline	160	−
6860	7-Chloro-2-β-diethylaminoethylaminoquinoxaline hydrochloride	160	−
6990	7-Chloro-2-γ-diethylaminopropylaminoquinoxaline hydrochloride	160	−
6736	7-Chloro-2-γ-piperidinopropylaminoquinoxaline hydrochloride	160	−
7109	6-Chloro-2-β-diethylaminoethylaminoquinoxaline	80	−
7034	6-Chloro-2-γ-piperidinopropylaminoquinoxaline	160	−
7318	2-Chloro-3-β-diethylaminoethylaminoquinoxaline *	80	+
		40	−
5987	2-Chloro-3-γ-diethylaminopropylaminoquinoxaline *	80	+
7216	2-β-Diethylaminoethylaminoquinoxaline	80	−
7215	2-γ-Diethylaminopropylaminoquinoxaline	80	−
7214	2 β-Diethylaminoethylamino-3-methylquinoxaline	80	−
7221	2-γ-Diethylaminopropylamino-3-methylquinoxaline	80	−
7310	2-β-Diethylaminoethylamino-3-hydroxyquinoxaline	160	−
7173	2-γ-Piperidinopropylamino-3-hydroxyquinoxaline	160	−
6479	*NN′*-Bis-(2 : 6-dichloro-3-quinoxalyl)ethylenediamine	80	−
7085	6-Chloro-1-ethyl-1 : 2 : 3 : 4-tetrahydro-1 : 4 : 9 : 10-tetra-aza-anthracene *	160	−
6599	6-Chloro-1 : 4-dimethyl-1 : 2 : 3 : 4-tetrahydro-1 : 4 : 9 : 10-tetra-aza-anthracene	160	−
6730	6-Chloro-1′-ethyl-1′ : 5′-diaza-2 : 3-pentamethylenequinoxaline	160	−

* Described in Part XXVII (*loc. cit.*) and included for comparison, or only subsequently tested.

The following compounds were also tested for prophylactic activity against *P. gallinaceum* in chicks by the method described elsewhere (Davey, *Ann. Trop. Med. Parasit.*, 1946, **40**, 453) but none showed activity: 5587 and 6736 at 160 mg./kg., 6219, 6479, 6480, 6730, 6860, 6946, 6991, 7034, 7085, 7109, 7215, 7216, 7219, 7221, and 7318 at 80 mg./kg., and 7214 at 40 mg./kg.

In Part XXVII (*loc. cit.*) the cyclisation of (I; R = Cl, R′ = $[CH_2]_2$·NEt_2) to give (XIII; R = Et, R′ = H, *n* = 2) was reported. This compound has been prepared again, for test as an antimalarial, together with the corresponding cyclisation product from (I; R = Cl, R′ = $[CH_2]_3$·NEt_2), namely 6-*chloro*-1′-*ethyl*-1′ : 5′-*diaza*-2 : 3-*pentamethylenequinoxaline* (XIII; R = Et, R′ = H, *n* = 3). The results of these tests against *P. gallinaceum* in chicks are shown in the Table in comparison with those of the corresponding compounds of type (I).

The inactivity of the former renders it unlikely that the activity of the 2 : 6-dichloro-3-dialkylaminoalkylaminoquinoxalines has any connection with their capacity to undergo cyclisation (which might have occurred *in vivo*), and this conclusion is supported by the activity of (*Ia*; R = Cl) which is incapable of such a transformation.

The synthesis of 2 : 6- and 2 : 7-dichloroquinoxaline mentioned above permitted the preparation of a number of 6- and 7-chloro-2-dialkylaminoalkylaminoquinoxalines of types (II and I; R = H) in addition to the γ-piperidinopropylamino-derivatives already referred to. The results of antimalarial tests on these compounds (described in the experimental section) are given in the Table. Their uniform inactivity, in contrast to the activity of the compounds of types (I and II; R = Cl), clearly indicated the importance of the 2-chlorine atom, and this was also demonstrated by the inactivity of 2-β-*diethylaminoethylaminoquinoxaline* (III; R = H, R′ = $[CH_2]_2$·NEt_2) and of the corresponding γ-*diethylaminopropylamino*-derivative (III; R = H, R′ = $[CH_2]_3$·NEt_2) which bear a similar relation to the slightly active 2-chloro-3-β-diethylaminoethylamino- and 2-chloro-3-γ-diethylaminopropylamino-quinoxaline (III; R = Cl, R′ = $[CH_2]_2$·NEt_2 and $[CH_2]_3$·NEt_2, respectively) described in Part XXVII. A methyl group in place of the chlorine atom in these last two compounds was incapable of conferring activity; 2-β-*diethylaminoethylamino*-3-*methylquinoxaline* (III; R = Me, R′ = $[CH_2]_2$·NEt_2) and 2-γ-*diethylaminopropylamino*-3-*methylquinoxaline* (III; R = Me, R′ = $[CH_2]_3$·NEt_2) were inactive at doses of 80 mg./kg. The condensation of 2-chloro-, 2-chloro-3-methyl-, 2 : 6-dichloro-, and 2 : 7-dichloro-quinoxaline with dialkylaminoalkylamines was carried out by heating with a large excess of the amine under reflux.

The non-equivalence of a methyl group and a chlorine atom for the display of antimalarial activity suggested that a reactive chlorine atom might be required in order to undergo hydrolysis *in vivo* to give the corresponding hydroxy-compound as the actual antimalarial substance. 6-Chloro-3-γ-piperidinopropylamino-2-hydroxyquinoxaline and some other compounds of a similar type were therefore tested, but none showed antimalarial activity. This series included 2-β-*diethylaminoethylamino*-3-*hydroxyquinoxaline* (III; R = OH, R′ = $[CH_2]_2$·NEt_2), prepared by hydrolysis of (III; R = Cl, R′ = $[CH_2]_2$·NEt_2), and 2-γ-*piperidinopropylamino*-3-*hydroxyquinoxaline* (III; R = OH, R′ = $[CH_2]_3$·N<$[CH_2]_4$>CH_2) which was formed during a preparation of 2-*chloro*-3-γ-*piperidinopropylaminoquinoxaline* (III; R = Cl, R′ = $[CH_2]_3$·N<$[CH_2]_4$>CH_2) in which the product was extracted with hot dilute hydrochloric acid.

Although the above work clearly demonstrated a difference in reactivity between the chlorine atoms in the 2- and 3-positions of 2 : 3 : 6-trichloroquinoxaline, all attempts to effect selective hydrolysis failed. With boiling 5N-hydrochloric acid the trichloro-compound was slowly hydrolysed to 6-chloro-2 : 3-dihydroxyquinoxaline, and with weaker acid only the same substance and unchanged material were isolated; it was unchanged by 2N-sodium hydroxide at room temperature, in contrast to the behaviour of 2 : 4-dichloroquinazoline which was hydrolysed to 2-chloro-4-hydroxyquinazoline by this treatment (Part XIV, Curd, Landquist, and Rose, *J.*, 1947, 775).

Experimental.

N-(4-*Chloro*-2-*nitrophenyl*)*glycine* (IV; R = Cl, R′ = R″ = H).—4-Chloro-2-nitroaniline (172·5 g.) and bromoacetic acid (139 g.) were stirred together at 125—130° for 1 hour under reflux, with a vigorous stream of air passing through the mixture to remove hydrogen bromide. The mixture was then cooled and extracted with hot water (500 c.c.) and sufficient ammonia to make the solution alkaline to brilliant-yellow. The filtered extract deposited the ammonium salt of the product on cooling. This was collected and the filtrate used for re-extraction of the reaction mixture, the process being repeated four times. The combined crops of ammonium salt were suspended in the final filtrates, and the mixture acidified hot with hydrochloric acid. The precipitated product was collected, washed with water, and dried (yield, 104 g.). Crystallisation from alcohol gave N-(4-*chloro*-2-*nitrophenyl*)*glycine* as golden yellow prisms, m. p. 194° (decomp.) (Found: C, 41·8; H, 2·9; N, 12·6. $C_8H_7O_4N_2Cl$ requires C, 41·6; H, 3·0; N, 12·15%).

7-*Chloro*-2-*hydroxy*-3 : 4-*dihydroquinoxaline* (V; R = Cl, R′ = H).—*N*-(4-Chloro-2-nitrophenyl)glycine (2·3 g.) was shaken in methanol (75 c.c.) with Raney nickel and hydrogen at room temperature and pressure until the theoretical amount of hydrogen had been absorbed. The mixture was filtered, the filtrates were evaporated to dryness, and the residue was crystallised from alcohol, to give the *product* as colourless plates (yield, 74%), m. p. 214—215° (decomp.) (Found: C, 52·4; H, 3·9; N, 15·2; Cl, 19·0. $C_8H_7ON_2Cl$ requires C, 52·6; H, 3·8; N, 15·3; Cl, 19·5%).

7-*Chloro*-2-*hydroxyquinoxaline* (VI; R = Cl, R′ = R″ = H).—Silver nitrate (65 g.) in water (250 c.c.) was treated with sufficient ammonia solution to dissolve the initial precipitate, and the solution added with stirring to a suspension of finely ground 7-chloro-2-hydroxy-3 : 4-dihydroquinoxaline (31·6 g.) in water (250 c.c.). The mixture was stirred and boiled under reflux for 1 hour, cooled, and filtered. The black residue was dried and repeatedly extracted with boiling 2-ethoxyethanol. The combined extracts were cooled, and the crystalline product was collected and washed with alcohol. Further

quantities of the same material were obtained by concentration of the 2-ethoxyethanol mother-liquors to small bulk and by similar treatment of the original aqueous filtrate (yield, 22·2 g.). 7-*Chloro*-2-*hydroxyquinoxaline* crystallised from 2-ethoxyethanol as practically colourless rods, m. p. 270° (decomp.) (Found: C, 53·6; H, 3·2; N, 15·1. $C_8H_5ON_2Cl$ requires C, 53·2; H, 2·8; N, 15·5%).

2 : 7-*Dichloroquinoxaline* (VII; R = Cl, R′ = R″ = H).—7-Chloro-2-hydroxyquinoxaline (11·85 g.) and phosphoryl chloride (150 c.c.) were heated under reflux for 20 minutes. Most of the excess of phosphoryl chloride was then removed by evaporation under diminished pressure, and crushed ice added to the residue. The resulting solid was collected, washed until acid-free with water, and dried in a vacuum over sodium hydroxide. Crystallisation from alcohol then gave 2 : 7-*dichloroquinoxaline* as colourless platelets, m. p. 141° (Found: C, 48·8; H, 1·9; N, 14·0; Cl, 35·1. $C_8H_4N_2Cl_2$ requires C, 48·2; H, 2·0; N, 14·1; Cl, 35·6%).

7-*Chloro*-2-*γ*-*piperidinopropylaminoquinoxaline* (Ia; R = H).—2 : 7-Dichloroquinoxaline (4 g.) and γ-piperidinopropylamine (15 c.c.) were heated under reflux for 2 hours, and the mixture was cooled and dissolved in water (50 c.c.) and hydrochloric acid (20 c.c.). The solution was treated with carbon, filtered, and made strongly alkaline with sodium hydroxide. The liberated oil was extracted with ether, and the extract dried (K_2CO_3) and evaporated. Fractionation of the residual oil gave 7-chloro-2-γ-piperidinopropylaminoquinoxaline (yield 5·1 g.), b. p. 220°/0·5 mm. Triturated with light petroleum (b. p. 40—60°) and a little water it solidified and then crystallised from aqueous methanol as colourless rods of the *dihydrate*, m. p. 80—82° (Found: C, 56·0; H, 7·1; N, 16·3; loss on drying in a vacuum at 60°, 10·5. $C_{16}H_{21}N_4Cl,2H_2O$ requires C, 56·4; H, 7·3; N, 16·4; H_2O, 10·6%). Treatment with methanolic picric acid gave the *picrate* which crystallised from 2-ethoxyethanol as yellow prisms, m. p. 216° (Found: C, 49·4; H, 4·6; N, 18·5; Cl, 6·3. $C_{16}H_{21}N_4Cl,C_6H_3O_7N_3$ requires C, 49·5; H, 4·5; N, 18·4; Cl, 6·7%). Treatment of a solution of the distilled base in ethyl acetate with alcoholic hydrogen chloride until no further precipitation occurred gave the *monohydrochloride* which crystallised from alcohol–ethyl acetate as colourless rods, m. p. 204—205° (Found: C, 56·6; H, 6·1; N, 16·4; Cl, 21·0. $C_{16}H_{21}N_4Cl,HCl$ requires C, 56·3; H, 6·45; N, 16·4; Cl, 20·8%) (6736). The *dihydrochloride* was obtained by dissolving the base in a large excess of warm alcoholic hydrogen chloride; precipitation commenced almost immediately; this salt crystallised from alcohol–ethyl acetate as colourless needles, m. p. 233° (Found: C, 50·6; H, 5·8; N, 14·9. $C_{16}H_{21}N_4Cl,2HCl$ requires C, 50·9; H, 6·15; N, 14·8%).

Ethyl 5-*Chloro*-2-*nitroanilinoacetate* (IV; R = H, R′ = Cl, R″ = Et).—10N-Sodium hydroxide (108 c.c.) was added with stirring and cooling to a mixture of ethyl aminoacetate hydrochloride (137·5 g.), water (74 c.c.), and benzene (300 c.c.). Anhydrous potassium carbonate was added to form a thick paste with the aqueous layer, and the benzene solution decanted. The residue was washed repeatedly with benzene, and the benzene solutions were combined and dried over potassium carbonate. To the filtered solution (700 c.c.), 4-chloro-1 : 2-dinitrobenzene (100 g.) (Laubenheimer, *Ber.*, 1875, **8**, 1623; 1876, **9**, 760) was added, and the mixture heated under reflux for 4 hours. Most of the solvent was then removed by evaporation, and light petroleum (b. p. 60—80°) added. The *product*, precipitated initially as an oil, rapidly solidified, and was then collected, washed with light petroleum (b. p. 60—80°), and crystallised from alcohol; it formed golden-yellow needles (yield, 61·3 g.), m. p. 100—101° (Found: C, 46·4; H, 4·3; N, 10·9. $C_{10}H_{11}O_4N_2Cl$ requires C, 46·4; H, 4·25; N, 10·8%).

Attempts to condense 4-chloro-1 : 2-dinitrobenzene with glycine and with ethyl aminoacetate hydrochloride failed.

6-*Chloro*-2-*hydroxy*-3 : 4-*dihydroquinoxaline* (V; R = H, R′ = Cl).—The preceding compound (61·3 g.) was stirred vigorously in alcohol (850 c.c.) for 30 hours in presence of Raney nickel with a rapid stream of hydrogen passing through the solution. The mixture was filtered and the filtrate evaporated to small bulk. The crystalline product which separated on cooling was collected, washed with alcohol, and dried. Crystallisation from water gave 6-*chloro*-2-*hydroxy*-3 : 4-*dihydroquinoxaline* as pale yellow needles (yield, 71%), m. p. 184° (Found: C, 52·4; H, 4·2; N, 15·9. $C_8H_7ON_2Cl$ requires C, 52·6; H, 3·8; N, 15·3%).

6-*Chloro*-2-*hydroxyquinoxaline* (VI; R = R″ = H, R′ = Cl).—The preceding dihydro-compound (25·1 g.) was stirred and boiled under reflux with water (500 c.c.), and a solution of ammoniacal silver nitrate [prepared from silver nitrate (52 g.) in water (100 c.c.)] added. After boiling for 2 hours the mixture was cooled and filtered, and the black residue washed with water. After drying, it was extracted with 2-ethoxyethanol (500 c.c.), and the filtrate cooled. The crystalline material which separated on cooling was collected and the filtrates were used for re-extraction. After the process had been repeated three times more, the combined crops of crystals were washed with methanol and dried. The pure *product* thus obtained (yield, 10·5 g.) had m. p. 305°. For analysis it was recrystallised from 2-ethoxyethanol giving minute colourless plates (Found: C, 52·9; H, 3·2; N, 15·4. $C_8H_5ON_2Cl$ requires C, 53·2; H, 2·8; N, 15·5%).

2 : 6-*Dichloroquinoxaline* (VII; R = R″ = H, R′ = Cl).—6-Chloro-2-hydroxyquinoxaline (10 g.) was treated with boiling phosphoryl chloride (100 c.c.) for 20 minutes. The excess of phosphoryl chloride was then removed by distillation under diminished pressure, and crushed ice added to the residue. The resulting solid was collected, washed with water, dried, and crystallised from alcohol to give the *product* as practically colourless needles, m. p. 159—160° (Found: C, 48·4; H, 2·3; N, 13·4; Cl, 35·7. $C_8H_4N_2Cl_2$ requires C, 48·2; H, 2·0; N, 14·1; Cl, 35·6%).

6-*Chloro*-2-*γ*-*piperidinopropylaminoquinoxaline* (IIa; R = H).—2 : 6-Dichloroquinoxaline (3 g.) and γ-piperidinopropylamine (11 c.c.) were boiled under reflux for 2 hours. The cooled reaction mixture was dissolved in a mixture of water (100 c.c.) and acetic acid (15 c.c.), leaving only a little insoluble material. The carbon-treated and filtered solution was made alkaline with sodium hydroxide and extracted with ether. The residue left after evaporation of the dried (K_2CO_3) solution was distilled to remove unchanged γ-piperidinopropylamine. Fractionation of the residue gave 6-*chloro*-2-*γ*-*piperidinopropylaminoquinoxaline* (yield, 78%), b. p. 192°/0·2 mm., which slowly crystallised and then separated from methanol as practically colourless plates, m. p. 109—110° (Found: C, 59·8; H, 7·1; N, 16·9. $C_{16}H_{21}N_4Cl,H_2O$ requires C, 59·6; H, 7·1; N, 17·4%) (7034). It formed a *dipicrate* which crystallised from 2-ethoxy-

ethanol as small yellow needles, m. p. 191—192° (Found : C, 44·5; H, 3·7; N, 18·8. $C_{16}H_{21}N_4Cl,2C_6H_3O_7N_3$ requires C, 44·05; H, 3·6; N, 18·4%).

Condensation of 2 : 3 : 6-*Trichloroquinoxaline with* γ-*Piperidinopropylamine.*—γ-Piperidinopropylamine (42·7 g.) was gradually added to a solution of 2 : 3 : 6-trichloroquinoxaline (70·2 g.) (see Part XXVII, *loc. cit.*) in boiling alcohol (400 c.c.), and the mixture heated under reflux for 18 hours. The alcohol was then removed by evaporation, the residue dissolved in 5N-acetic acid (200 c.c.), and the filtered solution made alkaline with sodium hydroxide. The precipitated oil gradually solidified when kept and was then collected and crystallised from methanol. The material which separated (yield, 62%) was recrystallised from methanol to give 2 : 6-*dichloro*-3-γ-*piperidinopropylaminoquinoxaline* (*Ia*; R = Cl) as colourless needles, m. p. 108° (Found : C, 56·7; H, 6·1; N, 16·2; Cl, 20·8. $C_{16}H_{20}N_4Cl_2$ requires C, 56·6; H, 5·9; N, 16·5; Cl, 20·9%) (6219). The corresponding *picrate* crystallised from 2-ethoxyethanol as yellow prisms, m. p. 228—230° (Found : C, 46·6; H, 4·2; N, 16·8. $C_{16}H_{20}N_4Cl_2,C_6H_3O_7N_3$ requires C, 46·5; H, 4·1; N, 17·3%). The original methanol filtrate from the separation of 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline was concentrated to about one-eighth of its original volume and allowed to stand. The material which separated (yield, 20%) was recrystallised from methanol to give 2 : 7-*dichloro*-3-γ-*piperidinopropylaminoquinoxaline* (*IIa*; R = Cl) as colourless rods, m. p. 76—77° (Found : C, 56·7; H, 5·7; N, 16·7. $C_{16}H_{20}N_4Cl_2$ requires C, 56·6; H, 5·9; N, 16·5%) (6991). This afforded a *picrate* which separated from 2-ethoxyethanol as minute yellow prisms, m. p. 191—193° (Found : C, 46·6; H, 4·2; N, 16·8. $C_{16}H_{20}N_4Cl_2,C_6H_3O_7N_3$ requires C, 46·5; H, 4·1; N, 17·3%).

Partial Reductive Dehalogenation of 2 : 6-*Dichloro*-3-γ-*piperidinopropylaminoquinoxaline.*—2 : 6-Dichloro-3-γ-piperidinopropylaminoquinoxaline (6·8 g.) in alcohol (100 c.c.) was shaken with hydrogen and Raney nickel until the calculated amount of hydrogen had been absorbed (7 hours). The catalyst was then removed by filtration, and the solvent evaporated under diminished pressure. The residue was boiled with 2N-hydrochloric acid (100 c.c.) for ½ hour to hydrolyse any unchanged material, and the solution then made alkaline with sodium hydroxide and extracted with ether. Removal of the solvent from the dried (K_2CO_3) ethereal extract left an oil (4·1 g.) which was crystallised from aqueous methanol to give a product, m. p. 80—81°, undepressed in admixture with authentic 7-chloro-2-γ-piperidinopropylaminoquinoxaline (Found : C, 56·8; H, 7·4; N, 16·7. Calc. for $C_{16}H_{21}N_4Cl,2H_2O$: C, 56·4; H, 7·3; N, 16·4%). With alcoholic picric acid it gave a picrate, m. p. 216—217° (from 2-ethoxyethanol), alone or admixed with an authentic specimen (Found : C, 49·2; H, 4·6; N, 18·1. Calc. for $C_{16}H_{21}N_4Cl,C_6H_3O_7N_3$: C, 49·5; H, 4·5; N, 18·4%).

Partial Reductive Dehalogenation of 2 : 7-*Dichloro*-3-γ-*piperidinopropylaminoquinoxaline.*—2 : 7-Dichloro-3-γ-piperidinopropylaminoquinoxaline (6·2 g.) was treated with hydrogen and Raney nickel, and the reaction mixture worked up as in the preceding experiment. The oily crude product (4·2 g.) crystallised from aqueous methanol and then had m. p. 110—111°, alone or in admixture with authentic 6-chloro-2-γ-piperidinopropylaminoquinoxaline (Found : C, 59·6; H, 7·3; N, 17·1. Calc. for $C_{16}H_{21}N_4Cl,H_2O$: C, 59·6; H, 7·1; N, 17·4%). With alcoholic picric acid it gave a picrate, m. p. 191—192° (decomp.) (from 2-ethoxyethanol), undepressed by admixture with the authentic dipicrate (Found : C, 44·1; H, 3·6; N, 18·0. Calc. for $C_{16}H_{21}N_4Cl,2C_6H_3O_7N_3$: C, 44·05; H, 3·6; N, 18·4%).

6-*Chloro*-3-γ-*piperidinopropylamino*-2-*mercaptoquinoxaline* (*Ia*; R = SH).—Hydrogen sulphide was passed into a solution of sodium (0·6 g.) in alcohol (40 c.c.) until the theoretical increase in weight (0·85 g.) for formation of sodium hydrogen sulphide had occurred. The solution was then added to a solution of 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline (8·5 g.) in warm alcohol (60 c.c.), and the mixture boiled under reflux for 2 hours with the continual passage of hydrogen sulphide into the mixture. After being filtered hot, the solution was evaporated under reduced pressure to about one-fifth of its volume. The material which separated on cooling was collected and crystallised from alcohol. After drying in a vacuum at 100° it was recrystallised from benzene–light petroleum (b. p. 80—100°) to give 6-*chloro*-3-γ-*piperidinopropylamino*-2-*mercaptoquinoxaline* as yellow needles (yield, 60%), m. p. 139° (Found : C, 56·7; H, 6·2; N, 16·5. $C_{16}H_{21}N_4ClS$ requires C, 57·0; H, 6·3; N, 16·6%) (7175.)

7-*Chloro*-3-γ-*piperidinopropylamino*-2-*mercaptoquinoxaline* (*IIa*; R = SH).—Prepared similarly from 2 : 7-dichloro-3-γ-piperidinopropylaminoquinoxaline, this *compound* crystallised from alcohol as clusters of small yellow prisms (yield, 45%), m. p. 178° (Found : C, 57·2; H, 6·0; N, 16·7. $C_{16}H_{21}N_4ClS$ requires C, 57·0; H, 6·3; N, 16·6%).

Desulphurisation of 6-*Chloro*-3-γ-*piperidinopropylamino*-2-*mercaptoquinoxaline.*—The thiol (2 g.), alcohol (120 c.c.), and Raney nickel (*ca.* 20 g.) were boiled under reflux with stirring for 5 hours. By filtration and evaporation of the solvent an oily product was obtained which crystallised from aqueous methanol and had m. p. 79—81°, alone or in admixture with 7-chloro-2-γ-piperidinopropylaminoquinoxaline. It afforded the picrate (crystallised from 2-ethoxyethanol), m. p. and mixed m. p. 216—217° (Found : C, 49·9; H, 4·6%), and dihydrochloride, m. p. 233°, undepressed by admixture with the dihydrochloride of (*Ia*; R = H).

A similar attempt to desulphurise 7-chloro-3-γ-piperidinopropylamino-2-mercaptoquinoxaline gave a dark green oil which did not crystallise.

6-*Chloro*-3-γ-*piperidinopropylamino*-2-*ethoxyquinoxaline* (*Ia*; R = OEt).—2 : 6-Dichloro-3-γ-piperidinopropylaminoquinoxaline (5·1 g.) was heated under reflux on the steam-bath for 6 hours with a solution of sodium (0·35 g.) in alcohol (30 c.c.). The reaction mixture was then filtered hot and the filtrate diluted with water to precipitate the *product* which was collected and crystallised from methanol to give colourless lozenge-shaped crystals (yield, 90%), m. p. 88° (Found : C, 61·6; H, 6·9; N, 15·8; Cl, 10·2. $C_{18}H_{25}ON_4Cl$ requires C, 62·0; H, 7·2; N, 16·1; Cl, 10·2%) (6946). It formed a *dipicrate*, small yellow plates, m. p. 178° (from 2-ethoxyethanol) (Found : C, 44·6; H, 4·1; N, 17·5. $C_{18}H_{25}ON_4Cl,2C_6H_3O_7N_3$ requires C, 44·6; H, 3·9; N, 17·4%).

The same compound was obtained from an attempted reductive dehalogenation of 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline in presence of sodium hydroxide as follows. 2 : 6-Dichloro-3-γ-piperidinopropylaminoquinoxaline (10·2 g.) was added to a solution of sodium hydroxide (1·2 g.) in alcohol (140 c.c.) containing a little water, and the mixture treated with hydrogen and Raney nickel. Uptake of hydrogen was slow. After 10 hours the mixture was filtered and evaporated to dryness, and

the residue dissolved in ether. The ether solution was shaken with 2N-acetic acid, and the acetic acid extract separated and made alkaline with sodium hydroxide. The precipitated product was isolated by extraction with ether and evaporation of the dried (K_2CO_3) solution. The remaining oil partly crystallised when kept. The crystals were freed from oil by trituration with a little light petroleum (b. p. 40—60°), collected, and recrystallised from methanol. The substance then had m. p. 82°, alone or mixed with authentic 6-chloro-3-γ-piperidinopropylamino-2-ethoxyquinoxaline (Found: C, 61·5; H, 6·9; N, 16·1; Cl, 10·0%). It was not further purified, but converted into its picrate, small yellow plates (from 2-ethoxyethanol), m. p. and mixed m. p. 176—178°.

6-*Chloro*-2 : 3-*diketo*-1 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (VIII).—6-Chloro-2 : 3-dihydroxyquinoxaline (2 g.) was dissolved in hot N-sodium hydroxide (60 c.c.), methyl sulphate (7·55 g.) added, and the mixture heated under reflux with stirring for 4 hours. The precipitated product was collected hot (a further quantity of less pure material separated on cooling), washed, and crystallised from alcohol to give the *quinoxaline* (VIII) as colourless needles, m. p. 192° (Found: C, 53·2; H, 3·8; N, 12·1. $C_{10}H_9O_2N_2Cl$ requires C, 53·5; H, 4·0; N, 12·5%).

6-*Chloro*-2 : 3-*dimethoxyquinoxaline*.—2 : 3 : 6-Trichloroquinoxaline (2·35 g.) was added to a solution of sodium (0·6 g.) in methanol (60 c.c.), and the mixture boiled under reflux for 1½ hours and filtered hot. On cooling the filtrate, the *product* separated as colourless needles (yield, 2·2 g.), m. p. 110—111° (Found: C, 53·8; H, 3·8; N, 12·5. $C_{10}H_9O_2N_2Cl$ requires C, 53·5; H, 4·0; N, 12·5%).

Hydrolysis of 2 : 6-*Dichloro*-3-γ-*piperidinopropylaminoquinoxaline with Hydrochloric acid*.—(*a*) A solution of 2 : 6-dichloro-3-γ-piperidinopropylaminoquinoxaline (4·2 g.) in 2N-hydrochloric acid (100 c.c.) was boiled for one hour and filtered hot. The crystalline product which separated on cooling was collected and then redissolved in water, and the solution carefully neutralised with sodium hydroxide to precipitate the base. A further small quantity was obtained by neutralisation of the reaction mother-liquors. Crystallisation of the combined crops from alcohol gave 6-*chloro*-3-γ-*piperidinopropylamino*-2-*hydroxyquinoxaline* as short colourless needles (yield, 77%), m. p. 193° (Found: C, 60·1; H, 6·4; N, 17·7. $C_{16}H_{21}ON_4Cl$ requires C, 59·9; H, 6·6; N, 17·5%) (7219).

(*b*) 2 : 6-Dichloro-3-γ-piperidinopropylaminoquinoxaline (3·4 g.) in 2N-hydrochloric acid (75 c.c.) was boiled under reflux for 12 hours with stirring. The precipitated solid was collected hot, washed, and dried. It was identified as 6-chloro-2 : 3-dihydroxyquinoxaline (yield, 72%) by methylation with methyl sulphate and alkali (see above) to give 6-chloro-2 : 3-diketo-1 : 4-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline, m. p. 189—190°, undepressed by admixture with authentic material.

Ethyl 4-*Chloro*-2-*nitro-oxanilate* (IX).—4-Chloro-2-nitroaniline (17·3 g., 0·1 g.-mol.) and ethyl oxalate (58·4 g., 0·4 g.-mol.) were heated in an oil-bath at 180—190° for 18 hours, the mixture was cooled, and the yellow crystalline product isolated by filtration. Further crops of the same material were obtained by reheating the mother-liquors twice. The crops were combined and extracted with boiling benzene. The insoluble material was collected (2 g.) and crystallised from nitrobenzene to give NN′-*di*-(4-*chloro*-2-*nitrophenyl*)*oxamide* as buff-coloured prisms, m. p. 296° (decomp.) (Found: C, 42·4; H, 2·0; N, 13·6. $C_{14}H_8O_6N_4Cl_2$ requires C, 42·1; H, 2·0; N, 14·0%). The benzene-soluble fraction consisted of the required *ethyl* 4-*chloro*-2-*nitro-oxanilate*. It crystallised from benzene as pale yellow needles (yield, 41%), m. p. 156° (Found: C, 44·4; H, 3·4; N, 10·3. $C_{10}H_9O_5N_2Cl$ requires C, 44·0; H, 3·3; N, 10·3%).

The quantity of *NN′*-di-(4-chloro-2-nitrophenyl)oxamide formed was very considerable when the proportion of ethyl oxalate was reduced below that given above.

N-(4-*Chloro*-2-*nitrophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide* (X; R = NO_2).—γ-Piperidinopropylamine (42·7 g., 0·3 g.-mol.) was added gradually to a stirred suspension of ethyl 4-chloro-2-nitro-oxanilate (81·8 g., 0·3 g.-mol.) in benzene (200 c.c.), and stirring then continued for a few minutes. Complete dissolution was obtained. Benzene (120 c.c.) was distilled off, and light petroleum (b. p. 80—100°) (360 c.c.) added to the hot solution. On cooling the mixture, N-(4-*chloro*-2-*nitrophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide* separated. Crystallised from benzene–light petroleum (b. p. 60—80°) it formed small pale cream prisms, m. p. 114° (Found: C, 52·6; H, 5·6; N, 15·2. $C_{16}H_{21}O_4N_4Cl$ requires C, 52·1; H, 5·7; N, 15·2%).

When ethyl 4-chloro-2-nitro-oxanilate was treated with an excess of γ-piperidinopropylamine alone, in the cold or at 130° for 3 hours, the products were 4-chloro-2-nitroaniline and NN′-*di*-(γ-*piperidinopropyl*)*oxamide*. The latter, separated by its solubility in 2N-acetic acid, crystallised from light petroleum (b. p. 60—80°) as small colourless needles, m. p. 112—113°, undepressed by admixture with material (m. p. 112—113°) made from γ-piperidinopropylamine and ethyl oxalate (Found: C, 63·7; H, 10·1; N, 16·9. $C_{18}H_{34}O_2N_4$ requires C, 63·9; H, 10·1; N, 16·6%).

Reaction of NN′-*Di*-(4-*chloro*-2-*nitrophenyl*)*oxamide with* γ-*Piperidinopropylamine*.—A mixture of γ-piperidinopropylamine (11·2 g.) and *NN′*-di-(4-chloro-2-nitrophenyl)oxamide (4 g.) was stirred in the cold for 18 hours. The resulting orange solution was diluted with water, the alkalinity to brilliant-yellow just removed by the addition of hydrochloric acid, and the insoluble material (3·1 g.) collected by filtration. It was identified as 4-chloro-2-nitroaniline, m. p. and mixed m. p. 115—116°. The filtrate was concentrated by evaporation under diminished pressure, and sodium hydroxide added to render the solution just alkaline to Clayton-yellow. The resulting precipitate was collected, washed with water, and dried (yield, 3·1 g.). It had m. p. 112°, alone or admixed with *NN′*-di-(γ-piperidinopropyl)-oxamide.

N-(4-*Chloro*-2-*aminophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide* (X; R = NH_2).—The corresponding nitro-compound (14·7 g.) was reduced in alcohol (120 c.c.) with hydrogen and Raney nickel at room temperature and pressure. Uptake of hydrogen was slow, but was complete after 12 hours. The catalyst was removed by filtration, the filtrate treated with carbon, again filtered, and evaporated to small bulk. The crystalline product which separated on cooling was collected and recrystallised from alcohol to give N-(4-*chloro*-2-*aminophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide* as small colourless needles, m. p. 99° after short drying at 70° and m. p. 120° after drying *in vacuo* at 80° (Found: C, 56·7; H, 6·8; N, 16·2; Cl, 10·6. $C_{16}H_{23}O_2N_4Cl$ requires C, 56·7; H, 6·8; N, 16·5; Cl, 10·5%).

Cyclisation of N-(4-*Chloro*-2-*aminophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide with Aqueous-alcoholic Hydrogen Chloride*.—*N*-(4-Chloro-2-aminophenyl)-*N′*-(γ-piperidinopropyl)oxamide (3·4 g.) was dissolved

in hot alcohol (40 c.c.), water (4 c.c.) and hydrochloric acid (8 c.c.) were added, and the mixture was boiled for 15 minutes. The product, which began to separate after about 3 minutes, was collected, after cooling, washed with alcohol, and dried (yield, 1·7 g.). It was shown to be 6-chloro-2 : 3-dihydroxyquinoxaline, (*a*) by methylation with methyl sulphate and sodium hydroxide to give 6-chloro-2 : 3-diketo-1 : 4-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline, m. p. and mixed m. p. 191—192°, and (*b*) by treatment with phosphorus pentachloride to give 2 : 3 : 6-trichloroquinoxaline, m. p. and mixed m. p. 144°.

5(or 6)-*Chloro*-2-*hydroxymethylbenziminazole* (XI; R = CH_2·OH).—A solution of 4-chloro-1 : 2-phenylenediamine (28·5 g.) and glycollic acid (22·8 g.) in 4N-hydrochloric acid (200 c.c.) was heated under reflux for 40 minutes, cooled, and neutralised with aqueous ammonia. The precipitated product was collected, washed with water, and crystallised from aqueous methanol to give 5(or 6)-*chloro*-2-*hydroxymethylbenziminazole* as practically colourless prisms (yield, 30·4 g.), m. p. 206—207° (Found : C, 52·6; H, 3·9; N, 15·6. $C_8H_7ON_2Cl$ requires C, 52·6; H, 3·9; N, 15·35%).

5(or 6)-*Chlorobenziminazole*-2-*carboxylic Acid* (XI; R = CO_2H).—5(or 6)-Chloro-2-hydroxymethylbenziminazole (5·5 g.) was dissolved in boiling water (400 c.c.), and N-sodium hydroxide (7 c.c.) added, followed by a solution of potassium permanganate (7 g.) in water (300 c.c.) which was added slowly with stirring during 1 hour. When the addition was complete, the mixture was boiled for a further ½ hour with stirring and then filtered hot, and the filtrate cooled and acidified with acetic acid. The precipitated product (3·7 g.) was crystallised from water (decolorising carbon), washed with ether, and dried by azeotropic distillation with benzene, to give the 5(or 6)-*chlorobenziminazole* 5(or 6)-*chlorobenziminazole*-2-*carboxylate*, m. p. 158—159° (decomp.) (Found : C, 51·4; H, 2·8; N, 16·2; Cl, 20·6. $C_8H_5O_2N_2Cl,C_7H_5N_2Cl$ requires C, 51·6; H, 3·1; N, 16·1; Cl, 20·3%). A sample of this material was extracted with aqueous sodium hydrogen carbonate, and the insoluble material extracted with ether. The ethereal extract was concentrated and treated with alcoholic picric acid to give 5(or 6)-chlorobenziminazole picrate (see below), m. p. and mixed m. p. 216°. The sodium hydrogen carbonate solution was acidified with acetic acid, and the precipitated product collected, washed with water, and dried in a vacuum over sulphuric acid, to give 5(or 6)-*chlorobenziminazole*-2-*carboxylic acid*, m. p. *ca.* 159° (decomp.) (dependent on the rate of heating) (Found : C, 48·0, 48·9; H, 2·9, 3·4; N, 14·5, 14·8. $C_8H_5O_2N_2Cl$ requires C, 48·9; H, 2·6; N, 14·25%). Consistent analyses could not be obtained.

5′(or 6′) : 5″(or 6″)-*Dichloro*-3 : 6-*diketodibenziminazolo*(1′ : 2′ : 1 : 2)(1″ : 2″ : 4 : 5)*piperazine* (XII).—5(or 6)-Chlorobenziminazole-2-carboxylic acid (5·9 g.) and thionyl chloride (35 c.c.) were boiled under reflux for 8 hours. After the mixture had been cooled, the solid was collected, ground with ice-water, filtered, and dried at 100° (yield, 3·8 g.). Crystallisation from nitrobenzene gave the *product* as pale yellow irregular plates, m. p. >350° (Found : C, 54·0; H, 2·0; N, 15·5. $C_{16}H_6O_2N_4Cl_2$ requires C, 54·0; H, 1·7; N, 15·7%).

5(or 6)-*Chlorobenziminazole*-2-*carboxy*-γ-*piperidinopropylamide* (XI; R = CO·NH·$[CH_2]_3$·N<$[CH_2]_4$>CH_2).—A mixture of the preceding compound (XII) (0·25 g.), γ-piperidinopropylamine (2 c.c.), and water (6 c.c.) was boiled under reflux gently for 20 minutes. Complete dissolution was quickly obtained. The mixture was cooled and diluted with water (35 c.c.), and the precipitated product collected. Crystallised from alcohol, 5(or 6)-*chlorobenziminazole*-2-*carboxy*-γ-*piperidinopropylamide* formed colourless needles, m. p. 173—174° (Found : C, 59·8; H, 6·3; N, 17·6. $C_{16}H_{21}ON_4Cl$ requires C, 59·9; H, 6·6; N, 17·5%).

5(or 6)-*Chlorobenziminazole* (XI; R = H).—A mixture of 4-chloro-1 : 2-phenylenediamine (10 g.) and 85% formic acid (25 c.c.) was boiled under reflux for 2 hours, cooled, and poured into excess of dilute aqueous ammonia. The precipitated product was collected and dried at 80° and then by azeotropic distillation with benzene. Crystallisation from benzene–light petroleum (b. p. 60—80°) then gave 5(or 6)-chlorobenziminazole, m. p. 124—126° (Found : C, 55·1; H, 3·4; N, 18·0. Calc. for $C_7H_5N_2Cl$: C, 55·1; H, 3·3; N, 18·4%). Repeated crystallisation from benzene–light petroleum (b. p. 60—80°) gave material, m. p. 117—118° (Found : C, 55·2; H, 3·1; N, 18·6%), which was considered to be a different form of the same substance (Fischer, *loc. cit.*, gives m. p. 125°). With alcoholic picric acid it gave a *picrate*, yellow needles, m. p. 215—216° (from alcohol) (Found : C, 41·0; H, 2·3; N, 18·8. $C_7H_5N_2Cl,C_6H_3O_7N_3$ requires C, 40·9; H, 2·1; N, 18·4%).

Cyclisation of N-(4-*Chloro*-2-*aminophenyl*)-N′-(γ-*piperidinopropyl*)*oxamide by Heat.*—*N*-(4-Chloro-2-aminophenyl)-*N*′-(γ-piperidinopropyl)oxamide (5·1 g.) was heated at 190—200° for 10 minutes. On cooling, the melt set to a glass which gradually crystallised. Recrystallisation from alcohol gave 5(or 6)-chlorobenziminazole-2-carboxy-γ-piperidinopropylamide (yield, 63%), m. p. 173—174°, undepressed by admixture with material made by the method described above.

This material (1·35 g.), dissolved in hydrochloric acid (40 c.c.), was boiled under reflux for 24 hours. The solution was diluted with water (100 c.c.), cooled, and made alkaline with aqueous ammonia. After filtration, the filtrate was acidified with acetic acid. The precipitated material was collected and crystallised from water to give colourless needles of 5(or 6)-chlorobenziminazole-2-carboxylic acid (yield, 74%), m. p. 157—158° (decomp.), undepressed by admixture with an authentic specimen. A portion of this acid (0·25 g.) was heated at 155—165° for 15 minutes, the resulting oil extracted with benzene, and the extract filtered and evaporated to small bulk. Addition of light petroleum (b. p. 40—60°) precipitated an oil which solidified on scratching. Recrystallisation from benzene–light petroleum (b. p. 60—80°) gave 5(or 6)-chlorobenziminazole, m. p. 117°, undepressed by admixture with authentic material of m. p. 117—118°. It afforded a picrate, m. p. 215—216°, alone or in admixture with authentic 5(or 6)-chlorobenziminazole picrate.

2 : 6-*Dichloro*-3-γ-*diethylaminopropylaminoquinoxaline* (I; R = Cl, R′ = $[CH_2]_3$·NEt_2).—γ-Diethylaminopropylamine (13 g.) was added to a solution of 2 : 3 : 6-trichloroquinoxaline (23·4 g.) in boiling alcohol (600 c.c.) and the whole boiled under reflux for 12 hours. The solvent was then removed by distillation, and the residue extracted with 2N-hydrochloric acid, a little unchanged 2 : 3 : 6-trichloroquinoxaline (2·6 g.) remaining undissolved. The filtered extract was made alkaline with sodium hydroxide, the precipitated oil extracted with ether, and the ethereal extract in turn extracted with

2N-acetic acid. Addition of sodium hydroxide to the acid extract gave the product which was isolated by extraction with ether and evaporation of the dried (K_2CO_3) extract. Vacuum-distillation of the residue gave 2 : 6-*dichloro*-3-*γ*-*diethylaminopropylaminoquinoxaline* as a pale orange oil, b. p. 170—175°/5 × 10^{-3} mm. (yield, 70%), which solidified when kept and then separated from aqueous methanol as practically colourless prisms, m. p. 66—67° (Found : C, 55·0; H, 6·1; N, 16·9; Cl, 21·9. $C_{15}H_{20}N_4Cl_2$ requires C, 55·1; H, 6·2; N, 17·1; Cl, 21·7%) (6231). The corresponding *picrate*, prepared from the base with alcoholic picric acid, crystallised from alcohol as pale yellow rods, m. p. 140—142° (Found : C, 45·1; H, 4·2; N, 17·4. $C_{15}H_{20}N_4Cl_2,C_6H_3O_7N_3$ requires C, 45·3; H, 4·2; N, 17·6%).

2 : 6-*Dichloro*-3-*δ*-*diethylamino*-*α*-*methylbutylaminoquinoxaline* (I; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2).—A mixture of 2 : 3 : 6-trichloroquinoxaline (11·7 g.), *δ*-diethylamino-*α*-methylbutylamine (7·9 g.), and alcohol (120 c.c.) was boiled under reflux for 20 hours with stirring, the solvent removed by distillation, and the residue extracted with 2N-hydrochloric acid. The filtered extract was made alkaline with sodium hydroxide and extracted with ether, and the dried extract evaporated. The resulting oil was twice vacuum-distilled, to give the *product* as a pale yellow oil, b. p. 156—157°/4 × 10^{-4} mm. (Found : C, 57·8; H, 6·8; N, 15·8. $C_{17}H_{24}N_4Cl_2$ requires C, 57·5; H, 6·8; N, 15·8%) (6480). The corresponding *picrate* crystallised from 2-ethoxyethanol as small yellow rods, m. p. 146—147° (Found : C, 47·4; H, 4·7; N, 17·0. $C_{17}H_{24}N_4Cl_2,C_6H_3O_7N_3$ requires C, 47·3; H, 4·7; N, 16·8%).

2 : 6-*Dichloro*-3-*γ*-*di*-n-*butylaminopropylaminoquinoxaline* (I; R = Cl, R′ = $[CH_2]_3$·NBu^n_2).—2 : 3 : 6-Trichloroquinoxaline (4·7 g.) and *γ*-di-*n*-butylaminopropylamine (3·7 g.) were allowed to react in boiling alcohol (120 c.c.) for 18 hours, the alcohol was distilled off, and the residue crystallised from water containing a little hydrochloric acid to give the *hydrochloride* as colourless irregular plates of indefinite melting point (174—183°) (Found : C, 54·0; H, 6·8; N, 13·4. $C_{19}H_{28}N_4Cl_2,HCl$ requires C, 54·4; H, 7·0; N, 13·4%) (6396). The corresponding base decomposed on attempted distillation in a high vacuum.

2 : 6-*Dichloro*-3-*β*-*dimethylaminoethylaminoquinoxaline* (I; R = Cl, R′ = $[CH_2]_2$·NMe_2).—*β*-Dimethylaminoethylamine (1·8 g.) (Turner, *J. Amer. Chem. Soc.*, 1946, **68**, 1607) was slowly added to a suspension of 2 : 3 : 6-trichloroquinoxaline (4·7 g.) in alcohol (120 c.c.) at 5°, with stirring. The mixture was then stirred at room temperature for 20 hours, the solvent removed by vacuum-evaporation at <30°, and the residue extracted with dilute acetic acid. After being filtered from undissolved material, the extract was made alkaline with sodium hydroxide. The precipitated solid was collected and crystallised first from aqueous methanol and then from light petroleum (b. p. 60—80°), to give 2 : 6-*dichloro*-3-*β*-*dimethylaminoethylaminoquinoxaline* as practically colourless prisms, m. p. 97° (the melt became turbid at 110° and completely solid at 140°, and finally remelted with decomposition at *ca.* 215°) (Found : C, 50·3; H, 4·9; N, 19·4. $C_{12}H_{14}N_4Cl_2$ requires C, 50·55; H, 4·95; N, 19·65%) (6991). With alcoholic picric acid it formed a *picrate* which crystallised from 2-ethoxyethanol as yellow prisms, m. p. 184° (decomp.) (Found : C, 42·1; H, 3·2; N, 19·0. $C_{12}H_{14}N_4Cl_2,C_6H_3O_7N_3$ requires C, 42·05; H, 3·3; N, 19·1%).

Cyclisation of 2 : 6-*Dichloro*-3-*β*-*dimethylaminoethylaminoquinoxaline by Heat.*—2 : 6-Dichloro-3-*β*-dimethylaminoethylaminoquinoxaline (1·79 g.) was heated to constant weight (1·65 g.) at 135—145°. The residue was extracted four times with light petroleum (b. p. 100—120°) (75, 75, 50, 30 c.c.) until the weight of undissolved material remained unchanged (0·5 g.). The combined light-petroleum extracts deposited crystals on cooling. Recrystallisation from the same solvent gave 6-*chloro*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra*-*aza*-*anthracene* (XIII; R = Me, R′ = H, *n* = 2) as practically colourless prisms, m. p. 169—170° (Found : C, 56·2; H, 4·6; N, 23·9. $C_{11}H_{11}N_4Cl$ requires C, 56·3; H, 4·7; N, 23·9%). With picric acid in alcoholic solution it afforded a *picrate* which crystallised from 2-ethoxyethanol as yellow needles of indefinite melting point [247—262° (decomp.)] (Found : C, 44·6; H, 3·2; N, 21·2. $C_{11}H_{11}N_4Cl,C_6H_3O_7N_3$ requires C, 44·0; H, 3·0; N, 21·15%). The *acetyl* derivative, prepared by boiling with acetic anhydride for 1 hour and isolated by pouring into water, crystallised from alcohol as almost colourless prisms, m. p. 180—181° (Found : C, 56·6; H, 4·3; N, 20·1. $C_{13}H_{13}ON_4Cl$ requires C, 56·4; H, 4·7; N, 20·25%). The corresponding *benzoyl* derivative, prepared by grinding with benzoyl chloride and aqueous sodium hydroxide, crystallised from alcohol as cream-coloured prisms, m. p. 239—240° (Found : C, 63·4; H, 4·6; N, 16·3. $C_{18}H_{15}ON_4Cl$ requires C, 63·8; H, 4·5; N, 16·5%).

The above material insoluble in light petroleum was readily soluble in water and was purified by crystallisation from ethyl acetate–alcohol. 6-*Chloro*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra*-*aza*-*anthracene dimethochloride* formed practically colourless prisms, m. p. 244° (decomp.) (Found, in material dried at 100° : C, 46·6; H, 5·2; N, 16·5. $C_{11}H_{11}N_4Cl,2CH_3Cl$ requires C, 46·5; H, 5·1; N, 16·7%). With picric acid in alcohol it gave the corresponding *methochloride methopicrate* which crystallised from 2-ethoxyethanol as orange-yellow needles, m. p. 231—232° (decomp.) (Found : C, 43·2; H, 3·7; N, 18·4; Cl, 13·4. $C_{11}H_{11}N_4Cl,CH_3Cl,CH_3·C_6H_2O_7N_3$ requires C, 43·2; H, 3·6; N, 18·6; Cl, 13·4%). The corresponding *methochloride methiodide*, obtained from the dimethochloride by treatment of an aqueous solution with potassium iodide, separated from alcohol as small rectangular prisms, m. p. 239—240° (decomp.) (Found : C, 36·9; H, 4·2; N, 13·2. $C_{11}H_{11}N_4Cl,CH_3Cl,CH_3I$ requires C, 36·6; H, 4·0; N, 13·1%).

Condensation of 2 : 3 : 6-*Trichloroquinoxaline with β-Dimethylaminoethylamine in Boiling Alcoholic Solution.*—2 : 3 : 6-Trichloroquinoxaline (18·6 g.) and *β*-dimethylaminoethylamine (7·1 g.) were allowed to react in boiling alcohol (250 c.c.) for 20 hours. The solvent was removed by evaporation and the residue extracted with 5N-acetic acid (180 c.c.). The insoluble material consisted of unchanged 2 : 3 : 6-trichloroquinoxaline (6·3 g.). The acetic acid extract was made alkaline with sodium hydroxide and the precipitated product crystallised from methanol. The material which separated first was recrystallised from methanol to give 7-*chloro*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra*-*aza*-*anthracene* (XIII; R = H, R′ = Me, *n* = 2) as colourless irregular plates or prisms (yield, 0·7 g.), m. p. 222—223° (Found : C, 56·0; 56·1; H, 4·6, 4·8; N, 23·7, 23·8. $C_{11}H_{11}N_4Cl$ requires C, 56·3; H, 4·7; N, 23·9%). With picric acid in alcohol it gave a *picrate* of indefinite melting point (*ca.* 258°) (Found : C, 44·0; H, 2·7; N, 21·2. $C_{11}H_{11}N_4Cl,C_6H_3O_7N_3$ requires C, 44·0; H, 3·0; N, 21·15%). Boiling with acetic anhydride for 1 hour, followed by pouring into water, gave the *acetyl* derivative which crystallised

from alcohol as almost colourless prisms, m. p. 167—169° (Found: C, 56·0; H, 4·5; N, 19·7. $C_{13}H_{13}ON_4Cl$ requires C, 56·4; H, 4·7; N, 20·25%). Mixed with the acetyl derivative of (XIII; R = Me, R′ = H, *n* = 2), it melted at 147—154°. The corresponding *benzoyl* derivative, prepared as in the case of the benzoyl derivative of the isomer, crystallised from alcohol as minute pale cream prisms, m. p. 207—208° (Found: C, 63·6; H, 4·2; N, 16·4. $C_{18}H_{15}ON_4Cl$ requires C, 63·8; H, 4·5; N, 16·5%). Mixed with the benzoyl derivative of (XIII; R = Me, R′ = H, *n* = 2), it melted at 193—226°.

Concentration of the methanol mother-liquors from the separation of (XIII; R = H, R′ = Me, *n* = 2), and addition of an equal volume of water precipitated another substance (yield, 2·35 g.), m. p. 157—158°. Even by repeated crystallisation from methanol the m. p. could not be raised above 160° (Found: C, 56·6; H, 4·7; N, 23·6; Cl, 15·3. Calc. for $C_{11}H_{11}N_4Cl$: C, 56·3; H, 4·7; N, 23·9; Cl, 15·1%), but the material was shown to be substantially 6-chloro-1-methyl-1 : 2 : 3 : 4-tetrahydro-1 : 4 : 9 : 10-tetra-aza-anthracene, possibly contaminated with a little of the 7-chloro-isomer. A mixed m. p. of this material with pure material, m. p. 169—170°, showed no depression. In addition, it afforded an acetyl derivative, m. p. 179—181°, and a benzoyl derivative, m. p. 239—240°, alone or mixed with the corresponding derivatives of (XIII; R = Me, R′ = H, *n* = 2).

Condensation of 2 : 3 : 6-*Trichloroquinoxaline with* NN′-*Dimethylethylenediamine*.—2 : 3 : 6-Trichloroquinoxaline (14 g.), *NN′*-dimethylethylenediamine (5·4 g.), and alcohol (200 c.c.) were boiled under reflux with stirring for 18 hours. The diamine dihydrochloride (1·7 g.) which had separated was removed by filtration. When the mixture cooled, unchanged 2 : 3 : 6-trichloroquinoxaline (7·1 g.) separated and was removed. The mother-liquors were evaporated to dryness, and the residue was extracted with 2N-hydrochloric acid. The filtered extract was made alkaline with sodium hydroxide and extracted with ether, and the extract dried (K_2CO_3) and evaporated. Crystallisation of the residual solid from methanol gave 6-*chloro*-1 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra-aza-anthracene* (XIII; R = R′ = Me, *n* = 2) as a colourless micro-crystalline powder (yield, 3 g.), m. p. 83° (Found: C, 57·9; H, 5·2; N, 22·6. $C_{13}H_{13}N_4Cl$ requires C, 57·9; H, 5·3; N, 22·5%) (6599). With alcoholic picric acid it gave a *picrate* which separated from 2-ethoxyethanol as yellow rods, m. p. 197—198° (Found: C, 45·5; H, 3·3; N, 20·4. $C_{12}H_{13}N_4Cl,C_6H_3O_7N_3$ requires C, 45·3; H, 3·4; N, 20·5%).

Condensation of 2 : 3 : 6-*Trichloroquinoxaline with Ethylenediamine*.—Ethylenediamine monohydrate (2·7 g.) was added slowly to a solution of 2 : 3 : 6-trichloroquinoxaline (11·7 g.) in boiling alcohol (300 c.c.), and the solution heated under reflux for 14 hours with stirring. Solid began to separate rapidly from the reaction mixture. After the mixture had been cooled, the product was collected, dried, and extracted with boiling light petroleum (b. p. 80—100°) to remove unchanged 2 : 3 : 6-trichloroquinoxaline. The insoluble residue (7·1 g.) crystallised from 2-ethoxyethanol to give NN′-*di*-(2 : 6-*dichloro*-3-*quinoxalyl*)*ethylenediamine* as almost colourless prisms, m. p. 258—260° (Found: C, 47·9; H, 2·9; N, 18·4. $C_{18}H_{12}N_6Cl_4$ requires C, 47·6; H, 2·7; N, 18·5%) (6479).

6-*Chloro*-1-*ethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra-aza-anthracene* (XIII; R = Et, R′ = H, *n* = 2).—Prepared as described in Part XXVII (*loc. cit.*) by heating 2 : 6-dichloro-3-β-diethylaminoethylaminoquinoxaline at 200°, and crystallised from alcohol, this compound had m. p. 189° (7085). With alcoholic picric acid it gave a *picrate* which crystallised from 2-ethoxyethanol as orange-yellow needles, m. p. 257—258° (Found: C, 45·1; H, 3·4; N, 20·6. $C_{12}H_{13}N_4Cl,C_6H_3O_7N_3$ requires C, 45·3; H, 3·4; N, 20·5%).

6-*Chloro*-1′-*ethyl*-1′ : 5′-*diaza*-2 : 3-*pentamethylenequinoxaline* (XIII; R = Et, R′ = H, *n* = 3).—2 : 6-Dichloro-3-γ-diethylaminopropylaminoquinoxaline (6·5 g.) was heated at 230—240° (oil-bath) for 1½ hours with stirring. After cooling, the dark product was extracted with boiling benzene, and the filtrate evaporated to dryness. The residue was in turn extracted with hot light petroleum (b. p. 60—80°), and the extract filtered. When it cooled, crystals of the *product* separated (yield 1·2 g.). Recrystallised from alcohol this formed pale yellow rhombs, m. p. 148° (Found: C, 59·1; H, 5·5; N, 21·1. $C_{13}H_{15}N_4Cl$ requires C, 59·4; H, 5·8; N, 21·3%) (6730).

6-*Chloro*-2-β-*diethylaminoethylaminoquinoxaline* (II; R = H, R′ = $[CH_2]_2{\cdot}NEt_2$).—2 : 6-Dichloroquinoxaline (3 g.) and β-diethylaminoethylamine (12 g.) were boiled under reflux for 2 hours, and the reaction mixture was cooled and dissolved in 2·5N-acetic acid (100 c.c.). The solution was treated with carbon, filtered, and made alkaline with sodium hydroxide. Extraction with ether and evaporation of the dried (K_2CO_3) solution gave an oil containing unchanged β-diethylaminoethylamine, which was removed by distillation at 10 mm. The higher-boiling residue was then fractionated, to give 6-*chloro*-2-β-*diethylaminoethylaminoquinoxaline* as a very pale yellow oil (yield, 79%), b. p. 157—160°/0·2 mm., which rapidly solidified and then separated from light petroleum (b. p. 60—80°) as practically colourless plates, m. p. 78—79° (Found: C, 60·3; H, 7·0; N, 20·6. $C_{14}H_{19}N_4Cl$ requires C, 60·3; H, 6·8; N, 20·1%) (7109).

7-*Chloro*-2-β-*diethylaminoethylaminoquinoxaline* (I; R = H, R′ = $[CH_2]_2{\cdot}NEt_2$).—Similarly prepared from 2 : 7-dichloroquinoxaline and β-diethylaminoethylamine, it formed a pale yellow oil (yield, 68%), b. p. 180°/0·6 mm. The *dihydrochloride*, prepared by treating a solution of the base in ethyl acetate with alcoholic hydrogen chloride to render it just acid to Congo-red, crystallised from alcohol–ethyl acetate as almost colourless rods, m. p. 180—182° (Found: C, 48·3; H, 6·5; N, 16·0. $C_{14}H_{19}N_4Cl,2HCl$ requires C, 47·8; H, 6·0; N, 15·9%) (6860).

7-*Chloro*-2-γ-*diethylaminopropylaminoquinoxaline* (I; R = H, R′ = $[CH_2]_3{\cdot}NEt_2$), prepared in an analogous manner from 2 : 7-dichloroquinoxaline and γ-diethylaminopropylamine, was obtained as a pale yellow oil (yield, 79%), b. p. 190°/0·3 mm. The *dihydrochloride* separated from alcohol–ethyl acetate as pale yellow needles, m. p. 197—198° (Found: C, 46·8; H, 6·6; N, 14·3. $C_{15}H_{21}N_4Cl,2HCl$ requires C, 47·0; H, 6·5; N, 14·6%) (6990).

2-β-*Diethylaminoethylaminoquinoxaline* (III; R = H, R′ = $[CH_2]_2{\cdot}NEt_2$), prepared similarly from 2-chloroquinoxaline (Gowenlock, Newbold, and Spring, *J.*, 1945, 622) and β-diethylaminoethylamine, formed a pale yellow oil (yield, 79%), b. p. 135°/0·1 mm. (Found: C, 66·7; H, 8·2; N, 22·4. $C_{14}H_{20}N_4,0{\cdot}5H_2O$ requires C, 66·4; H, 8·3; N, 22·1%) (7216). The *dipicrate*, prepared from the base in

methanol, crystallised from 2-ethoxyethanol as yellow plates, m. p. 183—186° (Found: C, 44·6; H, 3·5; N, 20·2. $C_{14}H_{20}N_4,2C_6H_3O_7N_3$ requires C, 44·4; H, 3·7; N, 20·0%).

2-*γ-Diethylaminopropylaminoquinoxaline* (III; R = H, R′ = $[CH_2]_3$·NEt_2), prepared analogously, was obtained as a pale yellow oil (yield, 70%) b. p. 153°/0·1 mm. (Found: C, 67·7; H, 8·5; N, 21·1. $C_{15}H_{22}N_4,0{\cdot}5H_2O$ requires C, 67·5; H, 8·6; N, 21·0%) (7215). In methanol it afforded a *dipicrate* which separated from alcohol as yellow needles, m. p. 127—129° (Found: C, 44·7; H, 3·2; N, 19·8. $C_{15}H_{22}N_4,2C_6H_3O_7N_3$ requires C, 45·25; H, 3·9; N, 19·6%).

2-*β-Diethylaminoethylamino*-3-*methylquinoxaline* (III; R = Me, R′ = $[CH_2]_2$·NEt_2).—Similarly prepared from 2-chloro-3-methylquinoxaline (Newbold and Spring, *J.*, 1948, 521) and β-diethylaminoethylamine, the *base* formed a pale yellow hygroscopic oil (yield, 81%), b. p. 148—150°/0·4 mm. (Found: C, 67·3; H, 8·2; N, 20·7. $C_{15}H_{22}N_4,0{\cdot}5H_2O$ requires C, 67·4; H, 8·6; N, 21·0%) (7214). Its *dipicrate* crystallised from alcohol as small yellow rods, m. p. *ca.* 130° (Found: C, 45·5; H, 4·4; N, 19·2. $C_{15}H_{22}N_4,2C_6H_3O_7N_3$ requires C, 45·25; H, 3·9; N, 19·6%).

2-*γ-Diethylaminopropylamino*-3-*methylquinoxaline* (III; R = Me, R′ = $[CH_2]_3$·NEt_2).—Prepared in a corresponding manner by use of γ-diethylaminopropylamine in place of β-diethylaminoethylamine, the *base* formed a pale yellow hygroscopic oil (yield, 66%), b. p. 155°/0·05 mm. (Found: C, 68·5; H, 8·4; N, 19·8. $C_{16}H_{24}N_4,0{\cdot}5H_2O$ requires C, 68·3; H, 8·9; N, 19·9%) (7221). The *dipicrate* crystallised from methanol as yellow needles, m. p. 155° (Found: C, 46·1; H, 4·1; N, 19·5. $C_{16}H_{24}N_4,2C_6H_3O_7N_3$ requires C, 46·0; H, 4·1; N, 19·2%).

2-*β-Diethylaminoethylamino*-3-*hydroxyquinoxaline* (III; R = OH, R′ = $[CH_2]_2$·NEt_2).—2-Chloro-3-β-diethylaminoethylaminoquinoxaline (3·1 g.) in 2N-hydrochloric acid (80 c.c.) was boiled gently under reflux for 1 hour. The solution was cooled and made just alkaline to litmus with sodium hydroxide. The *product*, which separated initially as an oil, soon solidified. It was collected and crystallised from aqueous alcohol as colourless micro-crystalline powder, m. p. 76—77° (Found: C, 60·6; H, 7·8; N, 20·0. $C_{14}H_{20}ON_4,H_2O$ requires C, 60·4; H, 8·0; N, 20·1%) (7310).

Condensation of 2 : 3-*Dichloroquinoxaline with γ-Piperidinopropylamine.*—γ-Piperidinopropylamine (3·6 g.) was added slowly to a solution of 2 : 3-dichloroquinoxaline (5 g.) in boiling alcohol (100 c.c.), and the mixture heated under reflux for 5½ hours. The solvent was then removed by distillation, and the solid residue extracted with hot dilute hydrochloric acid. The insoluble material (unchanged 2 : 3-dichloroquinoxaline, 0·8 g.) was removed by filtration and the filtrate neutralised with sodium hydroxide. The precipitated solid was collected, washed, and dried. Crystallisation from methanol afforded first 2-*γ-piperidinopropylamino*-3-*hydroxyquinoxaline* (III; R = OH, R′ = $[CH_2]_3$·N < $[CH_2]_4$ > CH_2) as elongated tablets (yield, 39%), m. p. 179—180° (Found: C, 67·0; H, 7·6; N, 19·5. $C_{16}H_{22}ON_4$ requires C, 67·1; H, 7·7; N, 19·6%) (7173). Concentration of the mother-liquors from this compound gave 2-*chloro*-3-*γ-piperidinopropylaminoquinoxaline* (III; R = Cl, R′ = $[CH_2]_3$·N < $[CH_2]_4$ > CH_2) which separated from light petroleum (b. p. 40—60°) as colourless needles (yield, 7%), m. p. 88° (Found: C, 63·1; H, 7·0; N, 18·2. $C_{16}H_{21}N_4Cl$ requires C, 63·0; H, 6·9; N, 18·4%). The *picrate* crystallised from 2-ethoxyethanol as minute yellow rods, m. p. 201—202° (Found: C, 49·4; H, 4·5; N, 18·2. $C_{16}H_{21}N_4Cl,C_6H_3O_7N_3$ requires C, 49·5; H, 4·5; N, 18·4%).

Acid Hydrolysis of 2 : 3 : 6-*Trichloroquinoxaline.*—2 : 3 : 6-Trichloroquinoxaline (4·7 g.) and 5N-hydrochloric acid (50 c.c.) were boiled under reflux for 4 hours with stirring. After the mixture had cooled, the solid was collected, dried, and extracted with hot light petroleum (b. p. 80—100°) (80 c.c.). Evaporation of the light petroleum gave unchanged 2 : 3 : 6-trichloroquinoxaline (2·1 g.). The material insoluble in light petroleum (1·95 g.) was shown to be 6-chloro-2 : 3-dihydroxyquinoxaline by methylation with methyl sulphate and sodium hydroxide to give 6-chloro-2 : 3-diketo-1 4-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline, m. p. and mixed m. p. 189—190°, in good yield.

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