157. *Synthetic Antimalarials. Part XXVII. Some Derivatives of Phthalazine, Quinoxaline, and* iso*Quinoline.*

By Robert D. Haworth and Stanley Robinson.

The reactions of amines with 1 : 4-dichlorophthalazine, 2 : 3-dichloroquinoxaline, and 1 : 3-dichloro- and 1-chloro-*iso*quinoline have been examined, and a series of derivatives of these heterocyclic bases has been prepared. The discovery of a quinoxaline derivative of marked antimalarial activity is of interest.

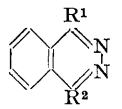
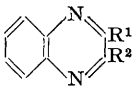
In previous work of this series special attention has been devoted to arylaminodialkylaminoalkylamino-heterocyclic compounds, and this communication describes some phthalazine and quinoxaline analogues of the quinazolines discussed in Part XIV (*J.*, 1947, 775). To the best of our knowledge antimalarial activity has never been reported with these systems, and the phthalazine ring has not been associated with biologically active molecules. On the other hand, the quinoxaline nucleus is now recognised in the riboflavin molecule, and the pyrazine structure is found in the pterins and folic acid.

The general procedure in the present researches involved the use of 1 : 4-dichlorophthalazine (I; $R^1 = R^2 = Cl$) and 2 : 3-dichloroquinoxaline (II; $R^1 = R^2 = Cl$), and the halogen atoms were replaced successively by amino-, substituted anilino- or dialkylaminoalkylamino-groups. 1 : 4-Dichlorophthalazine (I; $R^1 = R^2 = Cl$) was found to be stable towards water and alkalis, but its ready hydrolysis to 1-chloro-4-hydroxyphthalazine (I; $R^1 = Cl$; $R^2 = OH$) under weakly acid conditions presented certain difficulties in the synthetical applications. The condensation with δ-diethylamino-α-methyl-*n*-butylamine yielded a chlorine-containing basic oil, which reacted with *p*-chloroaniline, but, as all attempts to obtain crystalline derivatives failed, an alternative approach was adopted. 1 : 4-Dichlorophthalazine reacted with one mol. of aniline or *p*-chloroaniline in boiling alcoholic solution to yield 1-*chloro*-4-*anilino*- (I; $R^1 = NHPh$; $R^2 = Cl$) or 1-*chloro*-4-p-*chloroanilinophthalazine* (I; $R^1 = p\text{-}NH\cdot C_6H_4Cl$; $R^2 = Cl$). 1 : 4-*Dianilinophthalazine* (I; $R^1 = R^2 = NHPh$) was obtained by the action of two mols. of aniline on 1 : 4-dichlorophthalazine in boiling alcohol or alternatively from 1-chloro-4-anilinophthalazine by the action of excess of aniline at 200° or in boiling alcoholic solution in the presence of aniline hydrochloride. The catalytic influence of the latter is significant and is in agreement with the suggestion of Banks (*J. Amer. Chem. Soc.*, 1944, **66**, 1127) concerning reactions of this type. Conditions were not discovered for reaction between aromatic or dialkylaminoalkylamines and 1-chloro-4-hydroxyphthalazine, and the lack of reactivity is probably associated with the lactam structure of the hydroxyphthalazine molecule.

Condensation of 1-chloro-4-anilino- and -4-*p*-chloroanilino-phthalazine with dialkylaminoalkylamines was effected by heating with excess of amine at *ca.* 150°, and in this way 4-*anilino*-1-β-*diethylaminoethylaminophthalazine* (I; $R^1 = NHPh$; $R^2 = NH\cdot[CH_2]_2\cdot NEt_2$), 4-*anilino*-1-γ-*diethylaminopropylaminophthalazine* (I; $R^1 = NHPh$; $R^2 = NH\cdot[CH_2]_2\cdot NEt_2$), 4-p-*chloroanilino*-1-β-*diethylaminoethylaminophthalazine* (I; $R^1 = p\text{-}NH\cdot C_6H_4Cl$; $R^2 = NH\cdot[CH_2]_2\cdot NEt_2$), and 4-p-*chloroanilino*-1-γ-*diethylaminopropylaminophthalazine* (I; $R^1 = p\text{-}NH\cdot C_6H_4Cl$; $R^2 = NH\cdot[CH_2]_3\cdot NEt_2$), and 4-*p*-chloroanilino-1-δ-diethylamino-α-methyl-*n*-butylaminophthalazine (I; $R^1 = p\text{-}NH\cdot C_6H_4Cl$; $R^2 = NH\cdot CHMe\cdot[CH_2]_3\cdot NEt_2$), an oil giving a *picrate*, were obtained.

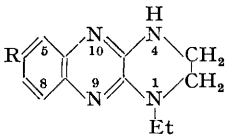
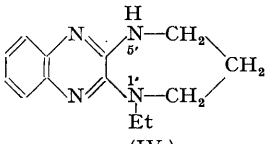
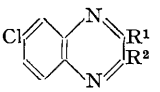
The greater stability of 2 : 3-dichloroquinoxaline (II; $R^1 = R^2 = Cl$) rendered its preparation and application more convenient than that of 1 : 4-dichlorophthalazine, although it was converted into 2 : 3-dihydroxyquinoxaline by boiling with dilute acids or alkalis. The reaction with aniline, examined under a variety of conditions, yielded 2 : 3-*dianilinoquinoxaline* (II; $R^1 = R^2 = NHPh$) (contrast Lockhart and Turner, *J.*, 1937, 424), and attempts to isolate

2-chloro-3-anilinoquinoxaline failed. 2 : 3-*Di*-p-*chloroanilinoquinoxaline* (II; $R^1 = R^2 =$ *p*-$NH{\cdot}C_6H_4Cl$) was obtained similarly from *p*-chloroaniline, but 2-*chloro*-3-p-*chloroanilino quinoxaline* (II; $R^1 =$ *p*-$NH{\cdot}C_6H_4Cl$; $R^2 = Cl$) was obtained by refluxing an aqueous

(I.)   (II.)

suspension of 2 : 3-dichloroquinoxaline and *p*-chloroaniline in the presence of very dilute hydrochloric acid. This observation was made at a relatively late stage of the research, and probably similar conditions would lead to the successful preparation of 2-chloro-3-anilino-quinoxaline (II; $R^1 = NHPh$; $R^2 = Cl$).

Dialkylaminoalkylamines reacted readily with 2 : 3-dichloroquinoxaline at ordinary temperatures, and 2-chloro-3-β-diethylaminoethylaminoquinoxaline (II; $R^1 = NH{\cdot}[CH_2]_2{\cdot}NEt_2$; $R^2 = Cl$) (*picrate*) and 2-chloro-3-γ-diethylaminopropylaminoquinoxaline (II; $R^1 = NH{\cdot}[CH_2]_3{\cdot}NEt_2$; $R^2 = Cl$) (*picrate* and *dihydrobromide*) were obtained in this way as oils which yielded crystalline picrates. When these chlorodialkylaminoquinoxalines were heated at 190—200°, ethyl chloride was eliminated and 1-*ethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra-aza-anthracene* (III; R = H) and 1′-*ethyl*-1′ : 5′-*diaza*-2 : 3-*pentamethylenequinoxaline* (IV) respectively were obtained. Early attempts to condense the chlorodialkylaminoalkylamino-quinoxalines with *p*-chloroaniline were unsuccessful; no reaction took place below 170—180°,

 (III.)  (IV.)  (V.)

and at this and higher temperatures intramolecular condensation occurred with elimination of ethyl chloride and the formation of the bases (III; R = H) and (IV). The parent 1 : 2 : 3 : 4-tetrahydro-1 : 4 : 9 : 10-tetra-aza-anthracene has been obtained (Bergstrom and Ogg, *J. Amer. Chem. Soc.*, 1931, **53**, 1846) by heating 2 : 3-dichloroquinoxaline with ethylenediamine at 150°, but the ready formation of base (III; R = H) and the hitherto undescribed heterocyclic type (IV) is noteworthy, and further experiments on these substances are in progress. The desired reaction between 2-chloro-3-dialkylaminoalkylaminoquinoxalines and *p*-chloroaniline was effected, however, in the presence of dilute hydrochloric acid at 100° (Banks, *loc. cit.*), and 2-p-*chloroanilino*-3-β-*diethylaminoethylaminoquinoxaline* (II; $R^1 =$ *p*-$NH{\cdot}C_6H_4Cl$; $R^2 = NH{\cdot}[CH_2]_2{\cdot}NEt_2$) and 2-p-*chloroanilino*-3-γ-*diethylaminopropylaminoquinoxaline* (II; $R^1 =$ *p*-$NH{\cdot}C_6H_4Cl$; $R^2 = NH{\cdot}[CH_2]_3{\cdot}NEt_2$) were prepared in this way.

When treated with warm alcoholic ammonia 2 : 3-dichloroquinoxaline gave excellent yields of 3-*chloro*-2-*aminoquinoxaline* (II; $R^1 = Cl$; $R^2 = NH_2$), which was converted into 2-*amino*-3-p-*chloroanilinoquinoxaline* (II; $R^1 =$ *p*-$NH{\cdot}C_6H_4Cl$; $R^2 = NH_2$) by heating with *p*-chloroaniline at 140°. This latter compound did not react with β-diethylaminoethyl chloride, probably because it exists as the isomeric 2-imino-modification. 2-Amino-3-chloroquinoxaline reacted with dialkylaminoalkylamines at 100°, and in this manner 2-*amino*-3-β-*diethylamino-ethylaminoquinoxaline* (II; $R^1 = NH{\cdot}[CH_2]_2{\cdot}NEt_2$; $R^2 = NH_2$) and 2-*amino*-3-γ-*diethyl-aminopropylaminoquinoxaline* (II; $R^1 = NH{\cdot}[CH_2]_3{\cdot}NEt_2$; $R^2 = NH_2$) were obtained.

2 : 3 : 6-Trichloroquinoxaline (V; $R^1 = R^2 = Cl$) was prepared by improved methods from *p*-chloroacetanilide in order to examine the influence of a chlorine atom in the benzene ring upon the biological activity of appropriate derivatives. The properties of 2 : 3 : 6-trichloroquinoxaline are very similar to those of the 2 : 3-dichloro-derivative. It was hydrolysed by boiling with acetic acid to 6-chloro-2 : 3-dihydroxyquinoxaline, but, whilst it was readily converted at 140° into 6-*chloro*-2 : 3-*di*-p-*chloroanilinoquinoxaline* (V; $R^1 = R^2 =$ *p*-$NH{\cdot}C_6H_4Cl$), it did not react in the presence of hydrochloric acid to yield the mono-*p*-chloroanilino-derivative. Reaction with ammonia and dialkylaminoalkylamines occurred readily with the production of aminodichloroquinoxalines in high yield. The structure of the homogeneous products has not been established, but it is assumed that the 3-chlorine atom is preferentially attacked by anionoid reagent, whilst the 2-chlorine atom is stabilised by conjugation with the chlorine atom in position 6. Such a pronounced difference in reactivity of the 2- and 3-chlorine atoms is

remarkable and the absence of isomeric aminodichloroquinoxaline is surprising. Thus 2 : 3 : 6-trichloroquinoxaline was converted by warm alcoholic ammonia into 2 : 6-*dichloro*-3-*aminoquinoxaline* (V; $R^1 = NH_2$; $R^2 = Cl$), which in turn reacted with *p*-chloroaniline at 160° and with β-diethylaminoethylamine at 100° to give 6-*chloro*-3-*amino*-2-p-*chloroanilinoquinoxaline* (V; $R^1 = NH_2$; $R^2 = p\text{-}NH\cdot C_6H_4Cl$) and 6-*chloro*-3-*amino*-2-β-*diethylaminoethylaminoquinoxaline* (V; $R^1 = NH_2$; $R^2 = NH\cdot[CH_2]_2\cdot NEt_2$). In other experiments, 2 : 3 : 6-trichloroquinoxaline was condensed with β-diethylaminoethylamine; in the cold, 2 : 6-*dichloro*-3-β-*diethylaminoethylaminoquinoxaline* (V; $R^1 = NH\cdot[CH_2]_2\cdot NEt_2$; $R^2 = Cl$) was obtained, but a reaction which was uncontrolled led to an impure specimen of the diamino-derivative (V; $R^1 = R^2 = NH\cdot[CH_2]_2\cdot NEt_2$). When 2 : 6-dichloro-3-β-diethylaminoethylaminoquinoxaline was heated at 200°, ethyl chloride was eliminated and 6-*chloro*-1-*ethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra-aza-anthracene* (III; R = Cl) produced, and, in the presence of dilute hydrochloric acid, *p*-chloroaniline condensed with 2 : 6-dichloro-3-β-diethylaminoethylaminoquinoxaline to yield 6-*chloro*-2-p-*chloroanilino*-3-β-*diethylaminoethylaminoquinoxaline* (V; $R^1 = NH\cdot[CH_2]_2\cdot NEt_2$; $R^2 = p\text{-}NH\cdot C_6H_4Cl$).

A few new derivatives of *iso*quinoline have been prepared. 1 : 3-Dichloro*iso*quinoline was stable towards boiling 2N-sodium hydroxide or 2N-hydrochloric acid, and it did not react with *p*-chloroaniline in the presence of dilute acids. When treated with *p*-chloroaniline in nitrobenzene or acetic acid solution, 1 : 3-dichloro*iso*quinoline was converted into a mixture of 1 : 3-*di*-p-*chloroanilino*iso*quinoline* and 3-*chloro*-1-p-*chloroanilino*iso*quinoline*, but the latter could not be condensed with β-dialkylaminoalkylamines. Similarly, 3-chloro-1-*p*-chloroanilino*iso*quinoline, obtained as an oil (*picrate*) by heating 1 : 3-dichloro*iso*quinoline with diethylaminoethylamine did not react smoothly with *p*-chloroaniline. The non-reactivity of the 3-chloro-atom in these experiments was confirmed by the behaviour of 3-chloro*iso*quinoline. This substance, prepared by a modification of the method of Gabriel (*Ber.*, 1886, **19**, 2354), was unreactive towards *p*-chloroaniline and β-diethylaminoethylamine. In marked contrast with the 3-chloro-isomer, 1-chloro*iso*quinoline reacted with *p*-chloroaniline either at 120° or in presence of dilute hydrochloric acid to give 1-p-*chloroanilino*iso*quinoline*, and with β-diethylaminoethylamine at 100° to yield 1-β-diethylaminoethylamino*iso*quinoline (*picrate* and *dihydrochloride*).

The following table gives the results of antimalarial tests carried out in the Research Laboratories of Imperial Chemical Industries Limited, Manchester.

The results which relate to tests against the blood invasive forms of *P. gallinaceum* in chicks are expressed in the same way as in previous papers of this Series.

Ref. no.	Compound.	Dose mg./kg.	Activity.
4759	4-*p*-Chloroanilino-1-β-diethylaminoethylaminophthalazine	160	+
		80	—
4998	2-Amino-3-*p*-chloroanilinoquinoxaline	320	—
		160	—
5017	2-Amino-3-γ-diethylaminopropylaminoquinoxaline	20	—
5325	2-*p*-Chloroanilino-3-β-diethylaminoethylaminoquinoxaline	80	—
5987	2-Chloro-3-γ-diethylaminopropylaminoquinoxaline	80	+
5326	2-*p*-Chloroanilino-3-γ-diethylaminopropylaminoquinoxaline	160	—
		80	—
5705	6-Chloro-3-amino-2-β-diethylaminoethylaminoquinoxaline	80	—
5706	6-Chloro-2-*p*-chloroanilino-3-β-diethylaminoethylaminoquinoxaline	80	—
5587	2 : 6-Dichloro-3-β-diethylaminoethylaminoquinoxaline	20	++
		10	+
5755	1-β-Diethylaminoethylamino*iso*quinoline	160	—
		80	—

None of the compounds showed any prophylactic activity against *P. gallinaceum* in chicks. The activity of **5587** is noteworthy since it is greater than that of mepacrine.

Experimental.

1 : 4-Dichlorophthalazine, prepared by the action of phosphorus pentachloride (3 parts) on phthalaz-1 : 4-dione at 150° (Drew and Holt, *J.*, 1937, 16), crystallised from acetone in long colourless needles, m. p. 161—162° (yield, 55%), and was rapidly hydrolysed to 1-chloro-4-hydroxyphthalazine by warm 2N-hydrochloric acid.

1-*Chloro*-4-*anilinophthalazine* (I; $R^1 = NHPh$; $R^2 = Cl$).—1 : 4-Dichlorophthalazine (6 g.) and aniline (2·8 g.) were refluxed in alcohol (60 c.c.) for 30 minutes. The mixture was basified with sodium hydroxide and diluted with water, and the solid collected and crystallised from acetone.

1-*Chloro*-4-*anilinophthalazine* (I; $R^1 = NHPh$; $R^2 = Cl$) (6 g.) was obtained as colourless felted needles, m. p. 200° (Found: C, 65·8; H, 4·0. $C_{14}H_{10}N_3Cl$ requires C, 65·8; H, 3·9%), and gave a

hydrochloride which was insoluble in cold water and crystallised from glacial acetic acid in needles, m. p. 270° (Found : ionisable Cl, 12·1. $C_{14}H_{10}N_3$,HCl requires ionisable Cl, 12·1%). 1-Chloro-4-anilinophthalazine was recovered after heating with excess of aniline in alcoholic solution for 7 hours.

1-*Chloro*-4-p-*chloroanilinophthalazine* (I; R^1 = *p*-NH·C_6H_4Cl; R^2 = Cl), prepared similarly, was isolated as the water-insoluble *hydrochloride*, needles, m. p. 256°, from glacial acetic acid (Found: ionisable Cl, 10·9. $C_{14}H_9N_3Cl_2$,HCl requires ionisable Cl, 10·8%), which was decomposed with sodium hydroxide, preferably in alcoholic solution. The base crystallised from acetone in colourless needles, m. p. 241° (Found : C, 57·8; H, 3·2. $C_{14}H_9N_3Cl_2$ requires C, 57·9; H, 3·1%).

1 : 4-*Dianilinophthalazine* (I; R^1 = R^2 = NHPh).—(*a*) 1 : 4-Dichlorophthalazine (3 g.), aniline (3 g.), and alcohol (60 c.c.) were refluxed for 30 minutes, and after basification with sodium hydroxide and dilution with water, the *base* (I; R^1 = R^2 = NHPh) was collected and crystallised from acetone; long, yellow, rectangular plates (2·5 g.), m. p. 223° (Found : C, 76·6; H, 5·2. $C_{20}H_{16}N_4$ requires C, 76·9; H, 5·1%), were obtained.

(*b*) 1-Chloro-4-anilinophthalazine (1 g.) and aniline (2 g., 5 mols.) were refluxed for 15 minutes; after basification, excess of aniline was removed in steam and the 1 : 4-dianilinophthalazine (1·2 g.) collected.

(*c*) 1-Chloro-4-anilinophthalazine (1 g.) and aniline hydrochloride (0·5 g.) were refluxed in alcohol for 7 hours. The solution was basified and diluted with water, and the product collected; crystallisation from acetone gave 1 : 4-dianilinophthalazine (0·7 g.) and unchanged 1-chloro-4-anilinophthalazine (0·4 g.).

4-*Anilino*-1-*β*-*diethylaminoethylaminophthalazine* (I; R^1 = NHPh; R^2 = NH·$[CH_2]_2$·NEt_2).—1-Chloro-4-anilinophthalazine (1 g.) and *β*-diethylaminoethylamine (0·91 g.) were heated for 3 hours at 150—160°. The viscous product was dissolved in dilute acetic acid, mixed with a little charcoal, and filtered, and the orange-coloured filtrate was basified with 20% sodium hydroxide. The product was taken up in chloroform and dried, and the solvent removed; the residual oil crystallised from petroleum (b. p. 90—120°) (charcoal and solid potassium hydroxide) in small cream-coloured prismatic needles (0·4 g.), m. p. 148—149° (Found : C, 71·3; H, 7·4. $C_{20}H_{25}N_5$ requires C, 71·6; H, 7·5%). The picrate, prepared in alcoholic solution, had m. p. 197—199°.

4-*Anilino*-1-*γ*-*diethylaminopropylaminophthalazine* (I; R^1 = NHPh; R^2 = NH·$[CH_2]_3$·NEt_2), prepared similarly (7 hours at 150—160°), crystallised from petroleum (b. p. 90—120°)–acetone in colourless platelets (yield 50%), m. p. 174° (Found : C, 72·0; H, 7·6. $C_{21}H_{27}N_5$ requires C, 71·9 H, 7·7%).

4-p-*Chloroanilino*-1-*β*-*diethylaminoethylaminophthalazine* (I; R^1 = *p*-NH·C_6H_4Cl; R^2 = NH·$[CH_2]_2$·NEt_2), prepared similarly (3 hours at 150° or 24 hours at 100°), crystallised from petroleum (b. p. 90—120°) in cream prismatic needles (yield 40%), m. p. 145° (Found : C, 65·0; H, 6·4. $C_{20}H_{24}N_5Cl$ requires C, 64·9; H, 6·5%).

4-p-*Chloroanilino*-1-*γ*-*diethylaminopropylaminophthalazine* (I; R^1 = *p*-NH·C_6H_4Cl; R^2 = NH·$[CH_2]_3$·NEt_2), prepared in 45% yield (36 hours at 100°), crystallised from acetone–ligroin in needles, m. p. 181—182° (Found : C, 65·3; H, 6·6. $C_{21}H_{26}N_5Cl$ requires C, 65·7; H, 6·8%).

4-*p*-Chloroanilino-1-δ-diethylamino-*α*-methyl-*n*-butylaminophthalazine (I; R^1 = *p*-NH·C_6H_4Cl; R^2 = NH·CHMe·$[CH_2]_3$·NEt_2) was obtained (3 hours at 140°) as an oil, b. p. 215—230/0·002 mm., giving a *dipicrate* which crystallised from acetic acid in needles, m. p. 203—204° (Found : C, 48·1; H, 4·5. $C_{23}H_{30}N_5Cl$,$2C_6H_3O_7N_3$ requires C, 48·2; H, 4·5%).

2 : 3-*Dianilinoquinoxaline* (II; R^1 = R^2 = NHPh).—2 : 3-Dichloroquinoxaline (II; R^1 = R^2 = Cl), m. p. 148°, obtained in 70% yield by the action of phosphorus pentachloride on 2 : 3-dihydroxyquinoxaline (Hinsberg and Pollak, *Ber.*, 1896, **29**, 784), was refluxed with aniline (5 mols.) for 10 minutes. Excess of aniline was removed in steam and the 2 : 3-dianilinoquinoxaline collected. It separated from acetic acid in long yellow needles, m. p. 123° (Lockhart and Turner, *loc. cit.*, give m. p. 223°), containing 1 mol. of acetic acid (Found : C, 70·3; H, 5·3; equiv., 375. $C_{20}H_{16}N_4$,$C_2H_4O_2$ requires C, 70·9; H, 5·4%; equiv., 372) which was lost in a vacuum at 100°. The unsolvated *base* was obtained from petroleum (b. p. 90—120°) in small yellow prisms, m. p. 138—139° (Found : C, 76·9; H, 5·3. $C_{20}H_{16}N_4$ requires C, 76·9; H, 5·2%). The hydrochloride crystallised from alcohol in small needles, m. p. 248—250°.

2-*Chloro*-3-p-*chloroanilinoquinoxaline* (II; R^1 = *p*-NH·C_6H_4Cl; R^2 = Cl).—2 : 3-Dichloroquinoxaline (2 g.), *p*-chloroaniline (1·3 g.), concentrated hydrochloric acid (1 c.c.), and water (100 c.c.) were refluxed for 24 hours. The solution was basified and steam distilled, and the residue collected, dried, taken up in ether, and precipitated as hydrochloride. The *base* was recovered and crystallised from alcohol; long yellow needles, m. p. 133—134°, were obtained (Found : C, 57·9; H, 3·4. $C_{14}H_9N_3Cl_2$ requires C, 57·9; H, 3·1%).

2 : 3-*Di*-p-*chloroanilinoquinoxaline* (II; R^1 = R^2 = *p*-NH·C_6H_4Cl), prepared as described above for the corresponding dianilino-derivative, crystallised from methyl alcohol–acetone in needles, m. p. 232° (Found : C, 63·0; H, 3·9. $C_{20}H_{14}N_4Cl_2$ requires C, 63·0; H, 3·7%).

2-*Chloro*-3-*β*-*diethylaminoethylaminoquinoxaline* (II; R^1 = NH·$[CH_2]_2$·NEt_2; R^2 = Cl).—*β*-Diethylaminoethylamine (2·32 g., 2 mols.) was gradually added with cooling to 2 : 3-dichloroquinoxaline (2 g.), and, after 1½ hours below 0°, the reaction was continued for 4 hours at 15°. After addition of dilute hydrochloric acid the mixture was filtered (charcoal), and the base, liberated by addition of sodium hydroxide, was taken up in ether, dried, and distilled. The pale yellow oil (1·7 g.), b. p. 160—170°/0·01 mm., gave a *picrate* which separated from propyl alcohol in yellow prisms, m. p. 153—154° (Found : C, 47·3; H, 4·45. $C_{14}H_{19}N_4Cl$,$C_6H_3O_7N_3$ requires C, 47·3; H, 4·35%)

2-*Chloro*-3-*γ*-*diethylaminopropylaminoquinoxaline* (II; R^1 = NH·$[CH_2]_3$·NEt_2; R^2 = Cl), obtained similarly, was an oil, b. p. 180—182°/0·015 mm., giving a *picrate* which crystallised from alcohol in stout yellow prisms, m. p. 159° (Found : C, 48·0; H, 4·3; Cl, 6·8. $C_{15}H_{21}N_4Cl$,$C_6H_3O_7N_3$ requires C, 48·3; H, 4·6; Cl, 6·8%), and a *dihydrobromide*, needles from alcohol–ether, m. p. 165° (Found : Br, 34·4. $C_{15}H_{21}N_4Cl$,2HBr requires Br, 35·2%).

1-*Ethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra*-*aza*-*anthracene* (III; R = H), obtained in 90% yield by heating 2-chloro-3-*β*-diethylaminoethylaminoquinoxaline in an oil-bath at 190° for 30 minutes,

crystallised from methyl alcohol (charcoal) in colourless prisms, m. p. 155—156° (Found: C, 67·2; H, 6·3; N, 26·8. $C_{12}H_{14}N_4$ requires C, 67·3; H, 6·5; N, 26·2%), and gave a *dihydrochloride*, m. p. 206° (decomp.) (Found: Cl, 24·5. $C_{12}H_{14}N_4$,2HCl requires Cl, 24·7%). The preparation was repeated, and the loss in weight on heating 2-chloro-3-β-diethylaminoethylaminoquinoxaline was found to be 24·9% (loss of C_2H_5Cl requires 23·2%). In a third experiment the evolved vapours were condensed and identified as ethyl chloride, b. p. 13°.

1′-*Ethyl*-1′ : 5′-*diaza*-2 : 3-*pentamethylenequinoxaline* (IV), prepared similarly, crystallised from petroleum (b. p. 90—120°) in very pale yellow prisms, m. p. 147° (Found: C, 68·1; H, 7·0; N, 25·0. $C_{13}H_{16}N_4$ requires C, 68·4; H, 7·0; N, 24·6%).

3-*Chloro*-2-*aminoquinoxaline* (II; $R^1 = Cl$; $R^2 = NH_2$).—2 : 3-Dichloroquinoxaline (10 g.) and alcohol (40 c.c.), saturated at 0° with ammonia, were refluxed for 20 hours. Most of the alcohol was removed, and, after dilution with water, the precipitate was collected, dried, and extracted with ether in a Soxhlet apparatus. The extract was saturated with hydrogen chloride and the precipitated *hydrochloride*, m. p. > 400° (Found: ionisable Cl, 16·2. $C_8H_6N_3Cl$,HCl requires ionisable Cl, 16·4%), was collected, dissolved in water, and basified. 3-*Chloro*-2-*aminoquinoxaline* crystallised from aqueous alcohol in colourless needles (6 g.), m. p. 139° (Found: C, 53·8; H, 3·5; Cl, 20·2. $C_8H_6N_3Cl$ requires C, 53·5; H, 3·4; Cl, 9·18%).

2-*Amino*-3-p-*chloroanilinoquinoxaline* (II; $R^1 = p$-$NH{\cdot}C_6H_4Cl$; $R^2 = NH_2$).—3-Chloro-2-aminoquinoxaline (3 g.) and *p*-chloroaniline (3 g.) were heated in an oil-bath. At 140° a vigorous exothermic reaction developed, and, after a few minutes at 190°, the mixture was cooled and the solid product was powdered, shaken with dilute hydrochloric acid, and filtered. The filtrate was basified and the *base* isolated with ether; it crystallised from acetone–ligroin in yellow stout prisms (3 g.), m. p. 193—194° (Found: C, 61·7; H, 4·1; Cl, 13·7. $C_{14}H_{11}N_4Cl$ requires C, 62·1; H, 4·1; Cl, 13·1%).

2-*Amino*-3-β-*diethylaminoethylaminoquinoxaline* (II; $R^1 = NH{\cdot}[CH_2]_2{\cdot}NEt_2$; $R^2 = NH_2$).—3-Chloro-2-aminoquinoxaline (0·85 g.) and β-diethylaminoethylamine (0·65 g.) were heated for 3 hours at 100°; and the resulting viscous oil was taken up in dilute hydrochloric acid and filtered. The *base*, liberated with sodium hydroxide and isolated with chloroform, crystallised from petroleum (b. p. 90—120°) in needles, m. p. 114—115° (Found: C, 64·3; H, 8·0. $C_{14}H_{21}N_5$ requires C, 64·8; H, 8·1%).

2-*Amino*-3-γ-*diethylaminopropylaminoquinoxaline* (II; $R^1 = NH{\cdot}[CH_2]_3{\cdot}NEt_2$; $R^2 = NH_2$), prepared similarly, crystallised from ether–ligroin in long rectangular prisms, m. p. 141—142° (Found: C, 65·0; H, 8·3. $C_{15}H_{23}N_5$ requires C, 65·9; H, 8·4%), which gave a low carbon value on analysis; the m. p. and the carbon values were, however, not changed by further crystallisation.

2-p-*Chloroanilino*-3-β-*diethylaminoethylaminoquinoxaline* (II; $R^1 = p$-$NH{\cdot}C_6H_4Cl$; $R^2 = NH{\cdot}[CH_2]_2{\cdot}NEt_2$).—2-Chloro-3-β-diethylaminoethylaminoquinoxaline (2·8 g.), *p*-chloroaniline (1·3 g.), concentrated hydrochloric acid (1 c.c.), and water (100 c.c.) were refluxed for 3 hours. The clear yellow solution was basified, unchanged *p*-chloroaniline removed in steam, and the *product* isolated with ether and distilled at 0·01 mm. The glass, b. p. 220°/0·01 mm., crystallised very slowly from aqueous alcohol in buff-coloured prisms, m. p. 90—92°, containing water of crystallisation (Found: C, 62·1; H, 6·7. $C_{20}H_{24}N_5Cl,H_2O$ requires C, 61·9; H, 6·7%).

2-p-*Chloroanilino*-3-γ-*diethylaminopropylaminoquinoxaline* (II; $R^1 = p$-$NH{\cdot}C_6H_4Cl$; $R^2 = NH{\cdot}[CH_2]_3{\cdot}NEt_2$), prepared similarly, crystallised from ligroin in stout, colourless prisms, m. p. 94—95° (Found: C, 65·3; H, 6·8; N, 18·6; Cl, 9·4. $C_{21}H_{26}N_5Cl$ requires C, 65·7; H, 6·8; N, 18·3; Cl, 9·3%).

2 : 3 : 6-*Trichloroquinoxaline* (V; $R^1 = R^2 = Cl$).—This was obtained by the following sequence of reactions: *p*-chloroacetanilide ⟶ *p*-chloro-*o*-nitroaniline ⟶ *p*-chloro-*o*-phenylenediamine ⟶ 6-chloro-2 : 3-dihydroxyquinoxaline ⟶ 2 : 3 : 6-trichloroquinoxaline.

The mononitration of *p*-chloroacetanilide (see Holleman, *Rec. Trav. chim.*, 1915, **34**, 204; de Bruyn, *ibid.*, 1916, **36**, 126; Hall and Turner, *J.*, 1945, 700) was effected as follows. A mixture of nitric acid (11 g., *d* 1·45) and concentrated sulphuric acid (25 c.c.) was added with stirring to a solution of *p*-chloroacetanilide (20 g.) in concentrated sulphuric acid (100 c.c.) at − 10°. Ten minutes after the completion of the additions, the solution was poured on ice, and the *p*-chloro-*o*-nitroacetanilide was collected and hydrolysed by refluxing with concentrated hydrochloric acid (125 c.c.). *p*-Chloro-*o*-nitroaniline, which was precipitated on addition of water, crystallised from benzene–ligroin in orange-red needles (18·4 g.), m. p. 115°. *p*-Chloro-*o*-phenylenediamine, obtained in 90% yield by reducing the above nitro-compound with stannous chloride (Ullmann and Mauthner, *Ber.*, 1903, **36**, 4027), was converted into 6-chloro-2 : 3-dihydroxyquinoxaline by refluxing with ethyl oxalate (10 volumes) for 2½ hours; the solution was cooled to 0° and the product, m. p. 380°, was collected and washed with ether (compare Kehrmann and Bener, *Helv. Chim. Acta*, 1925, **8**, 20). Treatment with phosphorus pentachloride at 180° as described by Kehrmann and Bener (*loc. cit.*) gave 2 : 3 : 6-trichloroquinoxaline (III; $R^1 = R^2 = Cl$), m. p. 143—144° from alcohol.

6-*Chloro*-2 : 3-*di*-p-*chloroanilinoquinoxaline* (V; $R^1 = R^2 = p$-$NH{\cdot}C_6H_4Cl$) was obtained in 70% yield by heating 2 : 3 : 6-trichloroquinoxaline and excess of *p*-chloroaniline in an oil-bath at 140°; the mixture was basified and steam-distilled, and the residual solid crystallised from acetone. After separation of a small amount of yellow matted crystals, m. p. 237—238°, which were not examined further, the mother liquors were evaporated and the residue crystallised from ethyl alcohol. The product (V; $R^1 = R^2 = p$-$NH{\cdot}C_6H_4Cl$) separated in yellow needles (Found: Loss in weight at 100°, 13·0; C, 58·6; H, 4·1; N, 11·6; Cl, 23·0. $C_{20}H_{13}N_4Cl_3,CH_3{\cdot}CO{\cdot}CH_3$ requires loss, 12·3; C, 58·3; H, 4·0; N, 11·8; Cl, 22·5%), which melted at 84°, resolidified, and melted again at 182—183°. The *base* separated from benzene–ligroin in yellow needles containing 0·5 mol. of benzene (Found: Loss in weight at 120°, 8·9; $C_{20}H_{13}N_4Cl_3,\frac{1}{2}C_6H_6$ requires loss, 8·6%) which melted at 135°, resolidified, and melted again at 180—181° (Found after drying at 120°: C, 57·6; H, 3·3; N, 13·4; Cl, 26·0. $C_{20}H_{13}N_4Cl_3$ requires C, 57·7; H, 3·1; N, 13·6; Cl, 25·6%).

2 : 6-*Dichloro*-3-*aminoquinoxaline* (V; $R^1 = NH_2$; $R^2 = Cl$), obtained in 60% yield by heating 2 : 3 : 6-trichloroquinoxaline with alcoholic ammonia as described for the preparation of 2-chloro-3-aminoquinoxaline, crystallised from alcohol or benzene in colourless needles, m. p. 221° (Found: C, 45·5; H, 2·6. $C_8H_5N_3Cl_2$ requires C, 44·9; H, 2·4%).

6-*Chloro*-3-*amino*-2-p-*chloroanilinoquinoxaline* (V; $R^1 = NH_2$; $R^2 = p$-NH·C_6H_4Cl), obtained by heating 2 : 6-dichloro-3-aminoquinoxaline and *p*-chloroaniline at 160° as described in similar cases, crystallised from acetone–petroleum (b. p. 90—120°) in yellow prismatic needles, m. p. 239° (decomp.) (Found : C, 55·5; H, 3·6; Cl, 23·5. $C_{14}H_{10}N_4Cl_2$ requires C, 55·1; H, 3·3; Cl, 23·3%).

6-*Chloro*-3-*amino*-2-β-*diethylaminoethylaminoquinoxaline* (V; $R^1 = NH_2$; $R^2 = NH{\cdot}[CH_2]_2{\cdot}NEt_2$), obtained by heating the dichloroamine with β-diethylaminoethylamine on the steam-bath, separated from ether–ligroin in rectangular prisms, m. p. 124·5—125·5° (Found : C, 57·6; H, 6·8. $C_{14}H_{20}N_5Cl$ requires C, 57·2; H, 6·8%).

2 : 6-*Dichloro*-3-β-*diethylaminoethylaminoquinoxaline* (V; $R^1 = NH{\cdot}[CH_2]_2{\cdot}NEt_2$; $R^2 = Cl$), prepared at 0° as described in a similar case, crystallised from aqueous methyl alcohol in stout elongated prisms, m. p. 83—84° (Found : C, 54·0; H, 5·6. $C_{14}H_{18}N_4Cl_2$ requires C, 53·7; H, 5·7%). The hydrochloride crystallised from alcohol–ether in colourless, feathery needles, m. p. 246° (decomp.). In a second experiment the temperature was allowed to rise to 120°; the product crystallised from ligroin in colourless prisms, m. p. 95—97° (Found : C, 58·8; H, 8·6; Cl, 9·5. $C_{20}H_{33}N_6Cl$ requires C, 61·2; H, 8·4; Cl, 9·0%), which were probably impure 6-*chloro*-2 : 3-*di*-(β-*diethylaminoethylamino*)*quinoxaline* (V; $R^1 = R^2 = NH{\cdot}[CH_2]_2{\cdot}NEt_2$).

6-*Chloro*-1-*ethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 4 : 9 : 10-*tetra-aza-anthracene* (III; R = Cl), obtained by heating (V; $R^1 = Cl$; $R^2 = NH{\cdot}[CH_2]_2{\cdot}NEt_2$) at 200° for 10 minutes, crystallised from alcohol in stout prisms, m. p. 187—188° (Found : C, 57·6; H, 5·5; Cl, 14·5. $C_{12}H_{13}N_4Cl$ requires C, 57·9; H, 5·2; Cl, 14·3%). The loss in weight during the experiment was 20·1%; the loss of 1 mol. of ethyl chloride requires 20·6%.

6-*Chloro*-2-p-*chloroanilino*-3-β-*diethylaminoethylaminoquinoxaline* (V; $R^1 = NH{\cdot}[CH_2]_2{\cdot}NEt_2$; $R^2 = p$-NH·C_6H_4Cl), prepared by refluxing the components in aqueous suspension in the presence of a little concentrated hydrochloric acid as described in similar cases, was a glass, b. p. 200—230°/0·005 mm., which crystallised very slowly from acetone–ligroin in needles, m. p. 82—83° (Found : C, 57·1, 56·8; H, 6·1, 6·0; N, 16·2; Cl, 17·1; loss in weight in a vacuum at 50°, 4·2. $C_{20}H_{23}N_5Cl_2,H_2O$ requires C, 56·8; H, 5·9; N, 16·6; Cl, 16·8; H_2O, 4·3%).

3-*Chloro*-1-p-*chloroanilino*- *and* 1 : 3-*Di*-p-*chloroanilino*-iso*quinoline*.—1 : 3-Dichloro*iso*quinoline (2 g.) (prepared from homophthalimide as described by Gabriel, *Ber.*, 1886, **19**, 2354) and *p*-chloroaniline (1·27 g.) were boiled for 3 hours in glacial acetic acid (7 c.c.). The solution was basified and steam distilled, and the dried residue (2 g.) crystallised from acetone–ligroin. 1 : 3-*Di*-p-*chloroanilino*iso*quinoline* was obtained in bright yellow crystals (0·8 g.), m. p. 233° (Found : C, 66·9; H, 3·7; N, 11·3; Cl, 18·8. $C_{21}H_{15}N_3Cl_2$ requires C, 66·3; H, 3·9; N, 11·1; Cl, 18·7%), and the mother liquor yielded 3-*chloro*-1-p-*chloroanilino*iso*quinoline* which separated from ligroin in long prismatic needles (0·4 g.), m. p. 140° (Found : C, 62·4; H, 3·4; N, 9·8; Cl, 24·8. $C_{15}H_{10}N_2Cl_2$ requires C, 62·3; H, 3·5; N, 9·7; Cl, 24·6%).

3-*Chloro*-1-β-*diethylaminoethylamino*iso*quinoline*, obtained as an oil (Found : Cl, 12·7. $C_{15}H_{20}N_3Cl$ requires Cl, 12·8%) by heating 1 : 3-dichloro*iso*quinoline and β-diethylaminoethylamine (1·2 parts) at 100° for 3 hours, gave a picrate, which crystallised from propyl alcohol in deep yellow prisms, m. p. 152—153°.

1-p-*Chloroanilino*iso*quinoline*.—1-Chloro*iso*quinoline was prepared by the method of Fisher and Hamer (*J.*, 1934, 1909), but the product, m. p. 23—24°, described by these authors is impure. When shaken with 2N-hydrochloric acid a residue of 1 : 4-dichloro*iso*quinoline, m. p. 89° (Found : Cl, 35·3. Calc. for $C_9H_5NCl_2$: Cl, 35·8%) (Gabriel, *Ber.*, 1886, **19**, 2354), was collected. Basification of the acidic filtrate gave 1-chloro*iso*quinoline, which separated from ligroin (b. p. 40—60°) in colourless plates, m. p. 36—37°, as described by Gabriel and Colman (*Ber.*, 1886, **19**, 2354; 1892, **25**, 2709). Condensation with *p*-chloroaniline (1 mol.) either (*a*) by heating at 120° for 5 minutes, or (*b*) by refluxing for 4 hours with water and a small amount of hydrochloric acid, yielded 1-p-*chloroanilino*iso*quinoline* which crystallised from acetone–ligroin (b. p. 90—120°) in long rectangular rods, m. p. 140° (Found : C, 70·5; H, 4·3; Cl, 14·1. $C_{15}H_{11}N_2Cl$ requires C, 70·7; H, 4·3; Cl, 14·0%). The *hydrochloride* crystallised from slightly acidified ethyl alcohol in stout prisms, m. p. 228—230° (Found : ionisable Cl, 12·0. $C_{15}H_{11}N_2Cl,HCl$ requires ionisable Cl, 12·2%).

1-β-Diethylaminoethylamino*iso*quinoline, b. p. 170—180°/0·01 mm., was obtained by heating 1-chloro*iso*quinoline and β-diethylaminoethylamine at 100° for 7 hours. The *picrate*, yellow needles, m. p. 139—141°, gave a low carbon value on analysis (Found : C, 52·5; H, 5·0. $C_{15}H_{21}N_3,C_6H_3O_7N_3$ requires C, 53·4; H, 5·1%). The *dihydrochloride*, prepared in ethereal solution, crystallised from methyl alcohol–ether in colourless needles, m. p. 225° (Found : Cl, 22·4. $C_{15}H_{21}N_3,2HCl$ requires Cl, 22·5%). The dihydrochloride, prepared in acetone solution, crystallised from methyl alcohol–ether in needles containing 1 molecule of acetone, which soften at 80° and melt at 220° (Found : Cl, 19·2. $C_{15}H_{21}N_3,2HCl,CH_3{\cdot}CO{\cdot}CH_3$ requires Cl, 19·0%); the solvent is lost on heating at 120° for 2 hours.

3-*Chloro*iso*quinoline*.—The following gave better results in our hands than published methods (Gabriel, *Ber.*, 1886, **19**, 2354). 1 : 3-Dichloro*iso*quinoline (1·5 g.), red phosphorus (0·5 g.), hydriodic acid (3 c.c.), and glacial acetic acid (7 c.c.) were refluxed for 6 hours. The mixture was basified and steam distilled; 3-chloro*iso*quinoline, which solidified in the early runnings, was collected, dissolved in 2N-hydrochloric acid, and filtered from the insoluble 1 : 3-dichloro*iso*quinoline. 3-Chloro*iso*quinoline (0·7 g.), recovered from the filtrate, had m. p. 46·5—47·5°.

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