357. *Synthetic Antimalarials. Part XXXII. Some 4-Arylamino- and 4-Arylthio-2-aminoalkylaminoquinazolines, and 2-Arylthio-4-aminoalkylaminoquinazolines.*

By F. H. S. Curd, E. Hoggarth, J. K. Landquist, and F. L. Rose.

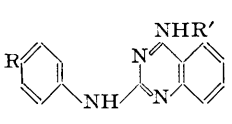
The investigation of quinazoline derivatives for antimalarial activity described in some of the earlier papers of this series (*J.*, 1947, 775, 890, and preceding paper) has been extended by the preparation of some 4-arylamino-2-aminoalkylaminoquinazolines and of some related derivatives carrying arylthio- and dialkylaminoalkylamino-groups in either the 2 : 4- or the 4 : 2- positions. None of these types exhibited any activity, and this is discussed in relation to the activity of the 2-arylamino-4-aminoalkylaminoquinazolines described in Part XIV and of the corresponding pyrimidine types.

In applying to the present quinazoline types the methods of synthesis earlier worked out for the analogous pyrimidine derivatives certain displacements of 4-arylamino- and arylthio-groups have been observed.

From previous investigations (Part XIV, Curd, Landquist, and Rose, *J.*, 1947, 775; Part XVI, Chapman, Gibson, and Mann, *ibid.*, p. 890; preceding paper) it was impossible to decide with any certainty whether the antimalarial activity of the 2-arylamino-4-aminoalkylaminoquinazolines of type (I; R′ = aminoalkyl) described in Part XIV originated from the same cause as that of the analogous 2-arylamino-4-aminoalkylamino-6-methylpyrimidines (III; X = NH, R′ = aminoalkyl). Had this indeed been the case, then it seemed reasonable to

expect that the isomeric 4-arylamino-2-aminoalkylaminoquinazolines (II; R′ = aminoalkyl), similarly related to the active 4-arylamino-2-aminoalkylamino-6-methylpyrimidines (IV: X = NH) described in Parts VI and IX (*J.*, 1946, 370, 720), would also show activity. Several quinazolines of type (II) have therefore been prepared, but antimalarial tests against *P. gallinaceum* in chicks conducted on these compounds by Dr. D. G. Davey failed to disclose any activity. This would seem to indicate a different mode of action for the quinazolines of type (I) as compared with the pyrimidines of type (III; X = NH), despite the obvious structural resemblance of the two types, and it is not without interest to discuss these results in the light of the hypothesis advanced in an earlier communication (Part XII, *J.*, 1947, 154) which sought to show that in certain antimalarial compounds positive activity was to be associated with the possibility of conjugation of a terminal alkylamino- or aminoalkylamino-group and an anilino-residue through a system made up of alternate carbon and nitrogen atoms. Such an arrangement would be provided in the case of the quinazolines by the polarised forms (or the tautomers corresponding thereto) represented by (I*a*) and (II*a*). If the conjugation hypothesis is applicable in the present instances then it must be that in type (I) the form (I*a*) provides a major contribution to a resonance hybrid whereas (II*a*) is insignificant with respect to type (II).

Alternatively, the biological results with type (II) may be compared with those yielded by the isosteric 4-arylamino-2-aminoalkylaminoquinolines (Part XVI, Curd, Raison, and Rose, *J.*, 1947, 899) which exhibit but feeble activity. In this respect then the quinazoline system may be regarded from the biological standpoint as a quinoline derivative, and further evidence in support of this view is provided by the considerable antimalarial activities found in the 4-dialkylaminoalkylaminoquinazolines described in Part XVI (*loc. cit.*) and the corresponding substituted quinolines (see D.R.-P. 683,692), activities which are enhanced in both instances by the introduction of chlorine into the 7-position.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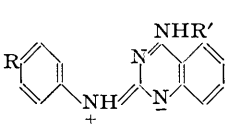
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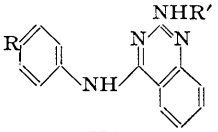
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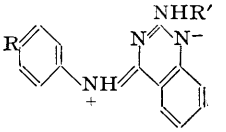
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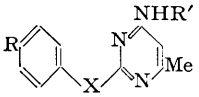
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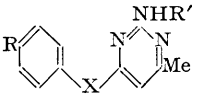
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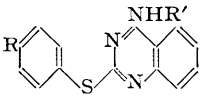
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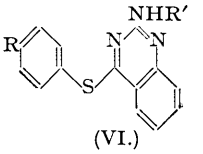
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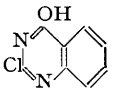
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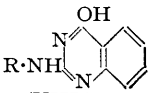
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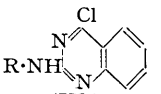
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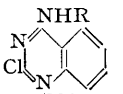
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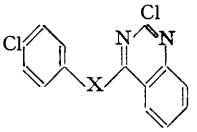
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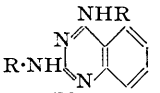
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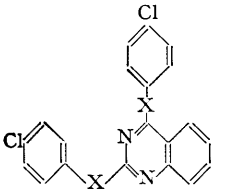
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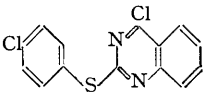

(XIV.)

A number of 4-dialkylaminoalkylamino-2-arylthio- and 2-dialkylaminoalkylamino-4-arylthio-quinazolines of types (V) and (VI) have also been prepared, but these showed no activity when tested against *P. gallinaceum* in chicks. The inactivity of the latter type is not very surprising in view of the inactivity of the analogous arylamino-type (II), but the former might have been expected to show some activity since it is related to the active quinazolines of type (I) in the same way that the dialkylaminoalkylamino-arylthiopyrimidines of types (III and IV; X = S) described in Part XV (Curd, Davis, Hoggarth, and Rose, *J.*, 1947, 783) are related to the corresponding anilino-types (III and IV; X = NH).

Compounds of type (II) were prepared from 2-chloro-4-hydroxyquinazoline (VII). This, by

reaction with aminoalkylamines, gave 2-aminoalkylamino-4-hydroxyquinazolines (VIII), and these were converted by treatment with phosphoryl chloride into 4-chloro-2-aminoalkylaminoquinazolines (IX) which reacted with arylamines to give the desired 4-arylamino-2-aminoalkylaminoquinazolines. In this way the following quinazolines of type (II) were prepared: 4-*p*-chloroanilino-2-β-diethylaminoethylamino- (II; R = Cl, R′ = $[CH_2]_2$·NEt_2) (characterised as its *dihydrochloride* and *dipicrate*), 4-p-*chloroanilino*-2-*γ*-*diethylaminopropylamino*- (II; R = Cl, R′ = $[CH_2]_3$·NEt_2), the corresponding *p*-methoxyanilino-derivative (II; R = OMe, R′ = $[CH_2]_3$·NEt_2) (isolated as its *dihydrochloride*), 4-p-*chloroanilino*-2-*γ*-*piperidinopropylamino*- (II; R = Cl, R′ = $[CH_2]_3$·N$<[CH_2]_4>CH_2$) and 4-*p*-chloroanilino-2-*γ*-di-*n*-butylaminopropylamino- (II; R = Cl, R′ = $[CH_2]_3$·NBu^n_2) as its *dihydrochloride*. The 4-chloro-2-aminoalkylaminoquinazolines of type (IX) served also as intermediates for the preparation of two representatives of type (VI), *viz.*, 2-β-*diethylaminoethylamino*-4-p-*chlorophenylthioquinazoline* (R = Cl, R′ = $[CH_2]_2$·NEt_2) and 2-*γ*-*diethylaminopropylamino*-4-p-*chlorophenylthioquinazoline* (R = Cl, R′ = $[CH_2]_3$·NEt_2).

The 4-aminoalkylamino-2-arylthioquinazolines of type (V) were prepared by a route analogous to that first worked out for the corresponding arylamino-compounds (I) and described in Part XIV (*loc. cit.*), namely, by condensation of a 2-chloro-4-aminoalkylaminoquinazoline with a thiophenol. Thus, 2-chloro-4-*γ*-diethylaminopropylaminoquinazoline (X; R = $[CH_2]_3$·NEt_2) when fused with *p*-chlorothiophenol and thio-*p*-cresol respectively gave 4-*γ*-*diethylaminopropylamino*-2-p-*chlorophenylthio*- (V; R = Cl, R′ = $[CH_2]_3$·NEt_2) and 4-*γ*-*diethylaminopropylamino*-2-p-*tolylthioquinazoline* (V; R = Me, R′ = $[CH_2]_3$·NEt_2) while 2-chloro-4-β-diethylaminoethylaminoquinazoline (X; R = $[CH_2]_2$·NEt_2) and *p*-chlorothiophenol gave 4-β-*diethylaminoethylamino*-2-p-*chlorophenylthioquinazoline* (V; R = Cl, R′ = $[CH_2]_2$·NEt_2).

When attempts were made to prepare the above 4-*p*-chloroanilino-2-aminoalkylaminoquinazolines (II) and the corresponding 4-*p*-chlorophenylthio-compounds (VI) by alternative methods from (XI; X = NH) and (XI; X = S) respectively, certain displacements of the substituents in the 4-position of the quinazoline nucleus were observed in a number of cases.

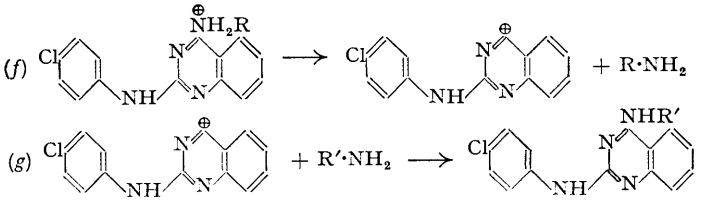
2 : 4-Dichloroquinazoline reacted with *p*-chloroaniline in cold aqueous suspension to give a compound which could not be satisfactorily purified but whose reactions showed it to be essentially 2-chloro-4-*p*-chloroanilinoquinazoline (XI; X = NH) since it condensed with *γ*-diethylaminopropylamine to give 4-*p*-chloroanilino-2-*γ*-diethylaminopropylaminoquinazoline (II; R = Cl, R′ = $[CH_2]_3$·NEt_2), and with *γ*-piperidinopropylamine to give the corresponding *γ*-piperidinopropylamino-derivative (II; R = Cl, R′ = $[CH_2]_3$·N$<[CH_2]_4>CH_2$). However, when (XI; X = NH) was heated with β-diethylaminoethylamine some of the expected 4-*p*-chloroanilino-2-β-diethylaminoethylaminoquinazoline (II; R = Cl, R′ = $[CH_2]_2$·NEt_2) was formed, but the major product proved to be 2 : 4-*bis*-β-*diethylaminoethylaminoquinazoline* (XII; R = $[CH_2]_2$·NEt_2) identical with that prepared from 2-chloro-4-β-diethylaminoethylaminoquinazoline and β-diethylaminoethylamine. The course of the reaction leading to (XII; R = $[CH_2]_2$·NEt_2) clearly involves displacement of the arylamino-residue from (XI; X = NH). Again, 2 : 4-dichloroquinazoline and sodium *p*-chlorothiophenoxide in ether gave 2-*chloro*-4-p-*chlorophenylthioquinazoline* (XI; X = S), and when this was boiled in alcoholic solution with β-diethylaminoethylamine two products were formed. One of these, separated by its insolubility in dilute acetic acid, proved to be 2 : 4-*bis*-p-*chlorophenylthioquinazoline* (XIII; X = S) and must have been formed by reaction of displaced *p*-chlorothiophenol with unaltered starting material. The second product, which was soluble in dilute acetic acid, proved to be not the expected 2-β-diethylaminoethylamino-4-*p*-chlorophenylthioquinazoline (VI; R = Cl, R′ = $[CH_2]_2$·NEt_2) but the isomeric 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline (V; R = Cl, R′ = $[CH_2]_2$·NEt_2). None of the former was isolated, and the amount formed must indeed have been very small in view of the yield of the latter and the substantial quantity of 2 : 4-bis-*p*-chlorophenylthioquinazoline also produced. A similar result was obtained starting with *γ*-diethylaminopropylamine, the products being 4-*γ*-diethylaminopropylamino-2-*p*-chlorophenylthioquinazoline (V; R = Cl, R′ = $[CH_2]_3$·NEt_2) and 2 : 4-bis-*p*-chlorophenylthioquinazoline. These results at first suggested that the initial reaction between 2 : 4-dichloroquinazoline and *p*-chlorothiophenol had taken the unexpected course to give not 2-chloro-4-*p*-chlorophenylthioquinazoline (XI; X = S) but its 4 : 2-isomer (XIV). This was proved not to be the case, however, since 2-chloro-4-hydroxyquinazoline condensed with *p*-chlorothiophenol gave 4-*hydroxy*-2-p-*chlorophenylthioquinazoline*, and this with phosphoryl chloride afforded 4-*chloro*-2-p-*chlorophenylthioquinazoline* (XIV) distinct from the isomer formed from 2 : 4-dichloroquinazoline and *p*-chlorothiophenol. Further proof of the assigned structures was provided by the conversion of each isomer into 2 : 4-bis-*p*-chlorophenylthioquinazoline

(XIII; X = S) on reaction with *p*-chlorothiophenol, and the observation that 4-chloro-2-*p*-chlorophenylthioquinazoline reacted with β-diethylaminoethylamine to give 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline (V; R = Cl, R′ = $[CH_2]_2$·NEt_2).

Some light was thrown on these displacement reactions by the fact that 2 : 4-bis-*p*-chlorophenylthioquinazoline heated with β-diethylaminoethylamine in alcoholic solution gave 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline (V; R = Cl, R′ = $[CH_2]_2$·NEt_2) with liberation of *p*-chlorothiophenol. This clearly demonstrated the lability of the 4-*p*-chlorophenylthio-group and further suggested that the formation of (V; R = Cl, R′ = $[CH_2]_2$·NEt_2) from 2-chloro-4-*p*-chlorophenylthioquinazoline and β-diethylaminoethylamine proceeded partially through the bis-*p*-chlorophenylthio-compound (XIII; X = S) as intermediate, so that the reactions (*a*) to (*d*) may be presumed to occur. Further it was shown that 2-β-diethylaminoethylamino-4-*p*-chlorophenylthioquinazoline (but not its 4 : 2-isomer) reacted with β-diethylaminoethylamine to give 2 : 4-bis-β-diethylaminoethylaminoquinazoline (XII; R = $[CH_2]_2$·NEt_2), and since this compound was not formed during the reaction between 2-chloro-4-*p*-chlorophenylthioquinazoline and β-diethylaminoethylamine the expected reaction (*e*) can only have occurred to a negligible extent.

(*a*) (XI; X = S) + NH_2·$[CH_2]_2$·NEt_2 ⟶ (X; R = $[CH_2]_2$·NEt_2) + *p*-HS·C_6H_4Cl
(*b*) (X; R = $[CH_2]_2$·NEt_2) + *p*-HS·C_6H_4Cl ⟶ (V; R = Cl, R′ = $[CH_2]_2$·NEt_2)
(*c*) (XI; X = S) + *p*-HS·C_6H_4Cl ⟶ (XIII; X = S)
(*d*) (XIII; X = S) + NH_2·$[CH_2]_2$·NEt_2 ⟶ (V; R = Cl, R′ = $[CH_2]_2$·NEt_2)
(*e*) (XI; X = S) + NH_2·$[CH_2]_2$·NEt_2 ⟶ (VI; R = Cl, R′ = $[CH_2]_2$·NEt_2)

The facile displacement of *p*-chlorothiophenol from, and its reaction with a further molecule of, 2-chloro-4-*p*-chlorophenylthioquinazoline was also demonstrated by the isolation of appreciable quantities of 2 : 4-bis-*p*-chlorophenylthioquinazoline when (XI; X = S) was boiled with alcoholic sodium hydroxide solution. Here the sodium hydroxide must be assumed to act in the same manner as the strongly basic dialkylaminoalkylamines in the reactions described above. By contrast, no reaction was detected when either 4-β-diethylaminoethylamino-2-*p*-chlorophenylthio- or 2 : 4-bis-β-diethylaminoethylamino-quinazoline was boiled with an alcoholic solution of *p*-chlorothiophenol.



Finally, a further example of the replacement of a 4-arylamino-residue may be recorded. When the hydrochloride of 2 : 4-bis-*p*-chloroanilinoquinazoline (XIII; X = NH) (prepared from 2 : 4-dichloroquinazoline and *p*-chloroaniline in chloroform solution, cf. Part XIV) was heated with β-diethylaminoethylamine some 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline (I; R = Cl, R′ = $[CH_2]_2$·NEt_2) was formed. The same product was obtained when the hydrochloride of 2-*p*-chloroanilino-4-β-hydroxyethylaminoquinazoline was heated with β-diethylaminoethylamine, in this case with displacement of a 4-alkylamino-residue. It seems possible that these displacements of 4-arylamino- and 4-alkylamino-residues may involve dissociation of a quinazolinium ion followed by recombination with a different amine, as in reactions (*f*) and (*g*), since no interaction was observed between 2 : 4-bis-*p*-chloroanilinoquinazoline (XIII; X = NH) and β-diethylaminoethylamine in the absence of hydrochloric acid. Certainly it would seem that these displacement reactions involving amino-residues differ in both facility and the necessary experimental conditions from those involving arylthio-groups.

Experimental.

2-β-Diethylaminoethylamino-4-hydroxyquinazoline (VIII; R = $[CH_2]_2$·NEt_2).—2-Chloro-4-hydroxyquinazoline (6·1 g.) and β-diethylaminoethylamine (5 c.c.) were heated for 1 hour at 140°. Excess of amine was then removed under diminished pressure. The residue was dissolved in hot acetic acid (20 c.c.) and poured into water, the solution made alkaline with sodium carbonate, and the liberated oil extracted with benzene. Evaporation of the dried extract and distillation of the residue in a high vacuum (0·001 mm.) from a bath at 188—195° gave the *product* as a colourless glass of indefinite m. p. (Found: C, 64·2; H, 7·7. $C_{14}H_{20}ON_4$ requires C, 64·6; H, 7·7%). On melting with a little water it formed a *hydrate* which crystallised from benzene–light petroleum (b. p. 60—80°) as colourless needles, m. p. 96—98° (Found: C, 60·7; H, 7·6. $C_{14}H_{20}ON_4,H_2O$ requires C, 60·4; H, 7·9%).

2-γ-*Diethylaminopropylamino*-4-*hydroxyquinazoline* (VIII; R = $[CH_2]_3$·NEt_2), prepared in a similar manner using γ-diethylaminopropylamine in place of β-diethylaminoethylamine and distilled from a bath at 185—190° under 0·001 mm., formed a colourless glass of indefinite m. p. (Found: C, 64·9; H, 8·3. $C_{15}H_{22}ON_4$ requires C, 65·7; H, 8·0%). The *hydrate* crystallised from light petroleum (b. p. 80—100°) as colourless laminæ, m. p. 96—97° (Found: C, 61·4; H, 8·6; N, 18·9. $C_{15}H_{22}ON_4,H_2O$ requires C, 61·5; H, 8·2; N, 19·2%).

2-γ-*Piperidinopropylamino*-4-*hydroxyquinazoline* (VIII; R = $[CH_2]_3$·N< $[CH_2]_4$ >CH_2).—2-Chloro-4-hydroxyquinazoline (4·5 g.) and γ-piperidinopropylamine (5 c.c.) were mixed, and when the resulting exothermic reaction had subsided the mixture was heated at 140—150° for 3·5 hours. The melt was dissolved in acetic acid (20 c.c.), and the solution poured into water (600 c.c.), treated with carbon, filtered, and made alkaline with ammonia. The precipitated product hardened on standing and was collected, dried, and crystallised from benzene–light petroleum (b. p. 60—80°) to give the *hemihydrate* as a microcrystalline solid, m. p. 117—119° (Found: C, 64·7; H, 7·5; N, 18·6; loss in a vacuum at 100°, 3·3. $C_{16}H_{22}ON_4,0{\cdot}5H_2O$ requires C, 65·0; H, 7·8; N, 19·0; H_2O, 3·5%).

2-γ-*Di*-n-*butylaminopropylamino*-4-*hydroxyquinazoline* (VIII; R = $[CH_2]_3$·NBu^{α}_2).—Prepared in a similar manner, the *hemihydrate* crystallised from aqueous methanol as faintly yellow plates, m. p. 103—104° (Found: C, 67·0, 67·3; H, 9·0, 9·1; N, 16·8. $C_{19}H_{30}ON_4,0{\cdot}5H_2O$ requires C, 67·2; H, 9·1; N, 16·5%).

4-*Chloro*-2-β-*diethylaminoethylaminoquinazoline* (IX; R = $[CH_2]_2$·NEt_2).—2-β-Diethylaminoethylamino-4-hydroxyquinazoline (8·1 g.) and phosphoryl chloride (25 c.c.) were refluxed for 1 hour, excess of phosphoryl chloride removed under reduced pressure, the residue poured on ice, and the solution treated with carbon and filtered. Addition of sodium hydroxide to the filtrate precipitated an oil which was extracted with ether and the ether extract dried (Na_2SO_4) and evaporated. Distillation of the residual oil from a bath at 170—175°/0·001 mm. gave 4-*chloro*-2-β-*diethylaminoethylaminoquinazoline* (Found: C, 60·5; H, 7·3. $C_{14}H_{19}N_4Cl$ requires C, 60·3; H, 6·8%). It formed a *sesquipicrate* which crystallised from acetic acid in large yellow needles, m. p. 205° (Found: C, 45·0; H, 4·2. $2C_{14}H_{19}N_4Cl,3C_6H_3O_7N_3$ requires C, 44·4; H, 3·8%).

4-*Chloro*-2-γ-*diethylaminopropylaminoquinazoline* (IX; R = $[CH_2]_3$·NEt_2), prepared similarly from 2-γ-diethylaminopropylamino-4-hydroxyquinazoline, formed a yellowish oil, b. p. 210—212°/0·2 mm. (Found: C, 61·8; H, 7·1. $C_{15}H_{21}N_4Cl$ requires C, 61·5; H, 7·2%).

4-*Chloro*-2-γ-*piperidinopropylaminoquinazoline* (IX; R = $[CH_2]_3$·N<$[CH_2]_4$ >CH_2), prepared in a corresponding manner from (VIII; R = $[CH_2]_3$·N < $[CH_2]_4$ > CH_2) and phosphoryl chloride, had b. p. 190—195°/0·15 mm. and then crystallised from light petroleum (b. p. 80—100°) as colourless plates, m. p. 71° (Found: N, 18·1. $C_{16}H_{21}N_4Cl$ requires N, 18·4%).

4-*Chloro*-2-γ-*di*-n-*butylaminopropylaminoquinazoline* (IX; R = $[CH_2]_3$·NBu^{α}_2).— 2-γ-Di-*n*-butylaminopropylamino-4-hydroxyquinazoline (5 g.) and phosphoryl chloride (15 c.c.) were heated under reflux for 1·25 hours at 120—130°. The mixture was poured on to a vigorously stirred mixture of ice (400 g.), 10N-sodium hydroxide (100 c.c.), and chloroform (100 c.c.), and, after being filtered, the chloroform layer was separated, washed with water, and dried (Na_2SO_4). The chloro-compound which remained on evaporation of the chloroform decomposed when its distillation was attempted. It was characterised as its *sesquipicrate*; microcrystalline nodules from alcohol, m. p. 157—159° (Found: C, 47·9; H, 4·8; N, 16·8. $2C_{19}H_{29}N_4Cl,3C_6H_3O_7N_3,H_2O$ requires C, 47·9; H, 4·9; N, 17·0%).

2-*Chloro*-4-p-*chloroanilinoquinazoline* (XI; X = NH).—2 : 4-Dichloroquinazoline (20 g.) and *p*-chloroaniline (12·8 g.), both finely powdered, were stirred at room temperature with a solution of sodium acetate (14 g.) in water (400 c.c.). After 24 hours, the mixture gave only a faint reaction for *p*-chloroaniline which was undiminished after 48 hours. The white solid was then collected, and washed with dilute hydrochloric acid and then with water. It became yellow on the surface when dried and melted at 210—215° (Found: Cl, 22·4. $C_{14}H_9N_3Cl_2$ requires Cl, 24·5%). Crystallisation from alcohol, 2-ethoxyethanol, *cyclo*hexane, or dimethylformamide, or sublimation in a high vacuum, either gave a less pure *product* or caused gross decomposition.

4-p-*Chloroanilino*-2-β-*diethylaminoethylaminoquinazoline* (II; R = Cl, R′ = $[CH_2]_2$·NEt_2).—4-Chloro-2-β-diethylaminoethylaminoquinazoline (5·8 g.) and *p*-chloroaniline (5 g.) were heated at 130—140° for 2 hours. The cooled melt was dissolved in acetic acid (30 c.c.), and the solution diluted with water (300 c.c.) and saturated with sodium acetate. Excess of *p*-chloroaniline was removed by filtration and extraction with ether, and the product precipitated from the aqueous layer by addition of ammonia. Isolated by extraction with chloroform, the base was obtained as an oil (6 g.) which afforded a *dihydrochloride* on treatment in acetone solution (100 c.c.) with 35% alcoholic hydrogen chloride (4·5 c.c.). This derivative crystallised from alcohol as colourless platelets, m. p. 262—263° (Found: C, 54·0; H, 5·9; N, 15·6, 15·7. $C_{20}H_{24}N_5Cl,2HCl$ requires C, 54·2; H, 5·9; N, 15·8%) (6223). The *dipicrate* separated from 2-ethoxyethanol as a yellow microcrystalline powder, m. p. 232—233° (Found: C, 46·3; H, 3·7; N, 18·7. $C_{20}H_{24}N_5Cl,2C_6H_3O_7N_3$ requires C, 46·4; H, 3·6; N, 18·6%).

4-p-*Chloroanilino*-2-γ-*diethylaminopropylaminoquinazoline* (II; R = Cl, R′ = $[CH_2]_3$·NEt_2).—(*a*) Prepared in a corresponding manner from 4-chloro-2-γ-diethylaminopropylaminoquinazoline and *p*-chloroaniline, the *base* crystallised from light petroleum (b. p. 100—120°) as colourless prisms, m. p. 107—108° (Found: C, 65·9; H, 7·2; N, 18·2. $C_{21}H_{26}N_5Cl$ requires C 65·7; H, 6·8; N, 18·3%) (3755).

(*b*) 2-Chloro-4-*p*-chloroanilinoquinazoline (10 g.) and γ-diethylaminopropylamine (6·5 c.c.) were heated under reflux for 2 hours at 120—130°. The resulting mixture was extracted with boiling 10% acetic acid (200 c.c.), and the solution made alkaline with ammonia and extracted with ether. Evaporation of the dried ethereal extract left a glass (2 g.) which gradually crystallised and then separated from light petroleum (b. p. 100—120°). It had m. p. 107—108° undepressed in admixture with material made by method (*a*).

4-p-*Methoxyanilino*-2-γ-*diethylaminopropylaminoquinazoline* (II; R = OMe, R′ = $[CH_2]_3$·NEt_2).—4-Chloro-2-γ-diethylaminopropylaminoquinazoline (2·6 g.) and *p*-anisidine (5 g.) were heated for 2 hours at 130—140°. A solution of the cooled melt in acetic acid (15 c.c.) was poured into 2% sodium acetate solution (200 c.c.), and the solution treated with carbon, filtered, and extracted with ether to remove

p-anisidine. The aqueous layer was made alkaline with ammonia and extracted with ether, and the extract dried and evaporated. The residue was extracted with boiling light petroleum (b. p. 100—120°), and the undissolved portion dissolved in acetone (50 c.c.) and treated with 35% alcoholic hydrogen chloride (3 c.c.). On standing, the *dihydrochloride* separated and was purified by crystallisation from alcohol–ethyl acetate. It formed a colourless microcrystalline solid, m. p. 228—230° (Found: C, 54·0; H, 7·0; N, 14·2. $C_{22}H_{29}ON_5$,2HCl requires C, 54·0; H, 7·2; N, 14·4%) (6315).

4-p-*Chloroanilino*-2-*γ*-*piperidinopropylaminoquinazoline* (II; R = Cl, R′ = $[CH_2]_3$·N<$[CH_2]_4$> CH_2). —(*a*) 4-Chloro-2-*γ*-piperidinopropylaminoquinazoline (2 g.), *p*-chloroaniline hydrochloride (1·1 g.), water (10 c.c.), and 10N-hydrochloric acid (0·1 c.c.) were boiled under reflux for 1 hour. The solution was then diluted further with water (10 c.c.), sodium acetate (2 g.) added, and the solution treated with carbon, filtered, and made alkaline with ammonia. The precipitated solid was collected, dried, and crystallised from light petroleum (b. p. 80—100°) to give the *base* as colourless platelets, m. p. 129° (Found: N, 17·3. $C_{22}N_{26}N_5Cl$ requires N, 17·7%). The *dihydrochloride*, prepared from the base in acetone solution with alcoholic hydrogen chloride, separated as a colourless microcrystalline powder, m. p. 238—240° (Found: Cl′, 15·0. $C_{22}H_{26}N_5Cl$,2HCl requires Cl′, 15·15%) (6234). The base formed a picrate which separated from 2-ethoxyethanol–alcohol as small yellow plates, m. p. 228—229°.

(*b*) 2-Chloro-4-*p*-chloroanilinoquinazoline (6 g.) and *γ*-piperidinopropylamine (5 c.c.) were heated at 130—140° under reflux for 3 hours. The cooled melt was extracted with boiling 20% acetic acid (150 c.c.), and the cooled, filtered extract made faintly alkaline with ammonia to precipitate the *acetate* which crystallised from ethyl acetate as colourless square plates, m. p. 114—115° (Found: C, 60·5; H, 7·0; N, 14·8; Cl, 7·5. $C_{22}H_{26}N_5Cl,CH_3{\cdot}CO_2H,H_2O$ requires C, 60·75; H, 6·8; N, 14·8; Cl, 7·5%). The free base liberated from this acetate with sodium hydroxide and crystallised from light petroleum (b. p. 80—100°) had m. p. 129° undepressed in admixture with base made by method (*a*).

4-p-*Chloroanilino*-2-*γ*-*di*-n-*butylaminopropylaminoquinazoline* (II; R = Cl, R′ = $[CH_2]_3$·NBu^n_2).— Prepared from 4-chloro-2-*γ*-di-*n*-butylaminopropylaminoquinazoline and *p*-chloroaniline as described above for 4-*p*-methoxyanilino-2-*γ*-diethylaminopropylaminoquinazoline, the *dihydrochloride* separated from ethyl acetate and a little alcohol as a colourless microcrystalline powder, m. p. 125—126° (Found: C, 56·4; H, 7·4; N, 12·9. $C_{25}H_{34}N_5Cl$,2HCl,H_2O requires C, 56·5; H, 7·15; N, 13·2%) (6277).

2-*β*-*Diethylaminoethylamino*-4-p-*chlorophenylthioquinazoline* (VI; R = Cl, R′ = $[CH_2]_2$·NEt_2).— 4-Chloro-2-*β*-diethylaminoethylaminoquinazoline (4·5 g.) and *p*-chlorothiophenol (4·5 g.) were heated to 130° by means of an oil-bath. When the vigorous reaction had subsided the mixture was cooled and dissolved in acetic acid (20 c.c.), and the solution poured on a mixture of ice and water. The unchanged *p*-chlorothiophenol thereby precipitated was filtered off and washed with water, and the united filtrates made alkaline with sodium hydroxide. The precipitated product was collected, washed with water, dried, and crystallised from light petroleum (b. p. 60—80°), giving 2-*β*-*diethylaminoethylamino*-4-p-*chlorophenylthioquinazoline* as yellow needles (yield, 2·1 g.), m. p. 92° (Found: C, 61·9; H, 5·8; S, 8·6. $C_{20}H_{23}N_4ClS$ requires C, 62·1; H, 5·9; S, 8·3%) (6225).

2-*γ*-*Diethylaminopropylamino*-4-p-*chlorophenylthioquinazoline* (VI; R = Cl, R′ = $[CH_2]_3$·NEt_2), prepared in a corresponding manner from 4-chloro-2-*γ*-diethylaminopropylaminoquinazoline and *p*-chlorothiophenol, crystallised from light petroleum (b. p. 60—80°) as pale yellow rhombs, m. p. 100° (Found: C, 62·6; H, 6·2. $C_{21}H_{25}N_4ClS$ requires C, 62·9; H, 6·2%) (6224).

4-*γ*-*Diethylaminopropylamino*-2-p-*chlorophenylthioquinazoline* (V; R = Cl, R′ = $[CH_2]_3$·NEt_2).— 2-Chloro-4-*γ*-diethylaminopropylaminoquinazoline hydrate (15 g.) (Part XIV) and *p*-chlorothiophenol (15 g.) were fused at 120—130° for 3 hours and the mixture worked up as described above for 2-*β*-diethylaminoethylamino-4-*p*-chlorophenylthioquinazoline. The *product* crystallised from benzene–light petroleum (b. p. 60—80°) as fine colourless needles (yield, 12·0 g.), m. p. 96° (Found: C, 63·2; H, 5·8; S, 8·6. $C_{21}H_{25}N_4ClS$ requires C, 62·9; H, 6·2; S, 8·0%) (5379).

4-*γ*-*Diethylaminopropylamino*-2-p-*tolylthioquinazoline* (V; R = Me, R′ = $[CH_2]_3$·NEt_2), similarly prepared from (X; R = $[CH_2]_3$·NEt_2) and thio-*p*-cresol, crystallised from light petroleum (b. p. 60—80°) or ether as colourless needles, m. p. 121° (Found: C, 69·6; H, 7·3; N, 15·1. $C_{22}H_{28}N_4S$ requires C, 69·5; H, 7·4; N, 14·75%) (3759).

4-*β*-*Diethylaminoethylamino*-2-p-*chlorophenylthioquinazoline* (V; R = Cl, R′ = $[CH_2]_2$·NEt_2), prepared in a corresponding manner, separated from light petroleum (b. p. 80—100°) as large colourless needles, m. p. 123° (Found: C,62·4; H, 6·4; S, 8·2. $C_{20}H_{23}N_4ClS$ requires C, 62·1; H, 5·9, S, 8·3%) (5331).

2 : 4-*Bis*-*β*-*diethylaminoethylaminoquinazoline* (XII; R = $[CH_2]_2$·NEt_2).—2-Chloro-4-*β*-diethylaminoethylaminoquinazoline hydrate (5·6 g.) and *β*-diethylaminoethylamine (2·5 c.c.) were heated for 2 hours at 130°, the mixture cooled and dissolved in dilute acetic acid, and the filtered solution basified with sodium hydroxide. The liberated oil was extracted with benzene, and the dried extract evaporated. Distillation of the residual oil gave the *product* (yield, 2·8 g.) as a pale yellow oil, b. p. 230—232°/0·1 mm. (Found: C, 66·5; H, 9·4. $C_{20}H_{34}N_6$ requires C, 67·1; H, 9·5%). It formed a *tripicrate* which was obtained in two distinct modifications: the first had m. p. 193—194° after two crystallisations from acetic acid (Found: C, 43·8; H, 4·3. $C_{20}H_{34}N_6,3C_6H_3O_7N_3$ requires C, 43·7; H, 4·1%); and the second had m. p. 213—214°, also from acetic acid (Found: C, 43·9, H, 4·5%), and was formed from the first on standing in contact with the solution. The *trihydrochloride* (6291) was obtained by dissolving the base (2·3 g.) in acetone (30 c.c.) and adding 35% alcoholic hydrogen chloride (2 c.c.). It separated first as an oil which crystallised on scratching, and after being collected and washed with acetone crystallised from alcohol as colourless prisms, m. p. 191—192° (Found: C, 49·3; H, 7·5; N, 16·9; Cl, 21·9. $C_{20}H_{34}N_6$,3HCl,H_2O requires C, 49·45; H, 8·0; N, 17·3; Cl, 21·9%).

Condensation of 2-*Chloro*-4-p-*chloroanilinoquinazoline with β-Diethylaminoethylamine.*—2-Chloro-4-*p*-chloroanilinoquinazoline (6 g.) and *β*-diethylaminoethylamine (5 c.c.) were heated under reflux for 3·5 hours at 120—130°. The cooled melt was extracted with boiling 10% acetic acid (120 c.c.), and the solution made alkaline with ammonia and extracted with ether. After drying, the ethereal extract was evaporated, and unchanged *β*-diethylaminoethylamine removed at 150—160°/15 mm. *p*-Chloroaniline was detected in the residue and was removed by ether extraction of a solution in 10% acetic acid containing sodium acetate (5 g.). The acid solution was then basified with sodium hydroxide, and the product

isolated by ether extraction. The residue obtained on evaporation of the dried ether extract was dissolved in acetone (40 c.c.), and 35% alcoholic hydrogen chloride (2 c.c.) added. The resulting oil solidified on scratching, and was then collected and crystallised from alcohol, giving 2 : 4-bis-β-diethylaminoethylaminoquinazoline trihydrochloride, m. p. and mixed m. p. 191—192°. Concentration of the acetone–alcoholic mother liquors afforded an impure hydrochloride which was converted into the base and thence into the picrate. Crystallisation of this picrate first from acetic acid and then from 2-ethoxyethanol afforded 4-*p*-chloroanilino-2-β-diethylaminoethylaminoquinazoline dipicrate, m. p. 230—232° undepressed in admixture with authentic material (see above).

2-*Chloro*-4-p-*chlorophenylthioquinazoline* (XI; X = S).—*p*-Chlorothiophenol (5·8 g.) was added to a solution of sodium (1·0 g.) in alcohol (50 c.c.), the solvent evaporated, and the dried residue ground to a fine powder. This sodium salt, suspended in dry ether (100 c.c.), was shaken with powdered 2 : 4-dichloroquinazoline (8·0 g.) for 4 hours and the mixture left overnight. Water (50 c.c.) and 10N-sodium hydroxide (10 c.c.) were added, the ether removed under diminished pressure at room temperature, and the solid collected, washed with water, and dried. Crystallised from light petroleum (b. p. 120—140°), 2-*chloro*-4-p-*chlorophenylthioquinazoline* formed large colourless needles, m. p. 156—157° (Found : C, 54·8; H, 2·9; S, 10·3. $C_{14}H_8N_2Cl_2S$ requires C, 54·7; H, 2·6; S, 10·4%).

4-*Hydroxy*-2-p-*chlorophenylthioquinazoline*.—2-Chloro-4-hydroxyquinazoline (3·6 g.) and *p*-chlorothiophenol (2·9 g.) were heated with stirring to 100°. The solid mass resulting from the vigorous reaction was cooled, powdered, and heated at 100° for a further hour, then cooled and crystallised directly from chlorobenzene, giving the *product* as colourless slender needles (yield, 5·2 g.), m. p. 246° (Found : C, 58·4; H, 3·2; S, 11·2. $C_{14}H_9ON_2ClS$ requires C, 58·2; H, 3·1; S, 11·2%). When this compound was crystallised from 2-ethoxyethanol only pearly leaflets of 2 : 4-dihydroxyquinazoline, m. p. 340°, were obtained.

4-*Chloro*-2-p-*chlorophenylthioquinazoline* (XIV).—The preceding compound (3·0 g.) and phosphoryl chloride (15 c.c.) were refluxed for 15 minutes, the mixture poured on ice, and the solid *product* collected, dried, and crystallised from light petroleum (b. p. 80—100°), giving colourless needles (yield, 1·8 g.), m. p. 126° (Found : C, 54·7; H, 2·8; S, 10·1. $C_{14}H_8N_2Cl_2S$ requires C, 54·7; H, 2·6; S, 10·4%).

2 : 4-*Bis*-p-*chlorophenylthioquinazoline* (XIII; X = S).—(*a*) 2-Chloro-4-*p*-chlorophenylthioquinazoline (3·1 g.) and *p*-chlorothiophenol (1·5 g.) were powdered together and heated in an oil-bath at 100°; a vigorous reaction ensued. The melt was cooled, powdered, and reheated at 100° for 1 hour. Crystallisation from xylene–light petroleum (b. p. 80—100°) then gave the *product* as clumps of colourless prisms (yield, 3·3 g.), m. p. 134—135° (Found : S, 15·7; Cl, 16·7. $C_{20}H_{12}N_2Cl_2S_2$ requires S, 15·4; Cl, 17·1%).

(*b*) The product from the interaction of 4-chloro-2-*p*-chlorophenylthioquinazoline (1·2 g.) and *p*-chlorothiophenol (0·6 g.) was worked up as in (*a*) to give the same compound, m. p. and mixed m. p. 134—136° (Found : S, 15·8%).

Condensation of 4-*Chloro*-2-p-*chlorophenylthioquinazoline with β-Diethylaminoethylamine*.—A solution of the chloroquinazoline (1·0 g.) and β-diethylaminoethylamine (0·5 g.) in alcohol (15 c.c.) was boiled for 2 hours, the solvent evaporated, and the residue treated with sodium hydroxide and extracted with ether. After evaporation of the ether extract the residue was dissolved in acetic acid (10 c.c.), poured into water (100 c.c.), and basified with sodium hydroxide. The precipitated solid was collected, dried, and crystallised from light petroleum (b. p. 60—80°) to give 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline (yield, 0·8 g.), m. p. and mixed m. p. 122° (Found : C, 61·7; H, 5·9; S, 8·8%).

Condensation of 2-*Chloro*-4-p-*chlorophenylthioquinazoline with β-Diethylaminoethylamine*.—A solution of the chloroquinazoline (XI; X = S) (6·0 g.) and β-diethylaminoethylamine (2·4 g.) in alcohol (100 c.c.) was boiled for 2 hours, and the solvent evaporated under reduced pressure and dissolved in hot acetic acid (50 c.c.). On addition of this solution to ice and water (500 c.c.) a solid was precipitated. This was collected, washed with water, and dried at 100° (yield, 1·4 g.) followed by crystallisation from light petroleum (b. p. 80—100°) to give colourless needles of 2 : 4-bis-*p*-chlorophenylthioquinazoline, m. p. and mixed m. p. 134—136° (Found : S, 15·7; Cl, 16·9%). The acetic acid filtrate from the above compound was basified with 10N-sodium hydroxide, and the precipitated product collected, washed with water, and dried at 80° (yield, 4·4 g., m. p. 120°). Crystallised from light petroleum (b. p. 60—80°), it formed colourless flat needles, m. p. 122° undepressed in admixture with 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline prepared as described above (Found : C, 62·4; H, 5·8%).

Condensation of 2-*Chloro*-4-p-*chlorophenylthioquinazoline and γ-Diethylaminopropylamine*.—A solution of γ-diethylaminopropylamine (2·5 g.) and (XI; X = S) (5·2 g.) in alcohol (85 c.c.) was boiled for 2 hours and then worked up as in the preceding experiment. The products isolated were 2 : 4-bis-*p*-chlorophenylthioquinazoline (0·8 g.), m. p. and mixed m. p. 135—136° (Found : S, 15·5%), and 4-γ-diethylaminopropylamino-2-*p*-chlorophenylthioquinazoline (1·8 g.), m. p. 94° undepressed in admixture with authentic material prepared as described above (Found : S, 8·0%).

Condensation of 2 : 4-*Bis*-p-*chlorophenylthioquinazoline with β-Diethylaminoethylamine*.—A solution of (XIII; X = S) (2·1 g.) and β-diethylaminoethylamine (0·6 g.) in alcohol (25 c.c.) and 2-ethoxyethanol (10 c.c.) was heated on the steam-bath for 6 hours and the solvent then removed under diminished pressure. The distillate was treated with 10N-sodium hydroxide (1 c.c.) and again evaporated, the residue dissolved in a little water, and the solution filtered (carbon) and acidified, giving colourless shining leaflets of *p*-chlorothiophenol (0·5 g.), m. p. 50—52°. The residue from the initial distillation was dissolved in acetic acid (10 c.c.), the solution poured into water, and the solid collected, dried, and crystallised from light petroleum (b. p. 80—100°), giving unchanged 2 : 4-bis-*p*-chlorophenylthioquinazoline (0·4 g.), m. p. and mixed m. p. 135—136° (Found : S, 15·5%). The acetic acid filtrate from this material was basified with sodium hydroxide solution, and the precipitated solid collected, dried, and purified by crystallisation from light petroleum (b. p. 80—100°). It was identified as 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline (yield, 1·3 g.), m. p. and mixed m. p. 123—124° (Found : S, 8·7%).

Condensation of 2-β-*Diethylaminoethylamino*-4-p-*chlorophenylthioquinazoline and β-Diethylaminoethylamine*.—The quinazoline (1·6 g.), β-diethylaminoethylamine (1·2 c.c.), and alcohol (10 c.c.) were refluxed for 24 hours and the solvent removed under diminished pressure. The residue was dissolved in hot acetic acid (10 c.c.), the solution poured into water (100 c.c.), and the precipitated solid collected.

This was purified by dissolution in dilute sodium hydroxide and reprecipitation with acetic acid to give *p*-chlorothiophenol (0·25 g.), m. p. and mixed m. p. 54°. The acetic acid filtrate from the original isolation of this material was made strongly alkaline with sodium hydroxide and the precipitated oil extracted with benzene. Evaporation of the dried benzene extract left an oil (free from sulphur) which was purified by vacuum distillation (b. p. 220—224°/0·1 mm.) and identified as 2 : 4-bis-β-diethylaminoethylaminoquinazoline. With picric acid in alcoholic solution it afforded a picrate which crystallised from acetic acid in large yellow needles, m. p. 213—214° undepressed in admixture with authentic picrate (see above) (Found : C, 43·4; H, 4·1%).

When 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline (1·6 g.) was used in a similar experiment in place of its 2 : 4-isomer it was recovered unchanged (1 g., m. p. 122°) (Found : S, 8·4%). No *p*-chlorothiophenol was detected.

Action of Sodium Hydroxide on 2-Chloro-4-p-chlorophenylthioquinazoline.—2-Chloro-4-*p*-chlorophenylthioquinazoline (3·1 g.) was added to a solution of sodium hydroxide (0·4 g.) in alcohol (25 c.c.) and water (10 c.c.), and the solution refluxed for 4 hours. It was then poured into water, and the precipitated solid collected, dried, and crystallised from light petroleum (b. p. 60—80°) to give 2 : 4-bis-*p*-chlorophenylthioquinazoline (0·9 g.), m. p. and mixed m. p. 134—135° (Found: C, 57·9; H, 3·2; N, 6·8. Calc. for $C_{20}H_{12}N_2Cl_2S_2$: C, 57·8; H, 2·9; N, 6·7%).

Attempted Reaction of 4-β-Diethylaminoethylamino-2-p-chlorophenylthioquinazoline with p-Chlorothiophenol.—The quinazoline (1·9 g.) and *p*-chlorothiophenol (1·5 g.) in alcohol (50 c.c.) were heated on the steam-bath for 10 hours. When worked up by evaporation and treatment with dilute acetic acid, only unchanged 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline, m. p. and mixed m. p. 124°, was isolated.

No reaction could be detected when the condensation of 2 : 4-bis-β-diethylaminoethylaminoquinazoline and *p*-chlorothiophenol was attempted under similar conditions.

2 : 4-*Bis*-p-*chloroanilinoquinazoline* (XIII; X = NH).—2 : 4-Dichloroquinazoline (10 g.) and *p*-chloroaniline (12·75 g.) in chloroform (125 c.c.) were stirred at room temperature for 6 hours. After a further 24 hours the precipitate was collected, washed with chloroform, dried, lixiviated with water, filtered off, and washed with water to remove *p*-chloroaniline hydrochloride. It was then obtained as a greyish crystalline powder, m. p. 340—345° undepressed in admixture with the hydrochloride of material made by the method described in Part XIV.

Condensation of 2 : 4-Bis-p-chloroanilinoquinazoline Hydrochloride with β-Diethylaminoethylamine.—2 : 4-Bis-*p*-chloroanilinoquinazoline hydrochloride (4·3 g.) and β-diethylaminoethylamine (4 c.c.) were heated at 130—140° under reflux for 3 hours, and the mixture extracted with boiling 10% acetic acid (40 c.c.) containing sodium acetate (1 g.). When cold, the extract deposited an oil which was removed by ether extraction and identified as *p*-chloroaniline. The aqueous solution was treated with hydrochloric acid (10 c.c.) and allowed to stand. The crystalline material which separated was collected and identified as 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride (Part XIV), m. p. and mixed m. p. 253°.

Condensation of 2-p-Chloroanilino-4-β-hydroxyethylaminoquinazoline Hydrochloride with β-Diethylaminoethylamine.—2-*p*-Chloroanilino-4-β-hydroxyethylaminoquinazoline hydrochloride (2·9 g.) (Part XIV) and β-diethylaminoethylamine (3 c.c.) were heated at 130—140° for 3 hours under reflux, and the mixture cooled and extracted with hot 10% acetic acid (50 c.c.). Addition of hydrochloric acid (15 c.c.) to the filtered extract precipitated a crystalline product, m. p. 253° undepressed in admixture with authentic dihydrochloride of (I; R = Cl, R′ = $[CH_2]_2{\cdot}NEt_2$).

IMPERIAL CHEMICAL INDUSTRIES LTD.,
RESEARCH LABORATORIES, BLACKLEY, MANCHESTER, 9. [*Received, December 22nd*, 1947.]