151. *Synthetic Antimalarials. Part XIV. Some 2-Arylamino-4-aminoalkylaminoquinazolines.*

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

The preparation of a series of 2-arylamino-4-aminoalkylaminoquinazolines is described. Many of the compounds show marked antimalarial activity against the endo-erythrocytic forms of *P. gallinaceum* in chicks but no activity against the exo-erythrocytic forms. In this respect they resemble the 2-arylamino-4-aminoalkylamino-6-methylpyrimidines (Part I, *J.*, 1946, 343) and the corresponding 5 : 6-disubstituted pyrimidine derivatives described in Part VII (*J.*, 1946, 378) to which they are related structurally.

The preparative methods employed comprise (*a*) the reaction of an aminoalkylamine with a 2-arylaminoquinazoline bearing a labile group (Cl, OEt, OPh, SMe) in the 4-position, and (*b*) the stepwise reaction of 2 : 4-dichloroquinazoline with an aminoalkylamine and an arylamine.

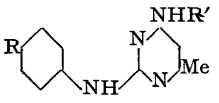
The discovery of a new type of antimalarial structure in the 2-arylamino-4-dialkylaminoalkylamino-6-methylpyrimidines (I) described by Curd and Rose in Part I (*loc. cit.*) provided a novel lead for chemotherapeutic investigations and it has been followed up in numerous directions with varied degrees of success.

At the inception of this work it appeared as if antimalarial activity was associated with the attachment to a heterocyclic nucleus of an aminoalkyl group and an aryl group through linkages capable of forming prototropic systems with the central nucleus, as in (I). The replacement of the pyrimidine nucleus in (I) by other nitrogen-containing heterocyclic systems was an obvious development, and some analogous quinazoline derivatives of type (II) are now described. In addition to its relationship to (I), type (II) was clearly even more closely related to the active 2-arylamino-4-aminoalkylamino-5 : 6-disubstituted pyrimidines such as for instance (III) described in Part VII (*loc. cit.*).

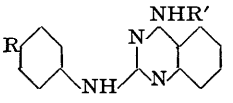
Previously, quinazoline derivatives have not been investigated to any great extent as antimalarials. In view of the interest in the quinoline nucleus this is rather surprising and may be connected with the statement of Magidson and Golovchinskaya (*J. Gen. Chem. Russia*, 1938, **8**, 1797) that 4-dialkylaminoalkylaminoquinazolines including those carrying an additional substituent such as chloro-, nitro-, or amino- in the 6-position are devoid of antimalarial activity.

However, the results given in Table I show that the earliest compounds of the type now described possessed considerable antimalarial activity and this activity persisted over a wide range of chemical variants subsequently investigated.

It is proposed to hold over discussion of the bearing of these results on the hypotheses we have advanced relating chemical structure with antiplasmodial activity in our various related types of compounds until several complementary investigations have been completed. It may be pointed out, however, that quinazolines of type (II) would be expected to show qualitatively similar resonance and tautomeric phenomena to the related pyrimidines of type (I) except in so far as these become modified by the presence of the extra fused benzene nucleus. Our subsequent investigations in this field have therefore been designed, *inter alia*, to throw light on this point.



(I.)



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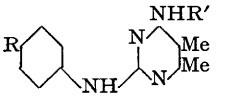

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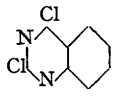
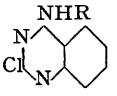
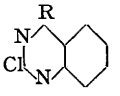


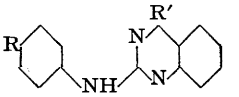
(IV.)



(V.)



(VI.)



(VII.)

The synthesis of compounds of type (II) was first essayed from 2 : 4-dichloroquinazoline (IV). The stepwise replacement of the two chlorine atoms in this compound with different amines, usually dyes or dye intermediates, has been described in E.P. 309,102 and in other patents, but while it was indicated that reaction probably occurred first at the 4-position no proof of this was given.

2 : 4-Dichloroquinazoline was found to react vigorously with two molecular proportions of γ-diethylaminopropylamine in the absence of a solvent to give 2 : 4-*bis*-(γ-*diethylaminopropylamino*)*quinazoline*, but with a cold dilute aqueous solution of the amine, using sodium hydroxide as acid-binding agent, only one chlorine atom was replaced and a compound formed that was later proved to be 2-*chloro*-4-γ-*diethylaminopropylaminoquinazoline* (V; R = $[CH_2]_3$·NEt_2). The latter reaction was then applied successfully to a number of other dialkylaminoalkylamines and substituted alkylamines such as ethanolamine. The yields were practically quantitative on the 2 : 4-dichloroquinazoline used and there was no evidence of the formation of any of the isomeric 4-chloro-2-substituted alkylaminoquinazolines. The compounds were found to be unexpectedly stable to hydrolysis by acid or alkali and could be distilled at pressures of 0·1 mm. or less.

Compounds of type (V) reacted smoothly with arylamines when heated together at 150°, or in a solvent such as acetic acid, or in boiling dilute hydrochloric acid (cf. Banks, *J. Amer. Chem. Soc.*, 1944, **66**, 1127, 1131) to give 2-arylamino-4-aminoalkylaminoquinazolines. Thus (V; R = $[CH_2]_3$·NEt_2) and *p*-anisidine gave 2-p-*anisidino*-4-γ-*diethylaminopropylaminoquinazoline* (II; R = OMe; R' = $[CH_2]_3$·NEt_2) while (V; R = $[CH_2]_2$·NEt_2) with *p*-chloroaniline gave 2-p-*chloroanilino*-4-β-*diethylaminoethylaminoquinazoline* (II; R = Cl, R' = $[CH_2]_2$·NEt_2).

The same compounds were also obtained in the following way. 2 : 4-Dichloroquinazoline was converted into 2-chloro-4-hydroxyquinazoline (VI; R = OH) (Lange and Sheibley, *J. Amer. Chem. Soc.*, 1931, **53**, 3867; 1933, **55**, 1188) by treatment with excess of 2N-sodium hydroxide (cf. E.P. 287,179). This on reaction with *p*-anisidine gave 2-p-*anisidino*-4-*hydroxyquinazoline* (VII; R = OMe, R' = OH), and with *p*-chloroaniline 2-p-*chloroanilino*-4-*hydroxyquinazoline* (VII; R = Cl, R' = OH), converted by the action of phosphoryl chloride into 4-chloro-2-*p*-anisidinoquinazoline (VII; R = OMe, R' = Cl) and 4-*chloro*-2-p-*chloroanilinoquinazoline* (VII; R = R' = Cl) respectively. (These two compounds were very labile and characterisation of the former was not possible.) Finally (VII; R = OMe, R' = Cl) was heated with γ-diethylaminopropylamine and (VII; R = R' = Cl) with β-diethylaminoethylamine. The identity of the final products made by the two methods lent support to the correctness of the assigned structures since there seemed little doubt that 2-chloro-4-hydroxyquinazoline had been correctly oriented. Thus, for instance, Lange and Sheibley (*J. Amer. Chem. Soc.*, 1932, **54**, 1994) brought this compound into reaction with aniline to give 2-anilino-4-hydroxyquinazoline (VII; R = H, R' = OH) identical with the product obtained

by condensing anthranilic acid with *N*-phenyl-*S*-methyl*iso*thiourea (cf. Wheeler, Johnson, and McFarland, *ibid.*, 1903, **25**, 797).

Further confirmatory proof of the structure of compounds of type (II), and therefore of their precursors of type (V; R = dialkylaminoalkyl), was provided by the following very convenient synthesis. It was known (Lange, Roush, and Asbeck, *J. Amer. Chem. Soc.*, 1930, **52**, 3696) that 2 : 4-dichloroquinazoline reacted with sodium phenoxide in ethanol to give 2-chloro-4-ethoxyquinazoline (VI; R = OEt) because reduction of this compound with zinc dust and acetic acid gave 4-ethoxyquinazoline identical with that made by the method of Bogert and May (*ibid.*, 1909, **31**, 510) from 4-chloroquinazoline and sodium ethoxide. *p*-Chloroaniline was therefore condensed with the 2-chloro-4-ethoxyquinazoline to give 2-p-*chloroanilino*-4-*ethoxyquinazoline* (VII; R = Cl, R′ = OEt) which was then brought into reaction with β-diethylaminoethylamine at 140—150°, with elimination of alcohol, to give (II; R = Cl, R′ = $[CH_2]_2$·NEt_2) identical with the compound made by the previous methods.

Similarly 2-chloro-4-phenoxyquinazoline (VI; R = OPh) (Lange, Roush, and Asbeck, *loc. cit.*) and 2-*chloro*-4-*methylthioquinazoline* (VI; R = SMe) (prepared by treating 2 : 4-dichloroquinazoline with one equivalent of sodium thiomethoxide in cold alcohol) reacted with *p*-chloroaniline to give respectively 2-p-*chloroanilino*-4-*phenoxyquinazoline* (VII; R = Cl, R′ = OPh) and 2-p-*chloroanilino*-4-*methylthioquinazoline* (VII; R = Cl, R′ = SMe) both of which reacted with β-diethylaminoethylamine to give (II; R = Cl, R′ = $[CH_2]_2$·NEt_2).

The greater lability of the 4-chlorine atom in 2 : 4-dichloroquinazoline noted by previous workers and confirmed in the present investigation differentiates this substance from 2 : 4-dichloropyrimidine and its homologues (2 : 4-dichloro-6-methyl- and 2 : 4-dichloro-5 : 6-dimethylpyrimidine) which yield a mixture of the two isomeric mono-condensation products on reaction with ammonia and amines. It resembles rather 2 : 4-dichloro-5-nitro- and 2 : 4-dichloro-5-nitro-6-methyl-pyrimidine in which mono-condensation occurs exclusively at the 4-position (cf. Isay, *Ber.*, 1906, **39**, 252; Gabriel and Colman, *ibid.*, 1901, **34**, 1234). Presumably the inductive effect of the aromatic nucleus in (IV), like a nitro-group in the pyrimidines mentioned above, renders the 4-position more accessible to attack by anionoid reagents.

The foregoing methods were used for the preparation of a variety of other quinazoline derivatives of type (II) in which the effect of variations in the aryl group and in the basic side chain was examined. In general these compounds formed colourless, crystalline, non-hygroscopic hydrochlorides which were used for biological tests.

The results of tests against the blood invasive forms of *P. gallinaceum* in chicks carried out by the method of Curd, Davey, and Rose (*Ann. Trop. Med. Parasit.*, 1945, **39**, 139) are given in Table I, the method of expressing antimalarial activity being the same as in Part I (*loc. cit.*). The detailed biological results will be published elsewhere.

Experimental.

2 : 4-*Dichloroquinazoline* (IV).—The following method based on the work of Baddiley and Topham (*J.*, 1944, 678) was preferred to the earlier methods in the literature (cf. Gabriel and Colman, *Ber.*, 1905, **38**, 3559). 2 : 4-Dihydroxyquinazoline (20 g.), phosphoryl chloride (60 c.c.), and dimethylaniline (9 c.c.) were refluxed for 5½ hours. The mixture was then cooled slightly and poured on crushed ice (700 g.). The precipitated dichloroquinazoline was filtered off, washed acid free with ice–water, and dried (yield, 18·6 g.); m. p. 116—117°. It was best purified further by vacuum distillation.

2 : 4-*Bis*-(γ-*diethylaminopropylamino*)*quinazoline*.—2 : 4-Dichloroquinazoline (4 g.) was added to γ-diethylaminopropylamine (5·5 g.). When the ensuing violent reaction had subsided the mixture was heated for 2 hours at 130°. The cooled reaction mixture was extracted with 5% acetic acid (50 c.c.), the solution made strongly alkaline, and the liberated base taken into ether. Evaporation of the dried (K_2CO_3) ether solution and distillation of the residue gave the *quinazoline* as a viscous pale yellow oil, b. p. 206—208°/0·02 mm. (Found: N, 21·7. $C_{22}H_{38}N_6$ requires N, 21·8%). It formed a *tripicrate* which crystallised from 2-ethoxyethanol as yellow laminæ, m. p. 180° (Found: C, 44·8; H, 4·5; N, 19·3. $C_{22}H_{38}N_6,3C_6H_3O_7N_3$ requires C, 44·7; H, 4·4; N, 19·55%).

2-*Chloro*-4-*aminoalkylaminoquinazolines* (V).—Finely ground 2 : 4-dichloroquinazoline (20 g., 0·1 g.-mol.), water (200 c.c.), and the appropriate aminoalkylamine (0·1 g.-mol.) were stirred at room temperature. After 1 hour the mixture was made just alkaline to Clayton-yellow by the addition of 10N-sodium hydroxide solution, and further additions were then made at intervals to maintain the alkalinity until approximately 0·1 g.-mol. had been added (4—12 hours). The solution was then acidified (to Congo-red) with hydrochloric acid and filtered from unreacted 2 : 4-dichloroquinazoline. Addition of excess of sodium hydroxide solution then precipitated the *quinazoline* (sometimes as a hydrate) as an oil or gum which crystallised on standing or, after decantation of the aqueous layer, on trituration with ether. The product was collected, washed well with water, and dried at room temperature. It was normally used without further purification but if necessary this was best effected by vacuum distillation. The compounds prepared are detailed in Table II.

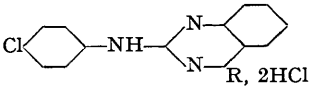
2-Chloro-4-hydroxyquinazoline (VI; R = OH).—2 : 4-Dichloroquinazoline (19·9 g.) (finely ground) and 2N-sodium hydroxide (150 c.c.) were stirred for 3 hours. After dilution with water (100 c.c.) and stirring for a further 10 minutes the solution was filtered from a little insoluble residue and the filtrate acidified with acetic acid. The precipitated product was filtered off, washed with water, and dried. Crystallised from alcohol it formed colourless needles, m. p. 218—220° (Found: C, 53·5; H, 2·95; Cl, 19·3. Calc. for $C_8H_5ON_2Cl$: C, 53·2; H, 2·8; Cl, 19·7%).

2-p-*Chloroanilino-4-hydroxyquinazoline* (VII; R = Cl, R′ = OH).—2-Chloro-4-hydroxyquinazoline (4·5 g.), *p*-chloroaniline (3·2 g.), water (30 c.c.), acetone (15 c.c.), and 10N-hydrochloric acid (0·5 c.c.) were

TABLE I.

Antimalarial Activities.

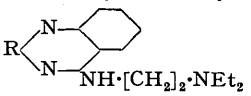
(*a*) 2-*p*-Chloroanilino-4-aminoalkylaminoquinazoline dihydrochlorides.



Reference No.	Nature of R.	Dose mg./kg.	Antimalaria activity.
3756	NH·[CH$_2$]$_2$·NEt$_2$	40	+ to ++
		20	±
3666	NH·[CH$_2$]$_3$·NEt$_2$ [1]	80	++
		40	+
		20	—
3915	NH·[CH$_2$]$_4$·NEt$_2$.	160	+ to ++
		80	+
4248	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	80	+
		40	+
4087	NMe·[CH$_2$]$_2$·NEt$_2$	160	—
		80	—
		40	—
5155	NMe·[CH$_2$]$_3$·NHMe	160	++
		80	—
3933	NH·[CH$_2$]$_2$·NMe$_2$	80	+ to ++
		40	—
3979	NH·[CH$_2$]$_3$·NMe$_2$	80	++
		40	++
		20	+
4601	NH·[CH$_2$]$_4$·NMe$_2$	40	++
		20	+
4870	NH·[CH$_2$]$_5$·NMe$_2$	80	++
		40	+ to ++
		20	±
4869	NH·[CH$_2$]$_6$·NMe$_2$	80	+
		40	—
4626	NH·[CH$_2$]$_3$·NMePr$^\beta$	80	++
		40	+
4214	NH·[CH$_2$]$_3$·NHBu$^\alpha$	160	++
		40	+
4524	NH·[CH$_2$]$_3$·NBu$^\alpha_2$	80	++
		40	+
4589	NH·[CH$_2$]$_4$·NBu$^\alpha_2$	120	+ to ++
		80	+
4252	NH·[CH$_2$]$_2$·N<[CH$_2$]$_3$>CH$_2$	80	+
		40	±
4251	NH·[CH$_2$]$_2$·N<[CH$_2$]$_4$>CH$_2$	80	+
		40	—
3932	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	80	++
		40	+
4575	NH·CHMe·CH$_2$·N<[CH$_2$]$_4$>CH$_2$	160	++
		80	±
		40	—
4600	NH·CH$_2$·CHMe·N<[CH$_2$]$_4$>CH$_2$	80	+
		40	±
4139	NH·[CH$_2$]$_2$·NH$_2$	120	+
		80	+
4496	NH·[CH$_2$]$_2$·NHAc	320	++
		80	—
4625	NH·[CH$_2$]$_6$·NH$_2$	160	+ to ++
		80	—
4608	NH·[CH$_2$]$_3$·NMe·[CH$_2$]$_2$·NEt$_2$ [2]	120	+
		80	±
		40	—

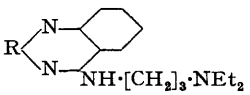
TABLE I—*contd.*

(*b*) 2-Arylamino-4-β-diethylaminoethylaminoquinazolines.



Reference No.	Nature of R.	Dose mg./kg.	Antimalarial activity.
3909	4-Methylthioanilino- [3]	80	++
		40	+
4086	*N*-Ethylanilino-	160	—
		80	—
		40	—
3761	2-Naphthylamino-	120	++
		80	+
		40	+
4103	6-Bromo-2-naphthylamino- [3]	80	+
		40	+
		20	—
4058	4 : 8-Dichloro-2-naphthylamino [3]	200	+
		120	±
		80	—
5131	4-Nitroanilino- [3]	80	++
		40	—

(*c*) 2-Arylamino-4-γ-diethylaminopropylaminoquinazolines.



3715	4-Anisidino-	80	++
		40	—
3758	Anilino-	80	+
3760	4-Toluidino-	80	++
		40	+
3757	2-Naphthylamino-	80	+
		40	+

(*d*) Miscellaneous quinazolines.

3975	2-Chloro-4-β-diethylaminoethylamino-	200	—
		120	—
		80	—
3690	2 : 4-Bis-(γ-diethylaminopropylamino)-	200	++

[1] Free base tested. [2] Trihydriodide. [3] Dihydrochloride.

TABLE II.

2-Chloro-4-aminoalkylaminoquinazolines (V).

R.	M.p.	Formula.	Analysis. Found, %.	Required, %.
$NH\cdot[CH_2]_2\cdot NMe_2$	96—98°	$C_{12}H_{15}N_4Cl$	Cl, 13·8	Cl, 14·2
$NH\cdot[CH_2]_3\cdot NMe_2$	74	$C_{13}H_{17}N_4Cl,2H_2O$	C, 51·8; H, 6·8; N, 18·7; Cl, 11·7	C, 51·8; H, 7·0; N, 18·6; Cl, 11·8
$NH\cdot[CH_2]_2\cdot NEt_2$	85 b. p. 185°/ 0·04 mm.	$C_{14}H_{19}N_4Cl$	C, 60·1; H, 6·8; Cl, 12·4	C, 60·3; H, 6·8; Cl, 12·75
	80—81	$C_{14}H_{19}N_4Cl,H_2O$	C, 56·8; H, 6·8; N, 18·9; Cl, 12·1	C, 56·7; H, 7·1; N, 18·9; Cl, 12·0
	202—203	$C_{14}H_{19}N_4Cl,HCl$ *	C, 53·6; H, 6·6; N, 17·9; Cl′, 10·9	C, 53·3; H, 6·35; N, 17·8; Cl′, 11·3
$NH\cdot[CH_2]_3\cdot NEt_2$	66—68	$C_{15}H_{21}N_4Cl,2H_2O$	N, 17·0	N, 17·0
$NH\cdot[CH_2]_4\cdot NEt_2$	71	$C_{16}H_{23}N_4Cl,H_2O$	N, 17·1; Cl, 11·3	N, 17·3; Cl, 10·9
$NH\cdot CHMe\cdot[CH_2]_3\cdot NEt_2$	oil, b. p. 200—203°/ 0·08 mm.	$C_{17}H_{25}N_4Cl$	N, 17·8	N, 17·5
$NMe\cdot[CH_2]_2\cdot NEt_2$	indefinite	$C_{15}H_{21}N_4Cl,3H_2O$	N, 16·5	N, 16·2
$NH\cdot[CH_2]_3\cdot N<[CH_2]_4>CH_2$	141	$C_{16}H_{21}N_4Cl,H_2O$	N, 17·3	N, 17·35
$NH\cdot[CH_2]_2\cdot NHAc$	206—207	$C_{12}H_{13}ON_4Cl$	Cl, 13·7	Cl, 13·4
$NH\cdot[CH_2]_2\cdot OH$	186	$C_{10}H_{10}ON_3Cl$	Cl, 15·6	Cl, 15·9

* Crystallised from aqueous hydrochloric acid.

refluxed for 1 hour. After cooling, the product was filtered off and washed with water. The *hydrochloride* was then dissolved in hot 2-ethoxyethanol, and the solution was made alkaline with ammonia and poured into water. The precipitated *base* was filtered off, dried, and crystallised from 2-ethoxyethanol; small colourless needles, m. p. 280—282° (Found: C, 61·9; H, 3·7; N, 15·4; Cl, 13·1. $C_{14}H_{10}ON_3Cl$ requires C, 61·9; H, 3·7; N, 15·5; Cl, 13·1%). The hydrochloride, which was also obtained by precipitation from a solution of the base in sodium hydroxide by the addition of hydrochloric acid, crystallised from 2-ethoxyethanol containing a little hydrochloric acid as colourless laminæ, m. p. 277° (Found: Cl, 23·2. $C_{14}H_{10}ON_3Cl,HCl$ requires Cl, 23·05%).

2-p-*Anisidino-4-hydroxyquinazoline* (VII; R = OMe, R′ = OH), prepared by the method given above for the corresponding *p*-chloroanilino-compound, crystallised from 2-ethoxyethanol in colourless thin prisms, m. p. 262—263° (Found: N, 16·1. $C_{15}H_{13}O_2N_3$ requires N, 15·7%).

4-*Chloro*-2-p-*chloroanilinoquinazoline* (VII; R = R′ = Cl).—2-*p*-Chloroanilino-4-hydroxyquinazoline (7·5 g.), phosphoryl chloride (30 c.c.), and dimethylaniline (5 c.c.) were refluxed for ¾ hour and the mixture poured on ice (300 g.) and sodium hydroxide solution (100 c.c. of 32%). The precipitated solid was filtered off, washed alkali-free with cold water, and dried in a vacuum. The crude material was extracted with boiling chloroform, and the extract evaporated to small bulk and allowed to crystallise. Collected and recrystallised from chloroform the *product* formed colourless needles, m. p. 177—178° (Found: Cl, 25·0. $C_{14}H_8N_3Cl_3$ requires Cl, 24·5%).

4-Chloro-2-*p*-anisidinoquinazoline (VII; R = OMe, R′ = Cl), prepared in a similar manner from 2-*p*-anisidino-4-hydroxyquinazoline, was not isolated from the crude material but treated directly with γ-diethylaminopropylamine.

2 : 4-*Bis*-p-*chloroanilinoquinazoline*.—2 : 4-Dichloroquinazoline (3·6 g.) and *p*-chloroaniline (18 g.) were heated at 140° for 3 hours. The cooled melt was thoroughly extracted with dilute hydrochloric acid to remove *p*-chloroaniline, the insoluble hydrochloride dissolved in alcoholic sodium hydroxide, and the solution diluted with water. The precipitated product was collected, washed with water, and crystallised from alcohol, giving the *quinazoline* as a practically colourless microcrystalline powder, m. p. 185° (Found: Cl, 18·9. $C_{20}H_{14}N_4Cl_2$ requires Cl, 18·65%). The same compound was obtained by interaction of 4-chloro-2-*p*-chloroanilinoquinazoline with *p*-chloroaniline under similar conditions.

2-p-*Chloroanilino-4-ethoxyquinazoline* (VII; R = Cl, R′ = OEt).—2-Chloro-4-ethoxyquinazoline (20·85 g.) and *p*-chloroaniline (12·8 g.) in alcohol (200 c.c.) were refluxed for 1 hour. The clear solution was cooled and poured into sodium carbonate solution (800 c.c. of 2·5%). The *quinazoline* was precipitated as an oil which solidified on standing. It was filtered off, washed with water, and crystallised from alcohol (yield, 23·5 g.); glistening white laminæ, m. p. 122° (Found: Cl, 12·1. $C_{16}H_{14}ON_3Cl$ requires Cl, 11·85%). The hydrochloride separated as faintly yellow prisms, m. p. 175°, on adding hydrochloric acid to a solution of the base in alcohol.

Hydrolysis of 2-p-*Chloroanilino-4-ethoxyquinazoline*.—2-*p*-Chloroanilino-4-ethoxyquinazoline (1 g.), hydrochloric acid (5 c.c.), and water (10 c.c.) were refluxed for 5 hours. The product which separated on cooling was filtered off, dissolved in 0·5N-sodium hydroxide, the solution filtered, and hydrochloric acid added. The resulting hydrochloride was dissolved in 2-ethoxyethanol, and the solution was made alkaline with ammonia and diluted with water. The precipitated product was filtered off, dried, and crystallised from 2-ethoxyethanol, giving 2-*p*-chloroanilino-4-hydroxyquinazoline, m. p. and mixed m. p. 280—282°.

2-p-*Chloroanilino-4-phenoxyquinazoline* (VII; R = Cl, R′ = OPh).—2-Chloro-4-phenoxyquinazoline (6·4 g.), *p*-chloroaniline (3·2 g.), and alcohol (30 c.c.) were boiled under reflux for 1 hour. The product began to separate as a mass of crystals after ½ hour. The mixture was poured into sodium carbonate solution (200 c.c. of 2·5%), and the precipitated product filtered off and washed with water. The *quinazoline* was separated from a high-melting product by extraction with glacial acetic acid and reprecipitation with water. It then crystallised from alcohol as long colourless felted needles (yield, 2·5 g.), m. p. 186—187° (Found: Cl, 10·0. $C_{20}H_{14}ON_3Cl$ requires Cl, 10·2%).

2-*Chloro*-4-*methylthioquinazoline* (VI; R = SMe).—Methylthiol was passed into a cooled solution of sodium (2·5 g.) in alcohol (40 c.c.) until it was present in excess. The solution was diluted with alcohol (40 c.c.) and shaken with finely powdered 2 : 4-dichloroquinazoline (19·9 g.) with ice–water cooling until no further heat evolution occurred. After 16 hours at laboratory temperature the mixture was diluted with water (800 c.c.), allowed to stand for 1 hour, and the solid filtered off and dried. The *quinazoline* separated from light petroleum (b. p. 60—80°) as long colourless prisms, m. p. 122° (Found: N, 13·1. $C_9H_7N_2ClS$ requires N, 13·3%).

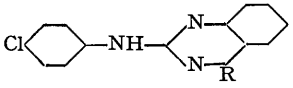
2-p-*Chloroanilino-4-methylthioquinazoline* (VII; R = Cl, R′ = SMe).—A solution of 2-chloro-4-methylthioquinazoline (5·26 g.) and *p*-chloroaniline (3·2 g.) in alcohol (50 c.c.) was refluxed for ½ hour. After a short time a felted mass of needles separated. The mixture was poured into sodium carbonate solution (200 c.c. of 2·5%), allowed to stand for some hours, and the product then filtered off. The *quinazoline* crystallised from alcohol as colourless needles, m. p. 176° (Found: S, 10·7. $C_{15}H_{12}N_3ClS$ requires S, 10·6%).

Preparation of 2-*Arylamino*-4-*aminoalkylaminoquinazolines*.—The methods used are illustrated by the following typical preparations. Details of the substances prepared are given in Tables III, IV, and V.

Method (*a*). 4-Chloro-2-*p*-chloroanilinoquinazoline (1·2 g.), β-diethylaminoethylamine (1 c.c.), and glacial acetic acid (5 c.c.) were heated at 95—100° for 1·5 hours; the mixture was then diluted with water (20 c.c.), boiled, and filtered from insoluble material. The filtrate was treated with hydrochloric acid (5 c.c.); 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride crystallised out on standing as colourless needles, m. p. 252—254°.

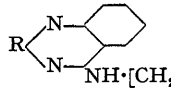
Method (*b*). 2-Chloro-4-β-diethylaminoethylaminoquinazoline (11·15 g., 0·04 g.-mol.), *p*-chloroaniline (10·5 g., 0·08 g.-mol.), and acetic acid (20 c.c.) were refluxed for 2 hours, and the solution cooled and poured into water (200 c.c.). Acet-*p*-chloroanilide (6 g.) separated and was filtered off. The filtrate was made alkaline with sodium hydroxide and steam distilled to remove *p*-chloroaniline. The gummy non-volatile base was separated, washed with water by decantation, and dissolved in 5% acetic acid (200 c.c.). The solution was treated with decolorising carbon and filtered, and hydrochloric acid (100

TABLE III.

2-p-*Chloroanilino*-4-*aminoalkylaminoquinazolines*, 

R.	Formula.	Method of preparation.	M. p.	Analysis. Found, %.	Analysis. Required, %.
NH·[CH_2]$_2$·NH_2	$C_{16}H_{16}N_5Cl$	*d*	142°	—	—
	$C_{16}H_{16}N_5Cl,2HCl,1{\cdot}5H_2O$	—	314—316	C, 46·5; H, 5·8; N, 17·4	C, 46·4; H, 5·1; N, 16·95
NH·[CH_2]$_6$·NH_2	$C_{20}H_{24}N_5Cl,2HCl,H_2O$	*d*	261—263	C, 51·7; H, 5·9; N, 15·0; Cl, 23·4; Cl′, 15·4	C, 52·0; H, 6·1; N, 15·2; Cl, 23·1; Cl′, 15·45
NH·[CH_2]$_2$·NMe_2	$C_{18}H_{20}N_5Cl,2HCl,2{\cdot}5H_2O$	*b*, *c*	267—268	C, 47·1; H, 5·45; N, 15·5	C, 47·05; H, 5·9; N, 15·25
NH·[CH_2]$_3$·NMe_2	$C_{19}H_{22}N_5Cl,2HCl,1{\cdot}5H_2O$	*b*	256—258	C, 50·2; H, 6·0; N, 15·6	C, 50·0; H, 5·9; N, 15·4
NH·[CH_2]$_4$·NMe_2	$C_{20}H_{24}N_5Cl,2HCl,H_2O$	*d*	261	C, 52·3; H, 5·5; N, 15·3; Cl′, 15·8	C, 52·05; H, 6·05; N, 15·2; Cl′, 15·4
NH·[CH_2]$_5$·NMe_2	$C_{21}H_{26}N_5Cl,2HCl,1{\cdot}5H_2O$	*d*	278	C, 52·3; H, 6·6; N, 14·7; Cl′, 14·4	C, 52·2; H, 6·4; N, 14·5; Cl′, 14·7
NH·[CH_2]$_6$·NMe_2	$C_{22}H_{28}N_5Cl,2HCl,1{\cdot}5H_2O$	*d*	156—158 (solidifies and remelts at 236°)	C, 53·0; H, 6·2; Cl′, 14·2	C, 53·0; H, 6·6; Cl′, 14·3
NH·[CH_2]$_2$·NEt_2	$C_{20}H_{24}N_5Cl$	*a*, *b*, *c*, *d*	111—112	C, 65·0; H, 6·4; N, 19·0	C, 65·0; H, 6·5; N, 18·95
	$C_{20}H_{24}N_5Cl,2HCl,2H_2O$	—	253—254	C, 50·5; H, 6·3; N, 14·3	C, 50·2; H, 6·3; N, 14·6
(Mono-acetyl derivative)	$C_{22}H_{26}ON_5Cl,2HCl$	—	248—249	Cl, 21·5; Cl′, 14·5	Cl, 21·9; Cl,′ 14·6
NH·[CH_2]$_3$·NEt_2	$C_{21}H_{26}N_5Cl,0{\cdot}5H_2O$	*a*	126—127	C, 64·2, 64·2; H, 6·8, 6·8; N, 17·9; Cl, 9·1	C, 64·2; H, 6·9; N, 17·85; Cl, 9·0
	$C_{21}H_{26}N_5Cl,2HCl,2H_2O$	—	274	Cl′, 14·2; Cl, 22·1	Cl′, 14·4; Cl, 21·6
NH·[CH_2]$_4$·NEt_2	$C_{22}H_{28}N_5Cl,2HCl,H_2O$	*b*	260—262	C, 53·9; H, 6·6; N, 14·0	C, 54·1; H, 6·55; N, 14·3
NH·CHMe·[CH_2]$_3$·NEt_2	$C_{23}H_{30}N_5Cl,2HCl,2H_2O$	*d*	122 (solidifies and remelts at 205°)	C, 52·8; H, 7·0; N, 13·2; loss on drying, 7·0	C, 52·9; H, 6·9; N, 13·45; 2H_2O, 6·9
NH·[CH_2]$_3$·NMePr$^\beta$	$C_{21}H_{26}N_5Cl,2HCl,2H_2O$	*d*	268—269	C, 51·2; H, 6·3; N, 14·2; Cl′, 14·8	C, 51·2; H, 6·5; N, 14·2; Cl′, 14·4
NH·[CH_2]$_3$·NHBu$^\alpha$	$C_{21}H_{26}N_5Cl,2HCl,H_2O$	*b*, *d*	254—256	C, 53·5; H, 6·8; N, 15·1	C, 53·2; H, 6·3; N, 14·75
NH·[CH_2]$_3$·NBu^α_2	$C_{25}H_{34}N_5Cl,2HCl,0{\cdot}5H_2O$	*d*	193—194	C, 57·0; H, 7·4; N, 13·7; Cl′, 12·9	C 57·5; H, 6·7; N, 13·45; Cl′, 13·6
NH·[CH_2]$_4$·NBu^α_2	$C_{26}H_{36}N_5Cl,2HCl,2H_2O$	*d*	181 (sinters at 151—152°)	C, 55·6; H, 6·9; N, 13·3; Cl′, 12·5	C, 55·45; H, 7·45; N, 12·45; Cl′, 12·65
NH·[CH_2]$_2$·N<[CH_2]$_3$>CH_2	$C_{20}H_{22}N_5Cl,2HCl,2{\cdot}5H_2O$	*d*	283—285	C, 49·1; H, 5·9; N, 14·5; Cl′, 15·3	C, 49·4; H, 6·0; N, 14·4; Cl′, 14·6
NH·[CH_2]$_2$·N<[CH_2]$_4$>CH_2	$C_{21}H_{24}N_5Cl,2HCl,0{\cdot}5H_2O$	*d*	276—278	C, 54·2; H, 5·6; N, 14·7; Cl′, 15·0	C, 54·3; H, 5·8; N, 15·1; Cl′, 15·35
NH·[CH_2]$_3$·N<[CH_2]$_4$>CH_2	$C_{22}H_{26}N_5Cl,2HCl,0{\cdot}5H_2O$	*b*, *c*	285—286	C, 54·8; H, 6·4; N, 14·9	C, 55·3; H, 6·1; N, 14·7
NH·CHMe·CH_2·N<[CH_2]$_4$>CH_2	$C_{22}H_{26}N_5Cl,2HCl,3H_2O$	*d*	274—275	C, 50·4; H, 6·3; N, 13·3; Cl′, 14·8	C, 50·45; H, 6·5; N, 13·4; Cl′, 13·6
NH·CH_2·CHMe·N<[CH_2]$_4$>CH_2	$C_{22}H_{26}N_5Cl,2HCl,H_2O$	*d*	283—286	C, 54·4; H, 5·8; N, 14·7; Cl′, 14·7	C, 54·3; H, 6·15; N, 14·4; Cl′, 14·6
NH·[CH_2]$_3$·NMe·[CH_2]$_2$·NEt_2	$C_{24}H_{33}N_6Cl,3HI,2H_2O$	*d*	229	C, 32·9; H, 4·6; N, 9·8; I, 44·2	C, 33·5; H, 4·65; N, 9·8; I, 44·3
NMe·[CH_2]$_2$·NEt_2	$C_{21}H_{26}N_5Cl,2H_2O$	*b*	76	C, 60·1; H, 7·1; N, 16·7	C, 60·0; H, 7·15; N, 16·7
NMe·[CH_2]$_3$·NHMe	$C_{19}H_{22}N_5Cl,2HCl,2{\cdot}5H_2O$	*d*	137—138	C, 47·9; H, 5·9; N, 14·8; Cl′, 15·0	C, 48·2; H, 6·1; N, 14·8; Cl′, 15.0
NH·[CH_2]$_2$·NHAc	$C_{18}H_{18}ON_5Cl$	*b*	183—184	C, 60·3; H, 5·0; N, 19·7	C, 60·7; H, 5·05; N, 19·7
NH·[CH_2]$_2$·OH	$C_{16}H_{15}ON_4Cl$	*b*, *d*	174	C, 61·0; H, 5·0; N, 17·6	C, 61·0; H, 4·8; N, 17·8
	$C_{16}H_{15}ON_4Cl,HCl,H_2O$	—	286—287	Cl, 19·0	Cl, 19·25

TABLE IV.

2-Arylamino-4-β-diethylaminoethylaminoquinazolines, 

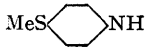
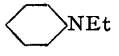
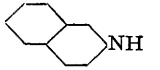
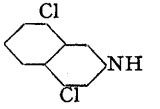
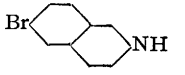
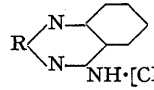
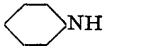
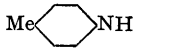
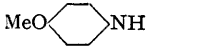
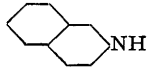
R.	Formula.	Method.	M. p.	Analysis. Found, %.	Required, %.
	$C_{21}H_{27}N_5S,2HCl,3H_2O$	*b*	130—131°	C, 49·3; H, 6·3; N, 13·8	C, 49·55; H, 6·9; N, 13·8
	$C_{20}H_{24}O_2N_6,2HCl,4H_2O$	*c*	286—287	C, 45·9; H, 4·8; N, 15·7; Cl′, 13·2	C, 45·7; H, 6·5; N, 16·0; Cl′, 13·5
	$C_{22}H_{29}N_5$	*b*	110	C, 72·7; H, 7·5; N, 19·3	C, 72·7; H, 8·0; N, 19·3
	$C_{24}H_{27}N_5$	*b*	126	C, 74·6; H, 6·8; N, 18·1	C, 74·75; H, 7·0; N, 18·2
	$C_{24}H_{25}N_5Cl_2,2HCl,H_2O$	*b*	284	C, 52·3; H, 5·3; N, 13·0	C, 52·8; H, 5·3; N, 12·85
	$C_{24}H_{26}N_5Br,2HCl,2H_2O$	*b*	284—285	C, 50·4; H, 5·8; N, 12·9	C, 50·25; H, 5·6; N, 12·25

TABLE V.

2-Arylamino-4-γ-diethylaminopropylaminoquinazolines, 

R.	Formula.	Method.	M. p.	Analysis. Found, %.	Required, %.
	$C_{21}H_{27}N_5$	*b*	112—114°	C, 72·0; H, 7·4; N, 19·9	C, 72·2; H, 7·7; N, 20·1
	$C_{22}H_{29}N_5$	*b*	94	C, 72·9; H, 7·8; N, 18·8	C, 72·7; H, 8·0; N, 19·3
	$C_{22}H_{29}ON_5$	*a*, *b*	114—115	C, 69·3; H, 7·4; N, 18·5	C, 69·7; H, 7·65; N, 18·5
	$C_{25}H_{29}N_5$		141	C, 75·2; H, 7·3; N, 17·2	C, 75·2; H, 7·25; N, 17·55

c.c.) added to the filtrate. 2-*p*-Chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride crystallised out. It was filtered off and recrystallised from water (yield, 11·5 g.).

Methods (*a*) and (*b*) were varied by carrying out the reaction at 130—140° for 3 hours in the absence of acetic acid.

Method (*c*). 2-Chloro-4-β-diethylaminoethylaminoquinazoline (11·15 g., 0·04 g.-mol.), *p*-chloroaniline hydrochloride (6·6 g., 0·04 g.-mol.), water (40 c.c.), and 10N-hydrochloric acid (0·2 c.c.) were refluxed for 1 hour. On cooling, 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride separated and was collected and recrystallised from water (yield, 10 g.).

Method (*d*). 2-*p*-Chloroanilino-4-ethoxyquinazoline (2·99 g., 0·01 g.-mol.) and β-diethylaminoethylamine (2·32 g., 0·02 g.-mol.) were heated under reflux at 140—150° for 2 hours. The cooled mixture was dissolved in acetic acid (10 c.c.), diluted with water (100 c.c.), and the solution boiled and filtered from a trace of insoluble matter. The filtrate was treated with hydrochloric acid (50 c.c.). On cooling, 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride separated; it was filtered off and recrystallised from water (yield, 4 g.). In some cases, *e.g.*, with δ-diethylamino-α-methylbutylamine and β-piperidino*iso*propylamine, a higher reaction temperature (180—190°) was found to be necessary.

Condensation of 2-p-*Chloroanilino-4-phenoxyquinazoline and β-Diethylaminoethylamine.*—2-*p*-Chloroanilino-4-phenoxyquinazoline (1 g.) and β-diethylaminoethylamine (1·5 g.) were mixed and heated at 140—150° for 2·5 hours. The cooled mixture was treated with 5% sodium hydroxide (10 c.c.), the oil extracted with ether, and the ether solution washed with sodium hydroxide and then with water. It was then extracted with 5% acetic acid (15 c.c.), and the acetic acid extract separated and treated with hydrochloric acid (5 c.c.). 2-*p*-Chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride separated and was filtered off and dried; m. p. and mixed m. p. 253—254° (see Table III) (yield, 0·9 g.).

Condensation of 2-p-*Chloroanilino-4-methylthioquinazoline and β-Diethylaminoethylamine.*—2-*p*-Chloroanilino-4-methylthioquinazoline (3·75 g.) and a large excess of β-diethylaminoethylamine were boiled under reflux for 6 hours. The cooled mixture was extracted with hot 5% acetic acid, and the solution filtered and treated with hydrochloric acid. On cooling, 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride separated, m. p. and mixed m. p. 253°.

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