356. *Synthetic Antimalarials. Part XXXI.* 2-p-*Chloroanilino*-4-β-*diethylaminoethylaminoquinazolines containing Various Substituents in the Quinazoline Nucleus.*

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

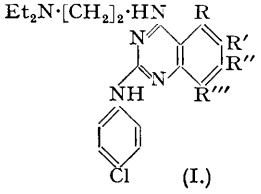
In continuation of the previous study of 2-arylamino-4-aminoalkylaminoquinazolines (Part XIV, *J.*, 1947, 775) as antimalarial agents the preparation of a series of 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazolines carrying various substituents (Cl, NO_2, NH_2, Me, OMe, and 6 : 7-benzo) in one or more positions of the quinazoline nucleus is now described. These new compounds were synthesised from the appropriately substituted 2 : 4-dihydroxyquinazolines through the corresponding 2 : 4-dichloroquinazolines and 2-chloro-4-β-diethylaminoethylaminoquinazolines (cf. Part XIV, *loc. cit.*). The required dihydroxyquinazolines were made by two general methods : (*a*) reaction of urea with a substituted anthranilic acid, and (*b*) reaction of sodium cyanate with a substituted anthranilic acid, ester, amide, or nitrile, and cyclisation of the resulting urea. By the first method the 7-nitro- and 6 : 7-benzo-compounds were prepared, and by the second the 6- and 7-chloro-, 7-nitro-, 7-methyl-, 5-, 6-, 7-, and 8-methoxy-, and 6 : 7-dimethoxy-derivatives.

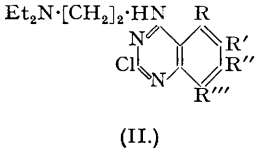
There appeared to be two possible origins of the antimalarial activity of the 2-arylamino-4-aminoalkylaminoquinazolines described in Part XIV (*J.*, 1947, 775). On the one hand there was their relationship to the 2-arylamino-4-aminoalkylamino-6-methylpyrimidines described in Parts I and II (*J.*, 1946, 343, 351) and the corresponding 5-alkyl derivatives (Part VII, *ibid.*, p. 378) on which they were modelled. Alternatively, the previously observed activity of 4-γ-diethylaminopropylaminoquinazoline (see Part XVI, *J.*, 1947, 890) suggested that the 2-arylamino-group might not be concerned with the display of antimalarial activity, although this appeared less likely in view of the greater activity of 2-*p*-chloroanilino-4-γ-diethylaminopropylaminoquinazoline compared with that of the compound less the arylamino-group. In any event it was thought to be of interest to examine the effect of introducing substituents into the *benz*-ring of the quinazoline nucleus, and indeed it was thought that such an investigation might throw some light on the questions at issue, particularly when compared with the work described in Part XVI. The disclosure (B.P. Appln. 27673/38) of the influence of analogous substitution, for example of halogen in the 7-position of the 4-dialkylaminoalkylaminoquinolines, added further point to these researches.

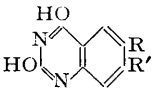
Taking as the parent compound the active 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline (Part XIV, *loc. cit.*), the following substituents were therefore introduced into the quinazoline nucleus : 6- and 7-chloro-, 6- and 7-nitro- (also reduced to the 6- and 7-amino-),

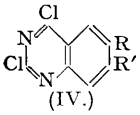
7-methyl, 5-, 6-, 7-, and 8-methoxy-, 6 : 7-dimethoxy- and 6 : 7-benzo-. Reference to the table of activities shows, however, that none of the substituted compounds prepared was more active than the parent substance, and most were less.

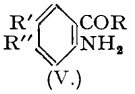
The new compounds of type (I) were prepared by the first method worked out for this type of compound and reported in Part XIV, *viz.*, by interaction of the appropriately substituted 2 : 4-dichloroquinazoline with β-diethylaminoethylamine to give a 2-chloro-4-β-diethylaminoethylaminoquinazoline which was caused to react with *p*-chloroaniline. As in the case of the parent 2 : 4-dichloroquinazoline there was no evidence of the intermediate formation of any of the isomeric 4-chloro-2-β-diethylaminoethylaminoquinazolines.

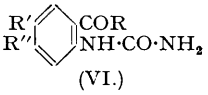

(I.)


(II.)


(III.)


(IV.)


(V.)


(VI.)

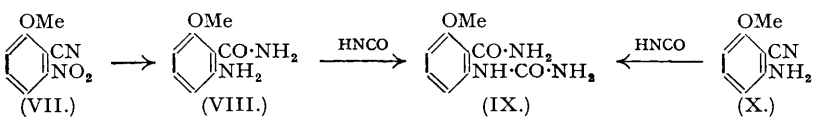
The established method of preparing 2 : 4-dichloroquinazoline involves treating 2 : 4-dihydroxyquinazoline with phosphorus pentachloride and phosphoryl chloride, and this procedure has been used for many of its derivatives described in this paper, although the use of phosphorus pentachloride was sometimes avoided by using phosphoryl chloride and dimethylaniline : this method of replacing hydroxyl groups by chlorine, found so convenient and widely applicable for pyrimidine compounds by Baddiley and Topham (*J.*, 1944, 679), promises to be equally valuable in the quinazoline series.

The various substituted 2 : 4-dihydroxyquinazolines were prepared as follows.

6-*Chloro*-2 : 4-*dihydroxyquinazoline* (III; R = Cl, R′ = H) was obtained by the action of sodium cyanate on methyl 5-chloroanthranilate (V; R = OMe, R′ = Cl, R″ = H) in acetic acid, followed by cyclisation of the resulting urea.

4-Chloroanthranilic acid (V; R = OH, R′ = H, R″ = Cl), prepared by a modification of Cohn's method (*Monatsh.*, 1901, **22**, 485), was treated with sodium cyanate to give (VI; R = OH, R′ = H, R″ = Cl) which, cyclised with alkali, afforded 7-chloro-2 : 4-dihydroxyquinazoline (III; R = H, R′ = Cl). 4-Nitroanthranilic acid, similarly prepared from 4-nitroacet-*o*-toluidide, furnished 7-*nitro*-2 : 4-*dihydroxyquinazoline* (III; R = H, R′ = NO_2) (*a*) by reaction with urea in boiling aqueous solution, and (*b*) by reaction with sodium cyanate to give 4-nitro-2-ureidobenzoic acid (VI; R = OH, R′ = H, R″ = NO_2) followed by cyclisation of this with boiling hydrochloric acid. 6-Nitro-2 : 4-dihydroxyquinazoline (III; R = NO_2, R′ = H) was prepared by nitration of 2 : 4-dihydroxyquinazoline (Bogert and Scatchard, *J. Amer. Chem. Soc.*, 1919, **41**, 2058).

2 : 4-Dihydroxy-7-methylquinazoline (III; R = H, R′ = Me), prepared previously by von Niementowski by heating 4-methylanthranilic acid or its amide with urea (*J. pr. Chem.*, 1889, **40**, 21) and by ring closure of ethyl 2-carboxyamido-5-methylphenylurethane (*ibid.*, 1895, **51**, 511), was obtained for the present work by the action of sodium cyanate on 4-methylanthranilic acid (V; R = OH, R′ = H, R″ = Me) or the corresponding amide followed by cyclisation of the intermediate 3-ureido-*p*-toluic acid (VI; R = OH, R′ = H, R″ = Me) and 3-ureido-*p*-toluamide (VI; R = NH_2, R′ = H, R″ = Me) respectively. It was also found to be the product of the action of sodium hydroxide or hydrochloric acid on 3-*ureido*-p-*tolunitrile*.


(VII.) (VIII.) (IX.) (X.)

Catalytic reduction of 2-nitro-6-methoxybenzonitrile (Lobry de Bruyn, *Rec. Trav. chim.*, 1883, **2**, 210) in methanol using Raney nickel gave mainly 2-amino-6-methoxybenzamide which

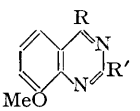
with sodium cyanate in acetic acid gave 2-*ureido*-6-*methoxybenzamide*. The same product was formed from 2-amino-6-methoxybenzonitrile and sodium cyanate. This is surprising in view of the resistance of the nitrile group in this compound to hydrolysis by the usual methods (Friedländer, Bruckner, and Deutsch, *Annalen*, 1912, **388**, 41), and the fact that all *o*-aminobenzonitriles do not hydrolyse during reaction with cyanate. 3-Amino-*p*-tolunitrile, for example, gives 3-ureido-*p*-tolunitrile, and not the amide. Ring closure of (IX) with boiling 30% sodium hydroxide gave the required 2 : 4-*dihydroxy*-5-*methoxyquinazoline* (XI; R = R′ = OH).

2 : 4-Dihydroxy-6-methoxyquinazoline (III; R = OMe, R′ = H) was prepared from 5-methoxyanthranilic acid (V; R = OH, R′ = OMe, R″ = H) which was converted by reaction with sodium cyanate into 2-ureido-5-methoxybenzoic acid (VI; R = OH, R′ = OMe, R″ = H), followed by ring-closure with hydrochloric acid.

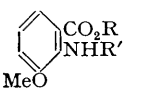
Whereas Mann and his co-workers (Part XVI, *loc. cit.*) prepared 2 : 4-dihydroxy-7-methoxyquinazoline by reaction of 4-methoxyanthranilic acid (V; R = OH, R′ = H, R″ = OMe) with cyanate and ring closure of the resulting 2-ureido-4-methoxybenzoic acid (VI; R = OH, R′ = H, R″ = OMe) with alkali, we have found it more convenient to proceed *via* the corresponding amide (VI; R = NH_2, R′ = H, R″ = OMe) which was cyclised with hydrochloric acid. The 2-ureido-4-methoxybenzamide was obtained from 4-methoxyanthranilamide (V; R = NH_2, R′ = H, R″ = OMe) which resulted, together with a smaller proportion of 2-amino-4-methoxybenzonitrile, from reduction of 2-nitro-4-methoxybenzonitrile with iron in alcohol.

2 : 4-Dihydroxy-8-methoxyquinazoline (XII; R = R′ = OH) was prepared by Froelicher and Cohen (*J.*, 1921, **119**, 1431) from 3-methoxyanthranilic acid (XIII; R = R′ = H) by

(XI.)



(XII.)



(XIII.)

reaction with sodium cyanate to give 2-ureido-3-methoxybenzoic acid (XIII; R = H, R′ = CO·NH_2) which was then ring closed by boiling with hydrochloric acid. We obtained better results by a variant of the process, starting with methyl 3-methoxyanthranilate (XIII; R = Me, R′ = H), converting it into methyl 2-ureido-3-methoxybenzoate (XIII; R = Me, R′ = CO·NH_2), and effecting the final ring closure merely by boiling with water.

Catalytic reduction of 6-nitroveratric acid in methanol solution over Raney nickel gave 6-aminoveratric acid which, without isolation, was caused to react with sodium cyanate to give 2-*ureido*-4 : 5-*dimethoxybenzoic acid* (VI; R = H, R′ = R″ = OMe). Treatment with sodium hydroxide gave 2 : 4-*dihydroxy*-6 : 7-*dimethoxyquinazoline* (III; R = R′ = OMe) accompanied by some hydrolysis of the ureido-group to 6-aminoveratric acid. This is the only instance, in this work, where such a hydrolysis was observed.

Antimalarial Activities.

2-p-*Chloroanilino*-4-*β*-*diethylaminoethylaminoquinazolines*.

Ref. no.	Substituent.	Dose (mg./kg.).	Activity.	Ref. no.	Substituent.	Dose (mg./kg.).	Activity.
3756	—	40	+ to ++	3931	7-Methyl-	160	+ to ++
		20	−			80	+
4258	6-Chloro-	80	++			40	−
		40	+	5124	5-Methoxy-	80	±
3918	7-Chloro-	200	+ to ++	4624	6-Methoxy-	80	+ to ++
		40	−			40	+
4537	6-Nitro-	80	++			20	−
		40	+ to ++	3963	7-Methoxy-	120	+ to ++
4259	7-Nitro-	120	++			80	±
		80	±	4609	8-Methoxy-	160	+
		40	−			80	−
4544	6-Amino-	160	+ to ++	4185	6 : 7-Dimethoxy-	80	+ to ++
		80	+			40	±
4213	7-Amino-	160	+ to ++	3964	6 : 7-Benzo-	400	++
		80	+			200	+ to ++
						120	+

For the preparation of 2 : 4-*dichloro*-6 : 7-*benzoquinazoline* (IV; RR′ = benzo), which is mentioned without details of preparation or description in B.P. 288,159, 2 : 4-*dihydroxy*-6 : 7-

benzoquinazoline (III; RR′ = benzo) was required and resulted from the reaction of 2-naphthylamine-3-carboxylic acid with urea in boiling phenol solution.

The variously substituted 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazolines described in this paper have been tested for antimalarial activity by Dr. D. G. Davey of these laboratories, using *P. gallinaceum* in chicks. His results are summarised in the following table where the activities are expressed at various doses as in Part I (*loc. cit.*). The results obtained with the parent 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride (**3756**) are included for comparison. The actual preparation (base, dihydrochloride, or trihydrochloride) used for biological test is indicated in the experimental section where the reference numbers are given in the appropriate place.

Experimental.

6-*Chloro*-2 : 4-*dihydroxyquinazoline* (III; R = Cl, R′ = H).—Methyl 5-chloroanthranilate (20 g.) (prepared by the method of Freundler, *Bull. Soc. chim.*, 1911, **9**, 606; cf. Part XVI, *loc. cit.*) in acetic acid (100 c.c.) was treated with a suspension of sodium cyanate (11 g.) in water (50 c.c.) while stirring, and the mixture then kept overnight at room temperature. The crystalline product was filtered off, washed with water, and dissolved in hot water (6 l.) and 10N-sodium hydroxide (30 c.c.). The filtered solution was then acidified with acetic acid and the 6-*chloro*-2 : 4-*dihydroxyquinazoline* filtered off, washed, and dried (yield, 14·5 g.); m. p. 345—348° (Found: Cl, 17·7. $C_8H_5O_2N_2Cl$ requires Cl, 18·1%).

2 : 4 : 6-*Trichloroquinazoline* (IV; R = Cl, R′ = H).—The preceding compound (14·5 g.), phosphorus pentachloride (30·65 g.), and phosphoryl chloride (15 c.c.) were heated under reflux until a clear solution was formed (5 hours). The phosphoryl chloride was then removed under reduced pressure, and the residue distilled from an oil-bath at 230—240°/15 mm., using a distillation flask with a wide side arm and short distillation path. The distillate solidified to an almost colourless solid which crystallised from light petroleum (b. p. 80—100°) as practically colourless needles of the *trichloro*-compound, m. p. 131° (Found: N, 12·0. $C_8H_3N_2Cl_3$ requires N, 12·0%).

4-*Chloroanthranilic acid* (V; R = OH, R′ = H, R″ = Cl).—4-Chloroacet-*o*-toluidide (183·5 g.), suspended in water (3 l.) containing anhydrous magnesium sulphate (360 g.), was stirred at 85—95° whilst potassium permanganate (360 g., 2·3 mols.) was added during 3 hours. Stirring was then continued for 2 hours, excess of sodium carbonate added, and manganese dioxide removed. The hot filtrate was acidified with hydrochloric acid and cooled, and the 4-chloro-2-acetamidobenzoic acid was collected and purified by dissolution in sodium carbonate and reprecipitation with acid (yield, 186 g.); m. p. 212°. This acetyl derivative (107 g.) was hydrolysed to 4-chloroanthranilic acid by warming it with hydrochloric acid (500 c.c.) until frothing moderated and then refluxing for 3 hours after the addition of a further quantity of hydrochloric acid (100 c.c.). The product was collected after cooling, washed well with water, and dried (yield, 71 g.); m. p. 224°.

7-*Chloro*-2 : 4-*dihydroxyquinazoline* (III; R = H, R′ = Cl).—In B.P. 315,451 it is mentioned that 7-chloro-2 : 4-dihydroxyquinazoline is prepared by heating 4-chloroanthranilic acid with urea or potassium cyanate, but the compound is not there characterised (cf. B.P. 288,159). 4-Chloroanthranilic acid (17·15 g.) was dissolved in water (180 c.c.) and sodium hydroxide (9·25 c.c. of 35%) at 40°, and sodium cyanate (7·2 g.) added with stirring. When the cyanate had dissolved, acetic acid (6 c.c.) was added, and stirring continued at room temperature for 6 hours. After being left overnight, the solution was filtered and the filtrate acidified with hydrochloric acid to give presumably 4-chloro-2-ureidobenzoic acid, m. p. 190° (yield, 8·7 g.). This compound (6·7 g.) was added to sodium hydroxide (10 c.c. of 30%). The mixture became very thick. It was extracted with boiling water (300 c.c.), and the sparingly soluble sodium salt (yield, 2·15 g.) filtered off. This gave 7-chloro-2 : 4-dihydroxyquinazoline, m. p. 347—348° (yield, 1·7 g.), on boiling with dilute hydrochloric acid. A further quantity of the same substance (2·83 g.), m. p. 346°, was obtained by acidifying the mother liquors from the isolation of the sodium salt with acetic acid.

2 : 4 : 7-*Trichloroquinazoline* (IV; R = H, R′ = Cl).—This was prepared by the method described above for the corresponding 2 : 4 : 6-trichloro-compound (method of B.PP. 288,159, 315,451; compound not characterised) and also by the following method. 7-Chloro-2 : 4-dihydroxyquinazoline (40 g.), phosphoryl chloride (150 c.c.), and dimethylaniline (15 c.c.) were refluxed for 5 hours. The cooled mixture was poured on ice, and the product extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue crystallised from light petroleum (b. p. 80—100°) to give 2 : 4 : 7-*trichloroquinazoline* as colourless needles, m. p. 127° (Found: N, 11·6. $C_8H_3N_2Cl_3$ requires N, 12·0%).

2 : 4-*Dichloro*-6-*nitroquinazoline* (IV; R = NO_2, R′ = H), prepared from 6-nitro-2 : 4-dihydroxyquinazoline (Bogert and Scatchard, *loc. cit.*) by the action of phosphoryl chloride and dimethylaniline as described for the preceding compound, crystallised from light petroleum (b. p. 80—100°) as pale yellow needles, m. p. 127—129° (Found: N, 17·3. $C_8H_3O_2N_3Cl_2$ requires N, 17·2%). This compound is mentioned but not characterised in B.PP. 287,179, 288,159. It is there stated to have been prepared by the action of phosphorus pentachloride–phosphoryl chloride on 6-nitro-2 : 4-dihydroxyquinazoline, and we have also used this method satisfactorily (procedure as for 2 : 4 : 6-trichloroquinazoline). The compound has b. p. 220—230°/16—20 mm.

4-*Nitroanthranilic acid* (V; R = OH, R′ = H, R″ = NO_2).—4-Nitroacet-*o*-toluidide (194 g.), water (4 l.), and magnesium sulphate (heptahydrate, 130 g.) were heated to 100° with stirring. Potassium permanganate (330 g.) was then added gradually during 2—3 hours with stirring (additions made as decolorisation occurred), the volume being kept constant by the addition of hot water. When all the permanganate had been added and decolorisation was complete, the mixture was filtered hot and the filter cake washed with hot water (700 c.c.). The filtrate and washings were combined and allowed to cool overnight. After filtration from unchanged material, acidification of the filtrate with hydrochloric

acid precipitated 4-nitro-2-acetamidobenzoic acid (yield, 145·5 g.). This was hydrolysed by boiling it with 5N-hydrochloric acid (1200 c.c.) for 1 hour with stirring. The clear solution was poured into water (3600 c.c.), and the precipitated 4-nitroanthranilic acid filtered off, washed, and dried (yield, 97 g.); m. p. 263—264°.

7-*Nitro*-2 : 4-*dihydroxyquinazoline* (III; R = H, R′ = NO_2).—(*a*) 4-Nitroanthranilic acid (18·2 g.), urea (50 g.), and water (50 c.c.) were stirred and boiled under reflux for 24 hours. The orange-coloured solution gradually deposited pale yellow crystals. These were filtered off hot, washed with boiling water, and extracted with boiling alcohol to leave 7-*nitro*-2 : 4-*dihydroxyquinazoline* (yield, 8 g.) as tan-coloured crystals, m. p. 338—339° (Found : N, 21·0. $C_8H_5O_4N_3$ requires N, 20·3%).

(*b*) 4-Nitroanthranilic acid (8·6 g.) was dissolved in hot water (250 c.c.) as the sodium salt, and the solution cooled to <30° and treated with potassium cyanate (10 g.) and 10N-hydrochloric acid (10 c.c.) with vigorous stirring. After 20 hours' stirring the resulting orange-yellow 4-nitro-2-ureidobenzoic acid was filtered off and crystallised from water; m. p. 224—225°. This compound (2·9 g.) when heated on the steam-bath for 2 hours with 10N-hydrochloric acid (10 c.c.) gave 7-nitro-2 : 4-dihydroxyquinazoline (isolated by dilution with water and filtration), m. p. 339°, identical with material made by method (*a*).

2 : 4-*Dichloro*-7-*nitroquinazoline* (IV; R = H, R′ = NO_2), prepared from the above compound by the action of phosphorus pentachloride–phosphoryl chloride and isolated by distillation of the reaction mixture from a bath at 250—270°/10 mm., formed a yellowish solid, m. p. 148—150° (Found : N, 17·4. $C_8H_3O_2N_3Cl_2$ requires N, 17·2%).

3-*Ureido*-p-*tolunitrile*.—3-Amino-*p*-tolunitrile (4·75 g.) (von Niementowski, *loc. cit.*) in acetic acid (20 c.c.) and water (5 c.c.) was treated with powdered sodium cyanate (2·1 g.) suspended in water (10 c.c.), and the mixture stirred for 4 hours and then left overnight. The crystalline product was filtered off, washed well with water, and crystallised from dilute alcohol. The *compound*, which sublimed readily when heated, formed yellowish needles, m. p. 225° (sealed tube) (Found : C, 60·5; H, 5·5; N, 23·3. $C_9H_9ON_3$, $0·25H_2O$ requires C, 60·1; H, 5·3; N, 23·4%).

2 : 4-*Dihydroxy*-7-*methylquinazoline* (III; R = H, R′ = Me).—(*a*) A solution of 4-methylanthranilic acid (15·1 g.) in hot water (20 c.c.) and hydrochloric acid (9 c.c.) was diluted to 200 c.c. with cold water and a suspension of sodium cyanate (8·4 g.) in water (30 c.c.) added. After stirring, the precipitated product, m. p. 187° (decomp.), presumably 3-ureido-*p*-toluic acid (VI; R = OH, R′ = H, R″ = Me), was filtered off, washed with water, and dried (yield, 8·1 g.). This was heated on the steam-bath for 1 hour with hydrochloric acid (15 c.c.) and water (4 c.c.), the mixture cooled and filtered, and the 2 : 4-dihydroxy-7-methylquinazoline collected. After purification *via* its sodium salt it had m. p. 320° (von Niementowski, *loc. cit.*, gives m. p. 317°).

(*b*) 4-Methylanthranilamide (13 g.) in acetic acid (80 c.c.) and water (20 c.c.) was treated with a suspension of sodium cyanate (8·4 g.) in water (40 c.c.) with stirring. In a short time the mixture set to a mass of crystals. After 2 hours these were filtered off, washed with water, and dried. This 3-ureido-*p*-toluamide, m. p. 188° (decomp.) [mixed m. p. with above 3-ureido-*p*-toluic acid, 174° (decomp.)] (yield, 16·6 g.), was not analysed but converted directly into 2 : 4-dihydroxy-7-methylquinazoline, m. p. and mixed m. p. 320°, by heating it on the steam-bath for 1 hour with hydrochloric acid (30 c.c.) and water (8 c.c.).

(*c*) 3-Ureido-*p*-tolunitrile (1·25 g.) and sodium hydroxide solution (20 c.c. of 35%) were refluxed for 20 minutes. The solid which had separated was filtered off when cold, dissolved in hot water, and the solution acidified with acetic acid to give 2 : 4-dihydroxy-7-methylquinazoline as colourless needles, m. p. and mixed m. p. 320° (yield, 0·52 g.).

3-Ureido-*p*-tolunitrile was also converted into (III; R = H, R′ = Me) by refluxing it (1·25 g.) with hydrochloric acid (20 c.c.) for 1 hour.

By treatment with phosphorus pentachloride–phosphoryl chloride, 2 : 4-dihydroxy-7-methylquinazoline was converted into 2 : 4-dichloro-7-methylquinazoline which distilled at 220—250° (bath temp.)/15—20 mm. and had m. p. 113° (cf. B.P. 288,159).

2-*Amino*-6-*methoxybenzamide* (VIII).—2-Nitro-6-methoxybenzonitrile (VII) (4·45 g.) (Lobry de Bruyn, *loc. cit.*) in methanol (100 c.c.) was reduced with hydrogen–Raney nickel at 20° and atmospheric pressure. On evaporation of the filtered, carbon-treated solution, 2-amino-6-methoxybenzamide crystallised in needles (yield, 2·3 g.), m. p. 149—150° undepressed by an authentic sample prepared by hydrolysis of 2-amino-6-methoxybenzonitrile (cf. Friedländer *et al.*, *loc. cit.*).

2-*Ureido*-6-*methoxybenzamide* (IX).—(*a*) 2-Amino-6-methoxybenzonitrile (X) (26·8 g.) (Lobry de Bruyn, *loc. cit.*) in acetic acid (175 c.c.) was stirred for 4 hours with finely powdered sodium cyanate (17·5 g.). After standing overnight the crystalline *product* was collected and washed with water (yield, 24 g.); m. p. 178—180° (decomp.). By crystallisation from water it was obtained as a cream-coloured solid, m. p. 198° (decomp.) (Found : N, 20·1. $C_9H_{11}O_3N_3$ requires N, 20·1%).

(*b*) 2-Amino-6-methoxybenzamide (VIII) (6·2 g.) in acetic acid (40 c.c.) was stirred with sodium cyanate (5 g.) suspended in water (20 c.c.) overnight. Next day the mixture was diluted with water (60 c.c.), and the product filtered off and washed with water (yield, 5·7 g.). It was shown to be identical (m. p. and mixed m. p.) with 2-ureido-6-methoxybenzamide made by method (*a*).

2 : 4-*Dihydroxy*-5-*methoxyquinazoline* (XI; R = R′ = OH).—The preceding compound (2·75 g.) was boiled with sodium hydroxide (10 c.c. of 35%). After 20 minutes the mixture was cooled, and the resulting sodium salt filtered off, dissolved in water (100 c.c.), treated with carbon, and precipitated with acetic acid. The *product* (2·4 g.) crystallised from aqueous alcohol; m. p. 308° (Found : N, 13·9, 13·9. $C_9H_8O_3N_2$, $0·5H_2O$ requires N, 13·9%). Treatment of this compound with phosphoryl chloride and dimethylaniline, in the manner described above for 2 : 4 : 7-trichloroquinazoline, gave 2 : 4-dichloro-5-methoxyquinazoline (XI; R = R′ = Cl) as colourless needles, m. p. 160—162°.

2 : 4-*Dichloro*-6-*methoxyquinazoline* (IV; R = OMe, R′ = H).—2-Nitro-5-methoxybenzoic acid (20 g.) (Part XVI, *loc. cit.*) was reduced catalytically using Raney nickel in methanol, and the crude 5-methoxyanthranilic acid obtained by filtration and evaporation of the methanol was dissolved in 2N-hydrochloric acid (60 c.c.) and stirred overnight with sodium cyanate (8·5 g.). The precipitated

2-ureido-5-methoxybenzoic acid [m. p. 186° (decomp.)] was filtered off, washed with water, and heated on the steam-bath with excess of hydrochloric acid for 1 hour to give 2 : 4-dihydroxy-6-methoxyquinazoline (not analysed), m. p. 316—318° (yield, 5 g.). This compound (7·5 g.) was heated under reflux with phosphorus pentachloride (16·3 g.) and phosphoryl chloride (10 c.c.) for 3 hours, the phosphoryl chloride removed under reduced pressure, and the residue distilled from a bath at 250—300°/15 mm. to give 2 : 4-*dichloro*-6-*methoxyquinazoline* as a yellowish crystalline solid, m. p. 171° (Found: Cl, 31·0. $C_9H_6ON_2Cl_2$ requires Cl, 31·0%).

4-*Methoxyanthranilamide* (V; R = NH_2, R′ = H, R″ = OMe).—Iron pin dust (80 g.), alcohol (400 c.c.), and hydrochloric acid (10 c.c.) were stirred and boiled under reflux for 10 minutes. 2-Nitro-4-methoxybenzonitrile (45 g.) (Cook, Heilbron, Reed, and Strachan, *J.*, 1945, 861) was added during 15 minutes, and the mixture then refluxed with stirring overnight. Sodium carbonate was added to precipitate dissolved iron, and the mixture was filtered hot, the residue being washed with a little boiling alcohol. The filtrate was concentrated to 100 c.c. On cooling, 4-methoxyanthranilamide was deposited (yield, 18·5 g.). It crystallised from alcohol in plates, m. p. 153° (Chapman, Gibson, and Mann, Part XVI, *loc. cit.*, give m. p. 155—155·5°) (Found: N, 16·7. Calc. for $C_8H_{10}O_2N_2$: N, 16·9%). Dilution of the alcoholic mother liquors from the 4-methoxyanthranilamide with water gave 2-amino-4-methoxybenzonitrile (yield, 12·4 g.) which crystallised from aqueous alcohol in colourless needles, m. p. 92° (Cook *et al.*, *loc. cit.*, give m. p. 96°) (Found: N, 19·3. Calc. for $C_8H_8ON_2$: N, 19·0%). The nitrile was converted into the amide by treatment with hydrogen peroxide in aqueous alcoholic sodium hydroxide, but in poor yield.

2-*Ureido*-4-*methoxybenzamide* (VI; R = NH_2, R′ = H, R″ = OMe).—4-Methoxyanthranilamide (18·5 g.) in acetic acid (100 c.c.) was treated with a suspension of sodium cyanate (11 g.) in water (50 c.c.) and stirred well. After 1 hour the 2-*ureido*-4-*methoxybenzamide* was collected, washed, and crystallised from water; colourless rhombic plates (yield, 21·75 g.), m. p. 208° (decomp.) (Found: N, 19·8. $C_9H_{11}O_3N_3$ requires N, 20·1%).

2 : 4-*Dihydroxy*-7-*methoxyquinazoline* (III; R = H, R′ = OMe).—2-Ureido-4-methoxybenzamide (21·5 g.) was heated with 8N-hydrochloric acid (45 c.c.) on the steam-bath for 1 hour. The resulting product was collected and stirred with 35% sodium hydroxide (50 c.c.) to form the sodium salt. This was filtered off and dissolved in hot water (500 c.c.), and the clarified solution precipitated with acetic acid to give 2 : 4-dihydroxy-7-methoxyquinazoline (yield, 11·2 g.) which crystallised from alcohol in colourless prisms, m. p. 300—301° (Found: C, 56·2; H, 4·2; N, 14·9. Calc. for $C_9H_8O_3N_2$: C, 56·2; H, 4·2; N, 14·6%) (Chapman, Gibson, and Mann, *loc. cit.*, give m. p. 299—301°).

2 : 4-*Dichloro*-7-*methoxyquinazoline* (IV; R = H, R′ = OMe).—The above 2 : 4-dihydroxy-7-methoxyquinazoline was converted into 2 : 4-dichloro-7-methoxyquinazoline by treatment with phosphorus pentachloride and phosphoryl chloride as described by Chapman *et al.* (*loc. cit.*). Instead of extracting the product with light petroleum we preferred isolation by distillation from a bath at 260—290°/15 mm. It crystallised from light petroleum (b. p. 100—120°) as practically colourless needles, m. p. 120—121° (lit. 121—121·5°) (Found: N, 12·3; Cl, 30·7. Calc. for $C_9H_6ON_2Cl_2$: N, 12·2; Cl, 31·0%).

2 : 4-*Dihydroxy*-8-*methoxyquinazoline* (XII; R = R′ = OH).—(*a*) 2-Nitro-3-methoxybenzoic acid (30·3 g.) (Hodgson and Beard, *J.*, 1926, 154) was refluxed with thionyl chloride (30 c.c.) for 1 hour, and the excess of the latter then removed under diminished pressure. The crystalline residue was cooled and treated with methanol (100 c.c.) under reflux, and the vigorous reaction was completed by subsequent boiling for 5 minutes. On cooling, methyl 2-nitro-3-methoxybenzoate (colourless plates, m. p. 140°, from methanol) separated (yield, 27·4 g.). Catalytic hydrogenation with Raney nickel in methanol afforded methyl 3-methoxyanthranilate (colourless thick elongated prisms, m. p. 45°, from methanol). (*b*) Methyl 3-methoxyanthranilate (12·5 g.) in acetic acid (30 c.c.) was treated with sodium cyanate (7 g.) suspended in water (15 c.c.) with stirring, and the mixture left for 48 hours. Water (50 c.c.) was added, and the crystalline product (methyl 2-ureido-3-methoxybenzoate, m. p. 148—150°) collected (yield, 10·55 g.) and boiled with water (100 c.c.) for 1 hour. The resulting 2 : 4-dihydroxy-8-methoxyquinazoline, collected hot, had m. p. 258—259° unchanged by purification by dissolution in sodium hydroxide solution and reprecipitation with acid (Found: C, 56·5; H, 4·2; N, 14·8. Calc. for $C_9H_8O_3N_2$: C, 56·2; H, 4·2; N, 14·6%).

2 : 4-*Dichloro*-8-*methoxyquinazoline* (XII; R = R′ = Cl).—Prepared from 2 : 4-dihydroxy-8-methoxyquinazoline, phosphorus pentachloride, and phosphoryl chloride, this *compound* distilled from a bath at 230—260°/20 mm. and formed a pale yellow solid, m. p. 154—156° (Found: Cl, 30·3. $C_9H_6ON_2Cl_2$ requires Cl, 31·0%).

2-*Ureido*-4 : 5-*dimethoxybenzoic acid* (VI; R = H, R′ = R″ = OMe).—6-Nitroveratric acid (45 g.) in methanol (300 c.c.) was reduced catalytically over Raney nickel, ammonia being added during the reduction to bring the acid into solution. When hydrogen absorption was complete the suspension was treated with sodium hydroxide, and, after removal of the methanol by steam distillation, the volume was reduced to 400 c.c. under reduced pressure. No product separated on neutralisation or faint acidification with acetic acid (Tiemann and Matsmoto, *Ber.*, 1876, **9**, 942, stated that free 6-aminoveratric acid could not be isolated, whereas Heidelberger and Jacobs, *J. Amer. Chem. Soc.*, 1919, **41**, 2142, described it as sparingly soluble in water), but a small portion of the solution treated with acetic anhydride gave 6-acetamidoveratric acid, m. p. 226° (Simonsen and Race, *J.*, 1918, **113**, 26, give m. p. 228°). The bulk of the solution, treated with sodium cyanate (15 g.) and acetic acid (15 c.c.), gave 2-*ureido*-4 : 5-*dimethoxybenzoic acid* (yield, 34·5 g.), m. p. 162—163° (decomp.) (Found: N, 10·6. $C_{10}H_{12}O_5N_2,H_2O$ requires N, 10·9%).

2 : 4-*Dihydroxy*-6 : 7-*dimethoxyquinazoline* (III; R = R′ = OMe).—The above 2-ureido-4 : 5-dimethoxybenzoic acid (38·5 g.) was stirred for 1 hour with sodium hydroxide (50 c.c. of 35%). The precipitated sodium salt was filtered off, dissolved in boiling water (500 c.c.), and the filtered solution poured into acetic acid (50 c.c.). The precipitated *product* was filtered off and dried (yield, 10·1 g.). It formed cream-coloured platelets, m. p. 323—325° (Found: N, 11·9. $C_{10}H_{10}O_4N_2,H_2O$ requires N, 11·7%). A further quantity was obtained by treating the original mother liquors from the sodium

salt with sodium cyanate (25 g.) and acidification with acetic acid followed by cyclisation of the resulting 2-ureido-4 : 5-dimethoxybenzoic acid by heating at 95—100° with hydrochloric acid (30 c.c.) and water (10 c.c.).

2 : 4-*Dichloro*-6 : 7-*dimethoxyquinazoline* (IV; R = R′ = OMe).—2 : 4-Dihydroxy-6 : 7-dimethoxyquinazoline (16 g.), phosphoryl chloride (45 c.c.), and dimethylaniline (4·5 c.c.) were refluxed for 4·5 hours, the reaction mixture poured on ice, and the product extracted with ether. Evaporation of the dried ether solution gave the *product* which crystallised from light petroleum (b. p. 80—100°) as colourless needles, m. p. 158° (Found : N, 10·8. $C_{10}H_8O_2N_2Cl_2$ requires N, 10·8%).

2 : 4-*Dihydroxy*-6 : 7-*benzoquinazoline* (III; RR′ = benzo).—2-Naphthylamine-3-carboxylic acid (30 g.), urea (60 g.), and phenol (150 g.) were fused together and the mixture stirred under reflux for ½ hour. The resulting melt was cooled to 100°, and alcohol (150 c.c.) added cautiously. The mixture was stirred until cold, and the colourless crystalline *product* then filtered off, washed with alcohol, and dried (yield, 31 g.); m. p. 356° raised to 358—359° by recrystallisation from phenol (Found : C, 67·3; H, 4·0; N, 13·2. $C_{12}H_8O_2N_2$ requires C, 67·8; H, 3·8; N, 13·2%). We are indebted to Dr. F. H. Slinger for this preparation.

2 : 4-*Dichloro*-6 : 7-*benzoquinazoline* (IV; R and R′ = benzo), prepared from the preceding compound by the action of phosphorus pentachloride and phosphoryl chloride and purified by distillation from a bath at 270—300°/10—15 mm., formed an orange-coloured solid, m. p. 184° (Found : N, 11·0. $C_{12}H_6N_2Cl_2$ requires N, 11·25%).

2 : 6-*Dichloro*-4-*β*-*diethylaminoethylaminoquinazoline* (II; R = R″ = R‴ = H, R′ = Cl).—Finely ground 2 : 4 : 6-trichloroquinazoline (9·6 g.), water (75 c.c.), and *β*-diethylaminoethylamine (5 g.) were stirred together at room temperature. After 1 hour, and subsequently at intervals, sodium hydroxide solution was added so as to maintain the alkalinity to Clayton-yellow. When the alkalinity no longer decreased, the mixture was stirred overnight and then acidified with hydrochloric acid. Unreacted 2 : 4 : 6-trichloroquinazoline was filtered off and washed with water. The filtrate was basified with ammonia, and the precipitated product (gummy) washed with water by decantation and triturated with ether; it then solidified. Crystallised from light petroleum (b. p. 100—120°), 2 : 6-*dichloro*-4-*β*-*diethylaminoethylaminoquinazoline* formed colourless crystals, m. p. 135—136° (Found : N, 17·9. $C_{14}H_{18}N_4Cl_2$ requires N, 17·9%).

Using the same method, the following 2-chloro-4-*β*-diethylaminoethylaminoquinazolines carrying different substituents were made by condensation of *β*-diethylaminoethylamine with the appropriate substituted 2 : 4-dichloroquinazoline. 2 : 7-*Dichloro*-4-*β*-*diethylaminoethylaminoquinazoline* (II; R = R′ = R‴ = H, R″ = Cl) was precipitated initially as a *dihydrate*, m. p. 84—85° (Found: Cl, 20·7; $C_{14}H_{18}N_4Cl_2,2H_2O$ requires Cl, 20·35%); the anhydrous compound crystallised from light petroleum (b. p. 80—100°) as faintly yellowish laminæ, m. p. 119° (Found : C, 53·6; H, 5·6; N, 17·6. $C_{14}H_{18}N_4Cl_2$ requires C, 53·6; H, 5·75; N, 17·9%). 2-*Chloro*-6-*nitro*-4-*β*-*diethylaminoethylaminoquinazoline* (II; R = R″ = R‴ = H, R′ = NO_2) formed yellow needles from light petroleum (b. p. 80—100°), m. p. 125—126° (Found : N, 21·9. $C_{14}H_{18}O_2N_5Cl$ requires N, 21·65%). 2-*Chloro*-7-*nitro*-4-*β*-*diethylaminoethylaminoquinazoline* (II; R = R′ = R‴ = H, R″ = NO_2) crystallised from light petroleum (b. p. 80—100°) as yellow laminæ, m. p. 117° (Found : N, 22·0. $C_{14}H_{18}O_2N_5Cl$ requires N, 21·65%). 2-*Chloro*-4-*β*-*diethylaminoethylamino*-7-*methylquinazoline* (II; R = R′ = R‴ = H, R″ = Me) separated from light petroleum (b. p. 80—100°) as colourless needles, m. p. 112° (Found : N, 19·3; Cl, 12·2. $C_{15}H_{21}N_4Cl$ requires N, 19·1; Cl, 12·1%). 2-*Chloro*-4-*β*-*diethylaminoethylamino*-5-*methoxyquinazoline* (II; R = OMe, R′ = R″ = R‴ = H) formed a trihydrate, m. p. 100—102° (Found : N, 15·7. $C_{15}H_{21}ON_4Cl,3H_2O$ requires N, 15·45%). 2-*Chloro*-4-*β*-*diethylaminoethylamino*-6-*methoxyquinazoline* (II; R = R″ = R‴ = H, R′ = OMe) was isolated as a hydrate, m. p. 65—66° (Found : N, 14·9. $C_{15}H_{21}ON_4Cl,4H_2O$ requires N, 14·7%). 2-Chloro-4-*β*-diethylaminoethylamino-7-methoxyquinazoline (II; R = R′ = R‴ = H, R″ = OMe) crystallised from light petroleum (b. p. 80—100°) as colourless needles, m. p. 110—111° (Found : C, 58·0; H, 6·9; N, 17·8. Calc. for $C_{15}H_{21}ON_4Cl$: C, 58·3; H, 6·8, N, 18·15%) (Chapman, Gibson, and Mann, *loc. cit.*, give m. p. 108—109°). 2-*Chloro*-4-*β*-*diethylaminoethylamino*-8-*methoxyquinazoline* (II; R = R′ = R″ = H, R‴ = OMe) formed a colourless crystalline solid, m. p. 134—135° (Found : N, 18·1. $C_{15}H_{21}ON_4Cl$ requires N, 18·15%). 2-*Chloro*-4-*β*-*diethylaminoethylamino*-6 : 7-*dimethoxyquinazoline* (II; R = R‴ = H, R′ = R″ = OMe) had m. p. 116—117° (Found : N, 14·6. $C_{16}H_{23}O_2N_4Cl,2H_2O$ requires N, 14·95%). 2-*Chloro*-4-*β*-*diethylaminoethylamino*-6 : 7-*benzoquinazoline* (II; R = R‴ = H, R′R″ = benzo) crystallised from light petroleum as pale yellow needles, m. p. 140—142° (Found : N, 15·8. $C_{18}H_{21}N_4Cl,H_2O$ requires N, 16·15%).

6-*Chloro*-2-p-*chloroanilino*-4-*β*-*diethylaminoethylaminoquinazoline* (I; R = R″ = R‴ = H, R′ = Cl).—2 : 6-Dichloro-4-*β*-diethylaminoethylaminoquinazoline (6·3 g.), *p*-chloroaniline (5·1 g.), and acetic acid (10 c.c.) were refluxed for 2 hours, and the solution then cooled and diluted with water (100 c.c.). After being filtered from acet-*p*-chloroanilide, the solution was made alkaline with sodium carbonate and steam distilled to remove unchanged *p*-chloroaniline. The residual oily base was washed with water by decantation and dissolved in 10% acetic acid (50 c.c.), the solution was treated with carbon and filtered, and hydrochloric acid (10 c.c.) was added. The precipitated *dihydrochloride* (4258) crystallised from water as colourless needles, m. p. 282° (Found : C, 47·3; H, 5·8; N, 13·5. $C_{20}H_{23}N_5Cl_2,2HCl,1·5H_2O$ requires C, 47·6; H, 5·6; N, 13·9%).

A similar method was used for the preparation of the following compounds of the same type. 7-Chloro-2-*p*-chloroanilino-4-*β*-diethylaminoethylaminoquinazoline (I; R = R′ = R‴ = H, R″ = Cl) crystallised from light petroleum (b. p. 80—100°) as yellowish nodular crystals, m. p. 121—122°, and gave a *dihydrochloride* (3918) which separated from water as small colourless needles, m. p. 280—283° (Found : C, 50·0; H, 5·4; N, 14·4. $C_{20}H_{23}N_5Cl_2,2HCl$ requires C, 50·3; H, 5·25; N, 14·7%). 6-*Nitro*-2-p-*chloroanilino*-4-*β*-*diethylaminoethylaminoquinazoline* (I; R = R″ = R‴ = H, R′ = NO_2) crystallised from alcohol as orange yellow needles, m. p. 200—201° (Found : C, 57·7; H, 5·2; N, 20·2. $C_{20}H_{23}O_2N_6Cl$ requires C, 57·9; H, 5·55; N, 20·3%), and its *dihydrochloride* (4537) from water as yellowish needles, m. p. 266° (Found : Cl′, 13·8. $C_{20}H_{23}O_2N_6Cl,2HCl,1·5H_2O$ requires Cl′, 13·8%). 7-*Nitro*-2-p-*chloro*-

anilino-4-β-diethylaminoethylaminoquinazoline (I; R = R′ = R‴ = H, R″ = NO_2) (4259) (dihydrochloride, m. p. 246°) crystallised from alcohol as reddish-orange laminæ, m. p. 159·5—160° (Found : C, 57·9; H, 5·5; N, 20·0. $C_{20}H_{23}O_2N_6Cl$ requires C, 57·9; H, 5·55; N, 20·3%). 2-p-*Chloroanilino-4-β-diethylaminoethylamino-7-methylquinazoline dihydrochloride* (as I; R = R′ = R‴ = H, R″ = Me) (3931) crystallised from dilute hydrochloric acid as colourless needles, m. p. 264° (Found : C, 54·8; H, 6·1; N, 15·7. $C_{21}H_{26}N_5Cl,2HCl$ requires C, 55·2; H, 6·1; N, 15·35%). 2-*p*-Chloroanilino-4-β-diethylaminoethylamino-6-methoxyquinazoline (I; R = R″ = R‴ = H, R′ = OMe) formed a *dihydrochloride* (4624) which separated from water as short colourless prisms, m. p. 248—249° (Found : C, 49·3; H, 6·3. $C_{21}H_{26}ON_5Cl,2HCl,2H_2O$ requires C, 49·6; H, 6·3%). 2-*p*-Chloroanilino-4-β-diethylaminoethylamino-7-methoxyquinazoline (I; R = R′ = R‴ = H, R″ = OMe) afforded a *dihydrochloride* (3963) which crystallised from water as colourless prisms, m. p. 230—232° (Found : C, 50·4; H, 6·5; N, 14·1. $C_{21}H_{26}ON_5Cl,2HCl,1·5H_2O$ requires C, 50·4; H, 6·2; N, 14·05%), and the corresponding 8-methoxy-compound (I; R = R′ = R″ = H, R‴ = OMe) was isolated as its *dihydrochloride* (4609) which separated from water as colourless prisms, m. p. 274—275° (Found : C, 51·6; H, 6·3; N, 13·8; Cl′, 14·4. $C_{21}H_{26}ON_5Cl,2HCl,H_2O$ requires C, 51·3; H, 6·1; N, 14·3; Cl′, 14·5%). 2-*p*-Chloroanilino-4-β-diethylaminoethylamino-6 : 7-dimethoxyquinazoline (I; R = R‴ = H, R′ = R″ = OMe) gave a *dihydrochloride* (4185) which crystallised from water as colourless laminæ, m. p. 255—256° (Found : C, 51·4; H, 6·1; N, 13·2. $C_{22}H_{28}O_2N_5Cl,2HCl,0·5H_2O$ requires C, 51·6; H, 6·05; N, 13·7%). 2-*p*-Chloroanilino-4-β-diethylaminoethylamino-6 : 7-benzoquinazoline (I; R = R‴ = H, R′ and R″ = benzo) formed a *dihydrochloride* (3964) which was precipitated from a hot aqueous solution by the addition of hydrochloric acid as small sulphur-yellow prisms, m. p. 286—287° (Found : C, 53·2; H, 6·2; N, 12·5. $C_{24}H_{26}N_5Cl,2HCl,3H_2O$ requires C, 52·7; H, 6·2; N, 12·8%).

2-p-*Chloroanilino-4-β-diethylaminoethylamino-5-methoxyquinazoline* (I; R′ = R″ = R‴ = H, R = OMe).—2-Chloro-4-β-diethylaminoethylamino-5-methoxyquinazoline (3 g.), *p*-chloroaniline hydrochloride (3·3 g.), water (20 c.c.), and 10N-hydrochloric acid (0·1 c.c.) were boiled for 1 hour, the resulting solution treated with carbon and filtered, and a few drops of hydrochloric acid added. The product separated slowly on cooling as the *dihydrochloride* (5124) which was recrystallised from very dilute hydrochloric acid; colourless micro-needles, m. p. 187—189° (Found: C, 49·3; H, 6·2; N, 13·8. $C_{21}H_{26}ON_5Cl,2HCl,2H_2O$ requires C, 49·6; H, 6·3; N, 13·8%).

6-*Amino*-2-p-*chloroanilino*-4-β-*diethylaminoethylaminoquinazoline* (I; R = R″ = R‴ = H, R′ = NH_2).—6-Nitro-2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline (6·5 g.) suspended in methanol (150 c.c.) was reduced catalytically over Raney nickel at room temperature and pressure. When the theoretical hydrogen-absorption had taken place, the solution was filtered from catalyst and evaporated to dryness. The residue was dissolved in 5% acetic acid (40 c.c.) (charcoal) and filtered, and hydrochloric acid (10 c.c.) added. The *trihydrochloride* (4544) which separated slowly was collected and recrystallised from water, forming practically colourless needles, m. p. 180° resolidifying and remelting at 286° (Found : C, 41·1; H, 6·5; N, 14·3; Cl′, 17·6. $C_{20}H_{25}N_6Cl,3HCl,5H_2O$ requires C, 41·2; H, 6·5; N, 14·4; Cl′, 18·25%).

7-*Amino*-2-p-*chloroanilino*-4-β-*diethylaminoethylaminoquinazoline* (I; R = R′ = R‴ = H, R″ = NH_2).—Prepared similarly by catalytic reduction of 7-nitro-2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline, this formed a *dihydrochloride* (4213) which separated from water in colourless hair-fine needles, m. p. 295—296° (Found : C, 49·8; H, 6·3; N, 17·6; Cl′, 15·1. $C_{20}H_{25}N_6Cl,2HCl,1·5H_2O$ requires C, 49·55; H, 6·2; N, 17·4; Cl′, 14·7%).

Imperial Chemical Industries Limited,
Research Laboratories, Blackley, Manchester, 9. [*Received, December 22nd*, 1947.]