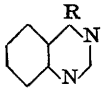
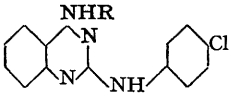
166. *Synthetic Antimalarials. Part XVI. 4-Dialkylaminoalkylamino-quinazolines. Variation of Substituents in the 6- and 7-Positions.*

By Norman B. Chapman, Geoffrey M. Gibson, and Frederick G. Mann.

A series of seven quinazolines having different dialkylaminoalkylamino-groups in the 4-position has been prepared. Series of 4-dialkylaminoalkylaminoquinazolines, having in addition the 6-chloro-, 7-chloro-, 7-nitro-, 6-methoxy-, and 7-methoxy-substituents, have also been synthesised. This wide range of quinazolines has been tested for antimalarial activity and some noteworthy variations have been revealed.

THIS investigation originated in the observation made in the laboratories of Imperial Chemical Industries Ltd. that 4-γ-diethylaminopropylaminoquinazoline (I; R = NH·[CH$_2$]$_3$·NEt$_2$) showed activity against *P. gallinaceum* in chicks. This result was apparently at variance with those of Magidson and Golovchinskaya (*J. Gen. Chem. Russia*, 1938, **8**, 1797) who first prepared this compound, its 6-chloro-derivative, and several other 6-substituted 4-dialkylaminoalkylaminoquinazolines and reported that they possessed no antimalarial activity. It appeared that the apparent discrepancy might possibly be due to a species specificity which these quinazoline derivatives might show in their antimalarial action, the Russian workers having probably tested the compounds against *P. præcox* (cf. Magidson *et al.*, *J. Microbiol. and Immunobiol.*, 1934, **13**, 685; *Trop. Dis. Bull.*, 1935, **32**, 419).

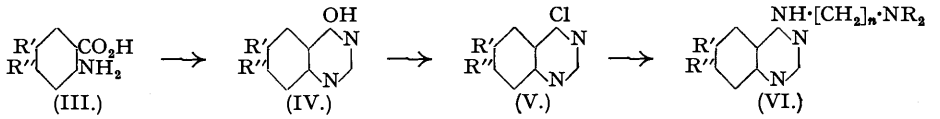
In view of the fact that 2-*p*-chloroanilino-4-dialkylaminoalkylaminoquinazolines of type (II; R = dialkylaminoalkyl) had also been shown to possess marked antimalarial activity against *P. gallinaceum* in chicks (Curd, Landquist, and Rose, Part XIV, this vol., p. 775) it became desirable to make a systematic study of the relationship between structure and antimalarial activity in 4-dialkylaminoalkylaminoquinazolines of type (I). Accordingly, we first prepared a series of compounds of type (I) having no substituent in the benzene ring, but

(I.)   (II.)

having in turn seven different dialkylaminoalkylamino-groups in the 4-position. We then prepared five similar series of compounds having in turn the 6-chloro-, 7-chloro-, 7-nitro-, 6-methoxy-, and 7-methoxy-substituents. Our choice both of these groups and their position was determined largely by the presence of the same groups in analogous positions in various quinoline and acridine compounds of known antimalarial activity. Thus, for instance, Magidson and Rubtsov (*J. Gen. Chem. Russia*, 1937, **7**, 1896) and Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) have reported on the antimalarial activity of 4-dialkylaminoalkylamino-6-methoxyquinolines, and D.R.-P. 683,692 relates *inter alia* to 7-halogeno-4-dialkylaminoalkylaminoquinolines which are stated to possess antimalarial activity. 7-Nitro-4-β-diethylaminoethylamino-3-ethoxyacridine (Magidson and Grigorowsky, *Ber.*, 1936, **69**, 396) is an example of an active antimalarial containing a nitro-group.

Over forty 4-dialkylaminoalkylaminoquinazolines have thus been prepared. In addition, some of the 4-hydroxyquinazoline derivatives utilised as intermediates in the synthesis of these quinazolines (*vide infra*) have also been submitted for test for prophylactic action because they were seen to be distantly related to Endochin (4-hydroxy-7-methoxy-3-*n*-heptylquinaldine) (C.I.O.S. Reports Nos. XXIII, 12, 13; XXIV, 20; XXV, 54, H.M. Stationery Office; see also Fitch, *Pharm. J.*, 1945, 182) which is stated to possess prophylactic activity against avian malaria.

The general route employed for the preparation of all these quinazolines consisted first in heating the appropriate anthranilic acid (or ester) (III) with formamide to obtain the



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

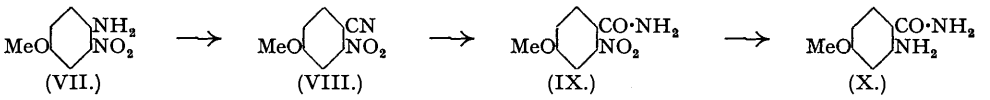
corresponding 4-hydroxyquinazoline (IV), which when suitably treated with a mixture of phosphorus pentachloride and phosphorus oxychloride gave the 4-chloroquinazoline (V). This when boiled in alcoholic solution with the dialkylaminoalkylamine furnished the 4-dialkylaminoalkylaminoquinazoline (VI), which was isolated either as the free base or directly as the hydrochloride.

The various substituted anthranilic acids and quinazoline intermediates were prepared as follows. Direct chlorination of methyl anthranilate (Freundler, *Bull. Soc. chim.*, 1911, **9**, 606) gave methyl 5-chloroanthranilate (as III; R′ = Cl, R″ = H) which readily condensed with formamide to give 6-chloro-4-hydroxyquinazoline (IV; R′ = Cl, R″ = H) and thence 4 : 6-dichloroquinazoline (V; R′ = Cl, R″ = H) (cf. Magidson *et al.*, *loc. cit.*). 4-Chloroanthranilic acid (III; R′ = H, R″ = Cl) was prepared by a modification (Curd *et al.*, forthcoming communication) of Cohn's method (*Monatsh.*, 1901, **22**, 485), 4-chloroaceto-*o*-toluidide being oxidised to 4-chloroacetylanthranilic acid, and then hydrolysed in turn to

4-chloroanthranilic acid. This acid furnished *7-chloro-4-hydroxyquinazoline* (IV; R′ = H, R″ = Cl) and 4 : 7-*dichloroquinazoline* (V; R′ = H, R″ = Cl). 4-Nitroanthranilic acid (III; R′ = H, R″ = NO_2), similarly prepared from 4-nitroaceto-*o*-toluidide, furnished 7-nitro-4-hydroxy- and *4-chloro-7-nitro-quinazolines* (IV and V; R′ = H, R″ = NO_2).

5-Methoxyanthranilic acid (III; R′ = OMe, R″ = H) was prepared by oxidising 2-nitro-5-methoxybenzaldehyde (Mason, *J.*, 1925, 1195) to 2-nitro-5-methoxybenzoic acid and reducing the latter. This acid gave *4-hydroxy-6-methoxy-* and *4-chloro-6-methoxy-quinazoline* (IV and V; R′ = OMe, R″ = H).

4-Methoxyanthranilamide (X) was prepared by converting 2-nitro-4-methoxyaniline (VII) into 2-nitro-4-methoxyphenyl cyanide (VIII) (cf., Cook, Heilbron, Reed, and Strachan, *J.*, 1945, 861), which on short treatment with sulphuric acid yielded *2-nitro-4-methoxybenzamide*



(IX) : reduction with ferrous hydroxide then gave (X). *4-Hydroxy-7-methoxyquinazoline* (IV; R′ = H, R″ = OMe) was readily prepared by the action of formic acid on this amide : it was also prepared, but less effectively, by the action of formamide on 4-methoxyanthranilic acid or its methyl ester. The usual treatment then furnished *4-chloro-7-methoxyquinazoline* (V; R′ = H, R″ = OMe).

In addition to the above quinazolines in which substituents in the pyrimidine ring were limited to the 4-position, the preparation of 2-amino-4-dialkylaminoalkylaminoquinazolines has been investigated, since Hull, Lovell, Openshaw, Payman, and Todd (Part III, *J.*, 1946, 357) have reported that the corresponding 2-amino-4-dialkylaminoalkylamino-5 : 6-dimethylpyrimidines possessed antiplasmodial activity. For this purpose 2-chloro-4-β-diethylaminoethylaminoquinazoline (XI; R = NH·$[CH_2]_2$·NEt_2) was heated with alcoholic ammonia to give *2-amino-4-β-diethylaminoethylaminoquinazoline* (XII; R = NH·$[CH_2]_2$·NEt_2), but the yield, which was never high, was markedly decreased by even small changes in the time and temperature of heating. 2-Chloro-4-β-diethylaminoethylaminoquinazoline (cf. Part XIV, *loc. cit.*) was very conveniently prepared by boiling 2 : 4-dichloroquinazoline (Lange, Roush, and Asbeck, *J. Amer. Chem. Soc.*, 1930, **52**, 3698) in alcoholic solution with one equivalent of β-diethylaminoethylamine. 2-Chloro-4-δ-diethylamino-α-methylbutylaminoquinazoline (XI; R = NH·CHMe·$[CH_2]_3$·NEt_2) was similarly prepared, but this compound could not be satisfactorily converted into the 2-amino-derivative by the action of either alcoholic ammonia or potassium phthalimide. Many attempts were also made to convert 2-chloro-4-methylthioquinazoline (XI; R = SMe) (Part XIV) and 2-chloro-4-phenoxyquinazoline (Lange *et al.*, *loc. cit.*) by the action of alcoholic ammonia into their 2-amino-derivatives, in the expectation that the 4-substituent might then be replaced by the δ-diethylamino-α-methylbutylamino-group, but conditions sufficiently vigorous to replace the 2-chlorine atom by the amino-group appeared always to replace similarly the 4-substituent.

Attempts to prepare the 2-amino-compound from *2-chloro-4-β-diethylaminoethylamino-7-methoxyquinazoline* also failed. This compound, although first prepared in the laboratories of Imperial Chemical Industries Ltd., has not yet been reported and is therefore described in this paper. Its synthesis involved the preparation of 2 : *4-dihydroxy-7-methoxyquinazoline* from *2-carbamido-4-methoxybenzoic acid*, followed by conversion into 2 : *4-dichloro-7-methoxyquinazoline* and condensation with β-diethylaminoethylamine.

The antimalarial activity (against the blood invasive forms of *P. gallinaceum*) of all the above 4-dialkylaminoalkylaminoquinazolines has been estimated by tests in chicks, by the method described by Curd, Davey, and Rose (*Ann. Trop. Med. Parasit.*, 1945, **39**, 139). The results are summarised in Table I where the usual method of expressing antimalarial activity is employed. For the antimalarial tests, certain of the 4-substituted quinazolines were weighed as free base (anhydrous or hydrated) which was then solubilised with dilute lactic acid : others were weighed as hydrochlorides or sulphates. The particular compound (base or salt) is accordingly indicated in column 4.

TABLE I.

Antimalarial Activity of 4-Substituted Quinazolines.

	Substituent:				
Ref. No.	6- or 7-position.	4-position.	Weighed as	Dose, mg./kg.	Activity.
5022	—	NH·[CH$_2$]$_2$·NEt$_2$	base	40	—
5023	—	NH·[CH$_2$]$_3$·NMe$_2$	,,	80	++
				60	+
				40	—
3623 *	—	NH·[CH$_2$]$_3$·NEt$_2$	,,	120	++
				40	—
5064	—	NH·[CH$_2$]$_3$·NHBu$^\alpha$	,,	160	±
				80	—
5024	—	NH·[CH$_2$]$_3$·NBu$^\alpha_2$	,,	40	—
5021	—	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	,,	60	++
				40	+
5026	—	NH·[CH$_2$]$_3$·O·[CH$_2$]$_2$·NEt$_2$	,,	80	—
5025	—	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	monohydrate	80	
5683	6-Cl	OH	base	20	—
5684	,,	NH·[CH$_2$]$_2$·NEt$_2$	monohydro-chloride	160	—
				80	—
				40	—
5688	,,	NH·[CH$_2$]$_3$·NMe$_2$	,,	160	+
				80	±
5685	,,	NH·[CH$_2$]$_3$·NEt$_2$	,,	160	±
				80	—
5689	,,	NH·[CH$_2$]$_3$·NBu$^\alpha_2$	,,	160	—
5687	,,	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	base	80	+ to ++
				40	
5686	,,	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	monohydro-chloride	160	—
5245	7-Cl	NH·[CH$_2$]$_2$·NEt$_2$	base	80	+ to ++
				40	—
5248	,,	NH·[CH$_2$]$_3$·NMe$_2$	,,	80	++
				40	+ to ++
				20	—
5247	,,	NH·[CH$_2$]$_3$·NEt$_2$	,,	80	++
				40	+
				20	±
5249	,,	NH·[CH$_2$]$_3$·NBu$^\alpha_2$	,,	160	++
				80	+
				40	—
5246	,,	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	,,	20	++
				10	—
5251	,,	NH·[CH$_2$]$_3$·O·[CH$_2$]$_2$·NEt$_2$	,,	80	++
				40	+
				20	±
5250	,,	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	hemihydrate	160	++
				80	+
5682	7-NO$_2$	OH	base	not tested	
5407	,,	NH·[CH$_2$]$_2$·NEt$_2$	monohydro-chloride	320	+ to ++
				160	—
5409	,,	NH·[CH$_2$]$_3$·NMe$_2$	,,	160	—
5408	,,	NH·[CH$_2$]$_3$·NEt$_2$	,,	160	—
5410	,,	NH·[CH$_2$]$_3$·NBu$^\alpha_2$	,,	160	±
				80	—
5406	,,	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	,,	320	++
				160	+ to ++
				80	—
5412	,,	NH·[CH$_2$]$_3$·O·[CH$_2$]$_2$·NEt$_2$	,,	160	—
5411	,,	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	,,	160	—
6123	6-OMe	OH	base	80	—
6117	,,	NH·[CH$_2$]$_2$·NEt$_2$	disulphate	140	—
6121	,,	NH·[CH$_2$]$_3$·NMe$_2$	base	80	+ to ++
6118	,,	NH·[CH$_2$]$_3$·NEt$_2$	disulphate	140	+
6122	,,	NH·[CH$_2$]$_3$·NBu$^\alpha_2$	,,	120	—
6120	,,	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	monohydrate	80	++
6119	,,	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	base	80	+
5681	7-OMe	OH	,,	not tested	
5252	,,	NH·[CH$_2$]$_2$·NEt$_2$	,,	160	++
				80	+

* Prepared by Dr. J. K. Landquist, Imperial Chemical Industries Ltd. (Dyestuffs Division).

TABLE I—*contd.*

Ref. No.	Substituent: 6- or 7-position.	Substituent: 4-position.	Weighed as	Dose, mg./kg.	Activity.
5256	7-OMe	$NH{\cdot}[CH_2]_3{\cdot}NMe_2$	base	80	++
				40	—
5253	,,	$NH{\cdot}[CH_2]_3{\cdot}NEt_2$	disulphate	160	+ to ++
				80	—
5257	,,	$NH{\cdot}[CH_2]_3{\cdot}NBu^{\alpha}_2$	,,	160	+
				80	—
5255	,,	$NH{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$	base	40	++
				20	+
5258	,,	$NH{\cdot}[CH_2]_3{\cdot}O{\cdot}[CH_2]_2{\cdot}NEt_2$	monohydrate	160	++
				80	±
5254	..	$NH{\cdot}[CH_2]_3{\cdot}N<[CH_2]_4>CH_2$	base	80	++
				40	+
5622	2-amino-4-β-diethylaminoethylamino-quinazoline		,,	40	++
				20	+

The following 4-hydroxyquinazolines were tested for prophylactic activity against *P. gallinaceum* in chicks by the method described by Davey (*Ann. Trop. Med. Parasit.*, 1945, **40**, in the press) but found to be inactive: 5681 and 5682 at 4 mg./50 g., and 5683 at 1 mg./50 g. In addition, 5622 was found to be inactive prophylactically at 8 mg./50 g., and 5246, which showed the highest activity against the blood forms of *P. gallinaceum* of all the 4-dialkylaminoalkylaminoquinazolines investigated, likewise showed no prophylactic activity (at 4 mg./50 g.).

Although the detailed biological results, summarised in Table I, will be published and discussed elsewhere, it may be noted that, in each of the six series of 4-dialkylaminoalkylaminoquinazolines investigated, highest activity was found in the compound containing the δ-diethylamino-α-methylbutylamino-side chain and that substitution by a chlorine atom in the 7-position led to the highest activity.

EXPERIMENTAL.

Notes on the Preparation of the Substituted Anthranilic Acids and/or their Derivatives.—Methyl 5-chloroanthranilate (as III: R′ = Cl, R″ = H). Direct chlorination of methyl anthranilate (405 g.) by Freundler's method (*loc. cit.*) gave methyl 3:5-dichloroanthranilate (174 g.) and methyl 5-chloroanthranilate (200 g.). The latter had m. p. 67—69° after recrystallisation from light petroleum (b. p. 60—80°), and contained a trace of methyl anthranilate which did not interfere with the preparation of 6-chloro-4-hydroxyquinazoline.

4-Chloroanthranilic acid (III; R′ = H, R″ = Cl) *and 4-nitroanthranilic acid* (III; R′ = H, R″ = NO_2). See Curd *et al.*, forthcoming communication.

5-Methoxyanthranilic acid (III; R′ = OMe, R″ = H). 2-Nitro-5-methoxybenzaldehyde (Mason, *loc. cit.*) was oxidised by alkaline permanganate at 20° to the corresponding acid in 92% yield; m. p. 132—133°. The nitro-acid was reduced to 5-methoxyanthranilic acid with hot stannous chloride and hydrochloric acid, the tin removed by addition of ammonia, a slight excess of acetic acid added to the filtrate, and the amino-acid isolated by continuous extraction with ether in a percolator; yield, 90%; m. p. 144—147° (decomp.).

2-Nitro-4-methoxybenzamide (IX) *and 4-methoxyanthranilamide* (X). Concentrated sulphuric acid (1 l.) and water (1 l.) were mixed and heated to boiling. 2-Nitro-4-methoxyphenyl cyanide (200 g.) (Cook *et al.*, *loc. cit.*) was then added during 2 minutes, and the mixture hand-stirred and gently boiled for 4 minutes. It was then rapidly cooled, diluted to 8 l. with ice and water, set aside for 1 hour, and the crude *2-nitro-4-methoxybenzamide* (IX) collected and extracted with ammonia. The 2-nitro-4-methoxybenzoic acid (39 g.) in the extract was converted into the amide in the usual way (thionyl chloride, aqueous ammonia), and added to the main portion (m. p. 150—157°) which was then suspended in a solution of hydrated ferrous sulphate (2200 g.) in water (3 l.). The mixture was boiled and stirred, and a slight excess of ammonia gradually added. When cold, the solid was collected and extracted with boiling alcohol. The extract afforded *4-methoxyanthranilamide* (X) (137 g.), m. p. 150—153°. A portion of the nitro-amide (IX) had m. p. 161—161·5° after recrystallisation from water (charcoal), unchanged after recrystallisation from alcohol (Found: N, 14·6. $C_8H_8O_4N_2$ requires N, 14·3%). A portion of the anthranilamide (X) had m. p. 155—155·5° after recrystallisation from water (charcoal), unchanged after recrystallisation from alcohol (Found: N, 17·4. $C_8H_{10}O_2N_2$ requires N, 16·9%).

In one reduction the amide–iron oxide mixture was dried, pulverised, and extracted with boiling acetone in an automatic apparatus. Removal of the solvent gave *2-isopropylideneamino-4-methoxybenzamide*, m. p. 196—196·5° after recrystallisation from much water (charcoal) (Found: C, 63·8; H, 7·0; N, 14·0. $C_{11}H_{14}O_2N_2$ requires C, 64·1; H, 6·8; N, 13·6%). This anil was hydrolysed to the anthranilamide in 95% yield on boiling for 20 minutes with 25% sulphuric acid.

2-Nitro-4-methoxybenzoic acid. The cyanide (VIII) (20 g.) was refluxed for 2·5 hours with sulphuric acid (75 c.c.) and water (100 c.c.), the mixture cooled and diluted with water, and the 2-nitro-4-methoxybenzoic acid purified by dissolution in ammonia (yield, 20·4 g.); m. p. 195—197° after recrystallisation from water (charcoal).

4-Methoxyanthranilic acid (III; R′ = H, R″ = OMe). This acid was prepared from 2-nitro-4-

methoxybenzoic acid in the same way as its 5-methoxy-isomer above, and was precipitated from the ammoniacal solution on addition of acetic acid. Since the amino-acid is nearly completely decarboxylated by boiling for 0·5 hour with 2N-hydrochloric acid, the reduction was carried out as rapidly as possible at 85—90°, and the solution then immediately cooled; yield, 85%; m. p. 166—166·5° (decomp.) after recrystallisation from water (charcoal). The methyl ester was prepared by boiling the hydrochloride of the acid with 10% methanolic hydrogen chloride for 3 hours, and purified by washing with ammonia and recrystallisation from aqueous methanol (charcoal); m. p. 75—77°.

Preparation of the 4-Hydroxyquinazolines.—4-Hydroxyquinazoline (IV; R′ = R″ = H) was obtained in 55% yield by heating anthranilic acid (1 mol.) and formamide (2 mols.) at 135° for 3 hours and recrystallising the product from alcohol.

6-Chloro-4-hydroxyquinazoline (IV; R′ = Cl, R″ = H) was prepared by heating methyl 5-chloroanthranilate (188 g.) and formamide (200 c.c.) at 180° for 9 hours, the methanol produced being allowed to escape. The product was extracted with cold 3% aqueous sodium hydroxide, the insoluble material (31 g.) removed, and the hydroxyquinazoline (129 g.) obtained from the extract by addition of aqueous ammonium chloride followed by recrystallisation from acetic acid. The alkali-insoluble material gave on recrystallisation from alcohol a *compound*, m. p. 220—221·5°, which appeared to be a 6-chloro-4-hydroxydihydroquinazoline (Found: C, 52·6; H, 3·9; N, 15·0; Cl, 19·5. $C_8H_7ON_2Cl$ requires C, 52·6; H, 3·8; N, 15·3; Cl, 19·5%).

7-Chloro-4-hydroxyquinazoline (IV; R′ = H, R″ = Cl) was obtained in 56% yield by heating 4-chloroanthranilic acid (1 mol.) and formamide (2 mols.) at 160° for 3 hours and recrystallising the product from alcohol.

7-Nitro-4-hydroxyquinazoline (IV; R′ = H, R″ = NO_2) was prepared by heating 4-nitroanthranilic acid (150 g.) and formamide (180 c.c.) at 160° for 6 hours, extracting the product with hot 3% aqueous sodium hydroxide, and acidifying the solution with acetic acid; yield, 152 g.

4-Hydroxy-6-methoxyquinazoline (IV; R′ = OMe, R″ = H) was prepared by heating 5-methoxy-anthranilic acid (84 g.) and formamide (100 c.c.) at 140° for 4·5 hours. The product was extracted with warm 10% aqueous sodium hydroxide, hydrochloric acid and then ammonia added, and the precipitated hydroxyquinazoline recrystallised from alcohol; yield, 75 g.

4-Hydroxy-7-methoxyquinazoline (IV; R′ = H, R″ = OMe). (*a*) 4-Methoxyanthranilamide (66 g.) and formic acid (*d*, 1·20; 70 c.c.) were refluxed at 140° for 2·5 hours. The product was treated with 5% aqueous sodium hydroxide, and hydrochloric acid followed by ammonia added to the extract; this precipitated the hydroxyquinazoline (66 g.).

(*b*) Methyl 4-methoxyanthranilate (4·2 g.) and formamide (4 c.c.) were heated at 140° for 3 hours. Extraction of the product with cold, dilute sodium hydroxide gave the hydroxyquinazoline (1·3 g.) and a compound (2·2 g.), m. p. 76—78°, which was probably the unchanged ester.

(*c*) 4-Methoxyanthranilic acid (5 g.) and formamide (3 c.c.) were heated at 140° for 3 hours. The product, boiled with alcohol and cooled, gave the hydroxyquinazoline (1 g.). The alcoholic filtrate was evaporated, and the residue extracted with ether in the presence of aqueous sodium hydroxide. The extract gave a solid (2·4 g.), m. p. 56·5—57·5° after recrystallisation from ether–light petroleum, which appeared to be formo-*m*-anisidide (Reverdin and Luc, *Ber.*, 1914, **47**, 1539, give m. p. 57°); it gave *m*-anisidine on hydrolysis with hydrochloric acid. The yield of hydroxyquinazoline was unaffected when the above reaction was carried out with a large excess of formamide. When the amino-acid (0·5 g.) and formamide (1 c.c.) were heated at 100° for 7 hours, the hydroxyquinazoline (0·03 g.) and an unidentified ammonia-soluble substance (0·15 g.), m. p. 189—190°, were obtained.

Preparation of the 4-Chloroquinazolines.—The hydroxyquinazoline (50—100 g., 1 mol.) was boiled with phosphorus pentachloride (1 mol.) and pure phosphorus oxychloride (150—300 c.c.) until the liquid was substantially clear (and no longer), the solvent removed by vacuum distillation, and the residue extracted with boiling light petroleum in a dry atmosphere. The extract deposited the 4-chloroquinazoline on cooling. This method gave products which were almost pure, and were collected as soon as the liquid was cold; otherwise, they tended to decompose. In this way, the following compounds were obtained, the reaction time, the b. p. of the light petroleum used for their isolation, and the yield being indicated in parenthesis: 4-chloroquinazoline (V; R′ = R″ = H) (2 hours, 60—80°, 45%); 4 : 6-dichloroquinazoline (V; R′ = Cl, R″ = H) (3 hours, 80—100°, 90%); *4 : 7-dichloroquinazoline* (V; R′ = H, R″ = Cl) (1 hour, 80—100°, 60%); *4-chloro-7-nitroquinazoline* (V; R′ = H, R″ = NO_2) (0·5 hour, 80—100°, 70%); *4-chloro-6-methoxyquinazoline* (V; R′ = OMe, R″ = H) (1·5 hours, 40—60°, 57%); *4-chloro-7-methoxyquinazoline* (V; R′ = H, R″ = OMe) (0·25 hour, 60—80°, 50%).

Preparation of the 4-Dialkylaminoalkylaminoquinazolines.—The appropriate 4-chloroquinazoline (10 g., 1 mol.) and the appropriate amine (1·1 mols.) were refluxed in alcohol (50 c.c.) for 0·5—1 hour; the required reaction had then occurred quantitatively. The material was then worked up in either of two ways: (*a*) the crystalline *4-dialkylaminoalkylaminoquinazoline monohydrochlorides*, which were occasionally deposited during the initial refluxing, were isolated either by direct addition of ether or by concentration and dissolution of the resulting syrup in acetone followed, if necessary, by addition of ether. Reference to these salts in Table II indicates when this method of working up was used for the particular compound in question. (*b*) The solutions were freed from solvent, the residues were taken up in acidulated water, sodium hydroxide was added, and the liberated *bases* were isolated by extraction with chloroform. When the bases were so hygroscopic as to be difficult to manipulate, or when it was desired to purify them through their salts, they were converted into their *disulphates* by dissolution in excess of concentrated alcoholic sulphuric acid followed by addition of acetone until just turbid; the salts crystallised out on being kept at 0° for a few hours.

The essential data concerning the above quinazolines and their derivatives are collected in Table II: the following notes give additional information concerning the properties and manipulation of certain of these compounds.

Simple quinazoline series. The dimethylaminopropylamino-compound was hygroscopic. The diethylaminoethoxypropylamino-compound was distilled (b. p. 196—200°/0·03 mm.) before the

Table II.

4-Substituted Quinazolines.

All compounds were colourless, except those of the nitro-series which were yellow (hydroxy-compound, brown).
All compounds are new except those indicated by a reference letter in the last column.

Benz-	Substituents: 4-Position.	Salt or hydrate.	S.	M. p.	Formula.	Analysis. Found, %. C.	H.	N.	Cl.	S.	Required, %. C.	H.	N.	Cl.	S.	Ref.
—	OH	—	A1	213°	$C_8H_6ON_2$	—	—	—	—	—	—	—	—	—	—	*a*
—	Cl	—	B1	98—100	$C_8H_5N_2Cl$	—	—	—	—	—	—	—	—	—	—	*b*
—	NH·[CH$_2$]$_2$·NEt$_2$	—	C1	124—125	$C_{14}H_{20}N_4$	68·7	8·5	22·9	—	—	68·9	8·2	23·0	—	—	—
—	NH·[CH$_2$]$_3$·NMe$_2$ [1]	—	B1	64—65	$C_{13}H_{18}N_4$	67·4	7·5	23·3	—	—	67·8	7·8	24·4	—	—	—
—	NH·[CH$_2$]$_3$·NHBu^a	—	—	Oil	$C_{15}H_{22}N_4$	70·1	8·4	21·3	—	—	69·8	8·5	21·7	—	—	—
—	NH·[CH$_2$]$_3$·NBu$^a_2$	—	B1	70—72	$C_{19}H_{30}N_4$	72·4	9·2	18·0	—	—	72·6	9·6	17·9	—	—	—
—	NH·CHMe·[CH$_2$]$_3$·NEt$_2$ [2]	—	B1	98	$C_{17}H_{26}N_4$	71·6	8·8	20·0	—	—	71·3	9·1	19·6	—	—	—
—	NH·[CH$_2$]$_3$·O·[CH$_2$]$_2$·NEt$_2$ [3]	—	B2	*ca.* 40	$C_{17}H_{26}ON_4$	67·2	8·5	18·1	—	—	67·5	8·6	18·6	—	—	—
—	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	H_2O	B1	106	$C_{16}H_{23}N_4,H_2O$	66·8	8·0	19·3	—	—	66·7	8·3	19·5	—	—	—
6-Cl	OH	—	D2	263—265	$C_8H_5ON_2Cl$	—	—	—	19·5	—	—	—	—	19·7	—	*c*
,,	Cl	—	B1	155—155·5	$C_8H_4N_2Cl_2$	—	—	—	35·4	—	—	—	—	35·7	—	*c*
,,	NH·[CH$_2$]$_2$·NEt$_2$	—	B3	138—138·5	$C_{14}H_{19}N_4Cl$	—	—	20·2	—	—	—	—	20·1	—	—	—
,,	,,	HCl	A3	242—243	$C_{14}H_{19}N_4Cl,HCl$	53·5	6·4	—	11·6 [4]	—	53·3	6·4	—	11·3 [4]	—	—
,,	NH·[CH$_2$]$_3$·NMe$_2$	—	B3	123—124	$C_{13}H_{17}N_4Cl$	—	—	20·9	—	—	—	—	21·2	—	—	—
,,	,,	HCl	A2	203—204	$C_{13}H_{17}N_4Cl,HCl$	51·4	5·9	—	11·8 [4]	—	51·8	6·0	—	11·8 [4]	—	—
,,	NH·[CH$_2$]$_3$·NEt$_2$	HCl	A2	162·5—163	$C_{15}H_{21}N_4Cl,HCl$	54·7	6·8	—	10·9 [4]	—	54·7	6·7	—	10·8 [4]	—	—
,,	NH·[CH$_2$]$_3$·NBu$^a_2$	—	B1	79—80	$C_{19}H_{29}N_4Cl$	—	—	16·1	—	—	—	—	16·1	—	—	—
,,	,,	HCl	A1	168·5—169·5	$C_{19}H_{29}N_4Cl,HCl$	59·5	7·8	—	9·1 [4]	—	59·2	7·8	—	9·2 [4]	—	—
,,	NH·CHMe·[CH$_2$]$_3$NEt$_2$	—	B1	112—113	$C_{17}H_{25}N_4Cl$	63·7	8·0	17·3	—	—	63·7	7·8	17·5	—	—	*c*
,,	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	—	B1	117—118	$C_{16}H_{21}N_4Cl$	—	—	18·4	—	—	—	—	18·4	—	—	—
,,	,,	HCl	A1	209—209·5 (decomp.)	$C_{16}H_{21}N_4Cl,HCl$	56·7	6·5	—	10·8 [4]	—	56·3	6·5	—	10·4 [4]	—	—
7-Cl	OH	—	A1	245 (decomp.)	$C_8H_5ON_2Cl$	53·1	3·1	15·8	—	—	53·2	2·8	15·5	—	—	—
,,	Cl	—	B4	132	$C_8H_4N_2Cl_2$	48·5	2·4	14·4	35·5	—	48·2	2·0	14·1	35·7	—	—
,,	NH·[CH$_2$]$_2$·NEt$_2$	—	B1	125	$C_{14}H_{19}N_4Cl$	60·3	6·9	20·4	—	—	60·3	6·8	20·1	—	—	—
,,	NH·[CH$_2$]$_3$·NMe$_2$	—	B1	102	$C_{13}H_{17}N_4Cl$	59·4	6·2	21·6	—	—	59·0	6·4	21·2	—	—	—
,,	NH·[CH$_2$]$_3$·NEt$_2$	—	B1	105	$C_{15}H_{21}N_4Cl$	61·6	7·2	19·5	—	—	61·6	7·2	19·1	—	—	—
,,	NH·[CH$_2$]$_3$·NBu$^a_2$	—	B1	81—82	$C_{19}H_{29}N_4Cl$	65·1	8·4	16·0	—	—	65·4	8·3	16·1	—	—	—
,,	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	—	B1	104—105	$C_{17}H_{25}N_4Cl$	63·8	7·7	17·8	—	—	63·7	7·8	17·5	—	—	—
,,	NH·[CH$_2$]$_3$·O·[CH$_2$]$_2$·NEt$_2$	—	B1	69—70	$C_{17}H_{25}ON_4Cl$	60·9	7·7	16·9	—	—	60·6	7·4	16·6	—	—	—
,,	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	0·5H_2O	B1	130—131	$C_{16}H_{21}N_4Cl,0·5H_2O$	61·3	7·3	18·1	—	—	61·3	7·0	17·9	—	—	—
7-NO_2	OH	—	D1	269—270	$C_8H_5O_3N_3$	—	—	—	—	—	—	—	—	—	—	*d*
,,	Cl	—	B4	146—147	$C_8H_4O_2N_2Cl$	—	—	—	16·6	—	—	—	—	16·9	—	—
,,	NH·[CH$_2$]$_2$·NEt$_2$	—	E1	151—151·5	$C_{14}H_{19}O_2N_5$	—	—	23·9	—	—	—	—	24·2	—	—	—
,,	,,	HCl	A3	213—214 (decomp.)	$C_{14}H_{19}O_2N_5,HCl$	51·7	6·4	21·4	10·7 [4]	—	51·6	6·1	21·5	10·9 [4]	—	—
,,	NH·[CH$_2$]$_3$·NMe$_2$	—	E1	132—132·5	$C_{13}H_{17}O_2N_5$	—	—	25·5	—	—	—	—	25·5	—	—	—
,,	,,	HCl	A3	238—239	$C_{13}H_{17}O_2N_5,HCl$	50·3	5·7	—	11·6 [4]	—	50·1	5·8	—	11·4 [4]	—	—

,,	NH·[CH$_2$]$_3$·NEt$_2$	—	B5	98—99	$C_{15}H_{21}O_2N_5$	—	—	23·1	—	—	—	—	23·1	—	—	—	—
,,	,,	HCl	A2	194·5—195·5	$C_{15}H_{21}O_2N_5$,HCl	53·1	7·0	20·3	10·5 [4]	—	53·0	6·5	20·6	10·5 [4]	—	—	—
,,	NH·[CH$_2$]$_3$·NBu^a$_2$	—	B1	79—80	$C_{19}H_{29}O_2N_5$	—	—	19·2	—	—	—	—	19·5	—	—	—	—
,,	,,	HCl	A2	180·5—182	$C_{19}H_{29}O_2N_5$,HCl	58·0	7·4	—	9·3 [4]	—	57·7	7·6	—	9·0 [4]	—	—	—
,,	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	—	E2	107—109	$C_{17}H_{25}O_2N_5$	—	—	21·4	—	—	—	—	21·1	—	—	—	—
,,	,,	HCl	A2	176—177	$C_{17}H_{25}O_2N_5$,HCl	55·8	7·2	—	10·0 [4]	—	55·5	7·1	—	9·7 [4]	—	—	—
,,	NH·[CH$_2$]$_2$·O·[CH$_2$]$_2$·NEt$_2$	—	—	69—71	$C_{17}H_{25}O_3N_5$	58·6	7·4	—	—	—	58·8	7·2	—	—	—	—	—
,,	,,	H_2O	C1	70—71	$C_{17}H_{25}O_3N_5$,H_2O	56·2	7·4	19·5	—	—	55·9	7·4	19·2	—	—	—	—
,,	,,	HCl	A2	142—143	$C_{17}H_{25}O_3N_5$,HCl	53·7	7·1	—	9·3 [4]	—	53·2	6·8	—	9·3 [4]	—	—	—
,,	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	—	E1	139—140	$C_{16}H_{21}O_2N_5$	—	—	22·6	—	—	—	—	22·2	—	—	—	—
,,	,,	HCl	A1	200—201	$C_{16}H_{21}O_2N_5$,HCl	54·4	6·6	—	10·3 [4]	—	54·6	6·3	—	10·1 [4]	—	—	—
6-OMe	OH	—	A1	242—243	$C_9H_8O_2N_2$	61·5	4·9	15·8	—	—	61·4	4·5	15·9	—	—	—	—
,,	Cl	—	B1	105—107	$C_9H_7ON_2Cl$	56·0	3·8	14·1	—	—	55·5	3·6	14·4	—	—	—	—
,,	NH·[CH$_2$]$_2$·NEt$_2$	—	B3	119—120	$C_{15}H_{22}ON_4$	—	—	20·6	—	—	—	—	20·4	—	—	—	—
,,	,,	HCl	A2	213—214	$C_{15}H_{22}ON_4$,HCl	—	—	—	11·6 [4]	—	—	—	—	11·4 [4]	—	—	—
,,	,,	2H_2SO_4	A3	162—164	$C_{15}H_{22}ON_4$,2H_2SO_4	38·6	5·4	11·8	—	12·7	38·3	5·5	11·9	—	13·6	—	—
,,	NH·[CH$_2$]$_3$·NMe$_2$	—	E2	132—133	$C_{14}H_{20}ON_4$	65·1	7·8	21·6	—	—	64·6	7·7	21·5	—	—	—	—
,,	NH·[CH$_2$]$_3$·NEt$_2$	—	B1	96—97	$C_{16}H_{24}ON_4$	—	—	19·6	—	—	—	—	19·4	—	—	—	—
,,	,,	2H_2SO_4	A3	187—190	$C_{16}H_{24}ON_4$,2H_2SO_4	39·9	6·0	11·7	—	12·6	39·7	5·8	11·6	—	13·2	—	—
,,	NH·[CH$_2$]$_3$·NBu^a$_2$	—	B1	78·5—79·5	$C_{20}H_{32}ON_4$	69·6	9·5	—	—	—	69·8	9·3	—	—	—	—	—
,,	,,	2H_2SO_4	A5	170—171	$C_{20}H_{32}ON_4$,2H_2SO_4	44·9	6·9	10·1	—	—	44·4	6·7	10·4	—	—	—	—
,,	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	H_2O	E2	144—147	$C_{18}H_{28}ON_4$,H_2O	64·8	8·8	17·2	—	—	64·7	9·0	16·8	—	—	—	—
,,	NH·[CH$_2$]$_2$·N<[CH$_2$]$_4$>CH$_2$	—	B3	110—111	$C_{17}H_{24}ON_4$	68·2	8·1	19·2	—	—	68·0	8·0	18·7	—	—	—	—
,,	,,	2H_2SO_4	A4	214—217	$C_{17}H_{24}ON_4$,2H_2SO_4	40·6	5·6	11·1	—	—	41·1	5·7	11·3	—	—	—	—
7-OMe	OH	—	A1	257—258	$C_9H_8O_2N_2$	61·0	4·4	16·0	—	—	61·4	4·5	15·9	—	—	—	—
,,	Cl	—	B1	141—142	$C_9H_7ON_2Cl$	—	—	14·6	18·0	—	—	—	14·4	18·3	—	—	—
,,	NH·[CH$_2$]$_2$·NEt$_2$	—	B5	109—110	$C_{15}H_{22}ON_4$	65·4	8·1	20·7	—	—	65·7	8·0	20·4	—	—	—	—
,,	NH·[CH$_2$]$_3$·NMe$_2$	—	C2	126—127	$C_{14}H_{20}ON_4$	64·4	7·6	22·0	—	—	64·6	7·7	21·5	—	—	—	—
,,	NH·[CH$_2$]$_3$·NEt$_2$	—	C3	65—66	$C_{16}H_{24}ON_4$	66·4	8·4	19·6	—	—	66·7	8·3	19·4	—	—	—	—
,,	,,	2H_2SO_4	A3	186—188	$C_{16}H_{24}ON_4$,2H_2SO_4	40·5	5·8	11·6	—	13·5	39·7	5·8	11·6	—	13·2	—	—
,,	NH·[CH$_2$]$_3$·NBu^a$_2$	—	—	54—57	$C_{20}H_{32}ON_4$	—	—	16·8	—	—	—	—	16·3	—	—	—	—
,,	,,	2H_2SO_4	A1	160—162	$C_{20}H_{32}ON_4$,2H_2SO_4	44·0	7·1	10·4	—	12·1	44·4	6·7	10·4	—	11·9	—	—
,,	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	—	—	92—93	$C_{18}H_{28}ON_4$	68·4	8·8	17·6	—	—	68·4	8·9	17·7	—	—	—	—
,,	NH·[CH$_2$]$_2$·O·[CH$_2$]$_2$·NEt$_2$	—	—	63—65	$C_{18}H_{28}O_2N_4$	64·7	8·4	—	—	—	65·1	8·4	—	—	—	—	—
,,	,,	H_2O	C3	65—67	$C_{18}H_{28}O_2N_4$,H_2O	61·9	8·7	16·0	—	—	61·7	8·6	16·0	—	—	—	—
,,	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	—	E2	121—122	$C_{17}H_{24}ON_4$	67·9	8·0	19·0	—	—	68·0	8·0	18·7	—	—	—	—

[1] *Dipicrate*, m. p. 215—217° (from alcohol) (Found: C, 43·8; H, 3·9; N, 20·2. $C_{13}H_{18}N_4$, 2$C_6H_3O_7N_3$ requires C, 43·6; H, 3·5; N, 20·4%).

[2] *Dipicrate monohydrate*, m. p. 185—187° (from methanolic picric acid) (Found: C, 46·2; H, 4·3; N, 18·2. $C_{17}H_{26}N_4$,2$C_6H_3O_7N_3$,H_2O requires C, 46·3; H, 4·5; N, 18·4%).

[3] *Dimethiodide monohydrate*, m. p. 129—131° (from alcohol–acetone) (Found: C, 37·8; H, 5·4; N, 9·0; I, 42·4. $C_{19}H_{32}ON_4I_2$,H_2O requires C, 37·8; H, 5·6; N, 9·3; I, 42·1%).

[4] Ionic chlorine.

Solvents (S.) used for recrystallisation are indicated: A1, alcohol. A2, alcohol–acetone. A3, alcohol + trace of water. A4, alcohol + trace of water + H_2SO_4. A5, alcohol + H_2SO_4 followed by precipitation with ether. B1, light petroleum (b. p. 60—80°). B2, light petroleum (b. p. 60—80°) at − 10°. B3, light petroleum (b. p. 60—80°) + trace of chloroform. B4, light petroleum (b. p. 80—100°). B5, light petroleum (b. p. 60—80°) + trace of benzene. C1, dry ether. C2, ether–benzene. C3, ether–light petroleum (b. p. 60—80°) at − 18°. D1, acetic acid. D2, aqueous acetic acid. E1, benzene. E2, benzene–light petroleum (b. p. 60—80°).

a, Niementowski, *J. pr. Chem.*, 1895, **51**, 564. *b*, Gabriel and Stelzner, *Ber.*, 1896, **29**, 1314. *c*, Magidson and Golovchinskaya, *J. Gen. Chem. Russia*, 1938, **8**, 1797. *d*, Bogert and Klaber, *J. Amer. Chem. Soc.*, 1908, **30**, 808.

recrystallisation indicated in Table II. The monobutylaminopropylamino-compound had b. p. 150—170°/0·0001 mm.

6-*Chloroquinazoline series.* During m. p. determinations on the diethylaminopropylamino-hydrochloride the melt occasionally solidified and then remelted at 186—187°. In the preparation of the dibutylaminopropylamino-hydrochloride, the cooled reaction mixture deposited waxy plates of a *compound* which had the same composition as γ-dibutylaminopropylamine dihydrochloride; m. p. 326—327° (decomp.) after recrystallisation from alcohol containing a trace of water (Found: C, 50·8; H, 11·1; N, 10·4; ionic Cl, 27·9. $C_{11}H_{26}N_2,2HCl$ requires C, 51·0; H, 10·8; N, 10·8; ionic Cl, 27·4%). Evidence that it was not identical with this diamine salt is: (*a*) a high m. p. and sparing solubility in pure alcohol would not be expected for such a salt; (*b*) addition of sodium hydroxide to its aqueous solution precipitated an almost odourless oil; (*c*) γ-dibutylaminopropylamine dihydrochloride was obtained, either by confinement over solid sodium hydroxide of a solution of the base in a slight excess of concentrated hydrochloric acid or by passing dry hydrogen chloride into a solution of the base in absolute ether, as an uncrystallisable syrup, an alcoholic solution of which failed to crystallise after being kept for several weeks either alone or after being seeded with the unidentified compound. The latter was encountered during the preparation of all the dibutylaminopropylaminoquinazolines reported in this paper, and evidently arose from an impurity in the γ-dibutylaminopropylamine used.

7-*Nitroquinazoline series.* The diethylaminopropylamino-, diethylaminomethylbutylamino-, dibutylaminopropylamino-, and diethylaminoethoxypropylamino-bases became dark brown on exposure to light. The last compound was hygroscopic, and formed a syrup on exposure to air. The syrup, which was a monohydrate, ultimately crystallised, and the pure anhydrous base was prepared from the purified hydrate by desiccation over sulphuric acid.

6-*Methoxyquinazoline series.* On very humid days the diethylaminopropylamino- and dibutylaminopropylamino-bases were hygroscopic, rapidly forming syrups on exposure to air. The piperidinopropylamino-disulphate underwent marked dissociation to the monosulphate on recrystallisation from slightly aqueous alcohol; the dibutylaminopropylamino-disulphate also dissociated when recrystallised in the absence of free sulphuric acid, although much less readily than the previous salt. The diethylaminomethylbutylamino-base monohydrate withstood the drying action of sulphuric acid, and hence must have considerable stability.

7-*Methoxyquinazoline series.* The diethylaminopropylamino-, dibutylaminopropylamino-, and diethylaminoethoxypropylamino-bases were hygroscopic, and formed syrups on exposure to air. The syrup from the last compound crystallised as the monohydrate on standing, and the pure anhydrous base was obtained from the purified monohydrate by confinement in a vacuum over sulphuric acid. The dibutylaminopropylamino-base could not be satisfactorily recrystallised, and was therefore prepared from its purified disulphate by basification, extraction with pure ether, and removal of solvent, finally in a desiccator over sulphuric acid. The diethylaminomethylbutylamino-base was hygroscopic to an extent depending on the climatic conditions, and was purified through its oxalate as follows: the crude base, dissolved in acetone, was added to excess of a dilute solution of hydrated oxalic acid in acetone. Next day, the acetone was decanted, and the hard residue boiled with alcohol to give a crystalline solid, m. p. 166—167° (decomp.) unchanged after recrystallisation from alcohol containing a trace of water. The constitution of this *compound* was uncertain, but it appeared to be either the base mono-oxalate monoalcoholate monohydrate or the dihydrated monoethyl oxalate salt of the base (Found for material dried in a vacuum over sulphuric acid: C, 55·9; H, 7·9; N, 12·0. $C_{18}H_{28}ON_4,C_2H_2O_4,C_2H_6O,H_2O$ or $C_{18}H_{28}ON_4,C_4H_6O_4,2H_2O$ requires C, 56·2; H, 8·1; N, 11·9%). The base was recovered from this salt by dissolution in water, addition of sodium hydroxide, and extraction with pure ether.

2-*Chloro*-4-β-*diethylaminoethylaminoquinazoline* (XI; R = NH·$[CH_2]_2$·NEt_2).—A mixture of 2 : 4-dichloroquinazoline (6 g.), β-diethylaminoethylamine (4 g., 1·1 mols.), and alcohol (25 c.c.) was refluxed for 30 minutes. After cooling, the hydrochloride of the quinazoline (XI; R = NH·$[CH_2]_2$·NEt_2) which had separated was collected and crystallised from alcohol (yield, 90%), m. p. 202° in agreement with Curd, Landquist, and Rose (Part XIV, *loc. cit.*) (Found: N, 17·5. Calc. for $C_{14}H_{19}N_4Cl,HCl$: N, 17·8%).

2-*Amino*-4-β-*diethylaminoethylaminoquinazoline* (XII; R = NH·$[CH_2]_2$·NEt_2).—Several experiments in which the degree and period of heating were varied showed the following conditions to be the most satisfactory. The above hydrochloride (10 g.) was dissolved in a minimum amount of warm alcohol and then treated with cold alcohol previously saturated with ammonia (50 c.c.). The solution was filtered to remove precipitated ammonium chloride and then heated at 120° for 2 hours. Alcohol and ammonia were then removed from the product by evaporation at 20 mm. pressure, the residue was treated with 30% aqueous sodium hydroxide, and the base extracted with ether and dried (K_2CO_3). After removal of the ether, the residual solid was first extracted with hot light petroleum (b. p. 60—80°) to remove unchanged chloro-compound, and then recrystallised from acetone. The 2-*amino-quinazoline* was obtained as colourless crystals, m. p. 144° (Found: C, 65·3; H, 8·2; N, 26·8. $C_{14}H_{21}N_5$ requires C, 64·9; H, 8·1; N, 27·0%).

When this reaction was carried out at higher temperatures, *e.g.*, 170°, intractable gummy mixtures were produced, from which the only pure constituent isolated was 2 : 4-dihydroxyquinazoline.

2-*Chloro*-4-δ-*diethylamino*-α-*methylbutylaminoquinazoline* (XI; R = NH·CHMe·$[CH_2]_3$·NEt_2).—A mixture of 2 : 4-dichloroquinazoline (10 g.), δ-diethylamino-α-methylbutylamine (8 g., 1·1 mols.), and alcohol (50 c.c.) was refluxed for 1 hour, and the alcohol then evaporated. The residual syrup was treated with 30% aqueous sodium hydroxide, and the liberated base extracted with ether and dried. Evaporation of the ether gave an oily residue which solidified when vigorously stirred with chilled light petroleum (b. p. 40—60°); recrystallisation from light petroleum then furnished the 2-chloro-compound as colourless crystals, m. p. 98° (Found: C, 63·7; H, 8·0; N, 17·8. Calc. for $C_{17}H_{25}N_4Cl$: C, 63·7; H, 7·8; N, 17·5%) (yield, 37%).

2 : 4-*Dihydroxy*-7-*methoxyquinazoline and its Derivatives.*—Sodium cyanate (2·5 g.) was added rapidly to a suspension of pure 4-methoxyanthranilic acid (5 g.) in acetic acid (15 c.c.) at 60°. The mixture was heated on the steam-bath until effervescence ceased, diluted with water, and the 2-*carbamido*-4-*methoxy*-

benzoic acid collected, washed with boiling alcohol to remove any traces of unchanged amino-acid, and further purified by dissolution in ammonia and reprecipitation with acetic acid; m. p. 185—186° (decomp.) (Found: N, 13·1. $C_9H_{10}O_4N_2$ requires N, 13·3%). The carbamido-acid was then boiled for 1 minute with 20% sodium hydroxide (30 c.c.), cooled, and the sodium salt of the dihydroxyquinazoline collected. The salt was dissolved in boiling water, dilute sulphuric acid followed by ammonia added, and the precipitated 2 : 4-*dihydroxy-7-methoxyquinazoline* collected and washed with alcohol (yield, 4·3 g.); m. p. 299—301° (Found: N, 14·4. $C_9H_8O_3N_2$ requires N, 14·6%).

The dihydroxyquinazoline (10 g.), phosphorus pentachloride (22 g.), and pure phosphorus oxychloride (32 c.c.) were boiled until the liquid was clear (10 minutes), the solvent distilled off under reduced pressure, and the residue extracted with boiling light petroleum (b. p. 60—80°) in a dry atmosphere. 2 : 4-*Dichloro-7-methoxyquinazoline* (7 g.) crystallised from the extract on cooling; m. p. 121—121·5° after recrystallisation from light petroleum (b. p. 60—80°) (Found: N, 12·2; Cl, 30·9. $C_9H_6ON_2Cl_2$ requires N, 12·2; Cl, 31·0%).

The dichloroquinazoline (5 g.) and β-diethylaminoethylamine (3·1 g., 1·2 mols.) were refluxed in alcohol (25 c.c.) for 10 minutes, the solvent was removed, the crystalline residue dissolved in water, aqueous sodium hydroxide added, and the liberated 2-*chloro*-4-*β-diethylaminoethylamino*-7-*methoxyquinazoline* isolated by extraction with chloroform and recrystallised from light petroleum (b. p. 60—80°) (yield, 5·8 g.); m. p. 108—109° (Found: N, 17·9; Cl, 11·4. $C_{15}H_{21}ON_4Cl$ requires N, 18·2; Cl, 11·5%).

The above chloroalkylamino-compound (1 g.) and alcohol saturated with ammonia at 0° (9 c.c.) were heated in a sealed tube at 160° for 3 hours. The solution was then distilled to remove solvent and ammonia, and the resulting syrup dissolved in dilute hydrochloric acid, basified with sodium hydroxide, and extracted with ether. Removal of the solvent left a small amount of resinous material which could not be crystallised, and from which crystalline salts could not be obtained.

This investigation was carried out as part of a wartime programme of antimalarial research sponsored by the Medical Research Council in collaboration with Imperial Chemical Industries Ltd. We are indebted to the former for grants (N. B. C. and G. M. G.) and to the latter for materials and for carrying out the biological tests. We are also greatly indebted to the workers of Imperial Chemical Industries for many discussions on the above work.

After this paper had been prepared for publication the following papers on quinazoline derivatives of related types appeared: Endicott, Wick, Mercury, and Sherrill (*J. Amer. Chem. Soc.*, 1946, **68**, 1299); Smith, Elisberg, and Sherrill (*ibid.*, p. 1301); Endicott, Alden, and Sherrill (*ibid.*, p. 1303); Price, Leonard, and Curtin (*ibid.*, p. 1305); Christensen, Graham, and Tomisek (*ibid.*, p. 1306), and Bunnett (*ibid.*, p. 1327).

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