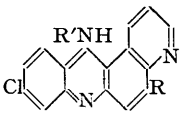
321. *Synthetic Antimalarials. Part XXII. Some Quinolylamino-substituted Pyrimidine Derivatives.*

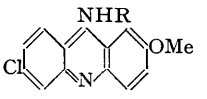
By F. H. S. Curd, W. Graham, (Miss) D. N. Richardson, and F. L. Rose.

By adapting the methods of preparation utilised for the corresponding anilino-compounds (see earlier papers in this series), series of 2-quinolylamino-4-dialkylaminoalkylamino- and 4-quinolylamino-2-dialkylaminoalkylamino-6-methylpyrimidines have been prepared. Whereas some of the former show activity against *P. gallinaceum* in chicks, the latter are all devoid of activity. Possible explanations for these observations are discussed.

The preparation of derivatives of 8-chloro-3 : 4 : 2′ : 3′-pyridoacridine (I; R = H, R′ = dialkylaminoalkyl), possessing considerable antimalarial activity against *P. gallinaceum* in chicks, has recently been reported by Dobson and Kermack (*J.*, 1946, 150). Such compounds may be considered as related to the mepacrine type of antimalarial (II), the 3-methoxy-group of the latter being replaced by the heterocyclic atom of the pyrido-ring. Reference to the structure (III) of the active 2-*p*-substituted anilino-4-dialkylaminoalkylamino-6-methylpyrimidines, described in Parts I and II (*J.*, 1946, 343, 351) showed that a related modification was possible with respect to the substituent R giving rise to quinoline derivatives of type (IV). Further incentive to the preparation of such compounds was provided by the known activity of (III; R = NMe_2, R′ = $[CH_2]_3{\cdot}NEt_2$) which suggested that activity might be encountered if the dimethylamino-group was replaced by the basic nitrogen atom of a fused heterocyclic ring.



(I.)



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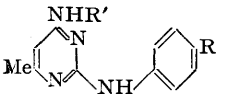

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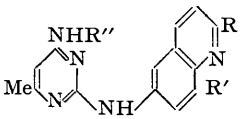

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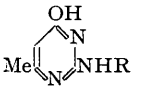

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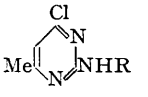


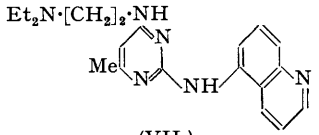
(VI.)

6-Aminoquinoline was therefore condensed with 4-hydroxy-2-methylthio-6-methylpyrimidine in boiling 2-ethoxyethanol solution to give 2-(6′-*quinolylamino*)-4-*hydroxy*-6-*methylpyrimidine* (V; R = 6-quinolyl), which was converted smoothly into 4-*chloro*-2-(6′-*quinolylamino*)-6-*methylpyrimidine* (VI; R = 6-quinolyl) by treatment with phosphoryl chloride. Condensation of this chloropyrimidine with β-diethylaminoethylamine, γ-diethylaminopropylamine, γ-dimethylaminopropylamine, δ-diethylaminobutylamine and δ-diethylamino-α-methylbutylamine then gave a series of 2-(6′-quinolylamino)-4-dialkylaminoalkylamino-6-methylpyrimidines (IV; R = R′ = H, R″ = $[CH_2]_2{\cdot}NEt_2$, $[CH_2]_3{\cdot}NEt_2$, $[CH_2]_3{\cdot}NMe_2$, $[CH_2]_4{\cdot}NEt_2$, and $CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$).

By a similar series of reactions using 6-aminoquinaldine in place of 6-aminoquinoline in the initial condensation with 4-hydroxy-2-methylthio-6-methylpyrimidine there were prepared, by way of (V; R = 6-quinaldyl) and (VI; R = 6-quinaldyl), 2-(6′-*quinaldylamino*)-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (IV; R = Me, R′ = H, R″ = $[CH_2]_2{\cdot}NEt_2$) and the corresponding 4-γ-*diethylaminopropylamino*-derivative (IV; R = Me, R′ = H, R″ = $[CH_2]_3{\cdot}NEt_2$).

All the above compounds showed some antimalarial activity when tested against *P. gallinaceum* in chicks (see table of activities) and it therefore became necessary to investigate the

effect of variations in the quinoline residue. Thus, the introduction of a substituent into the 8-position of the quinoline residue was indicated by the work of Hutchison and Kermack (this vol. p. 678) who were able to increase the activity of 8-chloro-5-γ-diethylaminopropylamino-3 : 4 : 2′ : 3′-pyridoacridine (I; R = H, R′ = $[CH_2]_3$·NEt_2) by substitution in the analogous position to give, for example, 2 : 8-dichloro- (I; R = Cl, R′ = $[CH_2]_3$·NEt_2) and 8-chloro-2-methyl-5-γ-diethylaminopropylamino-3 : 4 : 2′ : 3′-pyridoacridine (I; R = Me, R′ = $[CH_2]_3$·NEt_2). It also seemed desirable to investigate the effect of changing the orientation of the quinoline residue. The antimalarial activity of type (III) and related compounds appeared to be dependent on the presence of a substituent (Cl, NO_2, CN, etc.) in the benzene ring in the *p*-position to the imino-linkage. This substituent may be regarded as retained in type (IV) but this is not the case in the analogous 5- and 8-quinolyl derivatives. Utilising synthetic methods analogous to that outlined above for the 6-quinolyl derivatives of type (IV) a further series of compounds was therefore prepared which included the following 4-β-diethylaminoethylamino-6-methylpyrimidines: 2-(5′-*quinolylamino*)- (VII), 2-(8′-quinolylamino)- (VIII; R = R′ = H) (*dihydrochloride*), 2-(8′-methoxy-6′-quinolylamino)- (IV; R = H, R′ = OMe, R″ = $[CH_2]_2$·NEt_2) (*dihydrochloride*), and 2-(6′-methoxy-8′-quinolylamino)- (VIII; R = OMe, R′ = H) (*dihydrochloride*). The last named compound was considered to be of particular interest since it combines the 8-amino-6-methoxyquinoline nucleus found in pamaquin with essential features of the pyrimidine type of antimalarial (III).



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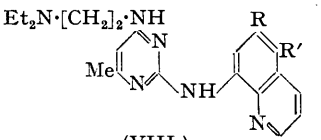
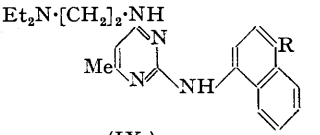
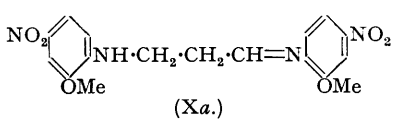


(VIII.)

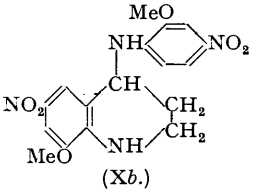


(IX.)

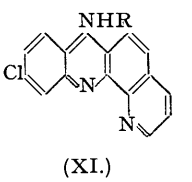
All the compounds of this further series were without antimalarial activity at the maximum tolerated doses. This result was particularly surprising in the case of 2-(8′-methoxy-6′-quinolylamino)-4-β-diethylaminoethylamino-6-methylpyrimidine (IV; R = H, R′ = OMe, R″ = $[CH_2]_2$·NEt_2) since this substance is a derivative of the active compound (IV; R = R′ = H, R″ = $[CH_2]_2$·NEt_2). However, it may also be regarded as a 3′ : 4′ : 5′-trisubstituted anilinopyrimidine analogous to (III), and it is known that the introduction of one additional substituent into a *m*-position of the active 2-*p*-substituted anilino-4-dialkylaminoalkylamino-6-methylpyrimidines of type (III) produces a dystherapeutic effect (Curd, Davis, and Rose, *J.*, 1946, 351) although the effect of trisubstitution has not been investigated in this series. The inactivity of (VIII; R = R′ = H) may be connected with the fact that it bears the same relationship to the active compounds of type (III) as the inactive 1 : 2 : 2′ : 3′-pyridoacridines (XI; R = dialkylaminoalkyl) described by Dobson and Kermack (*loc. cit.*) bear to mepacrine: in neither case does the added heterocyclic nucleus replace the important grouping removed but is fused into two neighbouring positions. Further, (VIII; R = R′ = H) is isosteric with the inactive 2-α-naphthylamino-4-β-diethylaminoethylamino-6-methylpyrimidine (IX; R = H) described in Part V (*J.*, 1946, 366). Introduction of a chlorine atom into the latter in the *p*-position to the imino-linkage to give 2-(4′-chloro-α-naphthylamino)-4-β-diethylaminoethylamino-6-methylpyrimidine (IX; R = Cl) largely restored activity, but an attempt



(X*a*.)



(X*b*.)



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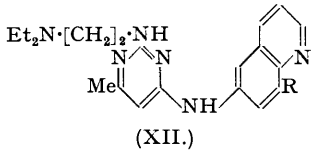
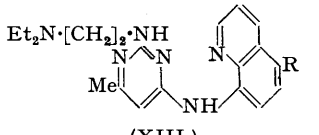


(XII.)



(XIII.)

to prepare the analogous quinoline compound, 2-(5′-bromo-8′-quinolylamino)-4-β-diethylaminoethylamino-6-methylpyrimidine (VIII; R = H, R′ = Br) was unsuccessful. It was found that

the bromine atom in 5-bromo-8-aminoquinoline was somewhat labile, and when the bromo-compound was heated with 4-hydroxy-2-methylthio-6-methylpyrimidine in 2-ethoxyethanol at 140°, hydrobromic acid, resulting from its decomposition, brought about hydrolysis of the pyrimidine intermediate to 4-methyluracil.

This investigation has also been concerned with the preparation of 2-dialkylaminoalkylamino-4-(quinolylamino)-6-methylpyrimidines of types (XII) and (XIII) in which the quinolylamino-substituent and the dialkylaminoalkylamino-side chain have been interchanged. 4-Chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (VI; R = $[CH_2]_2$·NEt_2) (Curd *et al.*, *J.*, 1946, 373) was condensed with 6-aminoquinoline by heating it at 140° to give 4-(6′-*quinolylamino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (XII; R = H) and with 8-aminoquinoline to give 4-(8′-quinolylamino)-2-β-diethylaminoethylamino-6-methylpyrimidine (XIII; R = H). Reactions of this type were also effected by boiling in dilute hydrochloric acid. In this way 6-amino-8-methoxyquinoline gave 4-(8′-*methoxy*-6′-*quinolylamino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (XII; R = OMe) and 5-bromo-8-aminoquinoline afforded 4-(5′-*bromo*-8′-*quinolylamino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (XIII; R = Br).

These compounds, like those of the previous series, were without antimalarial activity against *P. gallinaceum* in chicks. The contrast between the inactivity of 4-(6′-quinolylamino)-2-β-diethylaminoethylamino-6-methylpyrimidine (XII; R = H) and the activity of the isomeric 2-(6′-quinolylamino)-4-β-diethylaminoethylamino-6-methylpyrimidine (IV; R = R′ = H, R″ = $[CH_2]_2$·NEt_2), finds an analogy in the corresponding naphthylamino-derivatives. Thus 4-(6′-bromo-β-naphthylamino)-2-β-diethylaminoethylamino-6-methylpyrimidine and related compounds show little or no activity (Part VI, *J.*, 1946, 370), whereas the isomeric 2-(6′-bromo-β-naphthylamino)-4-β-diethylaminoethylamino-6-methylpyrimidine is highly active (Curd *et al.*, *J.*, 1946, 366).

TABLE I.

Antimalarial Activities.

The antimalarial tests were carried out, as in previous investigations of this series, by our colleague Dr. D. G. Davey using *P. gallinaceum* in chicks (cf. Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, **39**, 139; Davey, *ibid.*, 1946, **40**, 52). The results are expressed in the same way as in previous papers of this series.

(a) 2-(6′-*Quinolylamino*)- *and* 2-(6′-*quinaldylamino*)-4-*dialkylaminoalkylamino*-6-*methylpyrimidines.*

Ref. No.	Substituent at 2-position.	Substituent at 4-position.	Dose mg./kg.	Activity.
3749	Quinolyl	NH·$[CH_2]_2$·NEt_2	120	++
			80	+
3707	Quinolyl	NH·$[CH_2]_3$·NEt_2	160	+
			80	+
			40	−
3835	Quinolyl	NH·$[CH_2]_3$·NMe_2	160	+
			80	+
3878	Quinolyl	NH·$[CH_2]_4$·NEt_2	120	+
3864	Quinolyl	NH·CHMe·$[CH_2]_3$·NEt_2	120	±
			80	−
3750	Quinaldyl	NH·$[CH_2]_2$·NEt_2	80	+
			40	−
3692	Quinaldyl	NH·$[CH_2]_3$·NEt_2	120	++
			80	+

(b) 2-(*Quinolylamino*)-4-β-*diethylaminoethylamino*-6-*methylpyrimidines.*

Ref. No.	Substituent at 2.	Dose, mg./kg.	Activity.
5186	5′-Quinolyl	80	—
5187	8′-Quinolyl	80	—
5188	6′-Methoxy-8′-quinolyl	320	—
		240	—
5719	8′-Methoxy-6′-quinolyl	160	—

(c) 4-(*Quinolylamino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidines.*

Ref. No.	Substituent at 4.	Dose, mg./kg.	Activity.
5398	6′-Quinolyl	160	—
5399	8′-Quinolyl	160	—
5720	8′-Methoxy-6′-quinolyl	160	—
5721	5′-Bromo-8′-quinolyl	160	—

Some of the compounds were also tested for prophylactic action against *P. gallinaceum* in chicks by the method described by Davey (*Ann. Trop. Med. Parasit.*, 1946, **40**, 453); 5719, 5720, 5721, and 5398 at 160 mg./kg., 5188 at 240 mg./kg., and 5187 at 80 mg./kg., but all proved to be inactive.

The following points may be noted in connection with the preparation of the requisite quinoline intermediates. 5- and 8-Nitroquinolines, prepared from quinoline in 85% total yield by a method using fuming nitric acid and 20% oleum in place of the 40% oleum used by Meigen (*J. pr. Chem.*, 1908, **77**, 472) and 65% oleum by Fieser and Hershberg (*J. Amer. Chem. Soc.*, 1940, **62**, 1643), were reduced to the corresponding aminoquinolines with iron dust in dilute acetic acid (Dikshoorn, *Rec. Trav. chim.*, 1929, **48**, 153). 6-Nitro-8-methoxyquinoline was prepared by a modified Skraup reaction (cf. E.P. 394,416) using arsenic acid as oxidising agent. When sodium *m*-nitrobenzenesulphonate was used as oxidising agent the only product obtained was a yellow crystalline *substance*, presumed to be the 4-nitro-2-methoxyanil of β-4′-nitro-2′-methoxyanilinopropaldehyde (X*a*), or the cyclic analogue 4-(4′-nitro-2′-methoxyanilino)-6-nitro-8-methoxy-1 : 2 : 3 : 4-tetrahydroquinoline (X*b*), probable intermediates in the Skraup synthesis. Reduction of 6-nitro- to 6-amino-8-methoxyquinoline by means of stannous chloride (Fourneau *et al.*, *Ann. Inst. Pasteur*, 1930, **44**, 748) was not very satisfactory, and so attempts were made to increase the yield by reduction with iron dust and dilute acetic acid, iron dust and hydrochloric acid, or Raney nickel and hydrogen at 80 atmospheres and at 30 atmospheres. The best yield (50%) was obtained using the last named conditions.

Experimental.

2-(6′-*Quinolylamino*)-4-*hydroxy*-6-*methylpyrimidine* (V; R = 6-quinolyl).—4-Hydroxy-2-methylthio-6-methylpyrimidine (33·2 g.) (Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 478), 6-aminoquinoline (72 g.), and 2-ethoxyethanol (75 c.c.) were refluxed for 48 hours with stirring. Methylthiol was evolved. After cooling, the product was filtered off, washed well with hot alcohol, and dried (yield, 35 g.), m. p. 256—258°. The m. p. was unchanged by crystallisation from butanol from which the substance separated as colourless thick prisms (Found: C, 66·6; H, 4·7. $C_{14}H_{12}ON_4$ requires C, 66·7; H, 4·8%).

2-(6′-*Quinaldylamino*)-4-*hydroxy*-6-*methylpyrimidine* (V; R = 6-quinaldyl).—Prepared in an exactly similar manner using 6-aminoquinaldine in place of 6-aminoquinoline, the *compound* separated from 2-ethoxyethanol in clusters of small colourless needles, m. p. 284° (Found: C, 67·4; H, 5·3; N, 20·4. $C_{15}H_{14}ON_4$ requires C, 67·7; H, 5·3; N, 21·05%).

4-*Chloro*-2-(6′-*quinolylamino*)-6-*methylpyrimidine* (VI; R = 6-quinolyl).—The corresponding hydroxy-compound (28 g.) and phosphoryl chloride (95 c.c.) were refluxed for 4 hours. The excess of phosphoryl chloride was then removed under reduced pressure and the residue treated with a small amount of crushed ice. The solid product was filtered off, dissolved in hot water (150 c.c.) with hydrochloric acid (12·5 c.c.), and the resulting solution treated with decolorising carbon and filtered. The filtrate was cooled and hydrochloric acid (22·5 c.c.) added. The precipitated hydrochloride was filtered off, drained well, and dissolved in warm water (250 c.c.). Gradual addition of ammonia to the cooled solution precipitated the *base*, which was filtered off, dried in a vacuum, and crystallised from alcohol. It formed colourless prisms, m. p. 183—185° (Found: N, 20·5; Cl, 12·7. $C_{14}H_{11}N_4Cl$ requires N, 20·7; Cl, 13·1%).

4-*Chloro*-2-(6′-*quinaldylamino*)-6-*methylpyrimidine* (VI; R = 6-quinaldyl), prepared in an analogous manner from 2-(6′-quinaldylamino)-4-hydroxy-6-methylpyrimidine (33·25 g.) and phosphoryl chloride (85 c.c.), crystallised from 2-ethoxyethanol in colourless prisms, m. p. 235° (Found: N, 19·9; Cl, 12·5. $C_{15}H_{13}N_4Cl$ requires N, 19·85; Cl, 12·5%).

5- *and* 8-*Nitroquinoline*.—The method employed was essentially that of Fieser and Hershberg (*loc. cit.*). Quinoline sulphate, from quinoline (77·5 g.) and concentrated sulphuric acid (35 c.c.), dissolved in 20% oleum (210 g.), was nitrated with nitric acid (*d* 1·5; 105 g.) giving 5-nitroquinoline (42 g.) and 8-nitroquinoline (45 g.).

6-*Nitro*-8-*methoxyquinoline*.—A mixture of 2-amino-5-nitroanisole (100 g.), sulphuric acid (1000 g. of 70%), glycerol (200 g.), and arsenic acid (333 g. of 80%) was heated to boiling during ½ hour and then refluxed for 4 hours with stirring. The temperature of the boiling mixture dropped from 138° to 133° during the course of the reaction. After cooling, the reaction mixture was drowned into water (3 l.), and the solution stirred with decolorising carbon and filtered. Addition of sodium hydroxide solution to the filtrate precipitated 6-nitro-8-methoxyquinoline which was filtered off, washed with water, and crystallised from alcohol, m. p. 149—150° (yield, 82·5 g.). By recrystallisation from acetone the m. p. was raised to 152—153°. Fourneau *et al.* (*loc. cit.*) give m. p. 149°. In an experiment using sodium *m*-nitrobenzenesulphonate as oxidising agent the only material isolated was a *substance* crystallising from alcohol in yellow needles, m. p. 126—127°. This was presumed to be (X*a*) or (X*b*) (Found: C, 54·5; H, 4·2; N, 15·0. $C_{17}H_{18}O_6N_4$ requires C, 54·5; H, 4·8; N, 15·0%).

6-*Amino*-8-*methoxyquinoline*.—6-Nitro-8-methoxyquinoline (12 g.) dissolved in alcohol (600 c.c.) was hydrogenated in presence of Raney nickel (8 c.c. of sludge) in the cold at 30 atmospheres. After removal of the catalyst and on slight concentration of the alcohol solution a yellow solid separated which crystallised from alcohol–chloroform in yellow needles, m. p. *ca.* 350° (Found: C, 68·7; H, 4·3; N, 16·5%). Evaporation of the alcohol solution to dryness gave a dark red gummy solid from which, after several crystallisations from ethyl acetate, there was obtained 6-amino-8-methoxyquinoline (yield, 4·6 g.) as yellow laminæ, m. p. 167—169°. Fourneau *et al.* (*loc. cit.*) give m. p. 168°.

2-(8′-*Quinolylamino*)-4-*hydroxy*-6-*methylpyrimidine* (V; R = 8-quinolyl).—8-Aminoquinoline (34 g.), 4-hydroxy-2-methylthio-6-methylpyrimidine (34 g.), and 2-ethoxyethanol (40 c.c.) were heated together in an oil-bath at 135—145° for 70 hours. The mixture was then extracted several times with boiling alcohol leaving undissolved 2-(8′-*quinolylamino*)-4-*hydroxy*-6-*methylpyrimidine* (yield, 32·8 g.), m. p. 263—265°, unchanged after recrystallisation from 2-ethoxyethanol from which it separated in colourless prisms (Found: C, 66·5; H, 4·8. $C_{14}H_{12}ON_4$ requires C, 66·7; H, 4·8%).

2-(5′-*Quinolylamino*)-4-*hydroxy*-6-*methylpyrimidine* (V; R = 5-quinolyl).—Prepared in the same way from 5-aminoquinoline (10 g.) and 4-hydroxy-2-methylthio-6-methylpyrimidine (10 g.) in 2-ethoxyethanol (11·4 c.c.), this substance formed a fine white powder (yield, 8·1 g.), m. p. 286—290°, which could not be crystallised.

2-(6′-*Methoxy*-8′-*quinolylamino*)-4-*hydroxy*-6-*methylpyrimidine* (V; R = 6-methoxy-8-quinolyl), similarly obtained from 8-amino-6-methoxyquinoline (19 g.) and 4-hydroxy-2-methylthio-6-methylpyrimidine (15 g.) in 2-ethoxyethanol (25 c.c.), on crystallisation from 2-ethoxyethanol formed colourless needles (yield, 12·6 g.), m. p. 245—246° (Found: C, 64·2, 64·2; H, 4·5, 4·7. $C_{15}H_{14}O_2N_4$ requires C, 63·85; H, 5·0%).

2-(8′-*Methoxy*-6′-*quinolylamino*)-4-*hydroxy*-6-*methylpyrimidine* (V; R = 8-methoxy-6-quinolyl) was obtained in the same manner from 6-amino-8-methoxyquinoline (7·9 g.) and 4-hydroxy-2-methylthio-6-methylpyrimidine (6·8 g.) by reaction in 2-ethoxyethanol (9 c.c.). It formed a tan-coloured microcrystalline powder (yield, 5 g.), m. p. 231—235°, from alcohol (Found: C, 62·7; H, 4·7; N, 18·2. $C_{15}H_{14}O_2N_4$, $0{\cdot}5C_2H_5{\cdot}OH$ requires C, 62·95; H, 5·6; N, 18·35%).

4-*Chloro*-2-(8′-*quinolylamino*)-6-*methylpyrimidine* (VI; R = 8-quinolyl).—2-(8′-Quinolylamino)-4-hydroxy-6-methylpyrimidine (5 g.) and freshly distilled phosphoryl chloride (25 c.c.) were heated by means of an oil-bath for 4 hours at 125°. Excess of phosphoryl chloride was removed under diminished pressure and the residue treated with ice and dissolved in hydrochloric acid. The acid solution was filtered, carefully neutralised with ammonia, and the product filtered off, washed with water, and dried n a vacuum. It was then extracted thrice with boiling alcohol (200 c.c.) and filtered from insoluble material (1·5 g.). Concentration of the alcohol solution gave the *chloropyrimidine* which after recrystallisation from alcohol formed colourless prisms (yield, 3·4 g.), m. p. 146—148° (Found: C, 62·2; H, 4·3. $C_{14}H_{11}N_4Cl$ requires C, 62·1; H, 4·1%).

4-*Chloro*-2-(5′-*quinolylamino*)-6-*methylpyrimidine* (VI; R = 5-quinolyl).—The corresponding hydroxypyrimidine (11·5 g.) and freshly distilled phosphoryl chloride (45 c.c.) were heated at 120° in an oil-bath for 4 hours. After removal of the excess of phosphoryl chloride under reduced pressure at 100° the residue was treated with ice and dissolved in hydrochloric acid. After filtration, the solution was rendered alkaline with ammonia and the precipitated product filtered off, washed with water and dried in a vacuum. It crystallised from alcohol as colourless prisms (yield, 9·6 g.), m. p. 198—200° (Found: C, 62·5; H, 4·2. $C_{14}H_{11}N_4Cl$ requires C, 62·1; H, 4·1%).

4-*Chloro*-2-(6′-*methoxy*-8′-*quinolylamino*)-6-*methylpyrimidine* (VI; R = 6-methoxy-8-quinolyl), similarly obtained from 2-(6′-methoxy-8′-quinolylamino)-4-hydroxy-6-methylpyrimidine (9·7 g.) and phosphoryl chloride (39 c.c.), formed pale yellow prisms from alcohol (yield, 8·7 g.), m. p. 139—141° (Found: C, 59·7; H, 4·2. $C_{15}H_{13}ON_4Cl$ requires C, 59·9; H, 4·3%).

4-*Chloro*-2-(8′-*methoxy*-6′-*quinolylamino*)-6-*methylpyrimidine* (VI; R = 8-methoxy-6-quinolyl), prepared in the same way from the appropriate hydroxypyrimidine (5·2 g.) and phosphoryl chloride (21 c.c.), crystallised from benzene as pale yellow prismatic needles (yield, 5 g.), m. p. 213—215° (Found: C, 59·6; H, 4·1; N, 18·7. $C_{15}H_{13}ON_4Cl$ requires C, 59·9; H, 4·3; N, 18·6%).

Preparation of 2-*Quinolylamino*-4-*dialkylaminoalkylamino*-6-*methylpyrimidines*.—The 4-chloro-2-quinolylamino-6-methylpyrimidine (0·25 g.-mol.) and dialkylaminoalkylamine (0·25 × 1·15—2 g.-mol.) were heated at 125—135° (oil-bath) for 8 hours with stirring. After cooling, the resulting melt was dissolved in warm dilute hydrochloric acid, and the cooled solution basified with sodium hydroxide and extracted with chloroform. The chloroform extract was washed with water and shaken out several times with 5% acetic acid. The combined acid extracts were made alkaline with sodium hydroxide and the liberated base was taken into chloroform. After drying (K_2CO_3) and evaporation of the chloroform an oily base remained. This usually solidified on standing, or on trituration with warm light petroleum (b. p. 60—80°) and was then crystallised from light petroleum (b. p. 100—120°). Where the base could not be crystallised, it was converted into the dihydrochloride by dissolving it in 2N-hydrochloric acid and evaporation under reduced pressure at as low temperature as possible. The residue was dried and freed from adhering acid by repeated evaporation to dryness with alcohol–benzene and then purified by crystallisation. Table II details and gives a description of the compounds prepared.

5-*Bromo*-8-*aminoquinoline*.—8-Aminoquinoline was converted into its acetyl derivative and brominated in acetic acid. Contrary to the report of Claus and Setzer (*J. pr. Chem.*, 1896, **53**, 404) it was found that the hydrobromide of 5-bromo-8-acetamidoquinoline was dissociated in water. The acetyl derivative was hydrolysed to 5-bromo-8-aminoquinoline, the hydrochloride of which was likewise dissociated in water. After two crystallisations from alcohol, 5-bromo-8-aminoquinoline formed fine yellow needles, m. p. 109—110° (Found: C, 48·4; H, 3·5. Calc. for $C_9H_7N_2Br$: C, 48·4; H, 3·15%). Claus and Setzer (*loc. cit.*) give m. p. 104°.

Attempted Condensation of 5-*Bromo*-8-*aminoquinoline and* 4-*Hydroxy*-2-*methylthio*-6-*methylpyrimidine*.—The pyrimidine (9·6 g.), 5-bromo-8-aminoquinoline (15 g.), and 2-ethoxyethanol (11 c.c.) were heated in an oil-bath at 135—145° for 72 hours. From the dark red mixture the only products isolated were: (*a*) 4-methyluracil (5 g.), m. p. 312° (efferv.), identified by conversion into 5-bromo-4-methyluracil, m. p. 230° (Behrend, *Annalen*, 1885, **229**, 8), and (*b*) a water-soluble dark red gum (13 g.) which gave a positive test for ionised bromine. Ionised bromine was detected after 5-bromo-8-aminoquinoline had been heated with 2-ethoxyethanol at 140° for 8 hours, but the bromine in the acetyl derivative showed no such lability when heated with β-diethylaminoethylamine at this temperature.

4-(8′-*Quinolylamino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (XIII; R = H).—4-Chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (7·2 g.) (Curd *et al.*, *J.*, 1946, 373) and 8-aminoquinoline (5·4 g. 1·25 mol.) were heated in an oil-bath for 8 hours at 140°. The mixture was dissolved in dilute hydrochloric acid, the solution basified with sodium hydroxide, and extracted with chloroform. The chloroform extract was washed with water and then extracted several times with 5% acetic acid. The total acid extract was made alkaline with sodium hydroxide and the precipitated oil extracted with chloroform. The extract, after being washed and dried, was evaporated to dryness, giving the base as a red oil (7 g.) which could not be crystallised. This was dissolved in dilute hydrochloric acid and the solution evaporated to dryness under reduced pressure followed by repeated evaporation with alcohol–

TABLE II.

2-Quinolylamino-4-dialkylaminoalkylamino-6-methylpyrimidines.

Substituents, at position 2.	Substituents, at position 4.	Derivative.	M. p.	Formula.	Analysis. Found (%). C.	H.	N.	Required (%). C.	H.	N.
6-Quinolyl	NH·[CH_2]$_2$·NEt_2	—	124—126° (*a*)	$C_{20}H_{26}N_6$	68·0	7·0	23·8	68·6	7·4	24·0
,, ...	NH·[CH_2]$_3$·NEt_2	—	86—90 (*b*)	$C_{21}H_{28}N_6$,0·5H_2O	67·4	7·8	22·6	67·6	7·8	22·6
,, ...	NH·[CH_2]$_3$·NMe_2	—	153 (*a*) (*c*)	$C_{19}H_{24}N_6$	67·6	7·2	24·3	67·85	7·1	25·0
,, ...	NH·[CH_2]·NEt_2	—	119—120 (*d*)	$C_{22}H_{30}N_6$	69·6	7·9	22·2	69·8	7·9	22·2
,, ...	NH·CHMe·[CH_2]$_3$·NEt_2	—	120—122 (*a*)	$C_{23}H_{32}N_6$	70·1	8·0	21·5	70·4	8·2	21·4
6-Quinaldyl	NH·[CH_2]$_2$·NEt_2	—	132—133 (*a*)	$C_{21}H_{28}N_6$	69·1	7·5	22·5	69·2	7·7	23·1
,, ...	NH·[CH_2]$_3$·NEt_2	—	130—131 (*a*)	$C_{22}H_{30}N_6$	69·7	7·9	21·6	69·8	7·9	22·2
5-Quinolyl	NH·[CH_2]$_2$·NEt_2	—	110—111 (*d*)	$C_{20}H_{26}N_6$	68·6	7·4	23·9 Cl.	68·6	7·4	24·0 Cl.
		Trihydrochloride	258—260 (*e*)	$C_{20}H_{26}N_6$,3HCl,2·5H_2O	47·7	6·15	21·1	47·6	6·7	21·1
8-Quinolyl	,,	Dihydrochloride	267—270 (*d*)	$C_{20}H_{26}N_6$,2HCl,1·5H_2O	53·6	6·7	16·1	53·4	6·9	15·6
			(*f*)		53·7	6·8				
6-Methoxy-8-quinolyl	,,	,,	262—264 (*g*)	$C_{21}H_{28}ON_6$,2HCl,2·5H_2O	50·6	6·7	14·6	50·6	7·0	14·3
8-Methoxy-6-quinolyl	,,	,,	260—262 (*h*)	$C_{21}H_{28}ON_6$,2HCl,3·5H_2O	48·4	7·3		48·8	7·2	

(*a*) Colourless laminæ.
(*b*) Purified by preliminary vacuum distillation before crystallisation.
(*c*) Crystallised first from dilute alcohol.
(*d*) Colourless prisms.
(*e*) Crystallised from alcohol–ether; yellow needles.
(*f*) Crystallised from ether–alcohol.
(*g*) Crystallised from alcohol; colourless fine needles.
(*h*) Crystallised from alcohol–ether; slightly hygroscopic fine yellow needles, m. p. 202° (efferv.) solidifying and remelting at 260—262°. After drying for 2 hours in a vacuum at 100° it was deeper yellow in colour and had only one m. p. 260° (Found: N, 17·0; Cl, 14·2. $C_{21}H_{28}ON_6$,2HCl,2·5H_2O requires N, 16·9; Cl, 14·3%).

benzene. The remaining *dihydrochloride* crystallised from alcohol as colourless needles, m. p. 249—251° (Found: C, 54·0, 54·2; H, 6·9, 6·9; N, 19·5, 19·4. $C_{20}H_{26}N_6,2HCl,H_2O$ requires C, 54·4; H, 6·8; N, 19·1%).

4-(6′-*Quinolylamino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (XII; R = H), obtained in a similar manner from 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine and 6-aminoquinoline, crystallised from benzene–*cyclo*hexane in pale tan-coloured prisms, m. p. 160° (Found: C, 68·8, 68·7; H, 7·3, 7·5; N, 23·8. $C_{20}H_{26}N_6$ requires C, 68·6; H, 7·4; N, 24·0%). The corresponding *trihydrochloride* crystallised from alcohol, forming yellow needles, m. p. 258—261° (Found: C, 47·2; H, 6·8; N, 16·6. $C_{20}H_{26}N_6,3HCl,2·5H_2O$ requires C, 47·6; H, 6·7; N, 16·65%).

4-(8′-*Methoxy*-6′-*quinolylamino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (XII; R = OMe).—4-Chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (2·8 g., 1 mol.), 6-amino-8-methoxyquinoline (2 g., 1 mol.), concentrated hydrochloric acid (1·27 c.c., 1·1 mol.), and water (12·7 c.c.) were refluxed for 2 hours. The clear solution, when cold, was made alkaline with sodium hydroxide and worked up as described above for this type of compound, giving 4-(8′-*methoxy*-6′-*quinolylamino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (yield, 3·7 g.) which formed pale yellow needles from aqueous methanol, m. p. 201—203° (Found: C, 66·3; H, 7·2; N, 22·2. $C_{21}H_{28}ON_6$ requires C, 66·3; H, 7·3; N, 22·1%). The *trihydrochloride*, prepared in the usual manner, crystallised from alcohol in slightly yellow hygroscopic needles, m. p. 222—224° (Found: C, 47·4; H, 6·7. $C_{21}H_{28}ON_6,3HCl,2·5H_2O$ requires C, 47·15; H, 6·7%).

4-(5′-*Bromo*-8′-*quinolylamino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (XIII; R = Br).—4-Chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (2·9 g.), 5-bromo-8-aminoquinoline (2·67 g.), 10N-hydrochloric acid (1·32 c.c.), and water (13·2 c.c.) were boiled. Initially the mixed solids melted, and as the oil dissolved a solid began to separate. The mixture was refluxed for 2 hours and then left overnight. The 4-(5′-*bromo*-8′-*quinolylamino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine dihydrochloride* which separated was collected, dried, and crystallised from alcohol–ethyl acetate forming colourless needles (yield, 4·6 g.), m. p. 268—270° (Found: C, 47·6; H, 5·3; N, 16·5; Cl, 13·0. $C_{20}H_{25}N_6Br,2HCl$ requires C, 47·8; H, 5·4; N, 16·6; Cl, 14·1%). The free *base* was obtained by working up the hydrochloric acid mother liquor in the usual manner and also by treatment of the dihydrochloride with sodium hydroxide. It crystallised from light petroleum (b. p. 80—100°) as pale yellow rhombs, m. p. 133—134° (Found: C, 55·6; H, 5·7. $C_{20}H_{25}N_6Br$ requires C, 55·9; H, 5·8%).

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