148. *Synthetic Antimalarials. Part IX. 4-Arylamino-2-aminoalkylamino-6-methylpyrimidines. Further Variations.*

By F. H. S. Curd, (Miss) M. I. Davis, E. C. Owen, F. L. Rose, and G. A. P. Tuey.

Curd, Davis, Owen, Rose, and Tuey (Part VI, this vol., p. 370) described a series of 4-arylamino-2-aminoalkylamino-6-methylpyrimidines some of which showed antimalarial activity comparable with that of mepacrine when tested against *P. gallinaceum* in chicks. The present work comprises further syntheses of the same type of compound and series of 4-*p*-nitroanilino- and 4-*p*-cyanoanilino-2-aminoalkylamino-6-methylpyrimidines are described. Attention has also been paid to the effects of changes in position of the substituent in the anilino residue, introduction of more than one substituent, and additional substitution in the 5-position of the pyrimidine ring. The dystherapeutic effect of removal of the 6-methyl group now demonstrated for this type of compound is compared with the similar effect noted in Part VII (this vol., p. 378) for the isomeric 2-*p*-substituted-anilino-4-aminoalkylamino-6-methylpyrimidines and discussed.

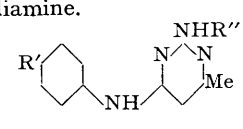
In view of the high antimalarial activity exhibited by 4-*p*-chloroanilino-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine (I; R′ = Cl, R″ = $[CH_2]_3\cdot NBu^n_2$) described in Part VI (this vol., p. 370) it was thought that compounds of type (I) might repay further study. The investigation has therefore been continued in a number of directions.

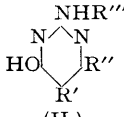
(a) *Variations in the dialkylaminoalkylamino group.* The incidence of high antimalarial activity in a compound containing the γ-di-*n*-butylaminopropylamino side chain was so unlike any other known series of antimalarial drugs that it was desirable to see how far activity persisted with less usual types of aminoalkylamino side chains. Reaction of 4-hydroxy-2-methylthio-6-methylpyrimidine with γ-(β′-diethylaminoethoxy)propylamine and γ-*N*-methyl-*N*-β′-diethylaminoethylaminopropylamine and treatment of the resulting 4-hydroxypyrimidines (II; R′ = H, R″ = Me, R‴ = $[CH_2]_3\cdot O\cdot[CH_2]_2\cdot NEt_2$) and (II; R′ = H, R″ = Me, R‴ = $[CH_2]_3\cdot NMe\cdot[CH_2]_2\cdot NEt_2$) with phosphoryl chloride to give respectively 4-*chloro*-2-γ-(β′-*diethylamino*-

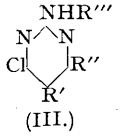
ethoxy)propylamino-6-methylpyrimidine (III; R′ = H, R″ = Me, R‴ = $[CH_2]_3$·O·$[CH_2]_2$·NEt_2) and 4-*chloro*-2-γ-N-*methyl*-N-(β′-*diethylaminoethyl*)*aminopropylamino*-6-*methylpyrimidine*

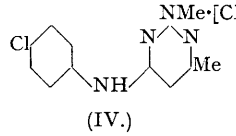
(III; R′ = H, R″ = Me, R‴ = $[CH_2]_3$·NMe·$[CH_2]_2$·NEt_2)

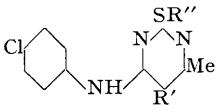
followed by condensation of these with *p*-chloroaniline gave compounds of type (I) in which the aminoalkylamino side chain was interrupted by oxygen and nitrogen. Using a similar method 4-p-*chloroanilino*-2-N-*methyl*-N-β-*diethylaminoethylamino*-6-*methylpyrimidine* (IV) was also prepared. For the preparation of 4-p-*chloroanilino*-2-β-*aminoethylamino*-6-*methylpyrimidine* (I; R′ = Cl, R″ = $[CH_2]_2$·NH_2) we had recourse to the second method of synthesis previously worked out for this type of compound (see Part VI, *loc. cit.*) and condensed 2-chloro-4-*p*-chloroanilino-6-methylpyrimidine (VII; R = H) with ethylenediamine. The same compound was also obtained by acid hydrolysis of 4-p-*chloroanilino*-2-β-*acetamidoethylamino*-6-*methylpyrimidine* (I; R′ = Cl, R″ = $[CH_2]_2$·NHAc) prepared by condensation of (VII; R = H) with acetylethylenediamine.

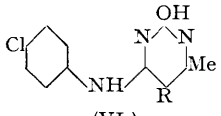

(I.)

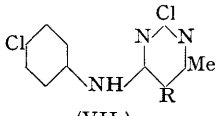

(II.)

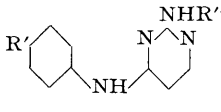

(III.)


(IV.)


(V.)


(VI.)


(VII.)


(VIII.)

(b) 4-p-*Nitroanilino*-2-*aminoalkylamino- and* 4-p-*cyanoanilino*-2-*aminoalkylamino*-6-*methylpyrimidines*. Our earlier work (Part VI, *loc. cit.*) on compounds of type (I) showed that 4-*p*-nitroanilino- (I; R′ = NO_2, R″ = $[CH_2]_2$·NEt_2) and 4-*p*-cyanoanilino-2-β-diethylaminoethylamino-6-methylpyrimidine (I; R′ = CN, R″ = $[CH_2]_2$·NEt_2) possessed higher activity against *P. gallinaceum* in chicks than the corresponding *p*-chloroanilino derivative (I; R′ = Cl, R″ = $[CH_2]_2$·NEt_2). As, moreover, replacement of the β-diethylaminoethylamino side chain in (I; R′ = Cl, R″ = $[CH_2]_2$·NEt_2) by certain other dialkylaminoalkylamino side chains led to a pronounced increase in antimalarial activity it was decided to investigate series of compounds of types (I; R′ = NO_2) and (I; R′ = CN) bearing a variety of different aminoalkylamino groups in the 2-position. Accordingly *p*-nitroaniline and *p*-cyanoaniline were each condensed with a variety of intermediates of type (III; R′ = H, R″ = Me, R‴ = aminoalkyl) in aqueous or aqueous acetone solution in presence of hydrochloric acid as catalyst. Details of the compounds prepared are given in Tables II and III.

(c) *Variation of the substituents in the anilino residue.* Although no extensive investigation has been carried out on the effect of changing the position of the substituent in the anilino residue of (I) or of introducing more than one substituent, similar to that recorded in Parts I and II (this vol., pp. 343, 351) for the isomeric 2-*p*-chloroanilino-4-aminoalkylamino-6-methylpyrimidines (IX), these points have received some attention in the present series and the following have been prepared: 4-m-*chloroanilino*-2-γ-*di*-n-*butylaminopropylamino*-, 4-m-*nitroanilino*-2-γ-*piperidinopropylamino*-, 4-(3′ : 4′-*dichloroanilino*)-2-γ-*di*-n-*butylaminopropylamino*-, and 4-(2′ : 4′-*dichloroanilino*)-2-γ-*di*-n-*butylaminopropylamino*-6-*methylpyrimidine*. The biological results (see Table I) indicated, however, that this line of investigation was probably not worth further study.

In the course of this work two compounds containing a *p*-hydroxyanilino residue have been prepared: 4-p-*hydroxyanilino*-2-γ-*diethylaminopropylamino*-6-*methylpyrimidine* (I; R′ = OH, R″ = $[CH_2]_3$·NEt_2) and the corresponding γ-*di*-n-*butylaminopropylamino* derivative (I; R′ = OH, R″ = $[CH_2]_3$·NBu^{α}_2). The hydroxyl group has not previously been introduced into the pyrimidine antimalarials but its inclusion seemed justified in view of the statement in E.P. 498,752 that certain 8-aminoalkylamino-6-hydroxyquinoline derivatives related to pamaquin have antimalarial activity and the probability that the drug Certuna (*Chem. Zentr.*, 1938, II, 3423; Kikuth, *Klin. Woch.*, 1938, **17**, 524; *Münch. med. Woch.*, 1939, **86**, 362) which received limited clinical trial before the war (Sioli, *Klin. Woch.*, 1938, **17**, 527; Muhlens, *Deut. med. Woch.*, 1938, **64**, 295; Chopra, Das Gupta and Sen, *Indian Med. Gaz.*, 1938, **73**, 667) belongs to this chemical type.

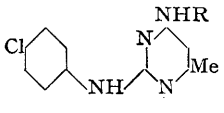
(d) *Variation of the substituents in the* 5 *and the* 6 *position.* In Part VII (Curd, Richardson, and Rose, this vol., p. 378) the dystherapeutic effect of removal of the 6-methyl group from the 2-arylamino-4-aminoalkylamino-6-methylpyrimidines of type (IX) was recorded. If, as is suggested in Part VIII (preceding paper), the antimalarial activity of this type of compound is connected with the tautomeric changes which can occur in such a molecule, such a dystherapeutic effect is difficult to interpret and it consequently appeared to be of interest to determine whether removal of the 6-methyl group produces a similar dystherapeutic effect in compounds of type (I).

We therefore prepared 4-p-*chloroanilino*- (VIII; R′ = Cl, R″ = $[CH_2]_3$·NBu^{α}_2) and 4-p-*nitroanilino*-2-γ-*di*-n-*butylaminopropylaminopyrimidine* (VIII; R′ = NO_2, R″ = $[CH_2]_3$·NBu^{α}_2). 4-Hydroxy-2-methylthiopyrimidine was condensed with γ-di-*n*-butylaminopropylamine to give (II; R′=R″=H, R‴=$[CH_2]_3$·NBu^{α}_2) which when treated with phosphoryl chloride afforded 4-*chloro*-2-γ-*di*-n-*butylaminopropylaminopyrimidine* (III; R′ = R″ = H, R‴ = $[CH_2]_3$·NBu^{α}_2). Reaction of this with *p*-chloroaniline then gave (VIII; R′ = Cl, R″ = $[CH_2]_3$·NBu^{α}_2) and with *p*-nitroaniline (VIII; R′ = NO_2, R″ = $[CH_2]_3$·NBu^{α}_2).

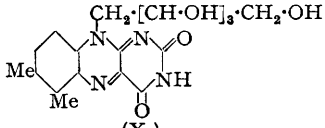
Reference to Table I shows that the antimalarial activity of these compounds is considerably less than that of the corresponding compounds carrying a methyl group in the 6-position. A possible explanation of this, which is applicable not only to compounds of type (I) but also to those of type (IX) and would be reconcilable with any theory relating the antimalarial activity of both types to tautomeric changes, is that the 6-methyl group merely functions as a blocking group. It has been shown (Kelsey *et al.*, *J. Pharm. Exp. Ther.*, 1944, **80**, 391) that quinine is enzymatically altered by the *in vitro* action of rabbit liver to give a degradation product which, as a result of the work of Mead and Koepfli (*J. Biol. Chem.*, 1944, **54**, 507), appears to be derived by the introduction of a hydroxyl group into the α-position of the quinoline nucleus, although no rigid proof of structure is given. It is possible, therefore, that in compounds of types (I) and (IX) the presence of the methyl group in the 6-position merely renders the substances of greater stability *in vivo* than the corresponding unmethylated compounds.

In a previous paper we drew attention to the formal resemblance of compounds of type (I) to riboflavin and suggested that because of this they might be capable of functioning as riboflavin antagonists. Although as yet no compounds of type (I) have been examined as riboflavin antagonists by the *Lactobacillus casei* technique (Madinaveitia, *Biochem. J.*, in the press) Dr. Madinaveitia, working in these laboratories, has demonstrated that *B. coli* adapted to withstand higher concentrations of mepacrine than the normal strain is also protected against 4-*p*-chloroanilino-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine. This affords evidence that compounds of type (I) share with mepacrine a common point of attack on *B. coli* which may extend to other micro-organisms including the parasites of malaria. That this is perhaps a flavine enzyme was suggested by the observations that mepacrine inhibits liver aldehyde oxidase (*idem*, private communication) and *d*-amino-acid oxidase (Wright and Sabine, *J. Biol. Chem.*, 1944, **155**, 315). In this case a further modification of compounds of type (I) was indicated.

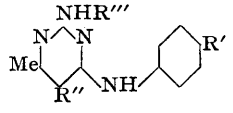
Emerson and Tishler (*Proc. Soc. Exp. Biol. Med.*, 1944, **55**, 184) have demonstrated the riboflavin antagonistic effect of 5 : 6-dimethyl-9-(*d*-1′-ribityl)*iso*alloxazine (*iso*riboflavin) and a comparison of the formula of this compound (X) with 4-arylamino-2-aminoalkylamino-6-methylpyrimidines carrying a 5-alkyl group (XI;



(IX.)



(X.)



(XI.)

R″ = alkyl) revealed a similarity which suggested that the latter might be enhanced riboflavin antagonists and in consequence possess antimalarial properties superior to that of compounds without the 5-alkyl group.

To examine this possibility, 4-chloro-2-ethylthio-5 : 6-dimethylpyrimidine was condensed with *p*-chloroaniline to give 4-p-*chloroanilino*-2-*ethylthio*-5 : 6-*dimethylpyrimidine* (V; R′ = Me, R″ = Et), hydrolysed by boiling with 48% hydrobromic acid to 4-p-*chloroanilino*-2-*hydroxy*-5 : 6-*dimethylpyrimidine* (VI; R = Me), which was then converted by boiling phosphoryl chloride into 2-*chloro*-4-p-*chloroanilino*-5 : 6-*dimethylpyrimidine* (VII; R = Me). Condensation of this with γ-diethylaminopropylamine and γ-dibutylaminopropylamine gave 4-p-*chloroanilino*-2-γ-*diethylaminopropylamino*- (XI; R′ = Cl, R″ = Me, R‴ = $[CH_2]_3$·NEt_2) and 4-p-*chloroanilino*-2-γ-*di*-n-*butylaminopropylamino*-5 : 6-*dimethylpyrimidine*

(XI; R′ = Cl, R″ = Me, R‴ = $[CH_2]_3$·NBu^{α}_2),

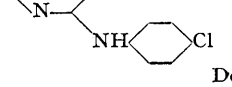
respectively. The preparation of the corresponding 5-ethyl derivatives and a number of related substances is also recorded in the experimental section, but no enhancement of activity resulted.

In an attempt to prepare a substance of the same type but containing a group other than alkyl in the 5-position, 4-*chloro*-5-*bromo*-2-*methylthio*-6-*methylpyrimidine* was prepared by the action of phosphoryl chloride

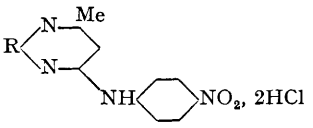
TABLE I.

Antimalarial activities.

The antimalarial activities quoted refer to *P. gallinaceum* in chicks and the symbols used to indicate activities have the same meaning as in earlier papers of this series. Detailed biological results will be published elsewhere.

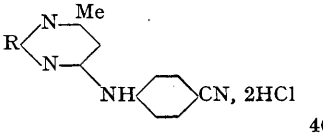
(*a*) Compounds of the type 

Ref. No.	R.	Dose, mg./kg.	Activity.
5153	NH·$[CH_2]_3$·NMe·$[CH_2]_2$·NEt_2 (trihydrochloride)	240	—
		120	—
5132	NH·$[CH_2]_3$·O·$[CH_2]_2$·NEt_2 (dihydrochloride)	160	—
		80	—
5096	NMe·$[CH_2]_2$·NEt_2	160	—
		80	—
5154	NH·$[CH_2]_2$·NH_2	120	++
		80	+
		40	—

(*b*) Compounds of the type 

Ref. No.	R.	Dose, mg./kg.	Activity.
4950	$NH\cdot[CH_2]_3\cdot NEt_2$	80	++
		40	+ to ++
		20	±
4631	$NH\cdot[CH_2]_3\cdot N<[CH_2]_4>CH_2$	40	++
		20	+ to ++
4630	$NH\cdot[CH_2]_3\cdot NBu^{\alpha}_2$	40	+ to ++
		20	+
5094	$NH\cdot[CH_2]_3\cdot NMe_2$ (1)	80	++
		40	+
5054	$NH\cdot CHMe\cdot[CH_2]_3\cdot NEt_2$	80	+ to ++
		40	+
5189	$NH\cdot[CH_2]_3\cdot NHBu^{\alpha}$ (1)	40	+ to ++
		20	+
5133	$NH\cdot[CH_2]_3\cdot O\cdot[CH_2]_2\cdot NEt_2$ (1)	160	++
		80	+

(1) Base.

(*c*) Compounds of the type 

5001	$NH\cdot[CH_2]_3\cdot NEt_2$	40	+
		20	−
4971	$NH\cdot[CH_2]_3\cdot N<[CH_2]_4>CH_2$	80	++
		40	+
5043	$NH\cdot[CH_2]_3\cdot NBu^{\alpha}_2$	20	++
5053	$NH\cdot CHMe\cdot[CH_2]_3\cdot NEt_2$ (2)	160	++
		120	++
		80	±

(2) Dihydrobromide.

(*d*) 4-Arylamino-2-aminoalkylamino-6-methylpyrimidines. Variation of substituents in the anilino residue.

4951	4-*m*-Chloroanilino-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine dihydrochloride	120	+
5042	4-*m*-Nitroanilino-2-γ-piperidinopropylamino-6-methylpyrimidine dihydrochloride	160	±
		80	−
5002	4-(3′ : 4′-Dichloroanilino)-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine dihydrochloride	40	±
		20	−
5000	4-(2′ : 4′-Dichloroanilino)-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine dihydrochloride	80	+
		40	±
4929	4-*p*-Hydroxyanilino-2-γ-diethylaminopropylamino-6-methylpyrimidine dihydrochloride	160	±
		80	−
4930	4-*p*-Hydroxyanilino-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine dihydrochloride	160	−
		80	−

(*e*) 4-Arylamino-2-aminoalkylaminopyrimidines. Variation of the substituents in the 5- and 6-positions.

4811	4-*p*-Chloroanilino-2-γ-di-*n*-butylaminopropylamino-pyrimidine dihydrochloride	80	Toxic
		40	−
5049	4-*p*-Nitroanilino-2-γ-di-*n*-butylaminopropylamino-pyrimidine	80	++
		40	±
5004	4-*p*-Chloroanilino-2-γ-di-*n*-butylaminopropylamino-5 : 6-dimethylpyrimidine dihydrochloride	80	+
		40	±
4230	4-*p*-Chloroanilino-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine dihydrochloride	40	+
		20	−
5050	4-*p*-Nitroanilino-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine	80	+ to ++
		40	+
		20	−
5051	4-*p*-Cyanoanilino-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine	80	+ to ++
		40	+ to ++
		20	±
5100	4-*p*-Chloroanilino-2-γ-di-*n*-butylaminopropylamino-6-methyl-5-ethylpyrimidine dihydrochloride	80	++
		40	−
		20	−

on 5-bromo-4-hydroxy-2-methylthio-6-methylpyrimidine (Part VII, *loc. cit.*) and condensed with *p*-chloroaniline to give (V; R′ = Br, R″ = Me) but attempts to hydrolyse the methylthio group in this compound with hydrobromic acid did not give (VI; R = Br) but led to removal of the bromine atom and the formation of 4-*p*-chloroanilino-2-hydroxy-6-methylpyrimidine (VI; R = H).

Experimental.

2-γ-(β′-Diethylaminoethoxy)propylamino-4-hydroxy-6-methylpyrimidine (II; R′ = H, R″ = Me, R‴ = $[CH_2]_3$·O·$[CH_2]_2NEt_2$).—4-Hydroxy-2-methylthio-6-methylpyrimidine (31·2 g.) and γ-(β′-diethylaminoethoxy)propylamine (34·8 g.) were stirred and heated at 150—160° for 3 hours leaving a colourless very viscous oil. It formed a *dipicrate* which crystallised from β-ethoxyethanol in yellow prisms, m. p. 161—163° (Found: C, 42·4; H, 4·3; N, 18·9. $C_{14}H_{26}O_2N_4,2C_6H_3O_7N_3$ requires C, 42·2; H, 4·3; N, 18·9%).

4-Chloro-2-γ-(β′-diethylaminoethoxy)propylamino-6-methylpyrimidine (III; R′ = H, R″ = Me, R‴ = $[CH_2]_3$·O·$[CH_2]_2$·NEt_2).—The above hydroxy compound (56·4 g.) and phosphoryl chloride (100 c.c.) were warmed until reaction occurred. When this had subsided the mixture was refluxed for 10 minutes, cooled, and poured on ice. The clear solution which resulted was made alkaline with sodium hydroxide and extracted with benzene. The benzene was then in turn extracted several times with 5% acetic acid. Addition of sodium hydroxide to the combined acetic acid extracts precipitated an oil which was again taken into benzene and the solution dried. Evaporation left *4-chloro-2-γ-(β′-diethylaminoethoxy)propylamino-6-methylpyrimidine* which was purified by distillation in a vacuum; b. p. 150—152°/0·15 mm. (Found: Cl, 11·7. $C_{14}H_{25}ON_4Cl$ requires Cl, 11·8%). It formed a *dipicrate* which crystallised from β-ethoxyethanol in yellow prisms, m. p. 111—113° (Found: C, 41·2; H, 4·1; N, 18·2. $C_{14}H_{25}ON_4Cl,2C_6H_3O_7N_3$ requires C, 41·1; H, 4·1; N, 18·4%).

4-p-Chloroanilino-2-γ-(β′-diethylaminoethoxy)propylamino-6-methylpyrimidine (I; R′=Cl, R″=$[CH_2]_3$·O·$[CH_2]_2$·NEt_2).—*p*-Chloroaniline (3·2 g.) was added to a solution of the above chloropyrimidine (7·5 g.) in water (25 c.c.) and 10N-hydrochloric acid (2·5 c.c.) and the mixture refluxed for 1 hour. The clear solution obtained was made alkaline with sodium hydroxide and extracted with chloroform. The product was then extracted from the chloroform with 5% acetic acid, and the extract made alkaline and shaken with chloroform. Evaporation of the dried chloroform solution left an oil which gave a *dipicrate*; yellow elongated prisms from β-ethoxyethanol, m. p. 148—150° (Found: C, 45·4; H, 4·0; N, 18·0. $C_{20}H_{30}ON_5Cl,2C_6H_3O_7N_3$ requires C, 45·2; H, 4·2; N, 18·1%). The *dihydrochloride* was prepared by dissolving the base in 2N-hydrochloric acid, evaporating the solution to dryness under reduced pressure, and crystallising the dried residue from alcohol–ethyl acetate. It formed colourless prisms, m. p. 178—180° (Found: C, 50·5; H, 7·7; N, 14·7; Cl′, 14·5. $C_{20}H_{30}ON_5Cl,2HCl,H_2O$ requires C, 49·8; H, 7·0; N, 14·6; Cl′, 14·7%) (5132).

2-γ-N-Methyl-N-(β′-diethylaminoethyl)aminopropylamino-4-hydroxy-6-methylpyrimidine (II; R′ = H, R″ = Me, R‴ = $[CH_2]_3$·NMe·$[CH_2]_2$·NEt_2).—4-Hydroxy-2-methylthio-6-methylpyrimidine (15·6 g.) and γ-*N*-methyl-*N*-(β′-diethylaminoethyl)aminopropylamine (18·75 g.) were heated at 150—160° for 3 hours giving a very viscous oil which afforded a *dipicrate*, purified by crystallisation from β-ethoxyethanol, m. p. 205—207° (decomp.) (Found: C, 43·0; H, 4·7; N, 20·3. $C_{15}H_{29}ON_5,2C_6H_3O_7N_3$ requires C, 43·0; H, 4·6; N, 20·45%).

4-Chloro-2-γ-N-methyl-N-(β′-diethylaminoethyl)aminopropylamino-6-methylpyrimidine (III; R′ = H, R″ = Me, R‴ = $[CH_2]_3$·NMe·$[CH_2]_2$·NEt_2).—The preceding hydroxypyrimidine (29·5 g.) was added to phosphoryl chloride (50 c.c.) and the mixture heated gradually to 100°. When the ensuing vigorous reaction had subsided the mixture was refluxed until a clear solution was obtained (*ca.* 30 mins.). After being cooled, the reaction mixture was poured on ice (250 g.) and the solution made alkaline with sodium hydroxide. The liberated product was taken up in benzene and extracted with 5% acetic acid. Treatment of the acid extract with sodium hydroxide and isolation with chloroform gave the *chloropyrimidine* as an oil, b. p. 142—144°/0·12 mm. (Found: C, 57·7; H, 8·9; N, 22·7. $C_{15}H_{28}N_5Cl$ requires C, 57·4; H, 8·9; N, 22·3%). The *tripicrate* (from β-ethoxyethanol) had m. p. 180—181° (Found: C, 40·0; H, 3·9; N, 19·5. $C_{15}H_{28}N_5Cl,3C_6H_3O_7N_3$ requires C, 39·6; H, 3·7; N, 19·6%).

4-p-Chloroanilino-2-γ-N-methyl-N-(β′-diethylaminoethyl)aminopropylamino-6-methylpyrimidine (I; R = Cl, R″ = $[CH_2]_3$·NMe·$[CH_2]_2$·NEt_2).—A mixture of the above chloropyrimidine (5·2 g.), *p*-chloroaniline (2·1 g.), water (15 c.c.), and 10N-hydrochloric acid (1·5 c.c.) was refluxed for 1 hour, cooled, and worked up as described above for the corresponding γ-diethylaminoethoxypropylamino derivative. The resulting oily base was converted into its *trihydrochloride* by solution in 2N-hydrochloric acid, evaporation of the solution under reduced pressure, and crystallisation of the residue, after drying, from alcohol–ethyl acetate; colourless prisms, m. p. 239—240° (decomp.) (Found: C, 46·9; H, 7·1; N, 16·5; Cl′, 19·7. $C_{21}H_{33}N_6Cl,3HCl,H_2O$ requires C, 47·4; H, 7·1; N, 15·8; Cl′, 20·0%) (5153).

2-N-Methyl-N-β-diethylaminoethylamino-4-hydroxy-6-methylpyrimidine, obtained by heating 4-hydroxy-2-methylthio-6-methylpyrimidine (15·6 g.) with *N*-methyl-*N*-β-diethylaminoethylamine (13 g.) at 140—150° for 3 hours, gave a *dipicrate* which formed yellow prisms and after several crystallisations from methanol had m. p. 167—169° (Found: C, 40·7; H, 4·0; N, 20·3. $C_{12}H_{22}ON_4,2C_6H_3O_7N_3$ requires C, 41·4; H, 4·0; N, 20·1%).

4-Chloro-2-N-methyl-N-β-diethylaminoethylamino-6-methylpyrimidine.—On adding phosphoryl chloride (30 c.c.) to the above hydroxypyrimidine (23·8 g.) reaction occurred immediately. After this had slackened the mixture was refluxed for 15 minutes to give a homogeneous solution. Excess of phosphoryl chloride was then removed under diminished pressure and the residue worked up as described previously for similar compounds. The *chloropyrimidine* was purified by distillation; b. p. 133—135°/0·8 mm. (Found: C, 56·3; H, 8·0; N, 21·4. $C_{12}H_{21}N_4Cl$ requires C, 56·1; H, 8·2; N, 21·8%). It formed a *picrate* which crystallised from methanol in yellow needles, m. p. 144—145° (Found: C, 44·2; H, 5·2; N, 20·1. $C_{12}H_{21}N_4Cl,C_6H_3O_7N_3$ requires C, 44·5; H, 5·0; N, 20·2%).

4-p-Chloroanilino-2-N-methyl-N-β-diethylaminoethylamino-6-methylpyrimidine (IV).—The above chloropyrimidine (9·6 g.), *p*-chloroaniline (4·8 g.), water (40 c.c.), and 10N-hydrochloric acid (3·75 c.c.) were boiled for 1 hour. After cooling, the solid which had separated was filtered off, dissolved in hot water, and reprecipitated with hydrochloric acid. Collected, dried, and crystallised from alcohol, the *dihydrochloride* formed colourless elongated prisms, m. p. 244—246° (Found: C, 50·9; H, 6·6; N, 16·9; Cl′, 17·1. $C_{18}H_{26}N_5Cl,2HCl$ requires C, 51·4; H, 6·7; N, 16·65; Cl′, 16·9%). The *base*, liberated from an aqueous solution of the hydrochloride with sodium hydroxide, crystallised from light petroleum (b. p. 80—100°) in tiny colourless prisms, m. p. 83—85° (Found: C, 62·0; H, 7·5; N, 19·9. $C_{18}H_{26}N_5Cl$ requires C, 62·2; H, 7·5; N, 20·1%) (5096).

4-p-Chloroanilino-2-β-acetamidoethylamino-6-methylpyrimidine (I; R′ = Cl, R″ = $[CH_2]_2$·NHAc).—2-Chloro-4-*p*-chloroanilino-6-methylpyrimidine (6·35 g.) and acetylethylenediamine (3·2 g.) were heated at 120—130° for 8 hours. The melt was dissolved in alcohol and the solution made alkaline with ammonia and poured into water. The precipitated product was filtered off and purified by crystallisation from methanol, forming colourless needles, m. p. 189—191° (Found: C, 56·6; H, 5·9; N, 21·7. $C_{15}H_{18}ON_5Cl$ requires C, 56·3; H, 5·6; N, 21·9%).

4-p-Chloroanilino-2-β-aminoethylamino-6-methylpyrimidine (I; R′ = Cl, R″ = $[CH_2]_2$·NH_2).—(*a*) 2-Chloro-4-*p*-chloroanilino-6-methylpyrimidine (6·35 g.) and ethylenediamine (14 g. of 65%) were heated on the steam-bath for 3 hours and then treated with dilute sodium hydroxide. The resulting solid was collected, dried, and crystallised from ethyl acetate forming colourless elongated prisms, m. p. 161—163° (Found: C, 56·2; H, 5·8; N, 25·1. $C_{13}H_{16}N_5Cl$ requires C, 56·2; H, 5·8; N, 25·2%) (5154).

(*b*) 4-*p*-Chloroanilino-2-β-acetamidoethylamino-6-methylpyrimidine (3 g.), alcohol (20 c.c.), water (10 c.c.), and

TABLE II.

4-p-*Nitroanilino*-2-*aminoalkylamino*-6-*methylpyrimidines*.

Substituent at 2.	Procedure.	Derivative.	Solvent used for crystn.; crystalline form.	Melting point.	Formula.	Analysis. Found, %. C.	H.	N.	Cl′.	Required, %. C.	H.	N.	Cl′.
$NH\cdot[CH_2]_3\cdot NEt_2$	(a)	Dihydrochloride	Dilute alcohol; pale yellow needles	273—275°	$C_{18}H_{26}O_2N_6,2HCl,0{\cdot}5H_2O$	49·5	6·5	—	15·9	49·1	6·6	—	16·1
$NH\cdot[CH_2]_3\cdot N<[CH_2]_4>CH_2$		—	Dilute alcohol; yellowish prisms	174—175	$C_{19}H_{26}O_2N_6,H_2O$	58·7	7·1	21·9	—	58·8	7·2	21·65	—
	(a)	Dihydrochloride	Dilute alcohol; pale yellow prisms	277—279	$C_{19}H_{26}O_2N_6,2HCl,2H_2O$	47·9	6·4	17·8	15·5	47·6	6·7	17·5	14·8
$NH\cdot[CH_2]_3\cdot NBu^{\alpha}{}_2$	(c)	—	Aqueous methanol; yellow prisms	118—119	$C_{22}H_{34}O_2N_6$	63·2	8·1	19·8	—	63·8	8·2	20·3	—
	(d)	Dihydrochloride	Alcohol–ethyl acetate; pale yellow prisms	224—225	$C_{22}H_{34}O_2N_6,2HCl,1{\cdot}5H_2O$	51·7	7·2	16·2	14·2	51·4	7·6	16·3	13·8
$NH\cdot[CH_2]_3\cdot NMe_2$	(c)	—	Toluene	184	$C_{16}H_{22}O_2N_6$	58·3	6·6	25·5	—	58·2	6·7	25·5	—
$NH\cdot CHMe\cdot[CH_2]_3\cdot NEt$		—	Oil										
		Dipicrate	β-Ethoxyethanol; yellow microcrystalline	173—176	$C_{20}H_{30}O_2N_6,2C_6H_3O_7N_3$	45·7	4·3	20·4	—	45·5	4·3	19·9	—
	(e)	Dihydrochloride	Alcohol–ethyl acetate; yellow rectangular prisms	*ca.* 116 *	$C_{20}H_{30}O_2N_6,2HCl,2H_2O$	48·0	7·3	16·9	14·9	48·5	7·3	17·0	14·4
$NH\cdot[CH_2]_3\cdot NHBu^{\alpha}$	(c)	—	Benzene	141—143	$C_{18}H_{26}O_2N_6$	59·8	7·3	23·6	—	60·3	7·3	23·5	—
$NH\cdot[CH_2]_3\cdot O\cdot[CH_2]_2\cdot NEt_2$	(c)	—	Benzene–light petroleum (b. p. 60—80°); yellow prisms	108—109	$C_{20}H_{30}O_3N_6$	59·7	7·2	20·6	—	59·7	7·5	20·9	—

* After being dried in air.

TABLE III.

4-p-*Cyanoanilino*-2-*aminoalkylamino*-6-*methylpyrimidines*.

Substituent at 2.	Procedure.	Derivative.	Solvent used for crystn.; crystalline form.	Melting point.	Formula.	Analysis. Found, %. C.	H.	N.	Cl′.	Required, %. C.	H.	N.	Cl′.
$NH\cdot[CH_2]_3\cdot NEt_2$	(a)	Dihydrochloride	Alcohol	274—275°	$C_{19}H_{26}N_6,2HCl,H_2O$	53·4	7·1	19·3	—	53·1	7·0	19·6	—
$NH\cdot[CH_2]_3\cdot N<[CH_2]_4>CH_2$	(a)	Dihydrochloride	Alcohol; colourless needles	280—282	$C_{20}H_{26}N_6,2HCl,0{\cdot}5H_2O$	55·4	6·5	19·0	—	55·5	6·7	19·4	—
$NH\cdot[CH_2]_3\cdot NBu^{\alpha}{}_2$	(a)	Dihydrochloride	Alcohol–ethyl acetate; colourless rectangular prisms	224—226	$C_{23}H_{34}N_6,2HCl$	59·0	7·6	17·9	15·1	59·1	7·7	18·0	15·2
$NH\cdot CHMe\cdot[CH_2]_3\cdot NEt_2$				B. p. 233—239°/ 0·15 mm.									
		Dipicrate	β-Ethoxyethanol; flat yellow prisms	199—200	$C_{21}H_{30}N_6,2C_6H_3O_7N_3$	48·2	4·4	—	—	48·2	4·4	—	—
	(b)	Dihydrobromide	Alcohol–ethyl acetate; colourless needles	216—220	$C_{21}H_{30}N_6,2HBr$	47·3	5·7	15·7	—	47·7	6·1	15·9	—

hydrochloric acid (10 c.c.) were refluxed for 4 hours. Addition of sodium hydroxide to the cooled solution precipitated the base as an oil which solidified on standing. It was collected, washed, and dried. After crystallisation from ethyl acetate it had m. p. 160—162° either alone or mixed with material made by method (*a*).

Preparation of 4-Arylamino-2-aminoalkylamino-6-methylpyrimidines.—The compounds described in Tables II, III, and IV were made by the following general method. The appropriate 4-chloro-2-aminoalkylamino-6-methylpyrimidine (0·025 g.-mol.) was dissolved in water (50 c.c.), or a mixture of water (40 c.c.) and acetone (10 c.c.) with 10N-hydrochloric acid (3·0 c.c.), the aniline (0·025 g.-mol.) added, and the mixture refluxed for 1—2 hours. Various procedures were used for the isolation of the products and are listed below, reference being made in the tables to the method used for each particular compound. Some of the dihydrochlorides separated on cooling the reaction mixture; these were filtered off, dried, and crystallised [Method (a)]. Where the dihydrochloride did not crystallise out on cooling it was sometimes found convenient to evaporate the reaction mixture to dryness under diminished pressure and to crystallise the residue [Method (b)]. The following method was, however, most commonly adopted. After being cooled, the reaction mixture was made strongly alkaline with sodium hydroxide to liberate the base which was extracted with chloroform and then re-extracted from the chloroform, or from the residue left after evaporation of the chloroform, with 5% acetic acid. Basification of the acid extract then liberated the base which was isolated with chloroform. If the base was obtained as a solid it was purified by vacuum distillation or by crystallisation and used for biological evaluation in this form [Method (c)]. Where the base was obtained as an oil it was usually characterised as its dipicrate and then converted into its dihydrochloride (or dihydrobromide) by dissolving in warm 2N-acid. Sometimes the salt separated on cooling and was filtered off and dried [Method (d)]. Otherwise the solution was evaporated to dryness under reduced pressure at 50—60° and the dried residue crystallised [Method (e)].

2-*γ-Di*-n-*butylaminopropylamino*-4-*hydroxypyrimidine* (II; R′ = R″ = H, R‴ = $[CH_2]_3$·Bu^n_2).—4-Hydroxy-2-methylthiopyrimidine (17 g.) (Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 478) and γ-di-*n*-butylaminopropylamine (22·3 g.) were heated at 170° for 2 hours. The product, left as a highly viscous oil on cooling, formed a *dipicrate* which crystallised from β-ethoxyethanol, m. p. 198—199° (Found: C, 44·3; H, 4·7; N, 18·4. $C_{15}H_{28}ON_4,2C_6H_3O_7N_3$ requires C, 43·9; H, 4·6; N, 19·0%).

4-Chloro-2-γ-di-*n*-butylaminopropylaminopyrimidine (III; R′ = R″ = H, R‴ = $[CH_2]_3$·NBu^n_2), prepared from the above hydroxy compound with phosphoryl chloride, followed by working up in the usual way, formed a viscous oil. The *dipicrate* crystallised from β-ethoxyethanol, m. p. 150—151° (Found: C, 43·4; H, 4·6; N, 17·9. $C_{15}H_{27}N_4Cl,2C_6H_3O_7N_3$ requires C, 42·8; H, 4·4; N, 18·5%).

4-p-*Chloroanilino*-2-γ-*di*-n-*butylaminopropylaminopyrimidine* (VIII; R′ = Cl, R″ = $[CH_2]_3$·NBu^n_2).—A mixture of 4-chloro-2-γ-di-*n*-butylaminopropylaminopyrimidine (7·5 g.), *p*-chloroaniline (3·2 g.), water (25 c.c.), and 10N-hydrochloric acid (2·5 c.c.) was refluxed for 1 hour and then evaporated to dryness under reduced pressure. The residue was dried by dissolving in alcohol and again evaporating to dryness. It was then crystallised from alcohol–ethyl acetate and gave colourless prisms of the *dihydrochloride*, m. p. 155—157° (Found: C, 53·2; H, 7·3; Cl′, 14·4. $C_{21}H_{32}N_5Cl,2HCl,0·5H_2O$ requires C, 53·4; H, 7·4; Cl′, 15·0%) (4811).

4-p-*Nitroanilino*-2-γ-*di*-n-*butylaminopropylaminopyrimidine* (VIII; R′ = NO_2, R″ = $[CH_2]_3$·NBu^n_2).—*p*-Nitroaniline (3·9 g.) was added to a solution of 4-chloro-2-γ-di-*n*-butylaminopropylaminopyrimidine (8·4 g.) in water (28 c.c.) and 10N-hydrochloric acid (2·8 c.c.), and the mixture refluxed for 1 hour. The cooled solution was made alkaline with sodium hydroxide, and the liberated product separated and dissolved in 5% acetic acid. After treatment with decolorising charcoal the acetic acid solution was treated with sodium hydroxide and extracted with chloroform. Evaporation of the dried extract gave the *base* which crystallised from benzene–light petroleum (b. p. 60—80°) in yellow prisms, m. p. 112—114° (Found: C, 62·8; H, 7·3; N, 21·0. $C_{21}H_{32}O_2N_6$ requires C, 63·0; H, 8·0; N, 21·0%) (5049). Its *dipicrate* separated from β-ethoxyethanol in yellow plates, m. p. 206—207° (Found: C, 46·1; H, 4·5. $C_{21}H_{32}O_2N_6,2C_6H_3O_7N_3$ requires C, 46·2; H, 4·4%).

4-p-*Chloroanilino*-2-*ethylthio*-5 : 6-*dimethylpyrimidine* (V; R′ = Me, R″ = Et).—A mixture of 4-chloro-2-ethylthio-5 : 6-dimethylpyrimidine (Chi and Kao, *J. Amer. Chem. Soc.*, 1936, **58**, 767) (10·1 g.), *p*-chloroaniline (6·4 g.), water (40 c.c.), acetone (10 c.c.), and 10N-hydrochloric acid (0·5 c.c.) was refluxed for 2 hours, cooled, and filtered. The collected solid was dissolved in alcohol with the addition of ammonia to give an alkaline reaction, the solution diluted with water, and the precipitated product isolated by filtration. After being washed with water it was crystallised from alcohol, forming colourless needles, m. p. 165—166° (Found: S, 10·9. $C_{14}H_{16}N_3ClS$ requires S, 10·9%) (yield, 8·2 g.).

4-p-*Chloroanilino*-2-*hydroxy*-5 : 6-*dimethylpyrimidine* (VI; R = Me).—The above ethylthiopyrimidine (10 g.) and 48% hydrobromic acid (100 c.c.) were refluxed for 40 hours and the resulting clear solution diluted with water and made alkaline with ammonia. The precipitated 4-p-*chloroanilino*-2-*hydroxy*-5 : 6-*dimethylpyrimidine* was filtered off and dried (yield, 8·2 g.). Crystallised from β-ethoxyethanol–alcohol it formed colourless thick prisms, m. p. 305—310° (decomp.) with previous marked darkening (Found: N, 16·8; Cl, 13·8. $C_{12}H_{12}ON_3Cl$ requires N, 16·8; Cl, 14·2%).

2-*Chloro*-4-p-*chloroanilino*-5 : 6-*dimethylpyrimidine* (VII; R = Me).—4-*p*-Chloroanilino-2-hydroxy-5 : 6-dimethylpyrimidine (29 g.) was treated with boiling phosphoryl chloride (65 c.c.) during 3 hours. After removal of the excess of phosphoryl chloride under diminished pressure the residue was treated with ice and water. After standing for some time the mixture was made alkaline with ammonia and the solid collected. Crystallisation from alcohol gave the *chloropyrimidine* as colourless prisms, m. p. 173—174° (yield, 19·8 g.) (Found: C, 53·9; H, 4·0; N, 15·8. $C_{12}H_{11}N_3Cl_2$ requires C, 53·7; H, 4·1; N, 15·7%).

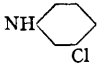
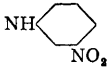
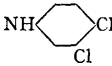
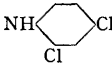
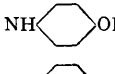
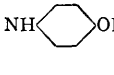
4-p-*Chloroanilino*-2-γ-*diethylaminopropylamino*-5 : 6-*dimethylpyrimidine* (XI; R′=Cl, R″=Me, R‴=$[CH_2]_3$·NEt_2).—2-Chloro-4-*p*-chloroanilino-5 : 6-dimethylpyrimidine (10 g.) and γ-diethylaminopropylamine (6 g.) were heated at 120—130° for 8 hours. The melt was then dissolved in warm dilute hydrochloric acid, and the solution made alkaline with sodium hydroxide and extracted with chloroform. The chloroform was extracted several times with 5% acetic acid, the extracts combined and added to excess of sodium hydroxide solution. The *base*, isolated by extraction with chloroform, crystallised from light petroleum (b. p. 60—80°); colourless prisms, m. p. 64—65° (Found: C, 60·1; H, 7·5; N, 18·6. $C_{19}H_{28}N_5Cl,H_2O$ requires C, 60·1; H, 7·9; N, 18·4%). The *dipicrate* crystallised from β-ethoxyethanol in yellow prisms, m. p. 175—176° (Found: C, 46·1; H, 4·5; N, 18·5. $C_{19}H_{28}N_5Cl,2C_6H_3O_7N_3$ requires C, 45·4; H, 4·1; N, 18·8%).

4-*p*-Chloroanilino-2-γ-di-*n*-butylaminopropylamino-5 : 6-dimethylpyrimidine (XI; R′ = Cl, R″ = Me, R‴ = $[CH_2]_3$·NBu^n_2), prepared in a similar manner using γ-di-*n*-butylaminopropylamine, was obtained as an oil. This gave a *dipicrate* which separated from β-ethoxyethanol–alcohol in yellow needles, m. p. 188—190° (Found: C, 47·9; H, 4·8; N, 17·3. $C_{23}H_{36}N_5Cl,2C_6H_3O_7N_3$ requires C, 48·0; H, 4·8; N, 17·6%) and a *dihydrochloride* (5004) which crystallised from alcohol–ethyl acetate and formed colourless needles, m. p. 204—205° (Found: C, 55·3; H, 7·4; N, 14·4; Cl′, 14·5. $C_{23}H_{36}N_5Cl,2HCl,0·5H_2O$ requires C, 55·3; H, 7·8; N, 14·0; Cl′, 14·2%).

4-*Chloro*-5-*bromo*-2-*methylthio*-6-*methylpyrimidine.*—5-Bromo-4-hydroxy-2-methylthio-6-methylpyrimidine (Part VII; *loc. cit.*) (20 g.) and phosphoryl chloride (65 c.c.) were refluxed for 1 hour. After removal of excess of phosphoryl chloride the residue was poured on ice and made alkaline with ammonia. The *chloropyrimidine* solidified on standing and was

Table IV.

4-Arylamino-2-aminoalkylamino-6-methylpyrimidines. Variation of the substituent in the anilino residue.

Substituent at 2.	Substituent at 4.	Procedure.	Derivative.	Solvent used for crystn.; crystalline form.	Melting point.	Formula.	Analysis. Found, %. C.	H.	N.	Cl'.	Required, %. C.	H.	N.	Cl'.
	$NH\cdot[CH_2]_3\cdot NBu^{\alpha}_2$	(d)	Dipicrate	β-Ethoxyethanol–alcohol; thick yellow laminæ	180—181°	$C_{22}H_{34}N_5Cl,2C_6H_3O_7N_3$	46·7	4·6	17·8	—	47·4	4·5	17·9	—
			Dihydrochloride	Butanol–ethyl acetate; colourless thick prisms	221—223	$C_{22}H_{34}N_5Cl,2HCl,0{\cdot}5H_2O$	54·4	7·4	15·0	14·4	54·4	7·6	14·4	14·6
	$NH\cdot[CH_2]_3\cdot N<[CH_2]_4>CH_2$	(d)	Dihydrochloride	Alcohol–water; colourless prisms	262—264	$C_{19}H_{26}O_2N_6,2HCl,1{\cdot}5H_2O$	48·8	6·2	17·5	15·3	48·5	6·6	17·9	15·1
	$NH\cdot[CH_2]_3\cdot NBu^{\alpha}_2$		Dipicrate	β-Ethoxyethanol–alcohol; thick yellow laminæ	192—193	$C_{22}H_{33}N_5Cl_2,2C_6H_3O_7N_3$	45·5	4·4	17·2	—	45·5	4·4	17·2	—
		(a)	Dihydrochloride	Methanol–ethyl acetate; colourless prisms	240—242	$C_{22}H_{33}N_5Cl_2,2HCl,H_2O$	50·1	7·2	13·1	12·8	49·9	7·0	13·2	13·4
	$NH\cdot[CH_2]_3\cdot NBu^{\alpha}_2$	(c)	—	—	50—52 (b. p. 220—222°/ 0·12 mm.)	$C_{22}H_{33}N_5Cl_2$	60·0	7·3	15·7	—	60·3	7·5	16·0	—
			Dipicrate	β-Ethoxyethanol	226—227°	$C_{22}H_{33}N_5Cl_2,2C_6H_3O_7N_3$	45·7	4·6	16·6	—	45·5	4·4	17·2	—
	$NH\cdot[CH_2]_3\cdot NEt_2$	(b)	Dihydrochloride	Aqueous alcohol; colourless needles	269—271	$C_{18}H_{27}ON_5,2HCl$	53·6	7·2	17·1	17·7	53·7	7·2	17·4	17·7
	$NH\cdot[CH_2]_3\cdot NBu^{\alpha}_2$	(b)	Dihydrochloride	Alcohol–ethyl acetate	120—122	$C_{22}H_{35}ON_5,2HCl,2H_2O$	53·2	8·0	14·2	14·2	53·4	8·3	14·2	14·3

then filtered off, pressed as dry as possible, and dissolved in benzene. After being dried, the benzene solution was evaporated and the residue crystallised from light petroleum (b. p. 60—80°); colourless needles, m. p. 72—73° (Found: S, 12·8. $C_6H_6N_2ClBrS$ requires S, 12·6%).

5-Bromo-4-p-chloroanilino-2-methylthio-6-methylpyrimidine (V; R′ = Br, R″ = Me).—4-Chloro-5-bromo-2-methylthio-6-methylpyrimidine (6·3 g.), *p*-chloroaniline (3·2 g.), water (20 c.c.), acetone (5 c.c.), and 10N-hydrochloric acid (0·25 c.c.) were refluxed for 3 hours. On cooling, the oily layer which had formed solidified. After filtration, it was dissolved in alcohol, and the solution made alkaline with ammonia and then diluted with water to precipitate the product. Crystallised from aqueous methanol it formed colourless blunt-ended needles, m. p. 116—117° (Found: C, 42·1; H, 3·5; N, 12·5. $C_{12}H_{11}N_3ClBrS$ requires C, 41·8; H, 3·2; N, 12·2%).

Hydrolysis of 5-Bromo-4-p-chloroanilino-2-methylthio-6-methylpyrimidine.—The methylthio compound (10 g.) was boiled with hydrobromic acid (100 c.c. of 48%) for 22 hours and the solution was then diluted with water and made alkaline with ammonia. The precipitated product was collected, washed with water, and dried. In view of its low solubility in solvents it was purified in the following manner. Sodium hydroxide was added to a suspension in alcohol and the mixture raised to the boil. After treatment with decolorising carbon the solution was filtered and cooled. The sodium salt which separated was filtered off and suspended in alcohol, and the suspension acidified with acetic acid and diluted with water. The precipitated product was filtered off, washed with water, and dried; m. p. >340° (Found: C, 56·3; H, 4·2; N, 17·8; Cl, 15·1. $C_{11}H_{10}ON_3Cl$ requires C, 56·05; H, 4·25; N, 17·8; Cl, 15·1%). The product was thus 4-*p*-chloroanilino-2-hydroxy-6-methylpyrimidine (VI; R = H). This was confirmed by conversion into the corresponding chloro compound (VII; R = H) with phosphoryl chloride; 2-chloro-4-*p*-chloroanilino-6-methylpyrimidine was thus obtained, m. p. 135—137° undepressed in admixture with authentic material (Part VI, *loc. cit.*).

2-γ-Diethylaminopropylamino-4-hydroxy-6-methyl-5-ethylpyrimidine (II; R′ = Et, R″ = Me, R‴ = $[CH_2]_3$·NEt_2).—4-Hydroxy-2-methylthio-6-methyl-5-ethylpyrimidine (Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 489) (36·8 g.) and γ-diethylaminopropylamine (26 g.) were heated to 130°. Evolution of methylthiol took place rapidly at this temperature and appeared to be complete after ½ hour. The temperature was then raised to 160° and this temperarure maintained for 2 hours to ensure complete reaction. On cooling, the product remained as an extremely viscous oil which could not be crystallised. The *dipicrate* formed yellow prisms from alcohol, m. p. 191—192° (Found: N, 19·1. $C_{14}H_{26}ON_4,2C_6H_3O_7N_3$ requires N, 19·3%).

4-Chloro-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine (III; R′ = Et, R″ = Me, R‴ = $[CH_2]_3$·NEt_2).—To the above hydroxy compound (53·2 g.) phosphoryl chloride (100 c.c.) was added at 25°. A vigorous reaction took place. When this had subsided the mixture was boiled for 2 minutes, cooled, and poured on ice with stirring. The resulting clear solution was immediately made strongly alkaline with sodium hydroxide, the temperature being kept below 40°, and the product extracted with benzene (4 extractions). The combined benzene extracts were washed with water and then shaken several times with 5% acetic acid. The product, liberated from the acid extracts with sodium hydroxide, was again extracted with benzene and the benzene solution washed twice with water, dried, and evaporated. The residual oil was distilled giving *4-chloro-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine* as a colourless oil, b. p. 138°/0·1 mm. Its *dipicrate* crystallised from β-ethoxyethanol in yellow prisms, m. p. 160—161° (Found: C, 41·8; H, 4·5; N, 19·0; Cl, 4·6. $C_{14}H_{25}N_4Cl,2C_6H_3O_7N_3$ requires C, 42·0; H, 4·2; N, 18·9; Cl, 4·8%).

4-p-Chloroanilino-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine
(XI; R′ = Cl, R″ = Et, R‴ = $[CH_2]_3$·NEt_2).

—4-Chloro-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine (8·5 g.), *p*-chloroaniline (11·5 g.), and *p*-chloroaniline hydrochloride (4·9 g.) were mixed and heated in an oil-bath at 170—175° for 2 hours. Repeated extraction of the cooled reaction mixture with hot benzene left the *dihydrochloride* which crystallised from methanol in colourless laminæ, m. p. 245—246° (Found: C, 53·5; H, 6·7; N, 15·6; Cl′, 15·6. $C_{20}H_{30}N_5Cl,2HCl$ requires C, 53·5; H, 7·1; N, 15·6; Cl′, 15·8%) (4230).

4-p-Nitroanilino-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine
(XI; R′ = NO_2, R″ = Et, R‴ = $[CH_2]_3$·NEt_2).

—4-Chloro-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine (7·1 g.), *p*-nitroaniline (3·45 g.), water (25 c.c.), and 10N-hydrochloric acid (2·5 c.c.) were refluxed for 1 hour, the resulting solution was cooled and made alkaline with sodium hydroxide. The precipitated base was taken into chloroform and then extracted with 5% acetic acid. The acid extract was treated with sodium hydroxide and the product isolated with chloroform. It separated from light petroleum (b. p. 100—120°) in yellow prisms, m. p. 126—128° (Found: C, 62·4; H, 7·6; N, 21·8. $C_{20}H_{30}O_2N_6$ requires C, 62·2; H, 7·8; N, 21·8%) (5050).

4-p-Cyanoanilino-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine
(XI; R′ = CN, R″ = Et, R‴ = $[CH_2]_3$·NEt_2).

—A mixture of (III; R′ = Et, R″ = Me, R‴ = $[CH_2]_3$·NEt_2) (7·1 g.), *p*-cyanoaniline (3·0 g.), water (25 c.c.), and 10N-hydrochloric acid (2·5 c.c.) was refluxed for 1 hour, and the solution cooled and made alkaline with sodium hydroxide. The product was precipitated as an oil which soon solidified. It was filtered off and purified by dissolution in 5% acetic acid and reprecipitation with sodium hydroxide. Crystallised from aqueous alcohol, *4-p-cyanoanilino-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine* formed colourless prisms, m. p. 151—152° (Found: C, 68·7; H, 8·3; N, 23·1. $C_{21}H_{30}N_6$ requires C, 68·8; H, 8·2; N, 23·0%) (5051).

2-γ-Di-n-butylaminopropylamino-4-hydroxy-6-methyl-5-ethylpyrimidine (II; R′=Et, R″=Me, R‴=$[CH_2]_3$·NBu^n_2).—γ-Di-*n*-butylaminopropylamine (8·2 g.) and 4-hydroxy-2-methylthio-6-methyl-5-ethylpyrimidine (8·3 g.) were mixed and fused at 160—170° for 2 hours leaving a highly viscous oil. With picric acid (one equivalent) it gave a *monopicrate* which crystallised from methanol; yellow prisms, m. p. 182—183° (Found: C, 52·5; H, 6·8; N, 17·5. $C_{18}H_{34}ON_4,C_6H_3O_7N_3$ requires C, 52·3; H, 6·7; N, 17·8%). The *dipicrate* was obtained by adding an alcoholic solution of picric acid (excess) to a solution of the base in β-ethoxyethanol. Crystallised from alcohol it formed stout yellow needles, m. p. 166—167° (Found: C, 46·2; H, 5·1; N, 18·4. $C_{18}H_{34}ON_4,2C_6H_3O_7N_3$ requires C, 46·15; H, 5·1; N, 17·9%).

4-Chloro-2-γ-di-n-butylaminopropylamino-6-methyl-5-ethylpyrimidine
(III; R′ = Et, R″ = Me, R‴ = $[CH_2]_3$·NBu^n_2).

—The above hydroxypyrimidine (6·2 g.) and phosphoryl chloride (25 c.c.) were warmed until reaction occurred. After this had subsided the mixture was refluxed for 2 minutes and worked up as in the preparation of the γ-diethylaminopropylamino derivative. The chloropyrimidine was thus obtained as an oil which was used for the following condensation without distillation. The *dipicrate* crystallised from methanol in flat yellow needles, m. p. 140—141° (Found: C, 45·1; H, 5·0; N, 17·5; Cl, 4·7. $C_{18}H_{33}N_4Cl,2C_6H_3O_7N_3$ requires C, 45·1; H, 4·9; N, 17·5; Cl, 4·4%).

4-p-Chloroanilino-2-γ-di-n-butylaminopropylamino-6-methyl-5-ethylpyrimidine
(XI; R′ = Cl, R″ = Et, R‴ = $[CH_2]_3$·NBu^n_2).

—The above chloropyrimidine (4·0 g.), *p*-chloroaniline (4·4 g.), and *p*-chloroaniline hydrochloride (1·9 g.) were mixed and fused at 160—170° for 2 hours. The resulting liquid reaction mixture was poured into benzene (1 l.) and the mixture

boiled for 5 minutes. The solid product obtained was filtered off and crystallised from methanol–ethyl acetate giving the *dihydrochloride*, m. p. 215—216° (Found : C, 56·7; H, 7·6; N, 13·9; Cl′, 14·3. $C_{24}H_{38}N_5Cl,2HCl$ requires C, 57·1; H, 7·9; N, 13·9; Cl′, 14·1%) (5100).

IMPERIAL CHEMICAL INDUSTRIES, LIMITED,
RESEARCH LABORATORIES, BLACKLEY, MANCHESTER, 9.

[*Received, February 14th,* 1946.]