152. *Synthetic Antimalarials. Part XV. Some Aryloxy- and Arylthio-dialkylaminoalkylaminopyrimidines.*

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The preparation of a number of 2(or 4)-dialkylaminoalkylamino-4(or 2)-aryloxy- and -arylthio-6-methylpyrimidines related to the 2-arylamino-4-dialkylaminoalkylamino- and -4-arylamino-2-dialkylaminoalkylamino-6-methylpyrimidines of previous papers in this series (*J.*, 1946, 343, 351, 370, 720) is described. Some of these new compounds show low antimalarial activity, and the theoretical implications of this are discussed.

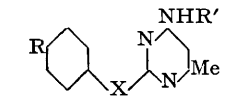
The 2-chloro-4-dialkylaminoalkylamino-6-methylpyrimidines prepared as intermediates in the synthesis of compounds of type (I; X = S, O) afford a further route to the corresponding 2-arylamino-derivatives (I; X = NH) first described in Parts I and II (*J.*, 1946, 343, 351).

In our original plan of work following the discovery of antimalarial activity in 2-arylamino-4-aminoalkylamino-6-methylpyrimidines such as (I; R = Cl, R′ = $[CH_2]_2$·NEt_2, X = NH), it was proposed to prepare compounds in which the imino-linkage between the aryl and the pyrimidine nucleus was replaced by other groups. In Part IV (Curd and Rose, *J.*, 1946, 362) the first step in this direction, the replacement of the imino-group by guanidino-, was described. The present communication deals with the preparation of compounds in which the conjugate grouping is a sulphide or ether linkage (*e.g.*, I; R′ = dialkylaminoalkyl, X = S or O). Since the compounds were also required for other chemotherapeutic investigations we have also prepared position isomers of this type, namely (II; X = S or O) analogous to the active 4-arylamino-2-aminoalkylamino-6-methylpyrimidines (II; X = NH) (Part VI; *J.*, 1946, 370; Part IX, *ibid.*, p. 720) and (III; X = S) corresponding to the inactive 4-arylamino-6-aminoalkylamino-2-methylpyrimidines (III; X = NH) (see Part VIII, *J.*, 1946, 713).

The interbond angle of imino-nitrogen is sufficiently close to those of oxygen and sulphur (with the greater divergence in the latter instance) to permit the formulation of molecules bearing a formal structural resemblance to riboflavin, and the possibility existed that they might be effective antimalarial agents on that account (cf. Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, **39**, 157). The new compounds were, however, primarily intended to throw light on the types of linking group necessary to promote antimalarial activity. The activity of types [I; X = NH or NH·C(:NH)·NH] and (II; X = NH) contrasted with the inactivity of compounds analogous to (I) in which the aryl group is attached directly to the pyrimidine nucleus (see Part I, *loc. cit.*) had earlier suggested that a linking group capable of forming a prototropic system with the pyrimidine nucleus was necessary.

In later communications (Part X, *J.*, 1946, 729; Part XII, this vol., p. 154) these theoretical arguments have been developed, largely as a result of the positive activity of types (I and II; X = NH) as compared with the lack of antimalarial action in type (III; X = NH) and the corresponding 1 : 3 : 5-triazine series, and the working hypothesis developed that marked therapeutic effect, *in the molecular species under discussion*, was dependent upon the existence within the molecule of aryl and alkyl groups linked by a conjugated chain made up of alternating nitrogen and carbon atoms. In order to demonstrate such a conjugated path within the molecule it was frequently essential either to formulate the drug molecules in the tautomeric form of that conventionally used by supposing a prototropic shift (compare I; X = NH and Ib), or to postulate a major contribution to a resonance hybrid of an excited state such as (Ia and IIa), but we were not prepared to indicate which might be the more important factor. Now it was evident that sulphide and ether linkages could not provide for prototropic changes analogous to that of (I; X = NH) ⟶ (Ib), except in the unlikely event of sulphonium or oxonium salt formation, so that the slight but undoubted activity observed in certain compounds of types (I and II; X = S) (see table) would appear to lend some support to the view that resonance features are predominantly important. The lower activity or complete inactivity of the compounds containing an oxygen linkage would suggest, if our views are correct, that the oxonium structures (Ia and IIa; X = O) must contribute less to the hybrid state of the molecules than the corresponding structures (Ia and IIa; X = S) and the latter in turn are less probable than the corresponding imino-types. This is in accord with the known order of O < S < N in the electropositive series.

The association of high antimalarial activity in compounds of types [I; X = NH or NH·C(:NH)·NH] and (II; X = NH) with the presence of a group such as halogen, nitro-, or cyano- in the para position of the aryl nucleus has previously been correlated with their powerful electron-attracting effect, although the exact significance of this was not understood. The observation now made that compounds of types (I and II; X = S) containing a methoxy group (R = OMe) possess higher antimalarial activity than those containing a chlorine substituent (R = Cl) suggests that the function of the substituent may be an influence on the resonance structure of the drug molecule. The electron donating (+ *T*) effect of the methoxy group will, by increasing electron availability at the sulphur atom, enhance the significance of structures such as (Ia and IIa; X = S), whereas the powerful inductive effect of the chlorine atom (— *I*) will operate to the disadvantage of such structures.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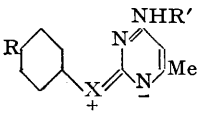
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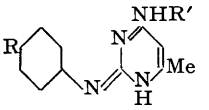
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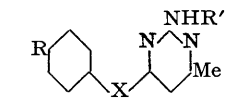
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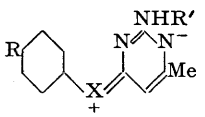
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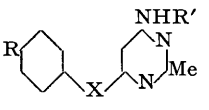
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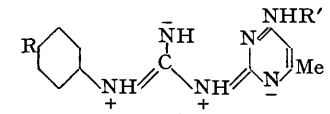
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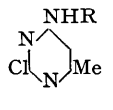
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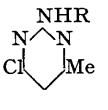
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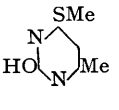
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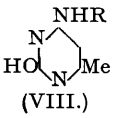
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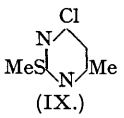
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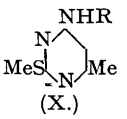
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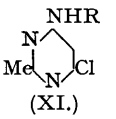
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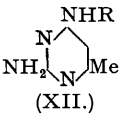
(XII.)

In addition to the views expressed above to account for the reduced activity of (I and II; X = S or O) as compared with (I and II; X = NH), it is desirable to consider a further factor which will operate in the same direction. The chemical lability of certain types of 2- or 4-alkylthiopyrimidines is well known, and we have demonstrated the anticipated greater lability of phenoxy- as opposed to anilino- by the reaction of 2-p-*chloroanilino*-4-*phenoxy*-6-*methylpyrimidine* with β-diethylaminoethylamine to give the corresponding 4-β-diethylaminoethyl-

amino-derivative and with γ-diethylaminopropylamine to give (I; R = Cl, R′ = $[CH_2]_3$·NEt_2, X = NH). It is conceivable, therefore, that the thioether and ether drugs are much less stable *in vivo* than the drugs of the imino-type.

For the preparation of compounds of types (I and II; X = S), 2-chloro-4-aminoalkylamino-6-methylpyrimidines (V) and 4-chloro-2-aminoalkylamino-6-methylpyrimidines (VI) were required. Substances of type (VI) had been prepared previously (see Part VI, *loc. cit.*) and a method has now been developed for the preparation of those of type (V). It was first demonstrated that 2-hydroxy-4-methylthio-6-methylpyrimidine (VII) underwent reaction with dialkylaminoalkylamines such as β-diethylaminoethylamine, γ-diethylaminopropylamine, and δ-diethylamino-α-methylbutylamine to give 4-dialkylaminoalkylamino-2-hydroxy-6-methylpyrimidines (VIII) which on treatment with phosphoryl chloride were converted into the required 2-chloro-4-dialkylaminoalkylamino-6-methylpyrimidines (V). The method was, however, an unattractive one as the preparation of the starting material (VII) involved a four stage synthesis from 4-hydroxy-2-methylthio-6-methylpyrimidine (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 431). A more convenient method was provided by the following: 4-chloro-2-methylthio-6-methylpyrimidine (*idem, ibid.*) (IX) was brought into reaction with a dialkylaminoalkylamine to give a 4-dialkylaminoalkylamino-2-methylthio-6-methylpyrimidine (X) which was then hydrolysed to the corresponding 4-dialkylaminoalkylamino-2-hydroxy-6-methylpyrimidine (VIII) (isolated as dihydrochloride), which was in turn converted by treatment with phosphoryl chloride into the 2-chloro-4-dialkylaminoalkylamino-6-methylpyrimidine (V). Using this method the following were prepared: 2-*chloro*-4-β-*diethylaminoethylamino*- (V; R = $[CH_2]_2$·NEt_2), 2-*chloro*-4-γ-*diethylaminopropylamino*- (V; R = $[CH_2]_3$·NEt_2) and 2-*chloro*-4-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine* (V; R = CHMe·$[CH_2]_3$·NEt_2).

These compounds of type (V) were then brought into reaction with thiophenols such as *p*-chlorothiophenol and *p*-methoxythiophenol, and a series of compounds of type (I; X = S) was thus obtained. Probably because of the intervention of side reactions attemps to condense the 2-chloro-4-dialkylaminoalkylamino-6-methylpyrimidines (V) with sodium *p*-chloro- or *p*-methoxy-thiophenoxide in boiling alcoholic solution were unsatisfactory, although both methods were successfully used for the corresponding conversion of the 4-chloro-2-dialkylaminoalkylamino-6-methylpyrimidines (VI) into type (II; X = S).

Because of the greater activity found in type (II; X = S) than (I; X = S) the exploration of compounds containing an oxygen linkage was carried out mainly in type (II; X = O), and the only compound of type (I) containing an oxygen linkage made was 4-δ-*diethylamino*-α-*methylbutylamino*-2-p-*chlorophenoxy*-6-*methylpyrimidine* (I; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = O) by melting together *p*-chlorophenol and (V; R = CHMe·$[CH_2]_3$·NEt_2). Of the compounds of type (II; X = O), 2-δ-*diethylamino*-α-*methylbutylamino*-4-p-*chlorophenoxy*-6-*methylpyrimidine* (II; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = O) resulted from the interaction of sodium *p*-chlorophenoxide with (VI; R = CHMe·$[CH_2]_3$·NEt_2) in alcoholic solution, while the sodium salt of quinol monomethyl ether melted with (VI; R = $[CH_2]_2$·NEt_2) gave 2-β-*diethylaminoethylamino*-4-p-*methoxyphenoxy*-6-*methylpyrimidine* (II; R = OMe, R′ = $[CH_2]_2$·NEt_2, X = O) and with (VI; R = $[CH_2]_3$·NEt_2) gave 2-γ-*diethylaminopropylamino*-4-p-*methoxyphenoxy*-6-*methylpyrimidine* (II; R = OMe, R′ = $[CH_2]_3$·NEt_2, X = O).

The 4-dialkylaminoalkylamino-6-*p*-chlorophenylthio-2-methylpyrimidines (III; R = Cl, R′ = $[CH_2]_3$·NEt_2, X = S) and (III; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = S) were prepared by melting *p*-chlorothiophenol with, respectively, 4-chloro-6-γ-diethylaminopropylamino-2-methylpyrimidine (XI; R = $[CH_2]_3$·NEt_2) and 4-chloro-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine (XI; R = CHMe·$[CH_2]_3$·NEt_2) which were available as the result of other work (forthcoming publication).

The discovery of a satisfactory method for the preparation of 2-chloro-4-dialkylaminoalkylamino-6-methylpyrimidines (V) (see above) opened up an alternative route for the preparation of compounds of type (I; X = NH). It was found that compounds of type (V) condensed with *p*-chloroaniline either at 150—160° (lower temperatures may be sufficient) or preferably in boiling aqueous solution as their monohydrochlorides in presence of a little extra hydrochloric acid as catalyst. Thus, 2-*p*-chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine (I; R = Cl, R′ = $[CH_2]_2$·NEt_2, X = NH) (2666) was prepared from (V; R = $[CH_2]_2$·NEt_2) 2-*p*-chloroanilino-4-γ-diethylaminopropylamino-6-methylpyrimidine (I; R = Cl, R′ = $[CH_2]_3$·NEt_2, X = NH) (3299) from (V; R = $[CH_2]_3$·NEt_2), and 2-*p*-chloroanilino-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (I; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = NH) (3300) from (V; R = CHMe·$[CH_2]_3$·NEt_2) (see Part I, *loc. cit.*). Similarly, by heating with alcoholic ammonia in a sealed tube at 180—200° (V; R = $[CH_2]_2$·NEt_2) was converted

into 2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine (XII; R = $[CH_2]_2$·NEt_2), and (V; R = CHMe·$[CH_2]_3$·NEt_2) into 2-amino-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (XII; R = CHMe·$[CH_2]_3$·NEt_2) (see Part III, *J.*, 1946, 357).

Table: Antimalarial Activities.

For interpretation of the results see Part I (*loc. cit.*).

Ref. No.	Pyrimidine.	Dose, mg./kg.	Activity.
5101	4-β-Diethylaminoethylamino-2-*p*-chlorophenylthio-6-methyl-	160	—
		80	—
5140	4-β-Diethylaminoethylamino-2-*p*-methoxyphenylthio-6-methyl	160	±
		80	—
5208	4-γ-Diethylaminopropylamino-2-*p*-chlorophenylthio-6-methyl-	160	—
5209	4-γ-Diethylaminopropylamino-2-*p*-methoxyphenylthio-6-methyl-	160	—
		80	—
5151	4-δ-Diethylamino-α-methylbutylamino-2-*p*-chlorophenylthio-6-methyl-	160	±
		80	—
5649	4-δ-Diethylamino-α-methylbutylamino-2-*p*-chlorophenoxy-6-methyl-	160	—
		80	—
4988	2-β-Diethylaminoethylamino-4-*p*-chlorophenylthio-6-methyl-	160	—
5019	2-β-Diethylaminoethylamino-4-*p*-methoxyphenylthio-6-methyl-	120	Toxic
		80	+
		40	+
5931	2-β-Diethylaminoethylamino-4-*p*-methoxyphenoxy-6-methyl-	160	—
		80	—
5037	2-γ-Diethylaminopropylamino-4-*p*-chlorophenylthio-6-methyl-	80	—
5020	2-γ-Diethylaminopropylamino-4-*p*-methoxyphenylthio-6-methyl-	80	+ to ++
		40	+
5932	2-γ-Diethylaminopropylamino-4-*p*-methoxyphenoxy-6-methyl-	160	+
		80	—
5045	2-δ-Diethylamino-α-methylbutylamino-4-*p*-chlorophenylthio-6-methyl-	160	Toxic
		80	—
5065	2-δ-Diethylamino-α-methylbutylamino-4-*p*-methoxyphenylthio-6-methyl-	160	+
		80	±
5150	2-δ-Diethylamino-α-methylbutylamino-4-*p*-chlorophenoxy-6-methyl-	160	Toxic
		80	—
5935	2-γ-Di-*n*-butylaminopropylamino-4-*p*-chlorophenylthio-6-methyl-	160	—
		80	—
5934	2-γ-Di-*n*-butylaminopropylamino-4-*p*-methoxyphenylthio-6-methyl-	160	—
		80	—
5342	4-γ-Diethylaminopropylamino-6-*p*-chlorophenylthio-2-methyl-	Not tested	
5727	4-δ-Diethylamino-α-methylbutylamino-6-*p*-chlorophenylthio-2-methyl-	Not tested	

Experimental.

4-β-Diethylaminoethylamino-2-methylthio-6-methylpyrimidine (X; R = $[CH_2]_2$·NEt_2).—4-Chloro-2-methylthio-6-methylpyrimidine (17·45 g.) and β-diethylaminoethylamine (12·8 g.) were heated (oil-bath) to 80° and when the resulting reaction had subsided the temperature was gradually raised to 150° during 1 hour. The mixture was then cooled, treated with sodium hydroxide solution, and extracted with benzene. The dried (Na_2SO_4) benzene solution on evaporation left an oil which was purified by vacuum distillation to give the *pyrimidine* (12·5 g.), b. p. 150—151·5°/1·2 mm. (Found: S, 12·5. $C_{12}H_{22}N_4S$ requires S, 12·6%). On treatment with water it formed a *monohydrate* which crystallised from light petroleum (b. p. 60—80°) in colourless prisms (Found: C, 53·0; H, 8·6; S, 11·5. $C_{12}H_{22}N_4S,H_2O$ requires C, 52·9; H, 8·8; S, 11·8%). The *dipicrate* separated from alcohol in clumps of yellow prisms, m. p. 155—157° (Found: C, 40·6; H, 4·2; N, 19·3. $C_{12}H_{22}N_4S,2C_6H_3O_7N_3$ requires C, 40·45; H, 3·9; N, 19·7%).

4-β-Diethylaminoethylamino-2-hydroxy-6-methylpyrimidine (VIII; R = $[CH_2]_2$·NEt_2).—(*a*) 2-Hydroxy-4-methylthio-6-methylpyrimidine (31 g.) and β-diethylaminoethylamine (23 g.) were heated at 160—170° for 2 hours. Crystallisation of the residue from chloroform–ethyl acetate gave the *product* as colourless prisms, m. p. 230—232° (Found: C, 56·7; H, 8·7; N, 24·7. $C_{11}H_{20}ON_4,0·5H_2O$ requires C, 56·7; H, 9·0; N, 24·0%). It formed a *dipicrate* which crystallised from 2-ethoxyethanol in yellow laminæ, m. p. 223—224° (Found: C, 40·0; H, 3·8; N, 20·4. $C_{11}H_{20}ON_4,2C_6H_3O_7N_3$ requires C, 40·5; H, 3·8; N, 20·5%).

(*b*) A solution of 4-β-diethylaminoethylamino-2-methylthio-6-methylpyrimidine (10 g.) in hydrochloric acid (100 c.c.) was boiled under reflux for 12 hours and the solution evaporated to dryness under reduced pressure. Crystallisation of the dried residual solid from alcohol gave *4-β-diethylaminoethylamino-2-hydroxy-6-methylpyrimidine dihydrochloride* as colourless needles, m. p. 258—260° (decomp.) (yield, 8·6 g.) (Found: C, 42·5; H, 7·4; N, 17·8. $C_{11}H_{20}ON_4,2HCl,H_2O$ requires C, 41·9; H, 7·6; N, 17·8%). This dihydrochloride was dissolved in water, and the solution exactly neutralised with sodium hydroxide solution and evaporated to dryness under reduced pressure. The product was extracted from the residue with chloroform, the solvent evaporated, and the material crystallised from alcohol–ethyl acetate; m. p. 230—232° (decomp.) (Found: C, 49·9; H, 7·9; N, 20·7. $C_{11}H_{20}ON_4,2H_2O$ requires C, 50·7; H, 7·9; N, 20·7%). It gave a dipicrate, m. p. 222—224° undepressed on admixture

with the picrate of the compound made by method (*a*). Probably because the substance formed different and indefinite hydrates, mixed melting point determinations were unsatisfactory for demonstrating the identity of the bases made by methods (*a*) and (*b*), but the evidence obtained from the identity of the picrates was substantiated by the identity of the chloropyrimidines prepared from the hydroxy-compound made by the two methods (see below).

2-Chloro-4-β-diethylaminoethylamino-6-methylpyrimidine (V; R = $[CH_2]_2$·NEt_2).—(*a*) 4-β-Diethylaminoethylamino-2-hydroxy-6-methylpyrimidine (40 g.), made by method (*a*) above, and phosphoryl chloride (60 c.c.) were refluxed for 2 hours. The mixture was cooled and poured on ice, and when the ice had melted the solution was made alkaline with sodium hydroxide. The liberated product was extracted with benzene and the solution dried (K_2CO_3). Distillation of the residue left after evaporation of the benzene gave the *pyrimidine* as a colourless oil, b. p. 144—146°/0·1 mm. (yield, 23·9 g.). On being stirred with water it formed a solid *hydrate* which crystallised from light petroleum (b. p. 60—80°); m. p. 55—56° (Found: N, 21·7; Cl, 12·9; loss on drying at 100°, 7·0. $C_{11}H_{19}N_4Cl,H_2O$ requires N, 21·5; Cl, 13·6; H_2O, 6·9%). The *dipicrate* crystallised from methanol in yellow prisms, m. p. 126—128° (Found: C, 39·4; H, 3·5; N, 19·4. $C_{11}H_{19}N_4Cl,2C_6H_3O_7N_3$ requires C, 39·4; H, 3·6; N, 20·0%).

(*b*) 4-β-Diethylaminoethylamino-4-hydroxy-6-methylpyrimidine dihydrochloride (52 g.), prepared by method (*b*) above, and phosphoryl chloride (500 c.c.) were refluxed until all the solid had dissolved (*ca.* 6 hours). The solution was then evaporated under reduced pressure to remove the excess of phosphoryl chloride and the residue poured on ice (1 kg.). Further working up was carried out as in (*a*) to give the chloropyrimidine, b. p. 160—162°/0·5 mm. (yield 50%) (Found: Cl, 14·2. $C_{11}H_{19}N_4Cl$ requires Cl, 14·6%). It gave a dipicrate, m. p. 126—128° undepressed by the dipicrate made from the compound obtained by method (*a*).

4-γ-Diethylaminopropylamino-2-methylthio-6-methylpyrimidine (X; R = $[CH_2]_3$·NEt_2).—4-Chloro-2-methylthio-6-methylpyrimidine (17·4 g.) and γ-diethylaminopropylamine (13 g.) were heated under a wide condenser. At 85—90° a vigorous reaction took place. When this had subsided the mixture was heated at 130—140° for ½ hour. It was then cooled, sodium hydroxide solution added, and the product extracted with benzene. Evaporation of the dried benzene solution and distillation of the residue gave the *product* as a yellow oil, b. p. 168—170°/1 mm. (yield 20 g.) (Found: S, 11·7. $C_{13}H_{24}N_4S$ requires S, 11·9%). The *dipicrate* crystallised from alcohol in yellow prisms, m. p. 125—127° (Found: C, 41·6; H, 4·1; N, 19·7. $C_{13}H_{24}N_4S,2C_6H_3O_7N_3$ requires C, 41·3; H, 4·1; H, 19·3%).

4-γ-Diethylaminopropylamino-2-hydroxy-6-methylpyrimidine (VIII; R = $[CH_2]_3$·NEt_2).—(*a*) 2-Hydroxy-4-methylthio-6-methylpyrimidine (5·2 g.) and γ-diethylaminopropylamine (4·9 g.) were heated at 150—160° for 3 hours. Crystallisation of the residue from chloroform–ethyl acetate gave the *pyrimidine* as colourless laminæ, m. p. 183—184° (Found: C, 60·2; H, 8·8; N, 22·8. $C_{12}H_{22}ON_4$ requires C, 60·5; H, 9·2; N, 23·5%).

(*b*) 4-γ-Diethylaminopropylamino-2-methylthio-6-methylpyrimidine (10 g.) and hydrochloric acid (100 c.c.) were refluxed for 24 hours. The solution was then evaporated to dryness under reduced pressure and the dried residue crystallised from alcohol, giving the *dihydrochloride* as colourless laminæ, m. p. 264—266° (yield, 9·5 g.) (Found: C, 46·3; H, 7·7; N, 18·0; Cl′, 22·1. $C_{12}H_{22}ON_4,2HCl$ requires C, 46·3; H, 7·7; N, 18·0; Cl′, 22·8%). The dihydrochloride (5 g.) was dissolved in water, and the solution neutralised with N-sodium hydroxide (33·15 c.c.) and evaporated to dryness under reduced pressure. After being dried by repeated evaporation to dryness with alcohol, the product was dissolved out with chloroform, the solution filtered, and ethyl acetate added. Crystallisation of the precipitated solid gave the base, m. p. 182—184° undepressed on admixture with that made from 2-hydroxy-4-methylthio-6-methylpyrimidine.

2-Chloro-4-γ-diethylaminopropylamino-6-methylpyrimidine (V; R = $[CH_2]_3$·NEt_2).—4-γ-Diethylaminopropylamino-2-hydroxy-6-methylpyrimidine dihydrochloride (62·5 g.) and phosphoryl chloride (500 c.c.) were refluxed for 8 hours. Excess of phosphoryl chloride was then removed under reduced pressure and the residue added to ice. The resulting solution was made alkaline with sodium hydroxide (cooling), the liberated oil extracted with benzene, and the solution dried (K_2CO_3). Evaporation gave the *pyrimidine* which was purified by vacuum distillation (b. p. 164—166°/0·9 mm.); it then set to a mass of crystals (yield, 26 g.) which separated from light petroleum (b. p. 40—60°); m. p. 45° (Found: C, 56·1; H, 8·1; Cl, 13·5. $C_{12}H_{21}N_4Cl$ requires C, 56·1; H, 8·2; N, 13·8%).

4-δ-Diethylamino-α-methylbutylamino-2-methylthio-6-methylpyrimidine (X; R=CHMe·$[CH_2]_3$·NEt_2).—4-Chloro-2-methylthio-6-methylpyrimidine (8·7 g.) and δ-diethylamino-α-methylbutylamine (17·4 g.) were gradually heated to 120°. At this temperature a vigorous reaction ensued, and when this had subsided the mixture was heated at 120—130° for 1 hour. It was then cooled, poured into water, and made alkaline with sodium hydroxide. The oily product was extracted with benzene and the extract dried and evaporated. Distillation of the residue gave the *pyrimidine*, b. p. 176—178°/0·9 mm. (yield, 8·8 g.) (Found: S, 11·0. $C_{15}H_{28}N_4S$ requires S, 10·8%).

4-δ-Diethylamino-α-methylbutylamino-2-hydroxy-6-methylpyrimidine (VIII; R = CHMe·$[CH_2]_3$·NEt_2).—(*a*) 2-Hydroxy-4-methylthio-6-methylpyrimidine (5·2 g.) and δ-diethylamino-α-methylbutylamine (5·3 g.) were heated in an oil-bath at 150—160° for 3 hours. The resulting mass was heated with benzene, cooled, and the insoluble material filtered off. Crystallisation from ethyl acetate gave the product as a *hemihydrate* of indefinite melting point (134—140°) (Found in material dried at 60—65°: C, 60·4; H, 9·6; N, 20·5. $C_{14}H_{26}ON_4,0·5H_2O$ requires C, 61·2; H, 9·8; N, 20·4%). It was slightly hygroscopic, and on storing turned to a sticky mass (Found in material dried in a vacuum at 80°: C, 62·7; H, 9·9; N, 20·9. $C_{14}H_{26}ON_4$ requires C, 63·2; H, 9·2; N, 21·1%). The *dipicrate* separated from 2-ethoxyethanol–alcohol in thick yellow prisms, m. p. 179—180° (Found: C, 43·0; H, 4·7; N, 19·6. $C_{14}H_{26}ON_4,2C_6H_3O_7N_3$ requires C, 43·1; H, 4·4; N, 19·3%).

(*b*) 4-δ-Diethylamino-α-methylbutylamino-2-methylthio-6-methylpyrimidine (10 g.) and hydrochloric acid (100 c.c.) were boiled under reflux for 24 hours. The solution was then evaporated to dryness under reduced pressure and the residue dried by repeated evaporation in the same way with alcohol and benzene. It was neither possible nor necessary to purify this hydrochloride for the preparation of 2-chloro-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (see p. 788). To obtain

the base, a portion of the hydrochloride was dissolved in water, and the solution neutralised with the calculated quantity of N-sodium hydroxide solution and evaporated to dryness. The dried residue was extracted with chloroform, and the solution filtered and precipitated with ethyl acetate. On account of its hygroscopic nature no attempt was made to demonstrate the identity of the base with that made by method (*a*). Instead, it was converted into the dipicrate, m. p. 177—179° either alone or admixed with the picrate of the compound made by method (*a*).

2-*Chloro*-4-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine* (V; R = CHMe·$[CH_2]_3$·NEt_2).—4-δ-Diethylamino-α-methylbutylamino-2-hydroxy-6-methylpyrimidine dihydrochloride (crude) (56·5 g.) and phosphoryl chloride (300 c.c.) were refluxed for 14 hours and the excess of phosphoryl chloride then removed under reduced pressure. The residue was poured on ice and the resulting solution made alkaline with sodium hydroxide, the solution being kept below 30° by addition of ice. The liberated base was extracted with benzene, and the extract dried and evaporated. Distillation of the residual oil gave the *pyrimidine*, b. p. 185—188°/1·2 mm. (yield, 34·5 g.) (Found: Cl, 12·2. $C_{14}H_{25}N_4Cl$ requires Cl, 12·5%).

4-β-*Diethylaminoethylamino*-2-p-*chlorophenylthio*-6-*methylpyrimidine* (I; R = Cl, R′ = $[CH_2]_2$·NEt_2, X = S).—2-Chloro-4-β-diethylaminoethylamino-6-methylpyrimidine (8 g.) and *p*-chlorothiophenol (9·6 g.) were heated in an oil-bath at 120° for 3 hours. Water (100 c.c.) and acetic acid (15 c.c.) were added, excess *p*-chlorothiophenol was removed by filtration, and the filtrate made strongly alkaline with sodium hydroxide solution. The oil was extracted with benzene, and the solution dried and evaporated. The residue was distilled to give the *pyrimidine* (yield, 10 g.) as a colourless oil, b. p. 202—204°/0·5 mm. (Found: Cl, 9·7; S, 9·1. $C_{17}H_{23}N_4ClS$ requires Cl, 10·1; S, 9·1%) which formed a *monohydrate*; colourless plates from light petroleum (b. p. 60—80°), m. p. 70° (Found: Cl, 9·5; S, 8·4. $C_{17}H_{23}N_4ClS,H_2O$ requires Cl, 9·65; S, 8·7%) (5101).

The following compounds were made in the same way. 4-β-*Diethylaminoethylamino*-2-p-*methoxyphenylthio*-6-*methylpyrimidine* (I; R = OMe, R′ = $[CH_2]_2$·NEt_2, X = S) was a pale yellow oil, b. p. 206—208°/1 mm., giving a *monohydrate* which crystallised from light petroleum (b. p. 60—80°); colourless prisms, m. p. 83° (Found: C, 59·7; H, 7·95; N, 16·2; S, 8·8; loss on drying in a vacuum at 100°, 4·9. $C_{18}H_{26}ON_4S,H_2O$ requires C, 59·3; H, 7·7; N, 15·4; S, 8·8; H_2O, 4·9%) (5140). 4-γ-*Diethylaminopropylamino*-2-p-*chlorophenylthio*-6-*methylpyrimidine* (I; R = Cl, R′ = $[CH_2]_3$·NEt_2, X = S) was a colourless oil, b. p. 228—230°/2 mm. (Found: Cl, 9·8; S, 8·4. $C_{18}H_{25}N_4ClS$ requires Cl, 9·7; S, 8·8%) (5208). 4-γ-*Diethylaminopropylamino*-2-p-*methoxyphenylthio*-6-*methylpyrimidine* (I; R = OMe, R′ = $[CH_2]_3$·NEt_2, X = S) was a pale yellow oil, b. p. 228—229°/2 mm. (Found: C, 62·9; H, 7·9; N, 15·4; S, 8·8. $C_{19}H_{28}ON_4S$ requires C, 63·3; H, 7·8; N, 15·5; S, 8·9%) (5209). 4-δ-*Diethylamino*-α-*methylbutylamino*-2-p-*chlorophenylthio*-6-*methylpyrimidine* (I; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = S) was a colourless oil, b. p. 208—210°/0·9 mm. (Found: C, 60·8; H, 7·0; Cl, 9·5; S, 8·1. $C_{20}H_{29}N_4ClS$ requires C, 61·2; H, 7·4; Cl, 9·05; S, 8·15%) (5151). 4-δ-*Diethylamino*-α-*methylbutylamino*-2-p-*chlorophenoxy*-6-*methylpyrimidine* (I; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = O), prepared from 2-chloro-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine and *p*-chlorophenol, was a pale yellow oil, b. p. 225—228°/0·1 mm. (Found: C, 63·6; H, 7·8; Cl, 9·7. $C_{20}H_{29}ON_4Cl$ requires C, 63·7; H, 7·7; Cl, 9·4%) (5649). 2-γ-*Di*-n-*butylaminopropylamino*-4-p-*chlorophenylthio*-6-*methylpyrimidine* (II; R = Cl, R′ = $[CH_2]_3$·NBu^n_2, X = S), prepared from 4-chloro-2-γ-dibutylaminopropylamino-6-methylpyrimidine and *p*-chlorothiophenol, had b. p. 192—194°/0·08 mm., m. p. 59—60° (Found: C, 63·2; H, 7·7; N, 13·6; Cl, 8·3; S, 8·0. $C_{22}H_{33}N_4ClS$ requires C, 62·9; H, 7·8; N, 13·3; Cl, 8·4; S, 7·6%); with picric acid in methanol it gave a *dipicrate* which crystallised from 2-ethoxyethanol as yellow prisms, m. p. 151—152° (Found: C, 46·5; H, 4·7; N, 16·0. $C_{22}H_{33}N_4ClS,2C_6H_3O_7N_3$ requires C, 46·45; H, 4·4; N, 15·9%) (5935). 2-γ-*Di*-n-*butylaminopropylamino*-4-p-*methoxyphenylthio*-6-*methylpyrimidine* (II; R = OMe, R′ = $[CH_2]_3$·NBu^n_2, X = S), prepared from 4-chloro-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine and *p*-methoxythiophenol, was a very pale yellow oil, b. p. 202—204°/0·09 mm. (Found: C, 66·1; H, 8·4; N, 13·7; S, 7·3. $C_{23}H_{36}ON_4S$ requires C, 66·3; H, 8·7; N, 13·5; S, 7·7%); it gave a *dipicrate*, yellow prisms from 2-ethoxyethanol, m. p. 154—156° (Found: C, 48·1; H, 4·7; N, 15·7. $C_{23}H_{36}ON_4S,2C_6H_3O_7N_3$ requires C, 48·1; H, 4·8; N, 16·0%) (5934).

2-β-*Diethylaminoethylamino*-4-p-*chlorophenylthio*-6-*methylpyrimidine* (II; R = Cl, R′ = $[CH_2]_2$·NEt_2, X = S).—Sodium (5 g.) was dissolved in absolute alcohol (500 c.c.), *p*-chlorothiophenol (29 g.) followed by 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (48 g.) were added, and the mixture was refluxed for 8 hours. Water (500 c.c.) was added, the liquid made strongly alkaline with sodium hydroxide solution, and the oil extracted with benzene. The dried extract was evaporated and the residue distilled, giving a colourless oil (yield, 23 g.), b. p. 201—212°/0·1 mm., which set to a crystalline solid and then crystallised from light petroleum (b. p. 60—80°) in large rosettes of colourless needles, m. p. 83° (Found: Cl, 10·3; S, 9·0. $C_{17}H_{23}N_4ClS$ requires Cl, 10·1; S, 9·1%) (4988).

The following compounds were made in the same way. 2-β-*Diethylaminoethylamino*-4-p-*methoxyphenylthio*-6-*methylpyrimidine* (II; R = OMe, R′ = $[CH_2]_2$·NEt_2, X = S) had b. p. 212—214°/0·8 mm.; it crystallised from light petroleum (b. p. 80—100°) in clumps of colourless needles, m. p. 68—69° (Found: C, 62·3; H, 7·35; S, 9·3. $C_{18}H_{26}ON_4S$ requires C, 62·4; H, 7·5; S, 9·3%) (5019). 2-γ-*Diethylaminopropylamino*-4-p-*chlorophenylthio*-6-*methylpyrimidine* (II; R = Cl, R′ = $[CH_2]_3$·NEt_2, X = S) was a colourless oil, b. p. 228—230°/0·7 mm., setting to a crystalline solid which crystallised from light petroleum (b. p. 80—100°) in large colourless plates, m. p. 83° (Found: C, 59·3; H, 6·9; Cl, 9·7; S, 8·8. $C_{18}H_{25}N_4ClS$ requires C, 59·3; H, 6·8; Cl, 9·7; S, 8·8%) (5037). 2-γ-*Diethylaminopropylamino*-4-p-*methoxyphenylthio*-6-*methylpyrimidine* (II; R = OMe, R′ = $[CH_2]_3$·NEt_2, X = S) had b. p. 228—230°/2 mm.; it separated from light petroleum (b. p. 80—100°) in large colourless prisms, m. p. 69—70° (Found: C, 63·1; H, 7·5; S, 9·0. $C_{19}H_{28}ON_4S$ requires C, 63·3; H, 7·8; S, 8·9%) (5020). 2-δ-*Diethylamino*-α-*methylbutylamino*-4-p-*chlorophenylthio*-6-*methylpyrimidine* (II; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = S) was a colourless oil, b. p. 224—226°/3 mm. (Found: Cl, 8·8; S, 8·3. $C_{20}H_{29}N_4ClS$ requires Cl, 9·05; S, 8·15%) (5045). 2-δ-*Diethylamino*-α-*methylbutylamino*-4-p-*methoxyphenylthio*-6-*methylpyrimidine* (II; R = OMe, R′ = CHMe·$[CH_2]_3$·NEt_2, X = S) was a colourless oil, b. p. 210—212°/1·5 mm. (Found: C, 64·5; H, 7·9; S, 8·1. $C_{21}H_{32}ON_4S$ requires C, 65·0; H, 8·2;

S, 8·2%) (5065). 2-δ-*Diethylamino-α-methylbutylamino*-4-p-*chlorophenoxy*-6-*methylpyrimidine* (II; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = O), prepared from 4-chloro-2-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine and *p*-chlorophenol, was first obtained as a colourless oil, b. p. 190—193°/0·1 mm., which set to a crystalline solid, m. p. 42° (Found: C, 63·7; H, 7·9; Cl, 9·7. $C_{20}H_{29}ON_4Cl$ requires C, 63·7; H, 7·7; Cl, 9·4%) (5150).

2-β-*Diethylaminoethylamino*-4-p-*methoxyphenoxy*-6-*methylpyrimidine* (II; R = OMe, R′ = $[CH_2]_2$·NEt_2, X = O).—Sodium (1·2 g.) was dissolved in alcohol (100 c.c.), quinol monomethyl ether (6·2 g.) added, and the solution evaporated to dryness under reduced pressure in an inert atmosphere. The residue was dried by evaporation twice with alcohol (10 c.c.) and then powdered in a mortar and added to 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (12·1 g.). The mixture was heated at 150° for 3 hours. The resulting melt was dissolved in acetic acid (50 c.c.) and the solution poured into water (250 c.c.). The clear solution was made alkaline with sodium hydroxide and extracted thrice with benzene. After being washed with water, the benzene solution was shaken twice with 25% acetic acid, the combined aqueous extracts were basified with sodium hydroxide, and the liberated oil was extracted with benzene. Evaporation of the dried benzene solution and distillation of the residue gave the *product*, b. p. 188—190°/0·05 mm., which solidified and then crystallised from light petroleum (b. p. 60—80°) as large colourless needles, m. p. 61° (Found: C, 65·0; H, 7·6. $C_{18}H_{26}O_2N_4$ requires C, 65·4; H, 7·9%) (5931).

2-γ-*Diethylaminopropylamino*-4-p-*methoxyphenoxy*-6-*methylpyrimidine* (II; R = OMe, R′ = $[CH_2]_3$·NEt_2, X = O) was prepared in a similar manner using 4-chloro-2-γ-diethylaminopropylamino-6-methylpyrimidine; it was a colourless oil, b. p. 194—195°/0·5 mm. (Found: C, 66·0; H, 7·7. $C_{19}H_{28}O_2N_4$ requires C, 66·3; H, 8·1%) (5932). The *dipicrate* crystallised from 2-ethoxyethanol in thick yellow laminæ, m. p. 155—156° (Found: C, 46·7; H, 4·3; N, 17·8. $C_{19}H_{28}O_2N_4,2C_6H_3O_7N_3$ requires C, 46·4; H, 4·2; N, 17·5%).

4-γ-*Diethylaminopropylamino*-6-p-*chlorophenylthio*-2-*methylpyrimidine* (III; R = Cl, R′ = $[CH_2]_3$·NEt_2, X = S).—Sodium (1·4 g.) was dissolved in alcohol (100 c.c.), *p*-chlorothiophenol (8·2 g.) and 4-chloro-6-γ-diethylaminopropylamino-2-methylpyrimidine (forthcoming publication) (15 g.) were added, and the solution was boiled under reflux for 6 hours. Water (200 c.c.) was added, and the solution made strongly alkaline with sodium hydroxide and extracted with benzene. Evaporation of the dried benzene extract and distillation of the residue gave the *pyrimidine*, b. p. 202—210°/2 mm., which set to a crystalline mass (yield, 13·6 g.) and then separated from light petroleum (b. p. 80—100°) in small colourless cubes, m. p. 75° (Found: C, 59·8; H, 7·2; S, 8·4. $C_{18}H_{25}N_4ClS$ requires C, 59·3; H, 6·8; S, 8·8%) (5342).

4-δ-*Diethylamino-α-methylbutylamino*-6-p-*chlorophenylthio*-2-*methylpyrimidine* (III; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = S).—*p*-Chlorothiophenol (14·5 g.) and 4-chloro-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine (forthcoming publication) (14·2 g.) were fused at 120° for 3 hours and the mixture worked up as described above. The *product* was obtained as a pale yellow oil, b. p. 220—222°/0·1 mm. (yield, 13·3 g.) (Found: C, 60·8; H, 7·2; Cl, 9·5; S, 8·3. $C_{20}H_{29}N_4ClS$ requires C, 61·2; H, 7·4; Cl, 9·05; S, 8·15%) (5727).

Condensation of 2-*Chloro*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine with* p-*Chloroaniline*.—2-Chloro-4-β-diethylaminoethylamino-6-methylpyrimidine (12·1 g.) and *p*-chloroaniline (12·5 g.) were heated at 150—160° for 6 hours. The resulting melt was dissolved in warm dilute hydrochloric acid, and the solution made strongly alkaline with sodium hydroxide and extracted with chloroform. The chloroform solution was dried and evaporated, leaving an oil which was distilled under reduced pressure, the fraction b. p. 204—208°/0·2 mm. being collected. Its identity with 2-*p*-chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine was proved by conversion into the dipicrate, m. p. 218—219°, either alone or mixed with authentic dipicrate (Part I, *loc. cit.*) (Found: C, 43·7; H, 4·1. Calc. for $C_{17}H_{24}N_5Cl,2C_6H_3O_7N_3$: C, 44·0; H, 3·8%), and the dihydrochloride, m. p. and mixed m. p. 267°.

2-*Amino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine*.—2-Chloro-4-β-diethylaminoethylamino-6-methylpyrimidine (4·5 g.) and saturated alcoholic ammonia (20 c.c.) were heated in a sealed tube at 175—185° for 6 hours. The mixture was evaporated to dryness, and the residue stirred with water, made alkaline with sodium hydroxide, and extracted with ether. Evaporation of the dried ethereal extract and distillation of the residue gave a product, b. p. 148—152°/0·15 mm., which then crystallised from light petroleum (b. p. 60—80°). It had m. p. 70—72° either alone or mixed with 2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine (Part III, *loc. cit.*), and gave a dipicrate, m. p. 216—217°, undepressed in admixture with that previously described.

Condensation of 2-*Chloro*-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine with* p-*Chloroaniline*.—2-Chloro-4-γ-diethylaminopropylamino-6-methylpyrimidine (5·12 g.) and *p*-chloroaniline (2·55 g.) were brought into reaction in a mixture of water (25 c.c.) and acetone (10 c.c.) (boiling) containing 10N-hydrochloric acid (2·2 c.c.) for 2 hours to give, after basification with sodium hydroxide and extraction with chloroform 2-*p*-chloroanilino-4-γ-diethylaminopropylamino-6-methylpyrimidine (I; R = Cl, R′ = $[CH_2]_3$·NEt_2, X = NH), b. p. 210—216°/0·15 mm., identified as its dipircate, m. p. 225—226°, which was identical with an authentic sample (Part I, *loc. cit.*). When the above reaction was attempted using only 0·2 c.c. of 10N-hydrochloric acid no appreciable condensation occurred during 2 hours' refluxing.

Condensation of 2-*Chloro*-4-δ-*diethylamino-α-methylbutylamino*-6-*methylpyrimidine with* p-*Chloroaniline*.—2-Chloro-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (5·68 g.) and *p*-chloroaniline (2·55 g.) were brought into reaction in boiling water (25 c.c.) containing 10N-hydrochloric acid (2·2 c.c.) during 2 hours. The cooled solution was made alkaline with sodium hydroxide and the precipitated oil separated. This was dissolved in 5% acetic acid, and the extract clarified with carbon, filtered, and made alkaline with sodium hydroxide. The liberated base was then extracted with chloroform, and the solution dried and evaporated. Distillation of the residual oil gave a product, b. p. 204—206°/0·15 mm., which afforded a dipicrate, m. p. 170—172°, identical with that of 2-*p*-chloroanilino-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (Part I, *loc. cit.*) (Found: C, 46·0; H, 4·4; N, 18·8. Calc. for $C_{20}H_{30}N_5Cl,2C_6H_3O_7N_3$: C, 46·1; H, 4·3; N, 18·5%).

2-*Amino*-4-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine*.—2-Chloro-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (5 g.) and saturated alcoholic ammonia (20 c.c.) were heated in a sealed tube for 6 hours at 180—190°. After evaporation to dryness, the contents of the tube were dissolved in water and made alkaline with sodium hydroxide. The product, isolated by extraction with chloroform, was purified by vacuum distillation, the fraction b. p. 148—150°/0·14 mm. being collected (yield, 4·1 g.). With picric acid in methanol it gave a *dipicrate* which crystallised from 2-ethoxyethanol–alcohol in yellow laminæ, m. p. 170—171°, not depressed in admixture with that prepared from the authentic compound (Part III, *loc. cit.*) (Found: C, 43·1; H, 4·5; N, 21·9. $C_{14}H_{27}N_5,2C_6H_3O_7N_3$ requires C, 43·2; H, 4·6; N, 21·3%).

2-p-*Chloroanilino*-4-*phenoxy*-6-*methylpyrimidine*.—Potassium hydroxide (11·2 g.) was treated with 4 drops of water and fused. Phenol (56·4 g.) was added and the mixture heated to 120—130°. 4-Chloro-2-*p*-chloroanilino-6-methylpyrimidine (Part I) (25·4 g.) was added gradually during 20 minutes with stirring. After being stirred at 120—130° for a further ½ hour, the mixture was cooled and treated with sodium hydroxide solution, and the product extracted with ether. After being washed with alkali and then with water, the ether solution was dried and evaporated and the residue crystallised from alcohol, giving the *pyrimidine* as colourless needles, m. p. 126° (Found: N, 13·5; Cl, 11·6. $C_{17}H_{14}ON_3Cl$ requires N, 13·5; Cl, 11·4%).

Condensation of 2-p-*Chloroanilino*-4-*phenoxy*-6-*methylpyrimidine with* β-*Diethylaminoethylamine*.—The above phenoxy-compound (15·5 g.), phenol (45 g.), and β-diethylaminoethylamine (7·25 g.) were stirred and heated at 120—130° for 8 hours. After cooling, water and sodium hydroxide were added and the insoluble material was taken into chloroform. The chloroform solution was shaken several times with 5% acetic acid (evaporation of the dried chloroform solution gave unchanged 2-*p*-chloroanilino-4-phenoxy-6-methylpyrimidine, 10·6 g.), and the combined acetic acid extracts were made alkaline with sodium hydroxide and extracted with chloroform. The chloroform was then extracted thoroughly with 2N-hydrochloric acid and the extract evaporated to dryness under reduced pressure. Crystallisation of the dried residue from alcohol gave 2-*p*-chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine dihydrochloride, m. p. and mixed m. p. 266—267° (yield, 28·6%). Separate experiments showed that β-diethylaminoethylamine mono- and di-hydrochlorides could be used in place of β-diethylaminoethylamine in the above condensation.

Condensation of 2-p-*Chloroanilino*-4-*phenoxy*-6-*methylpyrimidine and* γ-*Diethylaminopropylamine*.—2-*p*-Chloroanilino-4-phenoxy-6-methylpyrimidine (15·5 g.) and γ-diethylaminopropylamine (8·12 g.) were brought into reaction in phenol (45 g.), and the reaction mixture treated as in the previous experiment, giving unchanged 2-*p*-chloroanilino-4-phenoxy-6-methylpyrimidine (9·7 g.) and 2-*p*-chloroanilino-4-γ-diethylaminopropylamino-6-methylpyrimidine dihydrochloride (yield, 16·3%), m. p. (after one crystallisation) and mixed m. p. 246—248°.

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