251. *Synthetic Antimalarials. Part XXI. 4-Arylamino-6-aminoalkylaminopyrimidines. Further Variations.*

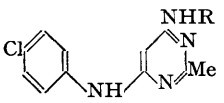
By F. R. Basford, F. H. S. Curd, E. Hoggarth, and F. L. Rose.

An alternative method of synthesis has been devised for the inactive 4-arylamino-6-aminoalkylamino-2-methylpyrimidines (type I) described in Part VIII (*J.*, 1946, 713), and, employing both this and the original route, substituents such as methyl, ethyl, and phenyl have been introduced into position 5 of the pyrimidine nucleus. These new derivatives were inactive, as were also related compounds in which the 2-methyl group was replaced by amino-.

The importance of the aminoalkylamino-side chain in the active 2-arylamino-4-aminoalkylamino- and 4-arylamino-2-aminoalkylamino-6-methylpyrimidines described earlier in this series (*J.*, 1946, 343, 351, 366, 370, 378) has been shown by the lack of activity in compounds, now synthesised, in which that grouping is replaced by primary amino-.

Differences in chemical reactivity of several related chloropyrimidine derivatives are discussed.

Chronologically the work described in this paper follows that reported in Part VIII (*J.*, 1946, 713) which concerned the synthesis of a variety of 4-arylamino-6-aminoalkylamino-2-methylpyrimidines including compounds of type (I; R = dialkylaminoalkyl). All these compounds were found to be without activity against *P. gallinaceum* in chicks. In the same paper we drew attention to the fact that in compounds of type (I) there do not exist two amidine units capable of independent tautomerism as are found in the two isomeric types (II) and (III).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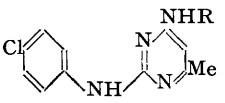
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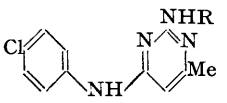
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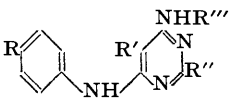
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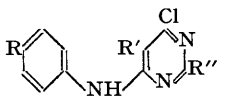
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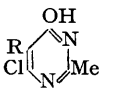
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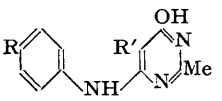
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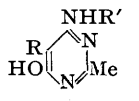
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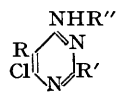
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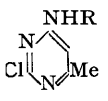
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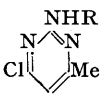
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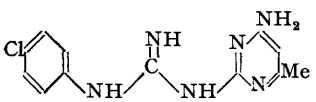
(XII.)

Since one important development of our work (see Part X, *J.*, 1946, 729) was in part based on the recognition of the possible significance of this difference, it seemed desirable to demonstrate with as much certainty as possible that antimalarial activity could not be developed in compounds of type (I). Thus, for example, in a series of simple 2-amino-4-aminoalkylaminopyrimidines, Hull, Lovell, Openshaw, Payman, and Todd (*J.*, 1946, 357) have shown that the introduction of a substituent into position 5 of the pyrimidine nucleus induced antimalarial activity. Clearly, this was a device that needed to be tried in the present instance, although it was appreciated that the two cases might not be comparable since it had been suggested (*idem, ibid.*) that the activity of the simple pyrimidines might be associated with an interference with nucleoside synthesis and the 5-substituent gave a closer structural resemblance to the purines, whereas we in the past have stressed the relationship of the anilinopyrimidines to riboflavin. The new preparations were of type (IV; R′ = Me, Et, or Ph; R″ = Me). Not all of these were made by the general method described in the earlier paper, namely through the reaction of an aminoalkylamine with the appropriately substituted 4-chloro-6-arylamino-2-methylpyrimidine (V; R″ = Me), itself obtained either directly by condensing a 4 : 6-dichloro-2-methylpyrimidine with an arylamine, or indirectly from a 4-chloro-6-hydroxy-2-methylpyrimidine (VI) by interaction with an arylamine followed by treatment of the resulting 4-arylamino-6-hydroxy-2-methylpyrimidine (VII) with phosphoryl chloride. A useful alternative method of synthesis has now been developed in which the arylamino- and aminoalkylamino-groups are introduced in the reverse order. The method is best illustrated by its application to the original type (I). β-Diethylaminoethylamine and γ-diethylaminopropylamine when heated with 4-chloro-6-hydroxy-2-methylpyrimidine (VI; R = H) gave respectively

4-β-diethylaminoethylamino- (VIII; R = H, R′ = $[CH_2]_2$·NEt_2) and 4-γ-diethylaminopropylamino-6-hydroxy-2-methylpyrimidine (VIII; R = H, R′ = $[CH_2]_3$·NEt_2) as their *hydrochlorides*. Treatment of these hydrochlorides with boiling phosphoryl chloride converted them into 4-*chloro*-6-β-*diethylaminoethylamino*- (IX; R = H, R′ = Me, R″ = $[CH_2]_2$·NEt_2) and 4-*chloro*-6-γ-*diethylaminopropylamino*-2-*methylpyrimidine* (IX; R = H, R′ = Me, R″ = $[CH_2]_3$·NEt_2) respectively. When a similar series of reactions was tried starting with δ-diethylamino-α-methylbutylamine it was found impossible to crystallise the intermediate 4-δ-diethylamino-α-methylbutylamino-6-hydroxy-2-methylpyrimidine hydrochloride, but treatment of the crude product with phosphoryl chloride gave 4-chloro-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine (IX; R = H, R′ = Me, R″ = CHMe·$[CH_2]_3$·NEt_2) in good yield. The above compounds of type (IX) underwent smooth reaction with *p*-chloroaniline in boiling aqueous solution as their monohydrochlorides in presence of a little extra hydrochloric acid, to give the corresponding 4-*p*-chloroanilino-6-dialkylaminoalkylamino-2-methylpyrimidines (I; R = $[CH_2]_2$·NEt_2, $[CH_2]_3$·NEt_2, or CHMe·$[CH_2]_3$·NEt_2) described in Part VIII (*loc. cit.*). In these reactions with *p*-chloroaniline no obvious differences could be detected between the reactivity of the 4-chloro-6-dialkylaminoalkylamino-2-methylpyrimidines and the isomeric 2-chloro-4-dialkylaminoalkylamino-6-methylpyrimidines (X) (see Part XV, this vol., p. **783**) and 4-chloro-2-dialkylaminoalkylamino-6-methylpyrimidines (XI) (Part VI, *J.*, 1946, **370**). No appreciable condensation occurred, even in the last two instances, when the chloropyrimidines were employed as free bases with addition of a trace of hydrochloric acid. The need for slightly more than one equivalent of acid to facilitate the reaction suggested that the chlorine atom was only labile after salt formation had occurred on the dialkylamino-group of the side chain.

A comparison with the three isomeric types of chlorodialkylaminoalkylaminomethylpyrimidines was provided by the corresponding unsubstituted amino-compounds. Like 2-chloro-4-amino- (X; R = H) and 4-chloro-2-amino-6-methylpyrimidine (XI; R = H), 4-chloro-6-amino-2-methylpyrimidine (IX; R = R″ = H, R′ = Me) reacted readily with *p*-chloroaniline in boiling aqueous solution in presence of only a little hydrochloric acid. The apparent normal reactivity of the 4-chloro-6-amino- and 4-chloro-6-dialkylaminoalkylamino-2-methylpyrimidines in comparison with their respective isomers was in direct contrast to that of the 4-chloro-6-arylamino-2-methylpyrimidines (IX; R = H, R′ = Me, R″ = aryl) which were found to be less reactive than the corresponding 2-chloro-4-arylamino- (X; R = aryl) and 4-chloro-2-arylamino-6-methylpyrimidines (XI; R = aryl) (see Part VIII, *loc. cit.*). This conforms with the suggestion there advanced that in arylaminopyrimidines there is a strong tendency for the linking nitrogen atom to conjugate with the benzene ring.

Several points may be noted in connection with the synthesis of compounds of type (IV; R″ = Me) described in detail in the experimental section. In the preparation of 4-*chloro*-6-p-*anisidino*-2 : 5-*dimethylpyrimidine* (V; R = OMe, R′ = R″ = Me), required for the synthesis of (IV; R = OMe, R′ = R″ = Me, R‴ = $[CH_2]_2$·NEt_2), by condensation of 4 : 6-dichloro-2 : 5-dimethylpyrimidine with *p*-anisidine in aqueous acetone catalysed by hydrochloric acid, no formation of di-condensation product was observed. Even the use of two molecular proportions of *p*-anisidine gave exclusively 4-chloro-6-*p*-anisidino-2 : 5-dimethylpyrimidine in contrast to the formation mainly of 4 : 6-di-*p*-anisidino-2-methylpyrimidine from 4 : 6-dichloro-2-methylpyrimidine and two equivalents of *p*-anisidine under identical conditions (see Part VIII). This steric effect of a 5-substituent was also noticed during the synthesis of 4-p-*chloroanilino*-6-γ-*diethylaminopropylamino*-2-*methyl*-5-*ethylpyrimidine* (IV; R = Cl, R′ = Et, R″ = Me, R‴ = $[CH_2]_3$·NEt_2). Whereas, as noted above, compounds of type (IX; R′ = Me, R″ = dialkylaminoalkyl) containing no substituent in the 5-position (R = H) condensed readily on boiling with *p*-chloroaniline in aqueous solution containing a little more than one equivalent of hydrochloric acid, no corresponding condensation occurred between 4-*chloro*-6-γ-*diethylaminopropylamino*-2-*methyl*-5-*ethylpyrimidine* (IX; R = Et, R′ = Me, R″ = $[CH_2]_3$·NEt_2) and *p*-chloroaniline under similar conditions. Higher temperatures were found to be necessary to effect condensation. The steric effect of a 5-phenyl group was even more marked than that of methyl or ethyl. Thus the reaction of *p*-chloroaniline with 4 : 6-*dichloro*-5-*phenyl*-2-*methylpyrimidine* to give 4-*chloro*-6-p-*chloroanilino*-5-*phenyl*-2-*methylpyrimidine* (V; R = Cl, R′ = Ph, R″ = Me) failed completely in boiling aqueous acetone with added hydrochloric acid, gave small yields in boiling alcohol, but succeeded at 115—120° in an equivalent of acetic acid. Tests using *P. gallinaceum* in chicks, carried out by our colleague, Dr. D. G. Davey, with the compounds of type (IV; R″ = Me), showed that the introduction of a substituent into the 5-position of type (I) failed to confer antimalarial activity.

The necessity for the aminoalkyl group (R) in types (II) and (III) to promote antimalarial

activity was shown by the inactivity in the same test of 4-*amino*-2-p-*chloroanilino*- (II; R = H) and 2-*amino*-4-p-*chloroanilino*-6-*methylpyrimidine* (III; R = H). The former was made by condensing (X; R = H) with *p*-chloroaniline, as mentioned above, and also by the action of ammonia on 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine at 140—150°. When, however, the action of ammonia on 4-chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine was tried with a view to the preparation of (XII), in order to assess the need for the aminoalkyl group in the active 2-*p*-chlorophenylguanidino-4-aminoalkylamino-6-methylpyrimidines described in Part IV (*J.*, 1946, 362), it was found that 2-amino-4-*p*-chloroanilino-6-methylpyrimidine was the main product. Hydrolysis of 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine with N-hydrochloric acid has been shown by Spinks and Tottey (*Ann. Trop. Med. Parasit.*, 1945, **39**, 190) to give *p*-chloroaniline, 2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine, ammonia, and carbon dioxide. Analogously, it is suggested that 4-chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine by ammonolysis gave *p*-chloroaniline and 4-chloro-2-amino-6-methylpyrimidine which then interacted to yield (III; R = H).

As a further extension of the investigation of compounds of type (IV) it seemed desirable to study compounds containing an amino-group in the 2-position (R″ = NH_2). The presence of such a group, in association with the anilino-residue, would provide the two linked independent amidine units which are a feature of types (II) and (III) without reference to the aminoalkylamino-group, and the only function required of the latter would be that of conditioning the pharmacology of the drug molecule.

Like 4 : 6-dichloro-2-methylpyrimidine, 4 : 6-dichloro-2-aminopyrimidine reacted with *p*-chloroaniline in boiling aqueous acetone in presence of a little hydrochloric acid as catalyst to give 4-*chloro*-2-*amino*-6-p-*chloroanilinopyrimidine* (V; R = Cl, R′ = H, R″ = NH_2). This condensed smoothly with dialkylaminoalkylamines at 150—160°. In this way the following were prepared: 2-*amino*-4-p-*chloroanilino*-6-β-*diethylaminoethylamino*- (IV; R = Cl, R′ = H, R″ = NH_2, R‴ = $[CH_2]_2$·NEt_2) and 2-*amino*-4-p-*chloroanilino*-6-γ-*diethylaminopropylamino-pyrimidine* (IV; R = Cl, R′ = H, R″ = NH_2, R‴ = $[CH_2]_3$·NEt_2) and the corresponding compounds containing the β-dimethylaminoethylamino-, γ-dimethylaminopropylamino-, and δ-diethylamino-α-methylbutylamino- side chains. 2-Amino-4-*p*-chloroanilino-6-β-diethylaminoethylaminopyrimidine was also obtained by reaction of *p*-chloroaniline hydrochloride with 4-*chloro*-2-*amino*-6-β-*diethylaminoethylaminopyrimidine* (IX; R = H, R′ = NH_2, R″ = $[CH_2]_2$·NEt_2) which resulted from condensation of β-diethylaminoethylamine with 4 : 6-dichloro-2-aminopyrimidine. The former method of synthesis was also employed for the preparation of 2-*amino*-4-p-*anisidino*- (IV; R = OMe, R′ = H, R″ = NH_2, R‴ = $[CH_2]_2$·NEt_2) and 2-*amino*-4-p-*toluidino*-6-β-*diethylaminoethylaminopyrimidine* (IV; R = Me, R′ = H, R″ = NH_2, R‴ = $[CH_2]_2$·NEt_2).

None of these compounds containing an amino-group in the 2-position of the pyrimidine nucleus exhibited any antimalarial activity, nor did any of the several 5-ethyl or 5-phenyl derivatives which were prepared (*vide infra*). Similar lack of activity characterised a series of 4-chloro-2-amino-6-aminolkylamino-5-ethyl- and -phenyl-pyrimidines which thus resemble the related 4-chloro-2-amino-6-dialkylaminoalkylamino-5-methylpyrimidines investigated by Hull, Lovell, Openshaw, and Todd (Part XI, this vol., p. 41).

Experimental.

4-β-*Diethylaminoethylamino*-6-*hydroxy*-2-*methylpyrimidine* (VIII; R = H, R′ = $[CH_2]_2$·NEt_2).—4-Chloro-6-hydroxy-2-methylpyrimidine (14·4 g.) (Part VIII, *loc. cit.*) and β-diethylaminoethylamine (11·6 g.) were heated at 150—160° for 8 hours to give 4-β-*diethylaminoethylamino*-6-*hydroxy*-2-*methylpyrimidine hydrochloride* which separated from moist alcohol–ethyl acetate as a hydrate which did not lose water on drying at 100°; colourless laminæ, m. p. 193—195° (Found: C, 47·9; H, 7·9; N, 20·7; Cl′, 13·0. $C_{11}H_{20}ON_4$,HCl,H_2O requires C, 47·4; H, 7·5; N, 20·1; Cl′, 12·8%).

4-γ-*Diethylaminopropylamino*-6-*hydroxy*-2-*methylpyrimidine* (VIII; R = H, R′ = $[CH_2]_3$·NEt_2).—By substituting γ-diethylaminopropylamine for the β-diethylaminoethylamine in the above preparation this was obtained as its *monohydrochloride* which crystallised from alcohol–ethyl acetate as colourless needles, m. p. 87—89° (after drying in air at room temperature) [Found: loss on drying at 100°, 6·4, 6·7. $C_{12}H_{22}ON_4$,HCl,1·5H_2O requires loss (for 1 H_2O), 6·0%] or 186—188° (after drying at 100°) (Found: C, 51·2; H, 8·4; N, 19·7; Cl′, 12·3. $C_{12}H_{22}ON_4$,HCl,0·5H_2O requires C, 50·8; H, 8·5; N, 19·75; Cl′, 12·5%).

4-*Chloro*-6-β-*diethylaminoethylamino*-2-*methylpyrimidine* (IX; R = H, R′ = Me, R″ = $[CH_2]_2$·NEt_2).—4-β-Diethylaminoethylamino-6-hydroxy-2-methylpyrimidine hydrochloride (20 g.) and phosphoryl chloride (75 c.c.) were boiled under reflux for 3 hours. After removal of most of the excess of phosphoryl chloride under reduced pressure, the residue was poured on ice, and the solution made strongly alkaline with sodium hydroxide and extracted with chloroform. The chloroform solution was shaken several times with 5% acetic acid and the combined acetic acid extracts were treated with sodium hydroxide and shaken with chloroform. Evaporation of the dried (K_2CO_3) extract gave the *chloropyrimidine* as

a colourless oil (yield, 9·9 g.), b. p. 136—137°/0·15 mm. (Found : C, 54·0; H, 7·8. $C_{11}H_{19}N_4Cl$ requires C, 54·4; H, 7·8%). It gave a *dipicrate* which crystallised from methanol as yellow laminæ, m. p. 144—145° (Found : C, 39·7; H, 3·8; N, 20·1. $C_{11}H_{19}N_4Cl,2C_6H_3O_7N_3$ requires C, 39·4; H, 3·6; N, 20·0%).

4-Chloro-6-γ-diethylaminopropylamino-2-methylpyrimidine (IX; R = H R′ = Me, R″ = $[CH_2]_3{\cdot}NEt_2$), prepared similarly from 4-γ-diethylaminopropylamino-6-hydroxy-2-methylpyrimidine hydrochloride (dried at 100°) (17·5 g.) and phosphoryl chloride (75 c.c.), was obtained as a colourless oil (yield, 8·7 g.), b. p. 143—145°/0·15 mm. (Found : C, 55·9; H, 8·1; N, 21·7; Cl, 13·4. $C_{12}H_{21}N_4Cl$ requires C 56·1; H, 8·2; N, 21·8; Cl, 13·8%). The *dipicrate* crystallised from methanol in yellow laminæ, m. p. 158—159° (Found : C, 40·2; H, 3·6; N, 19·8. $C_{12}H_{21}N_4Cl,2C_6H_3O_7N_3$ requires C 40·3; H, 3·8; N, 19·6%).

Condensation of 4-Chloro-6-β-diethylaminoethylamino-2-methylpyrimidine with p-*Chloroaniline*.—A mixture of (IX; R = H, R′ = Me, R″ = $[CH_2]_2{\cdot}NEt_2$) (4·85 g.), *p*-chloroaniline (2·55 g.), water (25 c.c.), and 10N-hydrochloric acid (2·2 c.c.) was refluxed for 6 hours. The cooled solution was treated with sodium hydroxide; the product then separated as an oil which soon solidified. The solid was collected and dissolved in 5% acetic acid, and the solution was treated with decolourising carbon and filtered. The product was then reprecipitated by the addition of sodium hydroxide, filtered off, dried, and crystallised from light petroleum (b. p. >120°) (yield, 86·2%); it had m. p. 148° undepressed on admixture with 4-*p*-chloroanilino-6-β-diethylaminoethylamino-2-methylpyrimidine (see Part VIII) (Found : C, 61·1; H, 7·0; N, 21·2; Cl, 10·3. Calc. for $C_{17}H_{24}N_5Cl$: C, 61·3; H, 7·2; N, 21·0; Cl, 10·5%).

Condensation of 4-Chloro-6-γ-diethylaminopropylamino-2-methylpyrimidine with p-*Chloroaniline*.—4-Chloro-6-γ-diethylaminopropylamino-2-methylpyrimidine (5·1 g.), *p*-chloroaniline (2·55 g.), water (25 c.c.), and 10N-hydrochloric acid (2·2 c.c.) were boiled under reflux for 2 hours, and the solution was cooled and made alkaline with sodium hydroxide. The precipitated oil, isolated with chloroform, was extracted with 5% acetic acid. Basification (with sodium hydroxide) of the clarified acetic acid solution and extraction with chloroform followed by evaporation of the dried solution gave the base which crystallised from light petroleum (b. p. >120°); it had m. p. 129—131° identical with 4-*p*-chloroanilino-6-γ-diethylaminopropylamino-2-methylpyrimidine made by the method of Part VIII (Found : C, 62·1; H, 7·5; N, 19·9. Calc. for $C_{18}H_{26}N_5Cl$: C, 62·2; H, 7·5; N, 20·1%).

4-Chloro-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine (IX; R = H, R′ = Me, R″ = $CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$).—4-Chloro-6-hydroxy-2-methylpyrimidine (28·9 g.) and δ-diethylamino-α-methylbutylamine (31·6 g.) were mixed and heated at 150—160° for 8 hours. To the cooled residue phosphoryl chloride (180 c.c.) was added, the mixture refluxed for 3 hours, excess of phosphoryl chloride removed under reduced pressure, and the residue poured on ice. The resulting solution was made alkaline with sodium hydroxide and extracted with chloroform. Evaporation of the dried (K_2CO_3) chloroform solution and distillation of the residual oil gave the *chloropyrimidine* (yield, 36·4 g.), b. p. 168—170°/0·125 mm. (Found : C, 59·2; H, 8·3; N, 19·5; Cl, 12·7. $C_{14}H_{25}N_4Cl$ requires C, 59·0; H, 8·8; N, 19·7; Cl, 12·5%). The *dipicrate* crystallised from alcohol–2-ethoxyethanol in small yellow laminæ, m. p. 171—173° (Found : C, 41·7; H, 4·2; N, 19·1. $C_{14}H_{25}N_4Cl,2C_6H_3O_7N_3$ requires C, 42·0; H, 4·2; N, 18·9%).

Condensation of 4-Chloro-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine with p-*Chloroaniline*.—4-Chloro-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine (5·7 g.), *p*-chloroaniline (2·55 g.), water (25 c.c.), and 10N-hydrochloric acid (2·2 c.c.) were refluxed for 2 hours, and the resulting solution was cooled and made alkaline with sodium hydroxide. The precipitated oil was collected and extracted with 5% acetic acid, and the acetic acid extract clarified with carbon, filtered, and added to excess of sodium hydroxide solution. The oily product was extracted with chloroform, and the solution dried and evaporated. Distillation of the residue gave 4-*p*-chloroanilino-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine, b. p. 220—225°/0·15 mm., identified as its *dipicrate*, m. p. 159—161° (Found : C, 46·2; H, 4·3; N, 18·2. $C_{20}H_{30}N_5Cl,2C_6H_3O_7N_3$ requires C, 46·1; H, 4·3; N, 18·5%). In Part VIII (*loc. cit.*) the m. p. of this picrate is given as 149—151°. The discrepancy is thought to be due to dimorphism, since repeat preparations of this picrate sometimes gave m. p. 149—151°, sometimes 159—161°, and sometimes intermediately. The exact conditions of crystallisation to obtain the two forms were not fully elucidated, but a preparation of the picrate from base made according to the method of Part VIII which had m. p. 159—161° (Found : C, 45·9; H, 4·3; N, 18·6%) showed no depression with the picrate described above.

*4-Amino-2-*p*-chloroanilino-6-methylpyrimidine* (II; R = H).—(*a*) 2-Chloro-4-amino-6-methylpyrimidine (7·2 g.), *p*-chloroaniline (6·4 g.), water (25 c.c.), and 10N-hydrochloric acid (0·5 c.c.) were refluxed for 1 hour. A clear solution was obtained after a few minutes refluxing, and the product then gradually separated. The mixture was diluted with water and made alkaline with ammonia, and the solid collected. The solid was dissolved in alcohol, and the solution made alkaline with ammonia and poured into water. The precipitated product was extracted with chloroform, and the solution dried (Na_2SO_4) and evaporated. Crystallisation of the residue from benzene–light petroleum gave colourless needles, m. p. 121—123°.

(*b*) 4-Chloro-2-*p*-chloroanilino-6-methylpyrimidine (10 g.) and aqueous ammonia (30 c.c.) were heated in a sealed tube at 140—150° for 12 hours. The contents of the tube were diluted with water and extracted with chloroform. Evaporation of the dried chloroform extract gave an oil which was purified by vacuum distillation (b. p. 190—192°/0·5 mm.). Crystallisation from benzene–light petroleum gave *4-amino-2-*p*-chloroanilino-6-methylpyrimidine*, m. p. 121—122° undepressed in admixture with material made by method (*a*) (Found : C, 56·7; H, 4·5; Cl, 15·1. $C_{11}H_{11}N_4Cl$ requires C, 56·3; H, 4·7; Cl, 15·1%) (4394).

*2-Amino-4-*p*-chloroanilino-6-methylpyrimidine* (III; R = H).—4-Chloro-2-amino-6-methylpyrimidine (7·2 g.), *p*-chloroaniline (6·4 g.), water (25 c.c.), and 10N-hydrochloric acid (0·5 c.c.) were refluxed for 1 hour. The reaction mixture was cooled, diluted with water, and made alkaline with ammonia. The precipitated product was filtered off, washed with water, and crystallised from aqueous alcohol, giving *2-amino-4-*p*-chloroanilino-6-methylpyrimidine* as colourless needles, m. p. 216—218° (Found : Cl, 15·2. $C_{11}H_{11}N_4Cl$ requires Cl, 15·1%) (4618).

Reaction of 4-*Chloro*-2-p-*chlorophenylguanidino*-6-*methylpyrimidine with Ammonia* (Experiment by Dr. P. A. Barrett).—4-Chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine (5 g.) and saturated alcoholic ammonia (25 c.c.) were heated in a sealed tube at 175° for 12 hours. The contents of the tube were evaporated to dryness and the residue was stirred with water. The resulting solid on fractional crystallisation from dilute alcohol gave 2-amino-4-*p*-chloroanilino-6-methylpyrimidine, m. p. and mixed m. p. 216—218° (Found: C, 56·2; H, 4·4; N, 23·7; Cl, 15·4. Calc. for $C_{11}H_{11}N_4Cl$: C, 56·3; H, 4·7; N, 23·9; Cl, 15·1%), as the less soluble fraction and *p*-chloroaniline as the more soluble.

4-*Amino*-6-p-*chloroanilino*-2-*methylpyrimidine* (I; R = H).—4-Chloro-6-amino-2-methylpyrimidine (7·2 g.), *p*-chloroaniline (6·4 g.), water (25 c.c.), and 10N-hydrochloric acid (0·5 c.c.) were refluxed for 1 hour. The reaction mixture was diluted with water and made alkaline with ammonia, and the product filtered off. The product was dissolved in alcohol, and the solution made alkaline with ammonia and poured into water. The precipitated product was filtered off and crystallised from aqueous alcohol, giving the *pyrimidine* as colourless flat prisms, m. p. 192—194° (Found: C, 56·4; H, 4·6; Cl, 15·2. $C_{11}H_{11}N_4Cl$ requires C, 56·3; H, 4·7; Cl, 15·1%).

4-*Chloro*-6-p-*chloroanilino*-2 : 5-*dimethylpyrimidine* (V; R = Cl, R′ = R″ = Me).—(*a*) 4 : 6-Dichloro-2 : 5-dimethylpyrimidine (8·85 g.) (Huber and Hölscher, *Ber.*, 1938, **71**, 87), *p*-chloroaniline (6·4 g.), water (40 c.c.), acetone (20 c.c.), and 10N-hydrochloric acid (2 c.c.) were refluxed for 2 hours. The resulting solution was diluted with water and ammonia added to give an alkaline reaction to Brilliant-yellow. The precipitated *base* was filtered off, dissolved in alcohol with the addition of a little ammonia, and poured into water. The solid was collected, washed with water, dried, and crystallised from alcohol, giving colourless thick prisms (9 g.), m. p. 176—177° (Found: C, 54·1; H, 3·9; N, 16·2; Cl, 26·2. $C_{12}H_{11}N_3Cl_2$ requires C, 53·7; H, 4·1; N, 15·7; Cl, 26·5%).

(*b*) 4 : 6-Dichloro-2 : 5-dimethylpyrimidine (5·3 g.) and *p*-chloroaniline (4·2 g.) were heated in acetic acid (30 c.c.), containing a crystal of potassium iodide, at 40° for 20 hours. Addition of sodium acetate (4 g.) and dilution with water gave 4-chloro-6-*p*-chloroanilino-2 : 5-dimethylpyrimidine which was filtered off, washed with water, and dried. It had m. p. and mixed m. p. 176° after crystallisation from benzene–light petroleum (Found: Cl, 26·5%).

4-*Chloro*-6-*hydroxy*-2 : 5-*dimethylpyrimidine* (VI; R = Me).—4 : 6-Dichloro-2 : 5-dimethylpyrimidine (25 g.), water (250 c.c.), and hydrochloric acid (100 c.c.) were boiled together under reflux for 1 hour (complete homogeneity was obtained after ½ hour). The solution was cooled, made alkaline with sodium hydroxide, and then acidified with acetic acid. The precipitated *product* was filtered off and purified by dissolution in ammonia and reprecipitation with acetic acid. After drying, it crystallised from alcohol in colourless slender prisms (yield 16·3 g.), m. p. 225° (Found: C, 45·5; H, 4·4; N, 17·5; Cl, 22·8. $C_6H_7ON_2Cl$ requires C, 45·4; H, 4·4; N, 17·7; Cl, 22·4%).

4-*Chloro*-6-β-*diethylaminoethylamino*-2 : 5-*dimethylpyrimidine* (IX; R = R′ = Me, R″ = $[CH_2]_2$·NEt_2).—4-Chloro-6-hydroxy-2 : 5-dimethylpyrimidine (25 g.) and β-diethylaminoethylamine (18·3 g.) were mixed and heated at 150—160° for 8 hours. A portion of the resulting solid, on treatment with excess of picric acid in methanol solution, gave 4-β-*diethylaminoethylamino*-6-*hydroxy*-2 : 5-*dimethylpyrimidine dipicrate* which crystallised from alcohol in yellow rectangular prisms, m. p. 154° (Found: C, 41·6; H, 4·2; N, 20·2. $C_{12}H_{22}ON_4,2C_6H_3O_7N_3$ requires C, 41·4; H, 4·0; N, 20·1%). The remainder of the hydrochloride was refluxed with phosphoryl chloride (220 c.c.) for 5 hours and the excess of phosphoryl chloride then removed by distillation under reduced pressure and the residue poured on ice. Addition of sodium hydroxide to the solution liberated the chloro-compound which was extracted with chloroform, and the extract was dried and evaporated. The residue was distilled in a vacuum giving 4-*chloro*-6-β-*diethylaminoethylamino*-2 : 5-*dimethylpyrimidine* (21·9 g.), b. p. 139°/0·085 mm. (Found: C, 56·1; H, 8·2; Cl, 13·5. $C_{12}H_{21}N_4Cl$ requires C, 56·1; H, 8·2; Cl, 13·8%). It formed a *hydrate* which crystallised from light petroleum (b. p. 60—80°) in colourless thick laminæ, m. p. 80° (Found: C, 52·6; H, 8·4; N, 20·3. $C_{12}H_{21}N_4Cl,H_2O$ requires C, 52·5; H, 8·4; N, 20·4%), and a *dipicrate* which separated from alcohol in yellow laminæ, m. p. 143° (Found: N, 19·5. $C_{12}H_{21}N_4Cl,2C_6H_3O_7N_3$ requires N, 19·6%).

4-δ-*Diethylamino*-α-*methylbutylamino*-6-*hydroxy*-2 : 5-*dimethylpyrimidine* (VIII; R = Me, R′ = CHMe·$[CH_2]_3$·NEt_2).—4-Chloro-6-hydroxy-2 : 5-dimethylpyrimidine (31·7 g.) and δ-diethylamino-α-methylbutylamine (31·6 g.) were mixed and heated at 150—160° for 8 hours with stirring to give, on cooling, a viscous mass of 4-δ-diethylamino-α-methylbutylamino-6-hydroxy-2-methylpyrimidine hydrochloride which could not be crystallised. The *dipicrate*, prepared from the hydrochloride with excess of picric acid in methanol, crystallised from alcohol; m. p. 163—164° (Found: C, 43·9; H, 4·8. $C_{15}H_{28}ON_4,2C_6H_3O_7N_3$ requires C, 43·9; H, 4·6%).

4-*Chloro*-6-δ-*diethylamino*-α-*methylbutylamino*-2 : 5-*dimethylpyrimidine* (IX; R = R′ = Me, R″ = CHMe·$[CH_2]_3$·NEt_2).—Phosphoryl chloride (225 c.c.) was added to the above crude hydrochloride (62 g.) and the mixture boiled under reflux for 4 hours. Most of the excess of phosphoryl chloride was removed under diminished pressure, the residue poured on ice, and, after solution had occurred, sodium hydroxide added to alkalinity, the oily product extracted with chloroform, and the extract dried and evaporated. Distillation of the residue gave the *chloropyrimidine* as a colourless oil (yield, 22·05 g.), b. p. 144—145°/0·055 mm. (Found: Cl, 12·1, 12·3. $C_{15}H_{27}N_4Cl$ requires Cl, 11·9%). A crystalline derivative was not obtained.

4-p-*Chloroanilino*-6-β-*diethylaminoethylamino*-2 : 5-*dimethylpyrimidine* (IV; R = Cl, R′ = R″ = Me, R‴ = $[CH_2]_2$·NEt_2).—(*a*) 4-Chloro-6-*p*-chloroanilino-2 : 5-dimethylpyrimidine (14·6 g.), β-diethylaminoethylamine (15 g.), and a crystal of potassium iodide were heated at 150—160° for 6 hours with stirring. The resulting melt was dissolved in dilute hydrochloric acid, and the solution made alkaline with sodium hydroxide and extracted with chloroform. After removal of the solvent the residue was stirred with 5% acetic acid, and the extract separated, stirred with decolourising carbon, and filtered. The filtrate was then made strongly alkaline with sodium hydroxide and extracted with chloroform, and the extract dried and evaporated. Distillation of the residual oil afforded 4-p-*chloroanilino*-6-β-*diethylaminoethylamino*-2 : 5-*dimethylpyrimidine* as a colourless oil (yield, 11·6 g.), b. p. 200°/0·07 mm. (Found: C, 61·6; H, 7·5; N, 19·7; Cl, 10·2. $C_{18}H_{26}N_5Cl$ required C, 62·2; H, 7·5; N, 20·1; Cl, 10·2%). The base was converted into its *dihydrochloride* by dissolving in 2N-hydrochloric acid and

evaporating the solution to dryness. The residue was dried and freed from adhering hydrochloric acid by dissolving in alcohol and evaporation to dryness under reduced pressure several times. Crystallisation from alcohol–ethyl acetate then gave thin colourless prisms, m. p. 263—264° (Found: C, 51·0; H, 6·4; N, 16·4; Cl′, 16·2. $C_{18}H_{26}N_5Cl,2HCl$ requires C, 51·4; H, 6·7; N, 16·65; Cl′, 16·9%) (3990).

(*b*) A mixture of 4-chloro-6-β-diethylaminoethylamino-2 : 5-dimethylpyrimidine (5·13 g.), *p*-chloroaniline hydrochloride (3·28 g.), and hydrochloric acid (0·25 c.c.) was heated at 150—160° for 6 hours. By direct crystallisation of the resulting solid melt from alcohol–ethyl acetate, 4-*p*-chloroanilino-6-β-diethylaminoethylamino-2 : 5-dimethylpyrimidine dihydrochloride was obtained (yield, 5·7 g.), m. p. and mixed m. p. 262—264° (Found: C, 51·2; H, 6·1; N, 16·4; Cl′, 16·5%).

4-p-*Chloroanilino*-6-γ-*diethylaminopropylamino*-2 : 5-*dimethylpyrimidine* (IV; R = Cl, R′ = R″ = Me, R‴ = $[CH_2]_3{\cdot}NEt_2$), prepared by method (*a*) above from 4-chloro-6-*p*-chloroanilino-2 : 5-dimethylpyrimidine and γ-diethylaminopropylamine, formed a colourless viscous oil, b. p. 204°/0·045 mm. (Found: C, 62·9; H, 7·8; N, 18·8; Cl, 9·8. $C_{19}H_{28}N_5Cl$ requires C, 63·1; H, 7·7; N, 19·4; Cl, 9·8%) which gave a *dihydrochloride* as colourless prisms from alcohol–ethyl acetate, m. p. 217—218° (Found: C, 48·8; H, 7·1; N, 14·9; Cl′, 15·1. $C_{19}H_{28}N_5Cl,2HCl,2H_2O$ requires C, 48·5; H, 7·2; N, 14·9; Cl′, 15·1%) (5507).

4-p-*Chloroanilino*-6-γ-*dimethylaminopropylamino*-2 : 5-*dimethylpyrimidine* (IV; R = Cl, R′ = R″ = Me, R‴ = $[CH_2]_3{\cdot}NMe_2$), prepared in a corresponding manner using γ-dimethylaminopropylamine, was obtained as colourless prisms from light petroleum (b. p. 60—80°), m. p. 105° (Found: C, 61·2; H, 7·0; N, 20·6. $C_{17}H_{24}N_5Cl$ requires C, 61·2; H, 7·2; N, 21·0%). It gave a *dihydrochloride* which crystallised from alcohol–ethyl acetate in tiny colourless prisms, m. p. 275—276° (decomp.) (the m. p. varied slightly with the rate of heating) (Found: C, 49·9; H, 6·3; N, 17·3; Cl′, 17·2. $C_{17}H_{24}N_5Cl,2HCl$ requires C, 50·2; H, 6·4; N, 17·2; Cl′, 17·5%) (4067).

4-p-*Chloroanilino*-6-δ-*diethylamino*-α-*methylbutylamino*-2 : 5-*dimethylpyrimidine* (IV; R = Cl, R′ = R″ = Me, R‴ = $CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$).—The condensate (150—160° for 6 hours) of 4-chloro-6-δ-diethylamino-α-methylbutylamino-2 : 5-dimethylpyrimidine (14·93 g.) and *p*-chloroaniline (8·2 g.) was dissolved in dilute hydrochloric acid, made alkaline with sodium hydroxide, and then extracted with chloroform. Evaporation of the dried chloroform extract and distillation of the residue gave the *base* (9·4 g.) as a colourless highly viscous oil, b. p. 208°/0·55 mm. (Found: C, 64·5; H, 7·8; Cl, 9·5. $C_{21}H_{32}N_5Cl$ requires C, 64·7; H, 8·2; Cl, 9·1%) (3988). No solid salt could be isolated.

4-p-*Bromoanilino*-6-β-*diethylaminoethylamino*-2 : 5-*dimethylpyrimidine* (IV; R = Br, R′ = R″ = Me, R‴ = $[CH_2]_2{\cdot}NEt_2$).—4-Chloro-6-β-diethylaminoethylamino-2 : 5-dimethylpyrimidine (10·26 g.) was mixed with *p*-bromoaniline hydrochloride (6·9 g.), a few drops of hydrochloric acid were added, and the whole was heated at 150—160° for 6 hours. The melt, originally fluid, was completely solid after 2·5 hours. Crystallisation from alcohol–ethyl acetate gave the *dihydrochloride* as colourless thick prisms, m. p. 265—266° (Found: C, 46·3; H, 6·4. $C_{18}H_{26}N_5Br,2HCl$ requires C, 46·45; H, 6·0%).

4-*Chloro*-6-p-*anisidino*-2 : 5-*dimethylpyrimidine* (V; R = Cl, R′ = OMe, R″ = Me).—(*a*) 4 : 6-Dichloro-2 : 5-dimethylpyrimidine (8·85 g.), *p*-anisidine (6·15 g.), water (40 c.c.), acetone (20 c.c.), and 10N-hydrochloric acid (1 c.c.) were refluxed for 3 hours. The mixture was diluted with water and made alkaline with ammonia. The filtered product was dissolved in 2-ethoxyethanol, and the solution made alkaline by the addition of a little ammonia and then poured into water. The precipitated solid was collected, washed with water, and dried. Crystallised from *n*-propanol, the *base* (9·5 g.) had m. p. 201° (Found: C, 58·8; H, 5·0; N, 15·8; Cl, 13·1. $C_{13}H_{14}ON_3Cl$ requires C, 59·2; H, 5·3; N, 15·9; Cl, 13·5%).

(*b*) 4 : 6-Dichloro-2 : 5-dimethylpyrimidine (5·31 g.), *p*-anisidine (4·5 g.), glacial acetic acid (30 c.c.), and 10N-hydrochloric acid (0·2 c.c.) were stirred at 40—45° for 20 hours. Sodium acetate (4 g.) was then added and the solution diluted with water (300 c.c.). On standing, the product gradually separated and was filtered off, washed with water, and dried. Crystallisation from benzene gave 4-chloro-6-*p*-anisidino-2 : 5-dimethylpyrimidine (6·4 g.) as colourless needles, m. p. and mixed m. p. 201° (Found: Cl, 13·4%).

4-p-*Anisidino*-6-β-*diethylaminoethylamino*-2 : 5-*dimethylpyrimidine* (IV; R = OMe, R′ = R″ = Me, R‴ = $[CH_2]_2{\cdot}NEt_2$).—The above chloropyrimidine (10 g.), β-diethylaminoethylamine (14 g.), and a crystal of potassium iodide were heated at 150—160° for 6 hours with stirring. The resulting reaction mixture was worked up as described previously for the corresponding *p*-chloroanilino-compound and gave the *base* (8·9 g.) as a colourless viscous oil, b. p. 203°/0·5 mm. (Found: C, 67·0; H, 9·3; N, 19·8. $C_{19}H_{29}ON_5$ requires C, 66·5; H, 8·5; N, 20·4%). The *dihydrochloride* crystallised from alcohol–ethyl acetate in clusters of colourless prisms, m. p. 254—255° (Found: C, 52·5; H, 7·7; N, 16·1; Cl′, 16·9. $C_{19}H_{29}ON_5,2HCl,H_2O$ requires C, 52·5; H, 7·6; N, 16·1; Cl′, 16·4%) (3962).

4-*Chloro*-6-p-*nitroanilino*-2 : 5-*dimethylpyrimidine* (V; R = NO_2, R′ = R″ = Me).—4 : 6-Dichloro-2 : 5-dimethylpyrimidine (5·22 g.), *p*-nitroaniline (4·55 g.), acetic acid (50 c.c.), and a crystal of potassium iodide were heated at 55—60° for 18 hours. Sodium acetate (3 g.) was then added and the solution diluted with water (500 c.c.). The precipitated solid was filtered off, washed with water, and dried. Crystallised from butanol, the *base* formed yellow prisms (yield, 5·2 g.), m. p. 208—210° (Found: Cl, 12·9; $C_{12}H_{11}O_2N_4Cl$ requires Cl, 12·7%).

4-p-*Nitroanilino*-6-β-*diethylaminoethylamino*-2 : 5-*dimethylpyrimidine* (IV; R = NO_2, R′ = R″ = Me, R‴ = $[CH_2]_2{\cdot}NEt_2$).—(*a*) An intimate mixture of 4-chloro-6-β-diethylaminoethylamino-2 : 5-dimethylpyrimidine (1·0 g.) and *p*-nitroaniline hydrochloride (0·68 g.) was heated at 150—160° for 6 hours with stirring in the initial stages. The cold melt was dissolved in hydrochloric acid, and the solution made alkaline with sodium hydroxide and extracted with chloroform. The chloroform solution was then extracted several times with 5% acetic acid and the combined acetic acid extracts were added to excess of sodium hydroxide. The precipitated oil was taken up in chloroform, and the solution dried and evaporated. Crystallisation of the residue from light petroleum (b. p. 80—100°) gave the *base* as thick yellow laminæ, m. p. 104—106° (Found: C, 60·4; H, 7·3, N, 23·1. $C_{18}H_{26}O_2N_6$ requires C, 60·3; H, 7·3; N, 23·5%).

(*b*) 4-Chloro-6-*p*-nitroanilino-5 : 6-dimethylpyrimidine (1·8 g.), β-diethylaminoethylamine (1·8 g.),

and a trace of potassium iodide were heated at 155—165° for 5 hours and the mixture was worked up in the same way as in (*a*) to give the base (1·8 g.) which was converted into its *dihydrochloride*. This crystallised from alcohol–ethyl acetate in yellowish rectangular prisms, m. p. 254—256° (Found: C, 50·1; H, 6·5; N, 19·4. $C_{18}H_{26}O_2N_6$,2HCl requires C, 50·1; H, 6·5; N, 19·5%) (4188).

4 : 6-*Dichloro*-2-*methyl*-5-*ethylpyrimidine*.—4 : 6-Dihydroxy-2-methyl-5-ethylpyrimidine (30 g.) (Ferris and Ronzio, *J. Amer. Chem. Soc.*, 1940, **62**, 606) and phosphoryl chloride (110 c.c.) were refluxed for 2 hours and the bulk of the excess of phosphoryl chloride was then removed under diminished pressure. The residue was poured on ice (200 g.), the product extracted with benzene, and the solution dried (Na_2SO_4). The benzene was then removed by distillation through a short fractionating column and the residue distilled giving 4 : 6-*dichloro*-2-*methyl*-5-*ethylpyrimidine* as a colourless oil, b. p. 212—214° (Found: Cl, 37·2. $C_7H_8N_2Cl_2$ requires Cl, 37·2%).

4-*Chloro*-6-*hydroxy*-2-*methyl*-5-*ethylpyrimidine* (VI; R = Et).—4 : 6-Dichloro-2-methyl-5-ethylpyrimidine (25 g.), water (250 c.c.), and hydrochloric acid (100 c.c.) were boiled under reflux for 2·5 hours. The resulting clear solution was cooled, made alkaline with ammonia, and then acidified with acetic acid. Next day the product was filtered off and purified by dissolution in dilute sodium hydroxide and reprecipitation with acetic acid. The dried *base* crystallised from alcohol in colourless elongated prisms (yield, 19·2 g.), m. p. 209° (Found: C, 49·0; H, 5·0; N, 16·4. $C_7H_9ON_2Cl$ requires C, 48·7; H, 5·2; N, 16·2%).

4-p-*Chloroanilino*-6-*hydroxy*-2-*methyl*-5-*ethylpyrimidine* (VII; R = Cl, R′ = Et).—4-Chloro-6-hydroxy-2-methyl-5-ethylpyrimidine (8·63 g.), *p*-chloroaniline (9·6 g.), and hydrochloric acid (0·5 c.c.) were mixed and heated at 160—170° for 8 hours. After cooling, the melt was dissolved in warm aqueous sodium hydroxide, and the solution treated with decolourising carbon and filtered. Addition of acetic acid to the filtrate gave the product which was filtered off, digested with aqueous ammonia, collected, and dried. 4-p-*Chloroanilino*-6-*hydroxy*-2-*methyl*-5-*ethylpyrimidine* crystallised from 2-ethoxyethanol in colourless needles (yield, 8·1 g.), m. p. 275° (Found: C, 59·0; H, 5·9; N, 16·1. $C_{13}H_{14}ON_3Cl$ requires C, 59·2; H, 6·1; N, 15·9%).

4-*Chloro*-6-p-*chloroanilino*-2-*methyl*-5-*ethylpyrimidine* (V; R = Cl, R′ = Et, R″ = Me).—(*a*) 4 : 6-Dichloro-2-methyl-5-ethylpyrimidine (5·73 g.) and *p*-chloroaniline (4·3 g.) were dissolved in acetic acid (30 c.c.), a crystal of potassium iodide was added, and the solution was stirred at 35—45° for 20 hours. Sodium acetate (3 g.) was then added and the solution drowned into water to precipitate the *base* which was filtered off, dried, and crystallised, first from benzene–light petroleum (b. p. 60—80°) and then from dilute alcohol; long colourless rectangular prisms, m. p. 166° (Found: C, 55·6; H, 4·4; N, 14·5; Cl, 25·2. $C_{13}H_{13}N_3Cl_2$ requires C, 55·3; H, 4·6; N, 15·0; Cl, 25·2%).

(*b*) 4-*p*-Chloroanilino-6-hydroxy-2-methyl-5-ethylpyrimidine (8·9 g.) and phosphoryl chloride (45 c.c.) were refluxed for 1½ hours, and the clear solution was cooled and poured on ice. After being stirred for ½ hour the solution was made alkaline with sodium hydroxide and the precipitated product filtered off, washed with water, and dried. On boiling it with benzene a small amount of unchanged hydroxy-compound remained undissolved. This was removed by filtration and the benzene evaporated. Crystallisation of the residue from dilute alcohol gave the same compound as in (*a*), m. p. and mixed m. p. 166° (Found: C, 55·6; H, 4·4; N, 14·8%).

4-γ-*Diethylaminopropylamino*-6-*hydroxy*-2-*methyl*-5-*ethylpyrimidine* (VIII; R = Et, R′ = $[CH_2]_3{\cdot}NEt_2$).—4-Chloro-6-hydroxy-2-methyl-5-ethylpyrimidine (34·5 g.) and γ-diethylaminopropylamine (26 g.) were heated at 150—160° for 8 hours, with stirring until the melt solidified. A small sample of the resulting hydrochloride of 4-γ-diethylaminopropylamino-6-hydroxy-2-methyl-5-ethylpyrimidine on treatment with picric acid in alcohol gave the *dipicrate* which crystallised from 2-ethoxyethanol–alcohol in flat yellow prisms, m. p. 188° (Found: C, 42·9; H, 4·7; N, 19·4. $C_{14}H_{26}ON_4$,2$C_6H_3O_7N_3$ requires C, 43·1; H, 4·4; N, 19·3%).

4-*Chloro*-6-γ-*diethylaminopropylamino*-2-*methyl*-5-*ethylpyrimidine* (IX; R = Et, R′ = Me, R″ = $[CH_2]_3{\cdot}NEt_2$).—The above hydrochloride (59·5 g.) was refluxed with phosphoryl chloride (225 c.c.) during 15 hours, and the reaction mixture worked up as described previously for this type of compound, giving the *chloropyrimidine* as a colourless oil, b. p. 142°/0·095 mm. (Found: N, 19·1; Cl, 12·1. $C_{14}H_{25}N_4Cl$ requires N, 19·7; Cl, 12·5%). It gave a *dipicrate* which crystallised from alcohol in yellow tables, m. p. 147—148° (Found: C, 42·0; H, 4·2; N, 18·8. $C_{14}H_{25}N_4Cl$,2$C_6H_3O_7N_3$ requires C, 42·0; H, 4·2; N, 18·85%).

4-p-*Chloroanilino*-6-β-*diethylaminoethylamino*-2-*methyl*-5-*ethylpyrimidine* (IV; R = Cl, R′ = Et, R″ = Me, R‴ = $[CH_2]_2{\cdot}NEt_2$).—4-Chloro-6-*p*-chloroanilino-2-methyl-5-ethylpyrimidine (2·0 g.), β-diethylaminoethylamine (2·0 g.), and a crystal of potassium iodide were stirred and heated at 140—150° for 6 hours. The resulting mixture was dissolved in dilute hydrochloric acid and the solution made alkaline with sodium hydroxide. The precipitate was separated by decantation and dissolved in 5% acetic acid, and the solution was filtered. On addition of sodium hydroxide to the filtrate, the base was obtained as an oil which was extracted with benzene, and the extract was dried and evaporated. The residual oily base gave a *dihydrochloride* which crystallised from alcohol–ethyl acetate in colourless thick prisms, m. p. 268—270° (decomp.) (Found: C, 52·3; H, 6·8; N, 16·0; Cl′, 16·3. $C_{19}H_{28}N_5Cl$,2HCl requires C, 52·5; H, 6·9; N, 16·1; Cl′, 16·3%) (4046).

4-p-*Chloroanilino*-6-γ-*dimethylaminopropylamino*-2-*methyl*-5-*ethylpyrimidine* (IV; R = Cl, R′ = Et, R″ = Me, R‴ = $[CH_2]_3{\cdot}NMe_2$).—Obtained similarly from 4-chloro-6-*p*-chloroanilino-2-methyl-5-ethylpyrimidine and γ-dimethylaminopropylamine, this gave a *dipicrate* which crystallised from alcohol in thick yellow laminæ, m. p. 171—173° (Found: C, 45·1; H, 4·5. $C_{18}H_{26}N_5Cl$,2$C_6H_3O_7N_3$ requires C, 44·7; H, 4·0%), and a *dihydrochloride* which crystallised from alcohol–ethyl acetate in colourless flat prisms, m. p. 278—279° (decomp.) (Found: C, 47·7; H, 7·3; N, 15·1; Cl′, 15·3. $C_{18}H_{26}N_5Cl$,2HCl,2H_2O requires C, 47·3; H, 7·0; N, 15·3; Cl′, 15·6%) (4017).

4-p-*Chloroanilino*-6-γ-*diethylaminopropylamino*-2-*methyl*-5-*ethylpyrimidine* (IV; R = Cl, R′ = Et, R″ = Me, R‴ = $[CH_2]_3{\cdot}NEt_2$).—4-Chloro-6-γ-diethylaminopropylamino-2-methyl-5-ethylpyrimidine (8·35 g.), *p*-chloroaniline (4·8 g.), and a few drops of hydrochloric acid were heated at 150—160° for 6 hours with stirring. The melt (cooled) was dissolved out with hydrochloric acid and the solution

made alkaline with sodium hydroxide. The liberated oil was extracted with benzene, and the extract dried and evaporated. Distillation of the remaining oil gave 4-p-*chloroanilino*-6-*γ-diethylaminopropylamino*-2-*methyl*-5-*ethylpyrimidine* (6·3 g.), b. p. 210°/0·065 mm. (Found: C, 63·5; H, 8·0. $C_{20}H_{30}N_5Cl$ requires C, 63·9; H, 8·0%), which formed a *dihydrochloride*, colourless prisms from alcohol–ethyl acetate, m. p. 162° (Found: C, 50·9; H, 7·1; N, 14·9; Cl′, 14·8. $C_{20}H_{30}N_5Cl,2HCl,H_2O$ requires C, 51·4; H, 7·3; N, 15·0; Cl′, 15·2%).

4-p-*Anisidino*-6-*hydroxy*-2-*methyl*-5-*ethylpyrimidine* (VII; R = OMe, R′ = Et).—4-Chloro-6-hydroxy-2-methyl-5-ethylpyrimidine (17·25 g.), *p*-anisidine (12·3 g.), and hydrochloric acid (1 c.c.) were heated at 160—170° for 3 hours. The mixture was dissolved in dilute sodium hydroxide solution, and the solution treated with decolourising carbon and filtered. Acidification of the filtrate with acetic acid gave a product which was freed from a small amount of unchanged 4-chloro-6-hydroxy-2-methyl-5-ethylpyrimidine by stirring with 10% aqueous ammonia for 3 hours and filtering. After being washed with water and dried, the *base* crystallised from alcohol in colourless thick prisms, m. p. 199—200° (Found: C, 65·0; H, 6·6; N, 16·3. $C_{14}H_{17}O_2N_3$ requires C, 64·9; H, 6·6; N, 16·2%).

4-*Chloro*-6-p-*anisidino*-2-*methyl*-5-*ethylpyrimidine* (V; R = OMe, R′ = Et, R″ = Me).—(*a*) 4 : 6-Dichloro-2-methyl-5-ethylpyrimidine (5·73 g.) and *p*-anisidine (4·1 g.) were kept in acetic acid (30 c.c.), with the addition of a crystal of potassium iodide, at 40—45° for 20 hours. After addition of sodium acetate (3 g.) the solution was drowned into water (300 c.c.), and the precipitated *product* filtered off, washed with water, and crystallised from dilute alcohol; colourless elongated prisms, m. p. 157° (Found: C, 60·6; H, 5·7; N, 15·2. $C_{14}H_{16}ON_3Cl$ requires C, 60·5; H, 5·8; N, 15·1%).

(*b*) 4-*p*-Anisidino-6-hydroxy-2-methyl-5-ethylpyrimidine (11·9 g.) and phosphoryl chloride (60 c.c.) were boiled under reflux for 1½ hours and the clear solution poured on ice. Addition of ammonia precipitated the product which was purified by crystallisation from dilute alcohol. It then had m. p. 157° either alone or in admixture with material made by method (*a*) (Found: C, 60·1; H, 5·4%).

4-p-*Anisidino*-6-*β-diethylaminoethylamino*-2-*methyl*-5-*ethylpyrimidine* (IV; R = OMe, R′ = Et, R″ = Me, R‴ = $[CH_2]_2{\cdot}NEt_2$).—4-Chloro-6-*p*-anisidino-2-methyl-5-ethylpyrimidine (2·75 g.) and β-diethylaminoethylamine (2·5 g.) were heated at 155—165° for 8 hours and the mixture worked up as in the case of the corresponding *p*-chloroanilino-compound, giving the *dihydrochloride* as colourless laminæ from alcohol–ethyl acetate, m. p. 250—251° (decomp.) (Found: C, 55·5; H, 7·5; N, 15·9; Cl′, 16·3. $C_{20}H_{31}ON_5,2HCl$ requires C, 55·8; H, 7·7; N, 16·3; Cl′, 16·5%) (4048).

4-p-*Anisidino*-6-*γ-dimethylaminopropylamino*-2-*methyl*-5-*ethylpyrimidine* (IV; R = OMe, R′ = Et, R″ = Me, R‴ = $[CH_2]_3{\cdot}NMe_2$).—4-Chloro-6-*p*-anisidino-2-methyl-5-ethylpyrimidine (2·75 g.) and γ-dimethylaminopropylamine (2·5 g.) were heated, with the addition of a trace of potassium iodide, at 150—160° for 8 hours with stirring. The melt was dissolved in dilute hydrochloric acid and the solution poured into excess of sodium hydroxide solution. The precipitated product was collected and purified by dissolution in 5% acetic acid and reprecipitation with sodium hydroxide. The *base*, isolated by extraction with benzene, crystallised from light petroleum (b. p. 80—100°) in colourless needles, m. p. 106—107° (Found: C, 66·2; H, 7·8; N, 20·3. $C_{19}H_{29}ON_5$ requires C, 66·5; H, 8·5; N, 20·4%) (4069).

4 : 6-*Dichloro*-5-*phenyl*-2-*methylpyrimidine*.—4 : 6-Dihydroxy-5-phenyl-2-methylpyrimidine (40 g.) (Dox and Yoder, *J. Amer. Chem. Soc.*, 1922, **44**, 361) and phosphoryl chloride (140 c.c.) were boiled under reflux for 2 hours. The excess of phosphoryl chloride was then removed under reduced pressure and the residue poured on a mixture of ice and water (300 g.). After ½ hour's stirring, the *product* which had separated was filtered off, washed acid-free with water, and crystallised from alcohol; colourless plates, m. p. 160° (Found: C, 55·2; H, 3·1; Cl, 29·1. $C_{11}H_8N_2Cl_2$ requires C, 55·2; H, 3·35; Cl, 29·7%).

4-*Chloro*-6-p-*chloroanilino*-5-*phenyl*-2-*methylpyrimidine* (V; R = Cl, R′ = Ph, R″ = Me).—4 : 6-Dichloro-5-phenyl-2-methylpyrimidine (11·95 g.) and *p*-chloroaniline (6·4 g.) were ground together, acetic acid (3 g.) was added, and the mixture was heated at 110—115° for 1 hour. The cooled melt was dissolved in alcohol, and the solution made alkaline with ammonia and poured into water. The precipitated *base* was filtered off, washed with water, and dried. Crystallised from light petroleum (b. p. >120°), it formed colourless prisms (9·5 g.), m. p. 155—156° (Found: C, 62·1; H, 4·1; N, 12·8; Cl, 21·2. $C_{17}H_{13}N_3Cl_2$ requires C, 61·8; H, 3·9; N, 12·7; Cl, 21·5%).

4-p-*Chloroanilino*-6-*β-diethylaminoethylamino*-5-*phenyl*-2-*methylpyrimidine* (IV; R = Cl, R′ = Ph, R″ = Me, R‴ = $[CH_2]_2{\cdot}NEt_2$).—The above chloropyrimidine (12·0 g.), β-diethylaminoethylamine (12·0 g.), and a crystal of potassium iodide were heated at 150—160° for 6 hours with stirring and then worked up to give the *pyrimidine* which crystallised from light petroleum (b. p. 40—60°) in colourless laminæ, m. p. 88—89° (Found: C, 67·0; H, 7·1; N, 17·5. $C_{23}H_{28}N_5Cl$ requires C, 67·4; H, 6·8; N, 17·1%).

4-p-*Chloroanilino*-6-*γ-diethylaminopropylamino*-5-*phenyl*-2-*methylpyrimidine* (IV; R = Cl, R′ = Ph, R″ = Me, R‴ = $[CH_2]_3{\cdot}NEt_2$), prepared in a similar manner using γ-diethylaminopropylamine in place of β-diethylaminoethylamine, crystallised from light petroleum (b. p. 40—60°) in colourless thick rectangular prisms, m. p. 77—78° (Found: C, 67·7; H, 6·8; N, 16·7. $C_{24}H_{30}N_5Cl$ requires C, 68·0; H, 7·1; N, 16·5%). A crystalline dihydrochloride could not be obtained either from this or the preceding compound.

4-*Chloro*-2-*amino*-6-p-*chloroanilinopyrimidine* (V; R = Cl, R′ = H, R″ = NH_2).—(*a*) 4 : 6-Dichloro-2-aminopyrimidine (12·3 g.) and *p*-chloroaniline (9·6 g.) were ground together, acetic acid (9·0 g.) was added, and the mixture was heated to 110°. After a few minutes at this temperature a vigorous reaction occurred, and the reaction mixture which had previously become fluid and homogeneous suddenly set solid. The cooled and ground melt was boiled with alcohol (150 c.c.) containing ammonia for 1½ hours, then diluted with water, and the *product* collected and dried. Crystallised from ethyl acetate it formed colourless prisms (yield, 11·6 g.), m. p. 242—243° (Found: C, 47·1; H, 3·2; N, 21·9; Cl, 28·1. $C_{10}H_8N_4Cl_2$ requires C, 47·1; H, 3·1; N, 22·0; Cl, 27·7%). Addition of hydrochloric acid to its alcoholic solution gave a *hydrochloride* as colourless needles, m. p. 252—254° (Found: N, 18·2; Cl, 33·6. $C_{10}H_8N_4Cl_2,HCl,H_2O$ requires N, 18·1; Cl, 34·4%).

(*b*) 4 : 6-Dichloro-2-aminopyrimidine (8·2 g.), *p*-chloroaniline (6·3 g.), water (40 c.c.), acetone (10 c.c.),

and 10N-hydrochloric acid (0·5 c.c.) were boiled under reflux for 2 hours. After cooling, the product was filtered off, washed with water, and dissolved in boiling 2-ethoxyethanol with the addition of ammonia to give an alkaline reaction. After dilution with water the precipitated product was filtered off, washed with water, dried, and crystallised from ethyl acetate; m. p. 241—242° either alone or admixed with the product from (*a*) above (yield, 6·5 g.).

4-*Chloro*-2-*amino*-6-p-*anisidinopyrimidine* (V; R = OMe, R′ = H, R″ = NH_2).—To an intimate mixture of 4 : 6-dichloro-2-aminopyrimidine (12·3 g.) and *p*-anisidine (9·2 g.), acetic acid (4·5 g.) was added and the mixture heated to 110°; a vigorous reaction then took place. After ½ hour at 110°, the melt was cooled, ground, and stirred with dilute ammonia for 2 hours. The resulting *base* was filtered off, washed with water, and crystallised from alcohol, giving colourless prisms (8·9 g.), m. p. 224—225° (Found: C, 53·1; H, 4·6; N, 22·1. $C_{11}H_{11}ON_4Cl$ requires C, 52·7; H, 4·4; N, 22·35%). The *hydrochloride* had m. p. 236° (decomp.) (Found: N, 19·3; Cl, 24·1. $C_{11}H_{11}ON_4Cl$,HCl requires N, 19·5; Cl, 24·7%).

4-*Chloro*-2-*amino*-6-p-*toluidinopyrimidine* (V; R = Me, R′ = H, R″ = NH_2), prepared similarly using *p*-toluidine in place of *p*-anisidine, crystallised from alcohol in colourless laminæ, m. p. 239—241° (Found: C, 56·1; H, 4·7; N, 23·8. $C_{11}H_{11}N_4Cl$ requires C, 56·3; H, 4·7; N, 23·9%). It formed a *hydrochloride*, m. p. 259—260° (decomp.) (Found: N, 20·3; Cl, 26·4. $C_{11}H_{11}N_4Cl$,HCl requires N, 20·3; Cl, 26·4%).

2-*Amino*-4-p-*chloroanilino*-6-*β*-*diethylaminoethylaminopyrimidine* (IV; R = Cl, R′ = H, R″ = NH_2, R‴ = $[CH_2]_2{\cdot}NEt_2$).—(*a*) 4-Chloro-2-amino-6-*p*-chloroanilinopyrimidine hydrochloride (9·7 g.) and *β*-diethylaminoethylamine (4·84 g.) were heated at 150—160° for 5 hours, and the mixture was cooled and dissolved in water. To the solution sodium hydroxide was added, and the precipitated product was extracted with chloroform. The chloroform solution was shaken several times with 5% acetic acid and the acid extracts were combined, made alkaline with sodium hydroxide, and extracted with chloroform. The dried chloroform solution, on evaporation, gave the *base* which crystallised from benzene in colourless laminæ (8 g.), m. p. 135° (Found: C, 57·4; H, 7·0; N, 24·7. $C_{16}H_{23}N_6Cl$ requires C, 57·4; H, 6·9; N, 25·1%) (3861).

(*b*) 4-Chloro-2-amino-6-*β*-diethylaminoethylaminopyridimine (6·1 g.) (see below) and *p*-chloroaniline hydrochloride (4·1 g.) were mixed and heated in an oil-bath at 170—180° for 6 hours. The resulting melt was dissolved in warm dilute hydrochloric acid and then worked up as in (*a*) to give 2-amino-4-*p*-chloroanilino-6-*β*-diethylaminoethylaminopyrimidine, m. p. and mixed m. p. 134—135°.

By method (*a*) above a number of other 2-*amino*-4-*arylamino*-6-*dialkylaminoalkylaminopyrimidines* were prepared. Details of these are given in Table I.

4-*Chloro*-2-*amino*-6-p-*chloroanilino*-5-*ethylpyrimidine* (V; R = Cl, R′ = Et, R″ = NH_2).—4 : 6-Dichloro-2-amino-5-ethylpyrimidine (19·2 g.) (v. Merkatz, *Ber.*, 1919, **52**, 869) and *p*-chloroaniline (12·75 g.) were ground together, acetic acid (6 g.) was added, and the mixture was heated at 100—110° for ½ hour with stirring. A homogeneous melt was obtained which suddenly solidified after about ½ hour. The cooled and ground melt was dissolved in boiling alcohol with the addition of ammonia to give an alkaline reaction, and the solution poured into water. The precipitated *product* was filtered off and dried. By crystallisation from benzene it was obtained as colourless tables (19·25 g.), m. p. 158—160° (Found: C, 51·2; H, 4·2; N, 19·4. $C_{12}H_{12}N_4Cl_2$ requires C, 50·9; H, 4·2; N, 19·8%). The *hydrochloride* crystallised from alcohol containing a little hydrochloric acid in long colourless prisms, m. p. >290° (Found: C, 45·6; H, 4·5; N, 17·6. $C_{12}H_{12}N_4Cl_2$,HCl requires C, 45·1; H, 4·1; N, 17·5%).

4-*Chloro*-2-*amino*-6-p-*cyanoanilino*-5-*ethylpyrimidine* (V; R = CN, R′ = Et, R″ = NH_2).—4 : 6-Dichloro-2-amino-5-ethylpyrimidine (12·8 g.) and *p*-cyanoaniline (7·86 g.) were mixed, and acetic acid (4 g.) was added. After being heated for some time at 120° the fluid mixture suddenly solidified. Heating at 120—130° was continued for 1 hour, and the melt then dissolved in 2-ethoxyethanol, ammonia added, and the solution poured into water. The dried precipitated *product* crystallised from butanol in colourless rhombs (10 g.), m. p. 230—232° (Found: C, 57·0; H, 4·1; N, 25·1. $C_{13}H_{12}N_5Cl$ requires C, 57·0; H, 4·4; N, 25·6%).

4 : 6-*Dichloro*-2-*amino*-5-*phenylpyrimidine*.—Guanidine nitrate (24·4 g.) was added to a hot solution of sodium (9·2 g.) in methanol (250 c.c.) and, after ½ hour's refluxing, ethyl phenylmalonate (47·2 g.) was added. The mixture was boiled under reflux for 3 hours and then allowed to cool. The solid was collected and the filtrate evaporated; the residue and the solid were combined and dissolved in warm water, and the solution was treated with decolourising carbon and filtered. The filtrate was acidified with acetic acid at 80°, and the product collected, washed with water, and dried (25·6 g.). This 2-amino-4 : 6-dihydroxy-5-phenylpyrimidine (20 g.) and phosphoryl chloride (90 c.c.) were boiled under reflux for 3 hours, and the resulting clear solution was poured on ice (600 g.) with stirring. After 2 hours' stirring, ammonia was gradually added until the mixture was neutral. The solid product was filtered off, washed with water, and dried. Purification by vacuum sublimation at 160—170°/14 mm. followed by crystallisation from alcohol, gave 4 : 6-*dichloro*-2-*amino*-5-*phenylpyrimidine* as colourless plates, m. p. 221—222° (Found: C, 50·3; H, 2·9; N, 17·3. $C_{10}H_7N_3Cl_2$ requires C, 50·0; H, 2·9; N, 17·5%).

4-*Chloro*-2-*amino*-6-p-*chloroanilino*-5-*phenylpyrimidine* (V; R = Cl, R′ = Ph, R″ = NH_2).—Acetic acid (3 g.) was added to an intimate mixture of 4 : 6-dichloro-2-amino-5-phenylpyrimidine (12·0 g.) and *p*-chloroaniline (6·45 g.) and the whole heated at 120—130° for 1·5 hours. The mixture gradually melted and then resolidified. After being ground and stirred with dilute ammonia, the solid product was dissolved in 2-ethoxyethanol, ammonia added to alkalinity, and the solution diluted with water. The crystalline *pyrimidine* which separated on standing was filtered off, dried, and crystallised from butanol; colourless laminæ, m. p. 228—229° (Found: C, 58·0; H, 3·6; N, 16·6. $C_{16}H_{12}N_4Cl_2$ requires C, 58·0; H, 3·6; N, 16·9%).

2-*Amino*-4-*arylamino*-6-*dialkylaminoalkylamino*-5-*substituted Pyrimidines*.—The appropriate 4-chloro-2-amino-6-arylaminopyrimidine was heated with excess of dialkylaminoalkylamine and a trace of potassium iodide for 6 hours at 160—165°. The resulting mixture was dissolved in dilute hydrochloric acid and the solution filtered, if necessary, from insoluble material. The filtrate was added to excess

TABLE I.

2-Amino-4-arylamino-6-dialkylaminoalkylaminopyrimidines.

Ref. No.	Substituent at 4.	Substituent at 6.	Solvent; appearance.	M. p.	Formula.	Analysis. Found, %.	Analysis. Required, %.
3925	C_6H_4Cl (*p*)	$[CH_2]_2\cdot NMe_2$	Benzene	139—140°	$C_{14}H_{19}N_6Cl$	C, 55·1; H, 6·4; N, 26·8	C, 54·8; H, 6·2; N, 27·4
3939	C_6H_4Cl (*p*)	$[CH_2]_2\cdot NEt_2$	Benzene–light petroleum (b. p. 60—80°); prisms	109—111	$C_{17}H_{25}N_6Cl$	C, 59·0; H, 7·7; N, 23·9	C, 58·5; H, 7·2; N, 24·1
3923	C_6H_4Cl (*p*)	$[CH_2]_3\cdot NMe_2$	Benzene; plates	132—134	$C_{15}H_{21}N_6Cl$	C, 56·4; H, 6·6; N, 25·7	C, 56·2; H, 6·6; N, 26·2
3934	C_6H_4Cl (*p*)	$CHMe\cdot[CH_2]_3\cdot NEt_2$	Benzene–light petroleum (b. p. 60—80°); prisms	128—130	$C_{19}H_{29}N_6Cl$	C, 60·9; H, 7·9; N, 21·8	C, 60·5; H, 7·7; N, 22·3
3913	$C_6H_4\cdot OMe$ (*p*)	$[CH_2]_2\cdot NEt_2$	Benzene; plates	123—125	$C_{17}H_{26}ON_6$	C, 62·3; H, 7·5; N, 25·4	C, 61·8; H, 7·9; N, 25·45
3922	$C_6H_4\cdot Me$ (*p*)	$[CH_2]_2\cdot NEt_2$	Benzene–light petroleum (b. p. 60—80°); tables	108—109	$C_{17}H_{26}N_6$	C, 65·0; H, 8·8; N, 26·2	C, 65·0; H, 8·3; N, 26·8

TABLE II.

2-Amino-4-p-chloroanilino-6-dialkylaminoalkylamino-5-substituted Pyrimidines.

Ref. No.	Substituent at 5.	Substituent at 6.	Solvent.	M. p.	Formula.	Analysis. Found, %.	Analysis. Required, %.
4072	Et	$[CH_2]_2\cdot NEt_2$	Light petroleum (b. p. 60—80°)	71—72°	$C_{18}H_{27}N_6Cl$	analysis sample lost	
4109	Et	$[CH_2]_3\cdot NEt_2$	Light petroleum (b. p. 80—100°)	102—103	$C_{19}H_{29}N_6Cl$	C, 60·6; H, 7·5; N, 22·3	C, 60·5; H, 7·7; N, 22·3
4108	Et	$[CH_2]_3\cdot NMe_2$	Light petroleum (b. p. 100—120°)	130—132	$C_{17}H_{25}N_6Cl$	C, 58·8; H, 7·1; N, 24·0	C, 58·5; H, 7·2; N, 24·1
*	Et	$[CH_2]_2\cdot NEt_2$	Benzene	151—152	$C_{19}H_{27}N_7$	C, 64·1; H, 7·6; N, 27·3	C, 64·6; H, 7·6; N, 27·8
4133	Ph	$[CH_2]_2\cdot NEt_2$	Alcohol	170—171	$C_{22}H_{27}N_6Cl$	C, 64·5; H, 6·4; N, 20·0	C, 64·3; H, 6·6; N, 20·4
4199	Ph	$[CH_2]_3\cdot NMe_2$	Alcohol	157—158	$C_{21}H_{25}N_6Cl$	C, 63·9; H, 6·4; N, 20·5	C, 63·6; H, 6·3; N, 21·2
4200	Ph	$[CH_2]_3\cdot NEt_2$	Alcohol	172—173	$C_{23}H_{29}N_6Cl$	C, 64·6; H, 6·5; N, 20·4	C, 65·0; H, 6·8; N, 19·8

All these compounds formed colourless laminæ, except the last two which were obtained as colourless thick prisms. * 4-*p*-Cyanoanilino-compound.

TABLE III.

4-Chloro-2-amino-6-aminoalkylaminopyrimidines.

Ref. No.	Substituent at 5.	Substituent at 6.	Solvent.	M. p.	Formula.	Analysis. Found, %.	Analysis. Required, %.
4284	H	$[CH_2]_2\cdot NEt_2$	Benzene–light petroleum (b. p. 60—80°) [1]	93—95°	$C_{10}H_{18}N_5Cl$	C, 49·6; H, 7·0; N, 28·4	C, 49·3; H, 7·4; N, 28·7
4552	H	$[CH_2]_3\cdot NEt_2$	Light petroleum (b. p. 100—120°) [2]	86—87	$C_{11}H_{20}N_5Cl$	C, 51·5; H, 7·8; N, 26·8	C, 51·3; H, 7·8; N, 27·2
4395	Et	$[CH_2]_2\cdot NEt_2$	Benzene–light petroleum (b. p. 60—80°) [2]	105—106	$C_{12}H_{22}N_5Cl$	C, 53·2; H, 7·6; N, 25·2	C, 53·4; H, 8·1; N, 25·8
4442	Et	$[CH_2]_3\cdot NEt_2$	Benzene [2]	115—116	$C_{13}H_{24}N_5Cl$	C, 54·4; H, 8·6	C, 54:6; H, 8·4
4441	Et	$[CH_2]_3\cdot N<[CH_2]_4>CH_2$	Toluene [2]	170—171	$C_{14}H_{24}N_5Cl$	C, 56·9; H, 8·2	C, 56·8; H, 8·1
4395	Ph	$[CH_2]_2\cdot NEt_2$	Benzene–light petroleum (b. p. 60—80°) [3]	138—139	$C_{16}H_{22}N_5Cl$	C, 59·6; H, 6·8; N, 21·7	C, 60·1; H, 6·9; N, 21·9
4320	Ph	$[CH_2]_3\cdot NEt_2$	Benzene–light petroleum (b. p. 60—80°) [3]	131—132	$C_{17}H_{24}N_5Cl$	C, 61·2; H, 6·7; N, 21·0	C, 61·2; H, 7·2; N, 21·0
4415	Ph	$[CH_2]_3\cdot N<[CH_2]_4>CH_2$	Benzene [3]	151—152	$C_{18}H_{24}N_5Cl$	C, 62·5; H, 6·4; N, 19·6	C, 62·5; H, 6·9; N, 20·3

[1] Colourless flat needles. [2] Colourless laminæ. [3] Colourless prisms.

of sodium hydroxide and the precipitated product either filtered off or (if liquid) extracted with chloroform. In either case purification was effected by extraction with 5% acetic acid and reprecipitation with sodium hydroxide. The precipitated product was collected and dried, or extracted with chloroform and the dried extract evaporated, and then crystallised. The *compounds* prepared are given in Table II.

4-*Chloro*-2-*amino*-6-*aminoalkylaminopyrimidines*.—The requisite 4 : 6-dichloro-2-aminopyrimidine was mixed with the aminoalkylamine (1 mol.) and acetic acid (1 mol.), and heated at 100—110° (115—120° in the case of the 5-phenyl compounds) for 3 hours. The cooled mixture was lixiviated with dilute hydrochloric acid and the solution filtered from unchanged pyrimidine. Addition of sodium hydroxide to the filtrate precipitated the product which was isolated either by filtration or by extraction with ether and then purified by dissolution in 5% acetic acid and reprecipitation with sodium hydroxide. If solid, the product was filtered off and dried; otherwise, it was extracted with ether, and the solution dried and evaporated. The product was then crystallised. Details of the *compounds* prepared are given in Table III.

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