

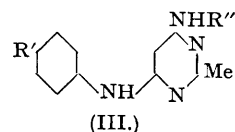
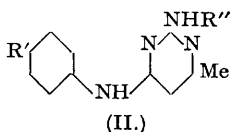
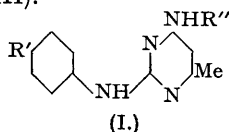
147. *Synthetic Antimalarials. Part VIII. Some 4-Arylamino-6-aminoalkylamino-2-methylpyrimidines.*

By F. R. BASFORD, F. H. S. CURD, and F. L. ROSE.

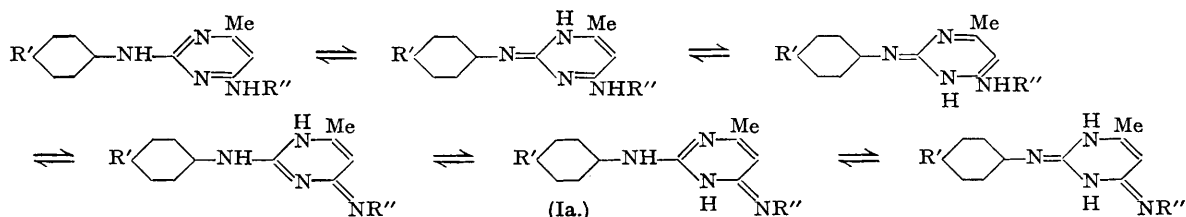
In continuation of the work on arylamino-aminoalkylaminopyrimidines described in some of the earlier papers of this series a number of 4-arylamino-6-aminoalkylamino-2-methylpyrimidines of type (III) have been prepared, but were devoid of antimalarial activity. Attention is drawn to a difference between the tautomeric

possibilities in compounds of type (III) on the one hand and the active isomeric 2-arylamino-4-aminoalkyl-amino- and 4-arylamino-2-aminoalkylamino-6-methylpyrimidines of types (I) and (II) on the other, which may have a bearing on the cause of antimalarial activity. Differences in reactivity between related pyrimidine derivatives are discussed; one possible explanation relates these also to the tautomeric behaviour of the molecules.

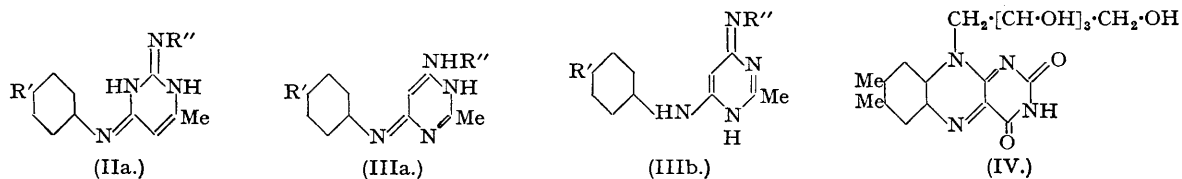
IN Parts I, II, and VI (this vol., pp. 343, 351, 370) we described the preparation of extensive series of 2-anilino-4-aminoalkylamino-6-methylpyrimidines (I) and 4-anilino-2-aminoalkylamino-6-methylpyrimidines (II) carrying substituents (R') in the *para* position of the anilino residue. Since compounds of both types (I) and (II) exhibited antimalarial activity against *P. gallinaceum* in chicks it was obviously desirable to examine the third isomeric type (III).



Quite apart from the possibility that the antimalarial activity of compounds of type (I) may be connected with their capability of functioning as riboflavin antagonists, from our initial work (Part I, *loc. cit.*) it appeared to be necessary for the aryl and pyrimidine nuclei to be linked by groupings capable of prototropic change. Compounds of type (II) are similarly constituted, but whereas type (I) conforms to the Schönhöfer hypothesis (*Z. physiol. Chem.*, 1942, 274, 1), according to which antimalarial activity is associated with an aminoalkyl-amino group in the γ -position relative to a heterocyclic nitrogen atom so as to allow tautomerism to a *p*-quinonoid structure, type (II) does not. With type (II), only *o*-quinonoid tautomerism is possible, and previously there do not appear to have been any indications that this had any significance for antimalarial activity. It will be seen, however, that types (I) and (II) do possess a common tautomeric feature. The various possibilities in type (I) are as follows :



Similar possibilities exist in type (II), so that in both types the NH-groups linking the phenyl and aminoalkyl residues to the pyrimidine nucleus are simultaneously capable of prototropy as in (Ia) and (IIa). In contrast to this, compounds of type (III), while capable of tautomerism to give the *p*-quinonoid structures (IIIa) and (IIIb), do not permit further prototropic change involving the second heterocyclic nitrogen atom analogous to (Ia) and (IIa). It was therefore considered that an examination of compounds of type (III) might throw further light on the relationship between antimalarial activity and structure.

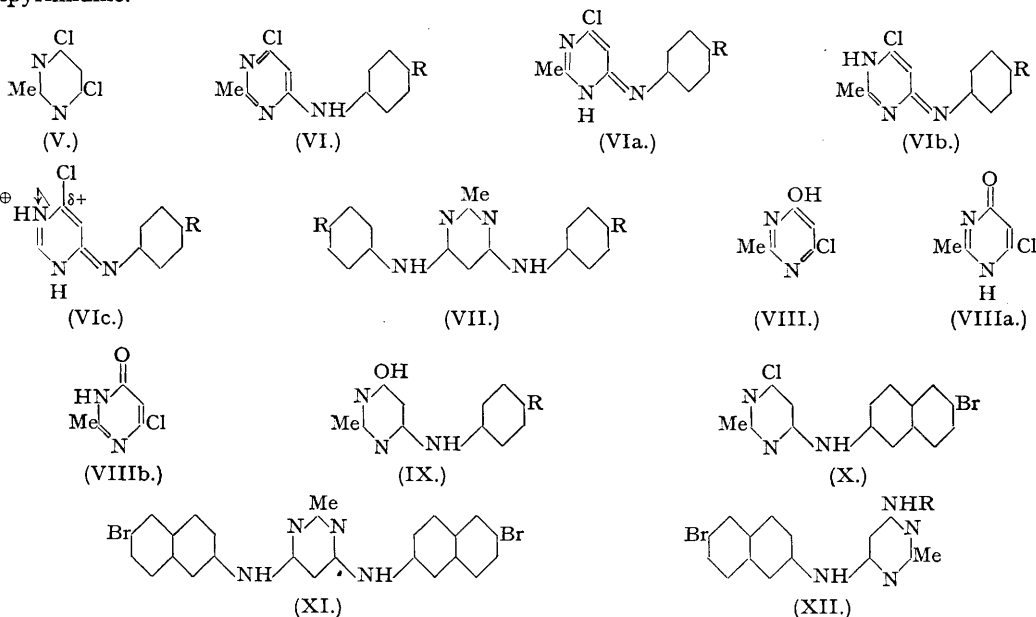


The structural resemblance to riboflavin (IV) discernible in the planar formulations of types (I) and (II) is in certain respects likewise a characteristic of type (III).

Although compounds of types (I) and (II) were not found to be easy of access by the stepwise replacement of the two chlorine atoms in 2 : 4-dichloro-6-methylpyrimidine by arylamino and aminoalkylamino groups respectively, because of the formation of isomeric products which were difficult to separate (see Part VI, this vol., p. 370), such a method had obvious possibilities for the synthesis of compounds of type (III) utilising 4 : 6-dichloro-2-methylpyrimidine (V). In this substance both chlorine atoms are positionally equivalent and the complication of the formation of isomers does not therefore arise. The stepwise replacement of the two chlorine atoms in (V) by amino-groups has been reported by Foldi, von Fodor, Demjén, Szkeres, and Halmos (*Ber.*, 1942, 75, 755) and by Baddiley, Lythgoe, McNeil, and Todd (*J.*, 1943, 383). Similarly, Huber and Hölscher (*Ber.*, 1938, 71, 87) found that 4 : 6-dichloro-2 : 5-dimethylpyrimidine required treatment with alcoholic ammonia at a much higher temperature for conversion into 4 : 6-diamino-2 : 5-dimethylpyrimidine than to give 4-chloro-6-amino-2 : 5-dimethylpyrimidine. Further, whereas theory predicts that the two chlorine atoms in 4 : 6-dichloro-2-methylpyrimidine should possess equivalent reactivity, it seemed unlikely that after one had reacted with an arylamine the remaining one would retain its original reactivity, since

new tautomeric possibilities would then have been introduced into the molecule. These considerations led to the hope that condensation of arylamines with (V) could be arrested at the mono-condensation stage.

Exploratory experiments on the condensation of *p*-chloroaniline with (V) to give (VI; R = Cl) showed, however, that this type of reaction proceeded much more readily than the corresponding reaction with ammonia, and in several experiments, even when equimolecular quantities were used, a certain proportion of the dicondensation product (VII; R = Cl) was isolated. The optimum conditions discovered, *viz.*, reaction in acetic acid at 40—50° in presence of a trace of potassium iodide, and in boiling aqueous acetone with the addition of a catalytic amount of hydrochloric acid, yielded products having m. p. 152° and 149—151° respectively. Examination of the latter appeared to indicate that it was not completely pure; the m. p. did not become constant on repeated crystallisation. Although no 4 : 6-*di-p*-chloroanilino-2-methylpyrimidine (VII; R = Cl) could be separated from this product, an examination of the solubility properties of (VII; R = Cl) (obtained by fusing together at 120° 4 : 6-dichloro-2-methylpyrimidine and two molecular proportions of *p*-chloroaniline with the addition of a little hydrochloric acid) indicated that removal of small quantities from 4-*chloro-6-p*-chloroanilino-2-methylpyrimidine (VI; R = Cl) would be difficult. Since the use of slightly less than one molecular equivalent of *p*-chloroaniline led to no improvement, it was decided to undertake the synthesis of (VI; R = Cl) by an alternative method in order to assess the purity of the preparations from 4 : 6-dichloro-2-methylpyrimidine.



Dr. P. A. Barrett has shown in these laboratories that (V) is hydrolysed by boiling for a short time with fairly concentrated hydrochloric acid to give 4-*chloro-6-hydroxy-2-methylpyrimidine* (VIII). On condensation with *p*-chloroaniline this was converted into 4-*p*-chloroanilino-6-*hydroxy-2-methylpyrimidine* (IX; R = Cl) which on treatment with boiling phosphoryl chloride yielded 4-*chloro-6-p*-chloroanilino-2-methylpyrimidine, m. p. 152—153°, thus showing that the product previously obtained was only slightly impure, and the reason for the earlier observed variation of the m. p. on repeated crystallisation has not been further investigated.

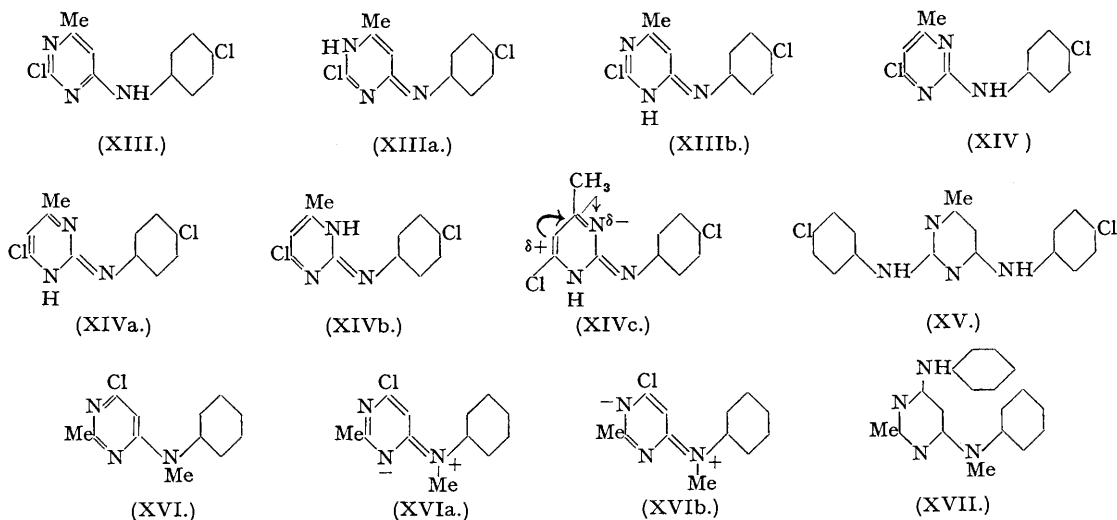
No difference was observed between the 4-*chloro-6-p*-anisidino-2-methylpyrimidine (VI; R = OMe) obtained by interaction of (V) and *p*-anisidine (1 mol.) in boiling aqueous acetone in presence of a small amount of hydrochloric acid and that from (VIII) via 4-*p*-anisidino-6-*hydroxy-2-methylpyrimidine* (IX; R = OMe). Interaction of 6-bromo-β-naphthylamine and (V), using equimolecular quantities, gave 4-*chloro-6-(6'-bromo-β-naphthylamino)-2-methylpyrimidine* (X) together with a small proportion of 4 : 6-*di-(6'-bromo-β-naphthylamino)-2-methylpyrimidine* (XI), but separation was easily accomplished in this case because of the insolubility of the dicondensation product in alcohol. The formation of (XI) was entirely prevented by reducing slightly the proportion of amine used. *p*-Nitroaniline reacted with (V) to give 4-*chloro-6-p*-nitroanilino-2-methylpyrimidine (VI; R = NO₂), either in acetic acid at 50—55° or in boiling aqueous acetone with hydrochloric acid, without any evidence of the formation of dicondensation product.

The further reaction of some of these 4-*chloro-6*-arylamino-2-methylpyrimidines with arylamines was then investigated, boiling aqueous acetone being used as solvent with the addition of small amounts of hydrochloric acid as catalyst. Using these conditions, it had previously been shown that both 2-*chloro-4-p*-chloroanilino-6-methylpyrimidine (XIII) and 4-*chloro-2-p*-chloroanilino-6-methylpyrimidine (XIV) condensed rapidly with a molecule of *p*-chloroaniline to give good yields of 2 : 4-*di-p*-chloroanilino-6-methylpyrimidine (XV). In contrast to this, no observable reaction had occurred after 2 hours between 4-*chloro-6-p*-chloroanilino-2-methylpyrimidine and *p*-chloroaniline, while 4-*chloro-6*-anilino-2-methylpyrimidine (VI; R = H)

and aniline, and 4-chloro-6-*p*-anisidino-2-methylpyrimidine (VI; R = OMe) and *p*-anisidine, gave only very small yields of the 4 : 6-diarylamino-compounds. As recorded above it had been observed earlier that the formation of dicondensation product was not easily avoided when 4 : 6-dichloro-2-methylpyrimidine (V) was caused to react with one molecular proportion of *p*-chloroaniline. Employing two molecular proportions of *p*-chloroaniline in aqueous acetone and a trace of hydrochloric acid, the amount of (VII; R = Cl) formed was appreciable. The behaviour of aniline and *p*-anisidine was very similar to that of *p*-chloroaniline except that they appeared to react with greater facility. The former gave approximately equal proportions of the mono- and di-condensation products (VI; R = H) and (VII; R = H), while *p*-anisidine gave almost exclusively (VII; R = OMe) and only a very small proportion of 4-chloro-6-*p*-anisidino-2-methylpyrimidine (VI; R = OMe). Assuming that the reaction proceeds by step-wise replacement of the chlorine atoms, these results suggested that the more difficult second stage, namely the condensation of the intermediate 4-chloro-6-arylamino-2-methylpyrimidine with the second molecule of arylamine, was facilitated by the presence of the equivalent of hydrochloric acid liberated in the first stage. Separate experiments showed this to be so, for when 4-chloro-6-anilino-2-methylpyrimidine and aniline reacted together in aqueous acetone with the addition of slightly more than one equivalent of hydrochloric acid 4 : 6-*dianilino*-2-methylpyrimidine was formed in amount comparable to that obtained from the reaction of (V) with aniline (2 mols.); similarly 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine and *p*-chloroaniline gave a significant amount of 4 : 6-di-*p*-chloroanilino-2-methylpyrimidine within the standard reaction time of two hours. Even so, the chlorine atom in the primary condensation products (VI) was much less reactive than that in the isomeric types (XIII) and (XIV).

One possible explanation of this might well be the tendency of the anilino nitrogen atom to conjugate with the benzene ring giving either (VIa) or (VIb) with the loss of the imino-chloride structure. A similar tendency might well exist with (XIII) and (XIV), giving (XIIIa) and (XIIIb), and (XIVa) and (XIVb), respectively. Of these, all but (XIVa) still retain an imino-chloride structure, and (XIVa) might still be expected to exhibit a labile chlorine by the mechanism (XIVc) (compare 4-chloroquinoline).

An attempt was made to check these speculations by preparing 4-chloro-6-*N*-methylanilino-2-methylpyrimidine (XVI), in which the methyl group would prevent tautomerism, and causing it to react with aniline by the aqueous acetone method. No (XVII) appeared to be formed, however. This result can be explained by assuming that the resonance forms (XVIa) and (XVIb) predominate, giving effects analogous to those obtained through tautomerism in (VIa) and (VIb). The activation of the chlorine atom in these latter structures by adding appreciable quantities of hydrochloric acid, as observed experimentally, might be explained by the formation of the cation leading to a charge displacement such as that displayed in (XIVc). The proton is there arbitrarily placed on a ring nitrogen atom, since such a disposition would exert the optimum effect on the reactivity of the chlorine atom. It might well be that the failure of added hydrochloric acid to activate (XVI) is due to attachment of the proton to the more distant extra-nuclear nitrogen atom, the basicity of which will have been appreciably increased by the methyl group attached to it.



Our inability to condense (VI; R = Cl) with *p*-chloroaniline in aqueous acetone with only a small proportion of added hydrochloric acid finds a parallel in the difficulty experienced in condensing 4-chloro-6-hydroxy-2-methylpyrimidine with *p*-chloroaniline under similar conditions; this may possibly be connected with a tendency for 4-chloro-6-hydroxy-2-methylpyrimidine to react as (VIIIa) or (VIIIb).

It should be emphasised that none of the condensations discussed above is impossible of achievement since they all proceed to completion at suitably raised temperatures, but the particular conditions used happen to have disclosed the interesting variations in reactivity between the different chloropyrimidines. A further

point of interest in the above experiments is the indication they provide that the nature of the substituent in the anilino group of (VI) affects the reactivity of the chlorine atom and, since we believe this may be bound up with the tautomeric behaviour of the heterocyclic system which also seems important for antimalarial activity, some interesting theoretical arguments can be developed. It is hoped that we shall later have an opportunity of testing these by experiment.

The compounds (VI; R = Cl, OMe, NO₂) and (X) were each condensed with representative aminoalkylamines to give series of substances of types (III) and (XII) which were tested against *P. gallinaceum* in chicks, but none showed any significant activity and in this respect differed from the compounds of types (I) and (II).

EXPERIMENTAL.

4-Chloro-6-hydroxy-2-methylpyrimidine (VIII).—4 : 6-Dichloro-2-methylpyrimidine (Baddiley, Lythgoe, McNeil, and Todd, *loc. cit.*) (25 g.), water (250 c.c.), and hydrochloric acid (100 c.c.) were boiled under reflux for $\frac{3}{4}$ hour. Complete solution of the chloropyrimidine had occurred after $\frac{1}{2}$ hour. After cooling, the reaction mixture was made alkaline with ammonia and then acidified with acetic acid. After being kept overnight, the precipitated product was filtered off, washed with water, and dried at 100° (yield, 18.4 g.). It crystallised from alcohol in colourless needles, m. p. 233° (Found: N, 19.4; Cl, 24.6. C₈H₈ON₂Cl requires N, 19.4; Cl, 24.6%). 4-Chloro-6-hydroxy-2-methylpyrimidine is soluble in dilute aqueous ammonia.

4-p-Chloroanilino-6-hydroxy-2-methylpyrimidine (IX; R = Cl).—The above chloropyrimidine (12.2 g.), *p*-chloroaniline (10.6 g.), water (87.5 c.c.), and hydrochloric acid (1.75 c.c.) were boiled under reflux for 6 hours. The reaction mixture was cooled, and the separated product was filtered off, washed with water, and purified by dissolution in warm sodium hydroxide and reprecipitation with acetic acid followed by extraction with dilute ammonia. The undissolved compound was crystallised from β -ethoxyethanol, forming small thick colourless prisms, m. p. 296—297° (yield, 7 g.) (Found: C, 55.8; H, 4.1; N, 17.8. C₁₁H₁₀ON₂Cl requires C, 56.05; H, 4.2; N, 17.8%).

4-Chloro-6-p-chloroanilino-2-methylpyrimidine (VI; R = Cl).—(a) A mixture of 4-*p*-chloroanilino-6-hydroxy-2-methylpyrimidine (5.8 g.) and phosphoryl chloride (30 c.c.) was refluxed for 3 hours. The excess of phosphoryl chloride was removed under reduced pressure and the residue added to ice and water. The solid product was collected and dissolved in alcohol with the addition of sufficient ammonia to give an alkaline reaction, and the solution was filtered and diluted with water. The precipitated 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine was collected, washed with water, and crystallised from dilute alcohol; thick colourless prisms, m. p. 152—153° (yield, 3.75 g.) (Found: C, 52.3; H, 3.7; N, 16.6; Cl, 27.7. C₁₁H₈N₃Cl₂ requires C, 52.0; H, 3.5; N, 16.5; Cl, 28.0%).

(b) 4 : 6-Dichloro-2-methylpyrimidine (4.89 g.) and *p*-chloroaniline (4.4 g.) in glacial acetic acid (30 c.c.) to which a crystal of potassium iodide had been added were stirred at 40—50° for 20 hours. The solution, at first clear, gradually deposited the hydrochloride of the product. After cooling to room temperature anhydrous sodium acetate (3 g.) was added and stirring continued until a clear solution had been obtained. This was then poured into water (250 c.c.), and the precipitated product was collected, washed, and dried. Crystallisation from benzene-light petroleum (b. p. 60—80°) gave (VI; R = Cl), m. p. 152°, undepressed in admixture with material made by method (a) above (yield, 7.3 g.) (Found: C, 51.8; H, 3.7; N, 16.2%).

(c) 4 : 6-Dichloro-2-methylpyrimidine (8.15 g.), *p*-chloroaniline (6.4 g.), water (40 c.c.), acetone (10 c.c.), and 10*N*-hydrochloric acid (1 c.c.) were refluxed gently for 1 hour. The solid which had separated was filtered off when cold, suspended in warm alcohol, and ammonia added until alkaline. The resulting solution was diluted with water giving an oil which quickly solidified. The solid was collected and crystallised once from dilute alcohol giving a product (yield, 9.8 g.), m. p. 149—151° undepressed when mixed with 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine made according to method (a) (Found: C, 52.3; H, 3.4; N, 16.8; Cl, 26.6, 26.5%).

4-p-Chloroanilino-6- β -diethylaminoethylamino-2-methylpyrimidine (III; R' = Cl, R'' = [CH₂]₂·NET₂).—4-Chloro-6-*p*-chloroanilino-2-methylpyrimidine (10.16 g.), β -diethylaminoethylamine (11.6 g.), and a crystal of potassium iodide were stirred and heated at 150—160° for 8 hours. The resulting melt was dissolved in warm dilute hydrochloric acid, and the solution was filtered from a small amount of insoluble matter and made alkaline with sodium hydroxide. The precipitated base was extracted with chloroform, the solvent evaporated, and the residue extracted with 5% acetic acid. After being stirred with decolorising carbon, the acetic acid extract was treated with sodium hydroxide and the product again taken into chloroform. Evaporation of the dried chloroform extract left 4-*p*-chloroanilino-6- β -diethylaminoethylamino-2-methylpyrimidine which crystallised from light petroleum (b. p. 100—120°) in colourless needles, m. p. 148—149° (yield, 8.4 g.) (Found: C, 61.6; H, 7.2; N, 20.8. C₁₇H₂₄N₅Cl requires C, 61.3; H, 7.2; N, 21.0%) (4070).

4-p-Chloroanilino-6- γ -diethylaminopropylamino-2-methylpyrimidine (III; R' = Cl, R'' = [CH₂]₃·NET₂).—4-Chloro-6-*p*-chloroanilino-2-methylpyrimidine (8.45 g.) and γ -diethylaminopropylamine (5.37 g.) were heated at 140—150° for 8 hours with stirring and the reaction mixture worked up as described above, giving a product which crystallised from light petroleum (b. p. 100—120°) as colourless prisms, m. p. 128° (Found: C, 61.8; H, 7.2; N, 20.0. C₁₈H₂₆N₅Cl requires C, 62.2; H, 7.5; N, 20.1%) (3597).

The following were prepared in a similar way.

4-p-Chloroanilino-6- γ -di-*n*-butylaminopropylamino-2-methylpyrimidine (III; R' = Cl, R'' = [CH₂]₃·NBU₂), from 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine (2.54 g.) and γ -di-*n*-butylaminopropylamine (3.72 g.), crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. 93—94° (Found: C, 65.1; H, 8.1; N, 17.3; Cl, 8.9. C₂₂H₃₄N₅Cl requires C, 65.4; H, 8.4; N, 17.4; Cl, 8.7%) (4562).

4-p-Chloroanilino-6- γ -piperidinopropylamino-2-methylpyrimidine (III; R' = Cl, R'' = [CH₂]₃·N<[CH₂]₄>CH₂), from 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine (7.65 g.) and γ -piperidinopropylamine (5.3 g.), crystallised from light petroleum (b. p. 100—120°) in flat colourless prisms, m. p. 110° (Found: C, 62.9; H, 6.9; N, 19.3; Cl, 10.1. C₁₉H₂₆N₅Cl requires C, 63.4; H, 7.2; N, 19.5; Cl, 10.0%) (5273).

4-p-Chloroanilino-6- δ -diethylamino- α -methylbutylamino-2-methylpyrimidine (III; R' = Cl, R'' = CHMe·[CH₂]₃·NET₂) (3720), from 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine and δ -diethylamino- α -methylbutylamine, formed a practically colourless oil, b. p. 222—224°/0.1 mm. (Found: Cl, 9.4. C₂₀H₃₀N₅Cl requires Cl, 9.4%). It gave a *dipicrate* which separated from β -ethoxyethanol in microscopic yellow plates, m. p. 149—151° (Found: C, 46.3; H, 4.4; N, 18.4. C₂₀H₃₀N₅Cl₂·2C₆H₅O₂N₃ requires C, 46.1; H, 4.3; N, 18.5%). The dihydrochloride was hygroscopic and could not be satisfactorily crystallised.

4-p-Chloroanilino-6- γ -(β' -diethylaminoethoxy)propylamino-2-methylpyrimidine (III; R' = Cl, R'' = [CH₂]₃·O·[CH₂]₂·NET₂), from 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine and γ -(β' -diethylaminoethoxy)propylamine, formed a colourless oil, b. p. 245—249°/0.15 mm. (Found: N, 17.9. C₂₀H₃₀ON₅Cl requires N, 17.9%). The *dipicrate* separated from β -ethoxyethanol as a yellow microcrystalline powder, m. p. 181—182° (Found: C, 45.0; H, 4.2; N, 18.0. C₂₀H₃₀ON₅Cl₂·2C₆H₅O₂N₃ requires C, 45.2; H, 4.2; N, 18.1%).

4-*p*-Anisidino-6-hydroxy-2-methylpyrimidine (IX; R = OMe).—4-Chloro-6-hydroxy-2-methylpyrimidine (8.0 g.) and *p*-anisidine (6.15 g.) were mixed, hydrochloric acid (0.5 c.c.) was added, and the mixture heated at 120–130° for 3 hours, with stirring until the melt solidified. The resulting solid mass was ground, dissolved in warm dilute sodium hydroxide, treated with decolorising carbon, and filtered. Addition of acetic acid to the filtrate precipitated the *product* which was purified by stirring with dilute ammonia followed by crystallisation from β -ethoxyethanol; colourless laminae, m. p. 266–268° (Found: C, 62.3; H, 5.3; N, 18.9. $C_{12}H_{13}O_2N_3$ requires C, 62.3; H, 5.6; N, 18.2%) (yield, 8 g.).

4-Chloro-6-*p*-anisidino-2-methylpyrimidine (VI; R = OMe).—(a) The above hydroxy compound (6 g.) and phosphoryl chloride (30 c.c.) were refluxed during 1.5 hours. The resulting mixture was poured on ice and made alkaline with ammonia. The solid obtained was filtered off, dissolved in alcohol with the addition of a little ammonia, and poured into water. The product reprecipitated in this way crystallised from dilute alcohol giving 4-chloro-6-*p*-anisidino-2-methylpyrimidine as thick colourless laminae, m. p. 142–143° (Found: C, 57.9; H, 4.7; N, 16.6; Cl, 14.1. $C_{12}H_{12}ON_3Cl$ requires C, 57.7; H, 4.8; N, 16.8; Cl, 14.2%) (yield, 3.7 g.).

(b) 4 : 6-Dichloro-2-methylpyrimidine (16.3 g.), *p*-anisidine (12.3 g.), water (80 c.c.), acetone (20 c.c.), and 10*N*-hydrochloric acid (2 c.c.) were boiled for 1 hour and the resulting solution cooled. The crystalline product which separated was collected, suspended in warm alcohol, and ammonia added until alkaline. When solution had occurred, water was added and the precipitated product was filtered off, washed with water, and purified by crystallisation from aqueous methanol giving material identical with (a) above, m. p. and mixed m. p. 141–143° (yield, 15.2 g.) (Found: C, 57.4; H, 4.9; N, 16.5; Cl, 13.7%).

4-*p*-Anisidino-6- β -diethylaminoethylamino-2-methylpyrimidine (III; R' = OMe; R'' = $[CH_2]_2 \cdot N \cdot Et_2$).—A mixture of the above chloropyrimidine (2.5 g.) and β -diethylaminoethylamine (2.5 g.) to which a crystal of potassium iodide had been added was heated at 150–160° for 8 hours. The whole was then dissolved in dilute hydrochloric acid and the solution made alkaline with sodium hydroxide. The precipitated product was filtered off and dissolved in 5% acetic acid, and the solution was treated with decolorising carbon and filtered. Addition of sodium hydroxide to the filtrate gave a solid which was collected, washed with water, and dried. Crystallised from light petroleum (b. p. 100–120°) the compound was obtained as colourless prisms, m. p. 146–148° (Found: C, 65.7; H, 7.7; N, 21.4. $C_{18}H_{27}ON_5$ requires C, 65.7; H, 8.2; N, 21.3%) (4071).

4-*p*-Anisidino-6- γ -diethylaminopropylamino-2-methylpyrimidine (III; R' = OMe, R'' = $[CH_2]_3 \cdot N \cdot Et_2$), obtained in a similar manner by using γ -diethylaminopropylamine in place of β -diethylaminoethylamine, formed flat colourless prisms from light petroleum (b. p. 100–120°), m. p. 130° (Found: C, 66.0; H, 8.3; N, 20.0. $C_{19}H_{29}ON_5$ requires C, 66.5; H, 8.5; N, 20.4%) (3610).

4-*p*-Anisidino-6- δ -diethylamino- α -methylbutylamino-2-methylpyrimidine (III; R' = OMe, R'' = $CHMe \cdot [CH_2]_3 \cdot N \cdot Et_2$).—4-Chloro-6-*p*-anisidino-2-methylpyrimidine (5.0 g.) and δ -diethylamino- α -methylbutylamine (4.8 g.) were mixed and fused at 150–160° for 7 hours. The cooled melt was dissolved in dilute hydrochloric acid and the solution made alkaline with sodium hydroxide and extracted with chloroform. The solvent was evaporated and the residue stirred with 5% acetic acid. The acid extract was clarified with decolorising carbon and then treated with sodium hydroxide. The liberated base was taken up in chloroform, and the chloroform solution was dried and evaporated. The *product* remained as an oil which crystallised on stirring with light petroleum (b. p. 40–60°). It was collected and purified by crystallisation from light petroleum (b. p. 60–80°); colourless prisms, m. p. 103° (Found: C, 68.0; H, 8.9; N, 19.2. $C_{21}H_{33}ON_5$ requires C, 67.9; H, 8.9; N, 18.9%) (3679).

4-Chloro-6-*p*-nitroanilino-2-methylpyrimidine (VI; R = NO₂).—(a) 4 : 6-Dichloro-2-methylpyrimidine (4.89 g.), *p*-nitroaniline (4.55 g.), glacial acetic acid (50 c.c.), and a crystal of potassium iodide were heated at 60–55° for 18 hours. Addition of sodium acetate (3 g.) and dilution with water (250 c.c.) gave 4-chloro-6-*p*-nitroanilino-2-methylpyrimidine which crystallised from butanol in yellow needles, m. p. 271–272° (Found: Cl, 13.5. $C_{11}H_9O_2N_4Cl$ requires Cl, 13.4%).

(b) 4 : 6-Dichloro-2-methylpyrimidine (16.3 g.), *p*-nitroaniline (13.8 g.), water (75 c.c.), acetone (25 c.c.), and 10*N*-hydrochloric acid (2 c.c.) were refluxed for 2 hours. After cooling, the product which had separated was filtered off and dried. It was then dissolved in hot β -ethoxyethanol with the addition of ammonia to make the solution alkaline to Brilliant Yellow, and the solution was diluted with a large volume of water. The precipitated chloropyrimidine was filtered off, washed with water, and dried. Crystallisation from β -ethoxyethanol gave the same product as (a), m. p. 271–272° (Found: C, 50.3; H, 3.6; N, 20.7. $C_{11}H_9O_2N_4Cl$ requires C, 49.9; H, 3.4; N, 21.2%).

4-*p*-Nitroanilino-6- β -diethylaminoethylamino-2-methylpyrimidine (III; R' = NO₂; R'' = $[CH_2]_2 \cdot N \cdot Et_2$).—4-Chloro-6-*p*-nitroanilino-2-methylpyrimidine (5.28 g.) and β -diethylaminoethylamine (4.6 g.) condensed together by heating at 150–160° for 6 hours and worked up in the usual way for this type of compound gave the *base* which crystallised from benzene in yellow prisms, m. p. 130–131° (Found: C, 59.2; H, 6.8; N, 24.4. $C_{17}H_{24}O_2N_6$ requires C, 59.3; H, 7.0; N, 24.4%) (4148).

4-*p*-Nitroanilino-6- γ -dimethylaminopropylamino-2-methylpyrimidine (III; R' = NO₂, R'' = $[CH_2]_3 \cdot N \cdot Me_2$), from the same chloropyrimidine and γ -dimethylaminopropylamine, separated from toluene in small yellow needles, m. p. 169° (Found: C, 58.3; H, 6.9; N, 25.2. $C_{16}H_{22}O_2N_6$ requires C, 58.2; H, 6.7; N, 25.45%) (4189).

4-*p*-Nitroanilino-6- γ -di-*n*-butylaminopropylamino-2-methylpyrimidine (III; R' = NO₂, R'' = $[CH_2]_3 \cdot N \cdot Bu_2$), prepared likewise using γ -di-*n*-butylaminopropylamine, crystallised from light petroleum (b. p. 80–100°) in small yellow needles, m. p. 101° (Found: C, 63.6; H, 8.5; N, 20.3. $C_{22}H_{34}O_2N_6$ requires C, 63.8; H, 8.2; N, 20.3%) (4563).

4-Chloro-6-(6'-bromo- β -naphthylamino)-2-methylpyrimidine (X).—(a) 4 : 6-Dichloro-2-methylpyrimidine (8.15 g.) and 6-bromo- β -naphthylamine (11.1 g.) were ground together, acetic acid (3 g.) was added, and the mixture heated to 120°; a vigorous reaction set in and the whole solidified. After being heated at 110–120° for 15 minutes the product was ground and stirred with water (100 c.c.) and ammonia (10 c.c.) for several hours. The resulting solid was filtered off, washed with water, and dried. It was then boiled with alcohol (250 c.c.) and a few drops of ammonia for $\frac{1}{2}$ hour and filtered hot, leaving an insoluble residue which was retained. The alcoholic filtrate was evaporated to dryness, the residue stirred with water, and the resulting solid dried. Crystallisation from toluene gave 4-chloro-6-(6'-bromo- β -naphthylamino)-2-methylpyrimidine as thick colourless prisms, m. p. 191–192° (Found: C, 52.1; H, 3.4; N, 12.05. $C_{15}H_{11}N_3ClBr$ requires C, 51.7; H, 3.2; N, 12.05%) (yield, 9 g.). The above residue, insoluble in alcohol, crystallised from glacial acetic acid in colourless hair-fine needles, m. p. 284–285° (Found: C, 56.2; H, 4.0; N, 10.6; Br, 30.0. $C_{26}H_{19}N_3Br_2$ requires C, 56.2; H, 3.4; N, 10.6; Br, 30.0%), and consisted of 4 : 6-di-(6'-bromo- β -naphthylamino)-2-methylpyrimidine (yield, 3.3 g.).

(b) 4 : 6-Dichloro-2-methylpyrimidine (8.15 g.), 6-bromo- β -naphthylamine (10.5 g.), water (60 c.c.), acetone (40 c.c.), and 10*N*-hydrochloric acid (1 c.c.) were refluxed gently for 1½ hours. During the course of the reaction a solid separated. This was filtered off, after cooling, and washed with water. It was then dissolved in hot alcohol with the addition of ammonia to give an alkaline reaction and the solution poured into water. The precipitated product was filtered off, washed with water, dried, and crystallised from toluene giving 4-chloro-6-(6'-bromo- β -naphthylamino)-2-methylpyrimidine, m. p. 191–192°, identical with that made by method (a) (yield, 10.45 g.) (Found: C, 52.0; H, 3.3; N, 12.3%).

When the amount of 6-bromo- β -naphthylamine used in the above experiment was increased to 11.1 g. (1 mol.)

there were obtained 4-chloro-6-(6'-bromo- β -naphthylamino)-2-methylpyrimidine (9.05 g.) and 4:6-di-(6'-bromo- β -naphthylamino)-2-methylpyrimidine (1.8 g.).

4-(6'-Bromo- β -naphthylamino)-6- β -diethylaminoethylamino-2-methylpyrimidine (XII; R = [CH₂]₂·NET₂).—4-Chloro-6-(6'-bromo- β -naphthylamino)-2-methylpyrimidine (4.5 g.) was heated with β -diethylaminoethylamine (3.6 g.) at 150–160° for 6 hours. A solution of the resulting product in dilute hydrochloric acid was made alkaline with sodium hydroxide and the precipitated oil taken into chloroform. After removal of the chloroform the residue was extracted with 5% acetic acid, the extract treated with sodium hydroxide, and the liberated product extracted with chloroform. Evaporation of the dried chloroform solution and crystallisation of the residue from light petroleum (b. p. 100–120°) afforded 4-(6'-bromo- β -naphthylamino)-6- β -diethylaminoethylamino-2-methylpyrimidine; clumps of colourless prisms, m. p. 129–131° (Found: C, 59.1; H, 6.6; N, 16.2. C₂₁H₂₆N₅Br requires C, 58.7; H, 6.1; N, 16.4%) (3960).

The following were prepared in a similar way.

4-(6'-Bromo- β -naphthylamino)-6- γ -diethylaminopropylamino-2-methylpyrimidine (XII; R = [CH₂]₃·NET₂), from (X) and γ -diethylaminopropylamine, crystallised from light petroleum (b. p. 100–120°) in flat colourless prisms, m. p. 129–130° (Found: C, 59.7; H, 6.7; N, 15.7; Br, 18.1. C₂₂H₂₈N₅Br requires C, 59.7; H, 6.3; N, 15.8; Br, 18.1%) (3948).

4-(6'-Bromo- β -naphthylamino)-6- γ -dimethylaminopropylamino-2-methylpyrimidine (XII; R = [CH₂]₃·NMe₂), from (X) and γ -dimethylaminopropylamine, crystallised from light petroleum (b. p. 100–120°); m. p. 132–134° (Found: C, 57.9; H, 5.6; N, 16.5. C₂₀H₂₄N₅Br requires C, 58.0; H, 5.8; N, 16.9%) (3989).

4-(6'-Bromo- β -naphthylamino)-6- γ -di-*n*-butylaminopropylamino-2-methylpyrimidine (XII; R = [CH₂]₃·NBu₂), from (X) and γ -di-*n*-butylaminopropylamine, crystallised from light petroleum (b. p. 60–80°) in colourless prisms, m. p. 91–93° (Found: C, 62.5; H, 6.7; N, 14.1. C₂₀H₂₄N₅Br requires C, 62.7; H, 7.2; N, 14.1%) (4564).

4-(6'-Bromo- β -naphthylamino)-6- δ -diethylamino- α -methylbutylamino-2-methylpyrimidine (XIII; R = CHMe·[CH₂]₃·NET₂), from (X) and δ -diethylamino- α -methylbutylamine, crystallised from light petroleum (b. p. 60–80°) in clumps of colourless prisms, m. p. 109–110° (Found: C, 61.3; H, 6.8; N, 15.1. C₂₄H₃₂N₅Br requires C, 61.3; H, 6.8; N, 14.9%) (3961).

2:4-Di-*p*-chloroanilino-6-methylpyrimidine (XV).—(a) 2:4-Dichloro-6-methylpyrimidine (10 g.) and *p*-chloroaniline (34 g.) were heated in boiling β -ethoxyethanol (100 c.c.) for 2½ hours. The reaction mixture was then poured into water, made alkaline with ammonia, and steam distilled to remove unchanged *p*-chloroaniline. The solid product was filtered off, washed with water, and dried. Crystallisation from alcohol gave fine colourless needles, m. p. 167–168° (Found: C, 59.0; H, 4.05; N, 16.1; Cl, 20.7. C₁₇H₁₄N₄Cl₂ requires C, 59.1; H, 4.05; N, 16.2; Cl, 20.6%).

(b) 2-Chloro-4-*p*-chloroanilino-6-methylpyrimidine (Curd *et al.*, this vol., p. 373) (5.1 g.), *p*-chloroaniline (2.55 g.), water (30 c.c.), acetone (15 c.c.), and 10*N*-hydrochloric acid (0.5 c.c.) were refluxed for 2 hours. The product began to separate after a few minutes. The filtered (cold) product was dissolved in hot alcohol with the addition of ammonia and then precipitated with water, collected, and dried. Crystallisation from ethyl acetate–light petroleum gave 2:4-di-*p*-chloroanilino-6-methylpyrimidine (6.1 g.), m. p. and mixed m. p. 167–168°.

(c) 4-Chloro-2-*p*-chloroanilino-6-methylpyrimidine (Part I, this vol., p. 349) (5.1 g.) and *p*-chloroaniline (2.55 g.) condensed together under the same conditions to give 2:4-di-*p*-chloroanilino-6-methylpyrimidine (6.2 g.), m. p. and mixed m. p. 167–168°.

4:6-Di-*p*-chloroanilino-2-methylpyrimidine (VII; R = Cl).—(a) 4:6-Dichloro-2-methylpyrimidine (3.2 g.) and *p*-chloroaniline (5.0 g.) were mixed, hydrochloric acid (5 drops) was added, and the mixture heated at 120° for 2 hours. Water was then added and the product collected. It was then suspended in hot alcohol and dissolved by the addition of ammonia. Addition of water precipitated 4:6-di-*p*-chloroanilino-2-methylpyrimidine which crystallised from alcohol in colourless prisms, m. p. 216–218° (Found: C, 59.6; H, 4.1; N, 16.3; Cl, 20.6. C₁₇H₁₄N₄Cl₂ requires C, 59.1; H, 4.1; N, 16.2; Cl, 20.6%).

(b) 4:6-Dichloro-2-methylpyrimidine (4.1 g.), *p*-chloroaniline (6.4 g.), water (20 c.c.), acetone (5 c.c.) and 10*N*-hydrochloric acid (0.5 c.c.) were refluxed for 2 hours. After cooling, the product which had separated was filtered off, dissolved in alcohol, and made alkaline with ammonia. Dilution with water precipitated a solid which was collected, dried, and crystallised from alcohol giving 4:6-di-*p*-chloroanilino-2-methylpyrimidine (2.4 g.), m. p. 215–217°, unaltered when mixed with material from (a). Dilution of the mother liquor with water precipitated 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine (3.55 g.), m. p. 146–148°.

Condensation of 4-Chloro-6-*p*-chloroanilino-2-methylpyrimidine with *p*-Chloroaniline.—4-Chloro-6-*p*-chloroanilino-2-methylpyrimidine (5.1 g.), *p*-chloroaniline (2.55 g.), water (30 c.c.), acetone (20 c.c.), and 10*N*-hydrochloric acid (2.25 c.c.) were boiled under reflux for 2 hours and then cooled. The filtered product was dissolved in alcohol with the addition of ammonia and then precipitated with water. By fractional crystallisation from alcohol it was separated into 4:6-di-*p*-chloroanilino-2-methylpyrimidine (1 g.), m. p. and mixed m. p. 216–217°, and unchanged starting material (3.6 g.). When the amount of 10*N*-hydrochloric acid in the above experiment was reduced to 0.5 c.c. only unchanged starting material could be isolated.

4-Anilino-6-hydroxy-2-methylpyrimidine (IX; R = H).—4-Chloro-6-hydroxy-2-methylpyrimidine (21.67 g.), aniline (13.95 g.), and hydrochloric acid (1 c.c.) were mixed and heated to 150–160°. A vigorous reaction ensued and the reaction mixture set solid. After being heated at the above temperature for 1 hour the cooled and ground melt was dissolved in dilute sodium hydroxide solution, treated with decolorising carbon, and filtered. The filtrate was acidified with acetic acid and the precipitated product filtered off. Purification from any unchanged 4-chloro-6-hydroxy-2-methylpyrimidine was then effected by stirring with dilute ammonia, and the product was again collected, washed with water, and dried. By crystallisation from β -ethoxyethanol the compound was obtained as thick colourless laminae, m. p. 276° (Found: C, 65.1; H, 5.5; N, 20.7. C₁₁H₁₁ON₃ requires C, 65.7; H, 5.5; N, 20.9%).

4-Chloro-6-anilino-2-methylpyrimidine (VI; R = H).—The above hydroxy pyrimidine (20 g.) and phosphoryl chloride (100 c.c.) were refluxed for 9 hours and the resulting mixture worked up as described for the preparation of the corresponding *p*-chloroanilino compound [method (a)] giving the chloropyrimidine as colourless prisms from light petroleum (b. p. 100–120°), m. p. 134–135° (Found: C, 60.0; H, 4.6; N, 19.6; Cl, 16.2. C₁₁H₁₀N₃Cl requires C, 60.1; H, 4.6; N, 19.1; Cl, 16.2%).

Condensation of 4:6-Dichloro-2-methylpyrimidine with Aniline.—4:6-Dichloro-2-methylpyrimidine (4.1 g.) and aniline (4.6 g.) were added to a mixture of water (20 c.c.) and acetone (5 c.c.) to which 10*N*-hydrochloric (0.5 c.c.) had been added, and the mixture was refluxed for 2 hours. After cooling, the clear solution was poured into dilute ammonia and the precipitated solid filtered off. To ensure complete basification the product was dissolved in a hot mixture of β -ethoxyethanol and alcohol, ammonia added to alkalinity, and the solution poured into water. Crystallisation of the dried precipitated product from *n*-propanol gave 4:6-dianilino-2-methylpyrimidine (3.1 g.) as flat colourless prisms, m. p. 242–243° (Found: C, 73.8; H, 5.6; N, 20.5. C₁₇H₁₆N₄ requires C, 73.9; H, 5.8; N, 20.3%). Dilution of the *n*-propanol mother liquors with water gave 4-chloro-6-anilino-2-methylpyrimidine (2 g.), m. p. and mixed m. p. 134–135°.

Condensation of 4-Chloro-6-anilino-2-methylpyrimidine with Aniline.—4-Chloro-6-anilino-2-methylpyrimidine (5.49 g.),

aniline (2.32 g.), water (40 c.c.), acetone (10 c.c.), and 10N-hydrochloric acid (0.5 c.c.) were heated under reflux for 2 hours. After dilution of the resulting reaction mixture with water and addition of ammonia the product was collected by filtration. It was then dissolved in hot β -ethoxyethanol, and the solution was made alkaline with ammonia and poured into water. The solid thus precipitated was collected, dried, and dissolved in the minimum quantity of hot alcohol. On cooling, 4 : 6-dianilino-2-methylpyrimidine (0.85 g.), m. p. and mixed m. p. 241—242°, separated. Dilution of the mother liquors with water yielded only unchanged starting material (3.6 g.), m. p. and mixed m. p. 135°.

Repetition of the above experiment using an increased amount of 10N-hydrochloric acid (3 c.c.) gave 4 : 6-dianilino-2-methylpyrimidine (2.8 g.) and unchanged 4-chloro-6-anilino-2-methylpyrimidine (2.4 g.).

Condensation of 4 : 6-Dichloro-2-methylpyrimidine with p-Anisidine.—4 : 6-Dichloro-2-methylpyrimidine (4.1 g.), *p*-anisidine (6.2 g.), water (20 c.c.), acetone (5 c.c.), and 10N-hydrochloric acid (0.5 c.c.) were refluxed for 2 hours. After cooling, the product which had separated was filtered off and dissolved in alcohol, and the solution, after being made alkaline with ammonia, was poured into water. The precipitated solid was filtered off, washed, and dried. Crystallisation from β -ethoxyethanol gave 4 : 6-di-*p*-anisidino-2-methylpyrimidine as colourless laminæ, m. p. 211—212° (Found : C, 67.9; H, 6.2; N, 17.3. $C_{19}H_{20}O_2N_4$ requires C, 67.9; H, 6.0; N, 16.7%) (yield, 4 g.). Dilution of the mother liquors with water gave 4-chloro-6-*p*-anisidino-2-methylpyrimidine (1 g.), m. p. and mixed m. p. 142—144°.

Condensation of 4-Chloro-6-p-anisidino-2-methylpyrimidine with p-Anisidine.—4-Chloro-6-*p*-anisidino-2-methylpyrimidine (3.3 g.) and *p*-anisidine (1.63 g.) were boiled with water (20 c.c.) and acetone (5 c.c.), to which 10N-hydrochloric acid (0.25 c.c.) had been added, during 2 hours. When worked up in the same way as in the previous experiment a crude product was obtained which on boiling with alcohol was separated into the insoluble 4 : 6-di-*p*-anisidino-2-methylpyrimidine (0.9 g.), m. p. 211°, and soluble 4-chloro-6-*p*-anisidino-2-methylpyrimidine (1.8 g.), m. p. 142°.

4-N-Methylanilino-6-hydroxy-2-methylpyrimidine.—This was prepared by condensation of 4-chloro-6-hydroxy-2-methylpyrimidine (14.45 g.) and methylaniline (10.7 g.), with the addition of hydrochloric acid (0.75 c.c.), at 150—160°, followed by working up as described for the corresponding anilino compound. The *base* separated from β -ethoxyethanol in thick colourless prisms, m. p. 263° (Found : C, 67.2; H, 6.4; N, 19.3. $C_{12}H_{13}ON_3$ requires C, 67.0; H, 6.0; N, 19.5%).

4-Chloro-6-N-methylanilino-2-methylpyrimidine.—(a) Treatment of the preceding hydroxypyrimidine (15 g.) with boiling phosphoryl chloride (75 c.c.) during 2 hours followed by working up in the manner described above for similar preparations gave the *chloro*-compound, which crystallised from aqueous methanol in flat colourless prisms, m. p. 74—75° (Found : C, 61.6; H, 5.15; Cl, 15.5. $C_{12}H_{12}N_3Cl$ requires C, 61.7; H, 5.1; Cl, 15.2%).

(b) 4 : 6-Dichloro-2-methylpyrimidine (8.2 g.) and methylaniline (5.35 g.) were added to a mixture of water (40 c.c.), acetone (10 c.c.), and 10N-hydrochloric acid (1 c.c.), and the whole was boiled under reflux for 6 hours. After dilution with water and addition of ammonia to give an alkaline reaction the product was filtered off. To ensure complete conversion of the hydrochloride into the base, the product was dissolved in alcohol, sufficient ammonia added to give an alkaline reaction, and the solution poured into excess of water. The precipitated product was then collected and crystallised from dilute methanol; m. p. 74—75° undepressed in admixture with material made by method (a).

4-Anilino-6-N-methylanilino-2-methylpyrimidine.—4-Chloro-6-anilino-2-methylpyrimidine (5.49 g.) and methylaniline (2.68 g.) were mixed, 10N-hydrochloric acid (0.5 c.c.) was added, and the mixture heated at 130—140° for 3 hours. The resulting melt (solid) was cooled, ground, and dissolved in boiling β -ethoxyethanol. The solution was then made distinctly alkaline by addition of ammonia and poured into excess of water. The precipitated *base* was filtered off, dried, and crystallised from *n*-propanol; thick colourless needles, m. p. 150° (Found : C, 74.1; H, 6.1. $C_{18}H_{18}N_4$ requires C, 74.5; H, 6.2%).

An attempt was made to prepare this compound by condensation of 4-chloro-6-*N*-methylanilino-2-methylpyrimidine (5.84 g.) and aniline (2.32 g.) in a mixture of water (40 c.c.) and acetone (10 c.c.) in presence of 10-N-hydrochloric acid (0.5 c.c.) by boiling for 2 hours. No detectable condensation occurred and only unchanged compound could be isolated. Increasing the amount of hydrochloric acid to 3 c.c. had no effect.

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