68. *Synthetic Antimalarials. Part I. Some Derivatives of Arylamino and Aryl Substituted Pyrimidines.*

By F. H. S. Curd and F. L. Rose.

The preparation of a series of 2-anilino-4-dialkylaminoalkylamino-6-methylpyrimidines carrying chlorine and methoxyl substituents in the anilino residue which represents a new type of antimalarial structure is described. The general method of preparation comprises the reaction of the appropriate aniline with 4-hydroxy-2-methylthio-6-methylpyrimidine to give a 2-anilino-4-hydroxy-6-methylpyrimidine which is converted into the corresponding 4-chloro-2-anilino-6-methylpyrimidine by the action of phosphoryl chloride, the 4-chlorine atom being then replaced by a dialkylaminoalkylamino group by heating with the dialkylaminoalkylamine at 120—130°.

Several other types of pyrimidine derivative have been prepared for examination as antimalarials. These include a variety of 2-anilino-4 : 6-dimethyl- and 4-anilino-2 : 6-dimethyl-pyrimidines carrying chlorine or methoxyl groups as substituents in the anilino residue and a series of similarly substituted 4-β-diethylaminoethylamino-2-phenyl-6-methylpyrimidines; none of these compounds exhibited any antimalarial activity.

In this series of papers we describe the synthetic work commenced in these laboratories in 1942 with the object of discovering new and improved drugs for the therapeutic and prophylactic treatment of malaria. A full account of the methods of testing employed and the results obtained will be given in detail in a related series of papers to be published in the *Annals of Tropical Medicine and Parasitology* but, in order to illustrate the direction of our investigations, we give an indication of the antimalarial activity of the various compounds in each paper of this series.

The properties to be possessed by the ideal antimalarial drug have been defined by Sinton (*Festschrift Bernhard Nocht zum 80 Geburtstag*, 1937, p. 240, Hamburg, Augustin), but the requirements are exacting and we set ourselves, initially, the more limited objective of finding a new synthetic substitute for quinine without the disadvantages of mepacrine.• Mepacrine, though a more effective schizonticide than quinine, sometimes produces symptoms of intolerance, such as gastro-intestinal disturbances; having dyestuff properties and being stored to some extent in cutaneous tissues, it may impart to the skin a yellow colour, which, though harmless, may be objectionable; its manufacture involves many stages, and it is, therefore, probably too expensive for the mass treatment of poor communities.

The main desiderata were therefore low toxicity, freedom from dyeing properties, and cheapness. We were impressed by the potentialities afforded by pyrimidine derivatives as a basis of antimalarials for a number of reasons.

The quinoline nucleus of pamaquin and the acridine nucleus of mepacrine are heterocyclic systems foreign to the animal body, and we considered that one feasible approach towards the synthesis of less toxic antimalarial drugs would be to build up antimalarial structures on the basis of some ring system of biological importance,

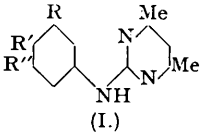
• The names mepacrine hydrochloride and pamaquin are now officially adopted in this country for atebrin and plasmoquine respectively (*British Pharmacopœia*, 1932, 3rd Addendum, p. 14; 4th Addendum, p. 24). We propose to use the British names in these communications, but for the sake of brevity mepacrine hydrochloride will be referred to as mepacrine.

since for such compounds the animal body would probably possess more tolerance because the development of new methods of detoxification would not be called for, but only an adaptation or modification of some process already developed and utilised.

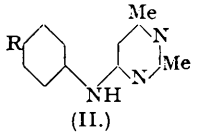
The malaria parasites, during the part of their life cycle in the human host, are generally believed to be intracellular, and the importance of pyrimidine derivatives, both by themselves and when built into purines, as constituents of the nucleic acids and certain vitamins and coenzymes, in cell chemistry needs no emphasis. It therefore seemed possible that there might be some undiscovered connection between pyrimidine derivatives and the biological processes of the malaria plasmodia.

Except for the investigation of sulphonamide derivatives of pyrimidine, little attention has been given to this heterocyclic nucleus as the basis of chemotherapeutic substances. Many heterocyclic systems have potential chemotherapeutic properties which become manifest by the attachment of suitable groupings, and there was no reason to suppose that pyrimidine would prove to be an exception. Moreover many types of pyrimidine derivative are easily synthesised, so that another of our prerequisites, namely simplicity, appeared capable of attainment. Unlike acridine this nucleus is also non-chromophoric.

We were led to the investigation of pyrimidine derivatives by a consideration of the antimalarial activity of the sulphonamide drugs discovered by Díaz de León (*Bol. Ofic. Sanit. Pan-Amer.*, 1937, **16**, 1039; English translation in *Publ. Hlth. Rep. Washington*, 1937, **52**, 1460). The structural resemblances between the other known antimalarial drugs have been pointed out by numerous workers, but the sulphonamides did not appear to conform to the general pattern. We therefore concluded either that their activity must be completely unrelated to that of the other antimalarials, or that some relationship must be sought. Consequently, before the demonstration by Marshall, Litchfield, and White (*J. Pharm. Exp. Ther.*, 1942, **75**, 89) that the antimalarial action of the sulphonamides is related to their antibacterial action, both being inhibited by *p*-aminobenzoic acid, we sought to explain the activity of this type of drug against the parasites of malaria on lines similar to those put forward by Magidson, Delektorskaya, and Lipowitsch (*Arch. Pharm.*, 1934, **272**, 74; see also Magidson and Grigorowsky, *Ber.*, 1936, **69**, 396) in connection with antimalarial drugs of the acridine and quinoline series. According to these workers different parts of the molecule have different functions. In their view the basic side chain is primarily of pharmacological importance, controlling the absorption and distribution of the drug in the host and aiding its penetration into the parasite and to the particular point where the toxic action is exerted, whereas the parasiticidal action is the function of the substituted acridine or quinoline nucleus. In a corresponding manner we regarded the sulphonamides as aniline derivatives in which the sulphonamide or substituted sulphonamide group performed the same pharmacological function as suggested for the basic side chain in the other types of antimalarials. Since, however, the attainment of very high blood levels is characteristic of the sulphonamide derivatives from 2-aminopyrimidine and 2-amino-4 : 6-dimethylpyrimidine we considered it possible that the introduction of these residues into other structures might confer similar properties on them, and we therefore examined compounds of type (I) and (II), which can be regarded as pyrimidine derivatives of aniline.



(I.)



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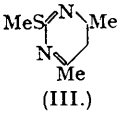


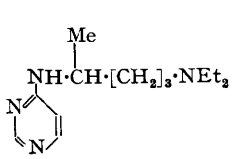
(III.)

A few compounds of types (I) and (II) were already known. St. Angerstein (*Ber.*, 1901, **34**, 3962) prepared 2-anilino-4 : 6-dimethylpyrimidine (I; R = R′ = R″ = H) by condensation of aniline with 2-chloro-4 : 6-dimethylpyrimidine, and Schmidt (*ibid.*, 1902, **35**, 1578) obtained 4-anilino-2 : 6-dimethylpyrimidine (II; R = H) by a similar method from 4-chloro-2 : 6-dimethylpyrimidine. In addition to the above the following have now been made by similar methods: 2-p-*anisidino*- (I; R = R″ = H, R′ = OMe), 2-p-*chloroanilino*- (I; R = R″ = H, R′ = Cl), and 2-(3′ : 5′-*dichloroanilino*)-4 : 6-*dimethylpyrimidine* (I; R = R″ = Cl, R′ = H) and 4-p-*anisidino*-2 : 6-*dimethylpyrimidine* (II; R = OMe), but all of these compounds are without activity against *P. gallinaceum* in chicks.

2-Anilino-4 : 6-dimethylpyrimidine was also obtained in very small yield by condensing aniline with 2-methylthio-4 : 6-dimethylpyrimidine (III) (Wheeler and Jamieson, *Amer. Chem. J.*, 1904, **32**, 356) at a high temperature. In view of the facility with which anilines react with 4-hydroxy-2-methylthio-6-methylpyrimidine with elimination of methylthiol (see below) the relative unreactivity of (III) is noteworthy. Our investigations have not so far included a sufficient variety of methylthiopyrimidines to enable any final conclusions to be drawn as to the exact structure necessary for lability of the methylthio-group, but in 4-hydroxy-2-methylthio-6-methylpyrimidine the tautomeric possibilities (XI) $\rightleftharpoons$ (X) allow the assumption of a structure similar to that found in methyl*iso*thiourea, where the methylthio-group is well known to be labile, whereas in 2-methylthio-4 : 6-dimethylpyrimidine no such tautomerism is possible.

Attention was next directed to the preparation of pyrimidine derivatives carrying dialkylaminoalkylamino groups which are characteristic of mepacrine and pamaquin. Such compounds have not been described previously, and the 4-dialkylaminoalkylamino derivatives appeared to be of particular interest since one tautomeric possibility in this type of compound [(IV) $\rightleftharpoons$ (V)] is exactly analogous to that which can occur

in mepacrine [(VI) ⇌ (VII)] and to which Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) has related the antimalarial activity of this substance.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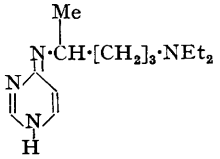
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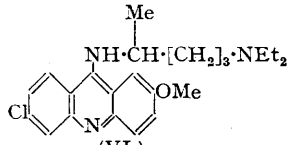
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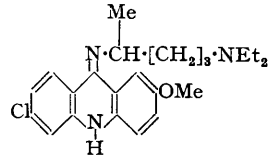
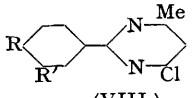

(VII.)

From this early stage in our investigations we were fortunate in having the collaboration of workers at Manchester University under the direction of Professor A. R. Todd, F.R.S., and their investigations, which began with simple pyrimidines, will form the subject of some papers in this series. We greatly appreciate this collaboration.

We selected certain 2-phenylpyrimidines containing a dialkylaminoalkylamino group in the 4-position, of the type (IX), for initial study since their molecular weights would lie between 300 and 400 which is a feature of the most potent antimalarials. Insertion of a chlorine atom or a methoxy group in the 2-phenyl group was included because such substituents are found in the fused benzene nuclei of the mepacrine molecule.

There are several recorded instances of the replacement of the 4-chlorine atom in compounds of type (VIII) (which are easily accessible by condensation of the appropriate benzamidine with ethyl acetoacetate followed by replacement of the hydroxy group in the resulting hydroxypyrimidine by a chlorine atom) by an amino group by reaction with ammonia at 150—160° or above (compare Johnson and Storey, *Amer. Chem. J.*, 1908, **40**, 1; Pinner, *Ber.*, 1887, **20**, 2363), so that a similar replacement by a dialkylaminoalkylamino group appeared feasible. Actually it was found that the reaction with a dialkylaminoalkylamine proceeded smoothly at 120—130° to give compounds of type (IX).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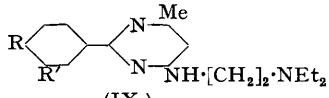

(IX.)

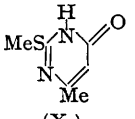
In this way 4-chloro-2-phenyl- (VIII; R = R′ = H), -2-*p*-methoxyphenyl- (VIII; R = OMe, R′ = H), -2-m-*methoxyphenyl*- (VIII; R = H, R′ = OMe) and -2-p-*chlorophenyl*-6-*methylpyrimidine* (VIII; R = Cl, R′ = H) have been condensed with β-diethylaminoethylamine to give the corresponding 4-β-*diethylaminoethylamino* compounds (IX; R = R′ = H), (IX; R = OMe, R′ = H), (IX; R = H, R′ = OMe) and (IX; R = Cl, R′ = H), respectively.

A pamaquin type of synthesis involving condensation of an aminopyrimidine with a dialkylaminoalkyl halide was rejected at the outset for several reasons. There was no recorded instance of an amino group in the α- or γ-position to a heterocyclic nitrogen atom having been converted into a dialkylaminoalkylamino group by such a condensation (a process of this type was mentioned but not exemplified in D.R.-P. 683,692) and the reaction would obviously be difficult since compounds with an amino group in this position tend in general to behave as if they were α- or γ-iminodihydro derivatives. There was also the possibility that, because of this behaviour, substitution might occur on one of the heterocyclic nitrogen atoms, and the constitution of the products would thus be open to doubt. This possible complication was considered to be even more likely in the projected preparation of other compounds of general formula (XIV; R′ = dialkylaminoalkyl).

Compounds of this type were considered to be of potential interest because they would combine in a different manner two of the structural features of mepacrine: a basic alkylamino heterocyclic system of the type referred to above and a chlorine- or methoxyl-substituted anilino residue which can be identified as fused components of the mepacrine molecule in one of its tautomeric forms (VII). Further, Schönhöfer (*loc. cit.*) has suggested that the antimalarial activity of pamaquin may be due to the possibility, which exises in a molecule of this orientation, that under biological conditions compounds of quinonoid character may be formed, and it was considered that the same possibility existed in 2-p-*anisidino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (XIV; R = OMe, R′ = $CH_2 \cdot CH_2 \cdot NEt_2$). The synthesis of this compound was therefore undertaken.

Several 4-chloro-2-anilinopyrimidines have already been described (see Wheeler and Bristol, *Amer. Chem. J.*, 1905, **33**, 437; Johnson and Heyl, *ibid.*, 1907, **38**, 237; Johnson and Storey, *ibid.*, 1908, **40**, 131). The method of synthesis utilised in the preparation of these compounds involved condensation of a 4-hydroxy-2-alkylthiopyrimidine and an aniline with elimination of alkylthiol to give a 2-anilino-4-hydroxypyrimidine followed by the replacement of the hydroxy group in the latter by a chlorine atom by reaction with phosphoryl chloride. A similar reaction sequence [(XI) ⟶ (XII; R = OMe) ⟶ (XIII; R = OMe)] has now been successfully utilised for the preparation of 4-*chloro*-2-p-*anisidino*-6-*methylpyrimidine*, and it has been found that the replacement of the 4-chlorine atom by a diethylaminoethylamino group to give 2-*p*-anisidino-4-β-diethylaminoethylamino-6-methylpyrimidine (XIV; R = OMe, R′ = $CH_2 \cdot CH_2 \cdot NEt_2$) takes place on heating with diethylaminoethylamine under conditions identical with those previously successful in a similar replacement of the 4-chlorine atom in 4-chloro-2-phenyl-6-methylpyrimidine and its derivatives.

The intermediate 2-p-*anisidino*-4-*hydroxy*-6-*methylpyrimidine* (XII; R = OMe) has also been obtained by condensation of *p*-anisylguanidine with ethyl acetoacetate. This is apparently the first recorded instance of the reaction of an aryl-substituted guanidine with a β-keto ester, although there are numerous examples of such condensations using guanidine itself (cf., *e.g.*, Behrend, *Ber.*, 1886, **19**, 220; Byk, *ibid.*, 1903, **36**, 1918). This can probably be attributed to the relative inaccessibility of the arylguanidines which, incidentally, prevented us from making this reaction a general method for the preparation of compounds of the type (XII). No indication was obtained of the formation of any second substance in the reaction; in this respect the condensation of an arylguanidine with a β-keto ester appears to differ from the behaviour of alkylguanidines, since Majima (*Ber.*, 1908, **41**, 180) has shown that the latter, when condensed with ethyl acetoacetate, give not only the expected 2-alkylamino-4-hydroxy-6-methylpyrimidine but also some of the isomeric 2-amino-4-methyl-1-alkyluracil.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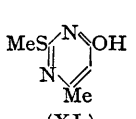
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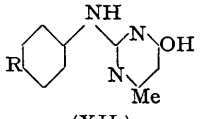
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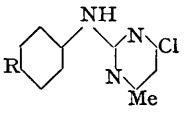
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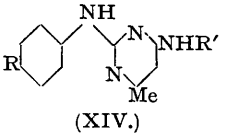
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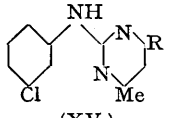
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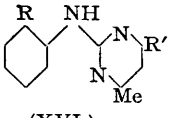
(XVI.)

We next applied the method outlined above to the preparation of 2-p-*chloroanilino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (XIV; R = Cl, R′ = CH_2·CH_2·NEt_2). Heating *p*-chloroaniline with 4-hydroxy-2-methylthio-6-methylpyrimidine gave 2-p-*chloroanilino*-4-*hydroxy*-6-*methylpyrimidine* (XII; R = Cl) which was converted into 4-*chloro*-2-p-*chloroanilino*-6-*methylpyrimidine* (XIII; R = Cl) by the action of phosphoryl chloride and thence into (XIV; R = Cl, R′ = CH_2·CH_2·NEt_2) by reaction with β-diethylaminoethylamine.

With the discovery of antimalarial activity in 2-*p*-chloroanilino- and 2-*p*-anisidino-4-β-diethylaminoethylamino-6-methylpyrimidine which represent a new type of antimalarial structure, a number of possibilities were open to us. We elected first to investigate the effect of varying the 4-dialkylaminoalkylamino group. In other series of antimalarial drugs significant variations in activity occur with variation of the basic alkyl side chain (see, *e.g.*, Fourneau, Tréfouel, Bovet, and Benoit, *Ann. Inst. Pasteur*, 1933, **50**, 731; Magidson and Grigorowsky, *loc. cit.*), and it seemed probable that similar variations would occur in the present series of compounds, particularly if the mechanism of their plasmodicidal action is, as we have suggested elsewhere (Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, in the press), an interference with the function of riboflavin in an enzyme system essential to the parasite and if some " molecular fit " or spacing of corresponding groups is involved. Further, even if the function of the basic alkyl side chain is purely of a pharmacological nature, it did not follow that the optimum basic side chain in the new pyrimidine type of antimalarial would necessarily be the same as in the pamaquin or mepacrine series, because the effect produced must to some extent be conditioned by the nature of the remainder of the molecule.

4-Chloro-2-*p*-chloroanilino-6-methylpyrimidine was accordingly condensed with a variety of dialkylaminoalkylamines to give the following 6-*methylpyrimidines*: 2-p-*chloroanilino*-4-γ-*diethylaminopropylamino*- (XIV; R = Cl, R′ = $[CH_2]_3$·NEt_2), 2-p-*chloroanilino*-4-γ-*dimethylaminopropylamino*- (XIV; R = Cl, R′ = $[CH_2]_3$·NMe_2), 2-p-*chloroanilino*-4-δ-*diethylaminobutylamino*- (XIV; R = Cl, R′ = $[CH_2]_4$·NEt_2), and 2-p-*chloroanilino*-4-δ-*diethylamino*-α-*methylbutylamino*- (XIV; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2). The results (see table) indicated that further variations of the side chain would be desirable, but these compounds will be described in a later paper.

Attention was next directed to the necessity for, and the positioning of, the substituent in the anilino residue. In order to investigate these points we prepared as dihydrochlorides the following 6-*methylpyrimidines*: 2-o-*chloroanilino*-4-β-*diethylaminoethylamino*- (XVI; R = Cl, R′ = NH·$[CH_2]_2$·NEt_2), -γ-*diethylaminopropylamino*- (XVI; R = Cl, R′ = NH·$[CH_2]_3$·NEt_2), 2-m-*chloroanilino*-4-γ-*diethylaminopropylamino*- (XV; R = NH·$[CH_2]_3$·NEt_2), 2-o-*anisidino*-4-β-*diethylaminoethylamino*- (XVI; R = OMe, R′ = NH·$[CH_2]_2$·NEt_2), and 2-*anilino*-4-β-*diethylaminoethylamino*- (XIV; R = H, R′ = $[CH_2]_2$·NEt_2).

The method outlined above for the preparation of the 2-anilino-4-dialkylaminoalkylamino-6-methylpyrimidines is only one of several which have been successfully applied. In this paper we describe one which involves a method of " building up " the alkylamino side chain. A similar process for introducing the side chain in stages is indicated in the patent literature as applicable to compounds of the mepacrine type (E.P. 363,392) and has been employed by Crum and Robinson (*J.*, 1943, 561) in their investigation of certain types of compounds related to pamaquin. Its interest lies in the possibilities it offers for the introduction of side chains, such as those with a terminal secondary amino group, which would be difficult by the usual methods. 4-Chloro-2-*p*-chloroanilino-6-methylpyrimidine (XIII; R = Cl) has been caused to react with β-aminoethyl alcohol to give 2-p-*chloroanilino*-4-β-*hydroxyethylamino*-6-*methylpyrimidine* (XIV; R = Cl, R′ = CH_2·CH_2·OH) which with phosphoryl chloride gave the *hydrochloride* of 2-*p*-chloroanilino-4-β-chloroethylamino-6-methyl-

pyrimidine (XIV; R = Cl, R′ = CH_2·CH_2Cl). Reaction of the last compound with diethylamine gave 2-*p*-chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine (XIV; R = Cl, R′ = CH_2·CH_2·NEt_2).

Certain points in connection with the reaction of chloropyrimidines and dialkylaminoalkylamines merit consideration. If the reactivity of the chlorine atoms is due to their iminochloride character it might have been anticipated that compounds of type (XIII), because of their tautomeric possibilities, would be less reactive than compounds of type (VIII). If, however, the resonance forms of both types are also taken into consideration it is evident that the proportion of molecules exhibiting an imino-chloride structure at any given moment is probably the same in both (VIII) and (XIII). A comparable reactivity therefore appeared most likely and, as pointed out above, both types were found to react with dialkylaminoalkylamines with equal facility under the conditions employed.

Banks (*J. Amer. Chem. Soc.*, 1944, **66**, 1127, 1131) has noted that the reaction between a number of chloropyrimidines and arylamines is accelerated by an increase in hydrogen-ion concentration, a fact of which we were already aware as the result of an investigation into possible methods of preparation of compounds isomeric with those of type (XIV) which will be reported later. Banks failed to obtain any evidence of condensation of chloropyrimidines with diethylaminopropylamine under similar conditions, and this also applies to the chloropyrimidines of type (XIII) which we have investigated. It therefore seems probable that the reaction between chloropyrimidines and dialkylaminoalkylamines proceeds by some mechanism other than that put forward by Banks for the reaction with aromatic amines, although the failure of dialkylaminoalkylamines to react under aqueous conditions for other reasons cannot yet be definitely excluded.

Antimalarial Activities.

The antimalarial activity of the various compounds was estimated by testing against *P. gallinaceum* in chicks by the method described by Curd, Davey, and Rose (*loc. cit.*). The activity at various doses is indicated as inactive (−), slight (+), or marked (++). Unless otherwise stated the drugs were administered orally.

Ref. No.	Formula of base.	Dose, mg./kg.	Activity.
	2-Anilino-4 : 6-dimethylpyrimidines and 4-anilino-2 : 6-dimethylpyrimidines.		
2637	I; R = R′ = R″ = H	500	−
2638	I; R = R″ = H, R′ = OMe	450	−
2775	I; R = R″ = H, R′ = Cl	500	−
2776	I; R = R″ = Cl, R′ = H	500	−
3196	II; R = H	60	−
3197	II; R = OMe	100	−
	4-β-Diethylaminoethylamino-2-aryl-6-methylpyrimidine dihydrochlorides.		
2587	IX; R = R′ = H	Not tested against *P. gallinaceum*	
2639	IX; R = OMe, R′ = H	250	−
2726	IX; R = H, R′ = OMe	100	−
2724	IX; R = Cl, R′ = H	160	−
	2-Arylamino-4-dialkylaminoalkylamino-6-methylpyrimidine dihydrochlorides.		
2665	XIV; R = OMe, R′ = $[CH_2]_2$·NEt_2	200	++
2666	XIV; R = Cl, R′ = $[CH_2]_2$·NEt_2	100	++
		80	++
		40	+
3299	XIV; R = Cl, R′ = $[CH_2]_3$·NEt_2	80	++
		40	+
3711	XIV; R = Cl, R′ = $[CH_2]_3$·NMe_2	40	++
		20	+
3338	XIV; R = Cl, R′ = $[CH_2]_4$·NEt_2	200	++
		80	+
3300	XIV; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2	200	++
		100	−
3381	XVI; R = Cl, R′ = NH·$[CH_2]_2$·NEt_2	200	±
		150	−
3466	XVI; R = Cl, R′ = NH·$[CH_2]_3$·NEt_2	200	−
3554	XV; R = NH·$[CH_2]_3$·NEt_2	200	+
		150	±
		80	−
3382	XVI; R = OMe, R′ = NH·$[CH_2]_2$·NEt_2	200	−
		100	−
2725	XIV; R = H, R′ = $[CH_2]_2$·NEt_2	80	−
	Miscellaneous derivatives.		
2598	XII; R = OMe	200 (intraperitoneally)	−
2792	XII; R = Cl	200 (intraperitoneally)	−
3608	XIV; R = Cl, R′ = CH_2·CH_2·OH	300	±
		100	−

Experimental.

2-*Anilino*-4 : 6-*dimethylpyrimidine* (I; R = R′ = R″ = H).—(a) 2-Chloro-4 : 6-dimethylpyrimidine (13·7 g.) and aniline (18·6 g.) were heated at 100—110° during 3 hours. Water was added, the precipitated solid extracted with benzene, and the solution dried. After removal of solvent and recrystallisation from light petroleum (b. p. 60—80°) the product (13·3 g.) formed colourless tables, m. p. 96—97° (Found: N, 21·0. Calc. for $C_{12}H_{13}N_3$: N, 21·1%). St. Angerstein (*loc. cit.*) gives m. p. 88—89°. The hydrochloride (2637), prepared by evaporating to dryness, under reduced pressure, a solution of the base in 2N-hydrochloric acid, crystallised from acetone as colourless thick prisms, m. p. 185—187° (Found: Cl, 15·4, 15·45. Calc. for $C_{12}H_{13}N_3$,HCl: Cl, 15·1%).

(b) 2-Methylthio-4 : 6-dimethylpyrimidine (15·4 g.) (Wheeler and Jamieson, *loc. cit.*) and aniline (18·6 g.) were refluxed for 20 hours. Dilution with water and steam distillation left a small amount of an oil which was extracted with benzene. Evaporation of the dried benzene solution and crystallisation of the residue from light petroleum (b. p. 60—80°) gave 2-anilino-4 : 6-dimethylpyrimidine (1·25 g.), m. p. 95—96° either alone or admixed with a specimen prepared by method (a) above.

2-p-*Anisidino*-4 : 6-*dimethylpyrimidine* (I; R = R″ = H, R′ = OMe), prepared from 2-chloro-4 : 6-dimethylpyrimidine (14·5 g.) and *p*-anisidine (25 g.) and crystallised from light petroleum (b. p. 60—80°), had m. p. 88—89° (yield, 16·75 g.) (Found: N, 18·4. $C_{13}H_{15}ON_3$ requires N, 18·3%). The *hydrochloride* (2638), prepared by adding excess hydrochloric acid to a solution of the base in 2N-hydrochloric acid, formed yellowish needles, m. p. 204—205° (Found: C, 51·7; H, 6·3; N, 14·0. $C_{13}H_{15}ON_3$,HCl,2H_2O requires C, 51·7; H, 6·6; N, 13·9%).

2-p-*Chloroanilino*-4 : 6-*dimethylpyrimidine* (I; R = R″ = H, R′ = Cl).—2-Chloro-4 : 6-dimethylpyrimidine (14·25 g.) and *p*-chloroaniline (12·75 g.) were heated at 100—110°. After a few minutes a vigorous reaction ensued. When this had subsided, heating was continued for 3 hours at the same temperature. The reaction mixture was then cooled and worked up as described above for the corresponding condensation with aniline. Crystallised from light petroleum (b. p. 60—80°) the *compound* formed colourless thick prisms, m. p. 118—120° (yield, 13·1 g.) (Found: C, 61·8; H, 5·1; N, 18·7. $C_{12}H_{12}N_3Cl$ requires C, 61·7; H, 5·1; N, 18·0%). The *methanesulphonate* (2775) formed colourless laminæ, m. p. 215—216° (Found: C, 46·9; H, 4·8; N, 13·0. $C_{12}H_{12}N_3Cl$,CH_4O_3S requires C, 47·3; H, 4·7; N, 12·7%).

2-(3′ : 5′-*Dichloroanilino*)-4 : 6-*dimethylpyrimidine* (I; R = R″ = Cl, R′ = H) (2776), prepared from 2-chloro-4 : 6-dimethylpyrimidine and 3 : 5-dichloroaniline, crystallised from alcohol as colourless thick prisms, m. p. 129—131° (Found: N, 15·5. $C_{12}H_{11}N_3Cl_2$ requires N, 15·7%).

4-Anilino-2 : 6-dimethylpyrimidine (II; R = H) (3196), prepared from 4-chloro-2 : 6-dimethylpyrimidine (11·6 g.) and aniline (15·15 g.), was obtained as colourless prisms, m. p. 104—105° in agreement with Schmidt (*loc. cit.*) (Found: N, 20·6. Calc. for $C_{12}H_{13}N_3$: N, 21·1%).

4-p-*Anisidino*-2 : 6-*dimethylpyrimidine* (II; R = OMe).—4-Chloro-2 : 6-dimethylpyrimidine (12·8 g.) and *p*-anisidine (22·1 g.) were heated at 100—110° for 3 hours, and the resulting melt dissolved in water and made alkaline with ammonia. After shaking with a small amount of benzene the insoluble material was filtered off and recrystallised from benzene giving 4-p-*anisidino*-2 : 6-*dimethylpyrimidine* (11·75 g.) as colourless prisms, m. p. 152—153° (Found: N, 18·3. $C_{13}H_{15}ON_3$ requires N, 18·3%). A further small quantity (1·75 g.) was obtained by drying the above benzene solution, evaporating to small bulk, adding light petroleum, and allowing to crystallise. The *hydrochloride* (3197) was prepared by dissolving the base in hot dilute hydrochloric acid, filtering, and adding excess of hydrochloric acid; it formed colourless needles, m. p. 254—256° (Found: C, 58·2; H, 5·8; Cl, 13·4. $C_{13}H_{15}ON_3$,HCl requires C, 58·8; H, 6·0; Cl, 13·4%).

4-*β-Diethylaminoethylamino*-2-*phenyl*-6-*methylpyrimidine* (IX; R = R′ = H).—4-Chloro-2-phenyl-6-methylpyrimidine (10·2 g.) (Forsyth and Pyman, *J.*, 1926, 2506) and *β*-diethylaminoethylamine (7·25 g.) were heated at 120—130° for 6 hours. After cooling, the resulting melt was dissolved in warm dilute hydrochloric acid, the solution poured into excess of aqueous sodium hydroxide, and the precipitated oil extracted with ether. The ether was then extracted twice with 5% acetic acid, and the acid extracts combined and made alkaline to Clayton yellow with sodium hydroxide. The oil was separated, dissolved in ether, and the ethereal solution dried over potassium carbonate and evaporated. Distillation of the residue in a vacuum gave 4-*β-diethylaminoethylamino*-2-*phenyl*-6-*methylpyrimidine* as a colourless oil, b. p. 166—168°/0·17 mm. (yield, 65%) (Found: C, 71·6; H, 8·4; N, 19·8. $C_{17}H_{24}N_4$ requires C, 71·8; H, 8·45; N, 19·7%). The *dipicrate*, prepared in methanol solution, crystallised from *β*-ethoxyethanol–alcohol as thick yellow prisms, m. p. 177—178° (Found: C, 47·1; H, 4·0; N, 19·1. $C_{17}H_{24}N_4$,2$C_6H_3O_7N_3$ requires C, 46·9; H, 4·0; N, 18·9%). The *dihydrochloride* (2587) was prepared from the base as described below for 2-*p*-chloroanilino-4-*β*-diethylaminoethylamino-6-methylpyrimidine dihydrochloride. It crystallised from alcohol–ethyl acetate as colourless prisms, m. p. 256—258° (Found: C, 52·4; H, 8·0; Cl, 17·7. $C_{17}H_{24}N_4$,2HCl,2H_2O requires C, 51·9; H, 7·6; Cl, 18·1%).

4-*β*-Diethylaminoethylamino-2-*p*-methoxyphenyl-6-methylpyrimidine (IX; R = OMe, R′ = H), prepared from 4-chloro-2-*p*-methoxyphenyl-6-methylpyrimidine (10·9 g.) (Gabriel and Colman, *Ber.*, 1899, **32**, 1528) and *β*-diethylaminoethylamine (7 g.) in a similar manner, gave a *dipicrate* which crystallised from *β*-ethoxyethanol–alcohol as flat yellow prisms, m. p. 184—185° (Found: C, 46·7; H, 4·1; N, 18·5. $C_{18}H_{26}ON_4$,2$C_6H_3O_7N_3$ requires C, 46·6; H, 4·1; N, 18·1%), and a *dihydrochloride* (2639) which separated from alcohol–ethyl acetate as colourless prisms, m. p. 244° (decomp.) (Found: C, 51·8; H, 7·4; Cl, 16·5. $C_{18}H_{26}ON_4$,2HCl,2H_2O requires C, 51·1; H, 7·6; Cl, 16·8%).

m-*Methoxybenzamidine Hydrochloride*.—*m*-Methoxybenzonitrile (29 g., unpublished work), dissolved in a mixture of absolute alcohol (30 c.c.) and dry chloroform (150 c.c.), was cooled to below 5°, and saturated with dry hydrogen chloride. After standing for 2 days it was evaporated to dryness under reduced pressure below 40° and the residue kept in a vacuum desiccator over potassium hydroxide until free from hydrogen chloride. The resulting iminoether hydrochloride was added to 500 c.c. of alcohol, previously saturated with ammonia at 0°, in a pressure bottle and heated at 40—45° for 10 hours. The solvent was then removed under reduced pressure at 40—45°, and the residue dissolved in water (300 c.c.) and extracted with benzene. After discarding the benzene extract the aqueous layer was decolourised with charcoal and evaporated to dryness under reduced pressure. Crystallisation of the residue from alcohol–ether gave m-*methoxybenzamidine hydrochloride* as colourless thick prisms, m. p. 165—166° (yield, 59%) (Found: C, 51·0; H, 6·1; N, 15·3. $C_8H_{10}ON_2$,HCl requires C, 51·5; H, 5·9; N, 15·0%).

4-*Hydroxy*-2-m-*methoxyphenyl*-6-*methylpyrimidine*.—To a solution of *m*-methoxybenzamidine hydrochloride (18·65 g.) in water (200 c.c.), ethyl acetoacetate (13 g.) was added, followed by a solution of sodium hydroxide (4 g. in 40 c.c. of water) added gradually. After standing for 2 days the *product* which had separated was filtered off, washed with water, and dried. Crystallised from ethanol it had m. p. 180—181° (yield, 10·8 g.) (Found: C, 67·2; H, 5·7; N, 13·4. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6; N, 13·0%).

4-*Chloro*-2-m-*methoxyphenyl*-6-*methylpyrimidine* (VIII; R = H, R′ = OMe).—The above hydroxy compound (9·5 g.) was refluxed with phosphoryl chloride (24 c.c.) for ½ hour, the clear solution poured on to ice, and the product isolated by extraction with ether. After drying and removing the solvent, the residue was crystallised from light petroleum (b. p. 60—80°) giving the *chloropyrimidine* (6·6 g.), m. p. 68—70° (Found: C, 61·3; H, 4·9; N, 11·7. $C_{12}H_{11}ON_2Cl$ requires C, 61·4; H, 4·7; N, 11·9%).

4-*β-Diethylaminoethylamino*-2-m-*methoxyphenyl*-6-*methylpyrimidine* (IX; R = H, R′ = OMe).—The condensation of 4-chloro-2-*m*-methoxyphenyl-6-methylpyrimidine (5·45 g.) and *β*-diethylaminoethylamine (3·5 g.) was carried out as described above for the corresponding 2-phenyl compound and gave the *base* as a colourless viscous oil, b. p. 193—198°/0·16 mm. (Found: C, 68·8; H, 8·1; N, 17·5. $C_{18}H_{26}ON_4$ requires C, 68·8; H, 8·3; N, 17·8%). The *dipicrate*, prepared in methanol solution, formed clusters of yellow needles from *β*-ethoxyethanol–alcohol, m. p. 165—167° (Found: C, 46·7; H, 3·9; N, 18·4. $C_{18}H_{26}ON_4,2C_6H_3O_7N_3$ requires C, 46·6; H, 4·1; N, 18·1%), and the *dihydrochloride* (2726), prepared by dissolving the base in 2N-hydrochloric acid, evaporating the solution to dryness under reduced pressure and crystallising the residue from alcohol, formed colourless needles, m. p. 234—236° (decomp.) (Found: C, 51·0; H, 7·2; Cl, 17·2. $C_{18}H_{26}ON_4,2HCl,2H_2O$ requires C, 51·1; H, 7·6; Cl, 16·8%).

4-*Hydroxy*-2-p-*chlorophenyl*-6-*methylpyrimidine*.—*p*-Chlorobenzamidine hydrochloride (21·72 g.) (Ekeley, Tieszen, and Ronzio, *J. Amer. Chem. Soc.*, 1935, **57**, 381) and ethyl acetoacetate (15·6 g.) were mixed, warmed to 45°, and a solution of sodium hydroxide (4·8 g.) in water (50 c.c.) was added. A homogeneous solution was quickly formed which soon began to deposit crystals. After heating at 40—45° for 1 hour the mixture was left for 2 days, and the crystalline product collected, washed with water, and stirred with dilute sodium hydroxide solution (450 c.c.). After filtering from undissolved material the solution was acidified with acetic acid and the precipitated product filtered off, washed with water, and dried. Crystallisation from alcohol gave 4-*hydroxy*-2-p-*chlorophenyl*-6-*methylpyrimidine* as colourless feathery needles, m. p. 233—234° (Found: C, 59·7; H, 4·4; N, 12·7. $C_{11}H_9ON_2Cl$ requires C, 59·9; H, 4·1; N, 12·7%).

4-*Chloro*-2-p-*chlorophenyl*-6-*methylpyrimidine* (VIII; R = Cl, R′ = H).—The above hydroxy compound (13 g.) was refluxed for 20 minutes with phosphoryl chloride (30 c.c.), and the clear solution cooled, poured on to ice and the precipitated product extracted with ether. The ether extract was washed with water, dried, and evaporated. The residue, crystallised from alcohol, gave 4-*chloro*-2-p-*chlorophenyl*-6-*methylpyrimidine* (11·2 g.), m. p. 108—109° (Found: C, 55·2; H, 3·3; N, 11·0. $C_{11}H_8N_2Cl_2$ requires C, 55·2; H, 3·3; N, 11·7%).

4-*β-Diethylaminoethylamino*-2-p-*chlorophenyl*-6-*methylpyrimidine* (IX; R = Cl, R′ = H).—Reaction of 4-chloro-2-*p*-chlorophenyl-6-methylpyrimidine (11·0 g.) and *β*-diethylaminoethylamine (8·7 g.) at 120—130° followed by working up in the usual manner gave the *base*, b. p. 186—190°/0·16 mm. (Found: C, 63·8; H, 6·9; N, 17·3. $C_{17}H_{23}N_4Cl$ requires C, 64·0; H, 7·2; N, 17·6%). The *dipicrate* crystallised from *β*-ethoxyethanol–alcohol in yellow laminæ, m. p. 197—198° (Found: C, 45·1; H, 3·8; N, 17·8. $C_{17}H_{23}N_4Cl,2C_6H_3O_7N_3$ requires C, 44·8; H, 3·7; N, 18·0%), and the *dihydrochloride* (2724) separated from alcohol in colourless needles, m. p. 235—237° (Found: C, 47·5; H, 6·8; Cl, 25·5. $C_{17}H_{23}N_4Cl,2HCl,2H_2O$ requires C, 47·7; H, 6·8; Cl, 24·9%).

2-p-*Anisidino*-4-*hydroxy*-6-*methylpyrimidine* (XII; R = OMe).—(a) 4-Hydroxy-2-methylthio-6-methylpyrimidine (15·6 g.) (Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 478) and *p*-anisidine (30·75 g.) were heated at 125—130° for 24 hours. The mixture, which soon became completely molten and homogeneous, gradually solidified as the evolution of methylthiol slackened. After cooling it was ground, boiled with alcohol (100 c.c.), cooled, and the product filtered (yield, 89%). Crystallisation from *β*-ethoxyethanol gave 2-p-*anisidino*-4-*hydroxy*-6-*methylpyrimidine* (2598) as colourless needles, m. p. 213—214° (Found: C, 62·0; H, 6·1; N, 17·9. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·6; N, 18·2%).

(b) Sodium (1·15 g.) was dissolved in methyl alcohol (65 c.c.), and *p*-anisylguanidine sulphate (10·7 g.) (prepared by method privately communicated by Sir Robert Robinson) and ethyl acetoacetate (16·25 g.) were added. The mixture was refluxed for 48 hours, then allowed to cool and the product filtered off, washed well with water to remove inorganic salts, and dried. It was 2-*p*-anisidino-4-hydroxy-6-methylpyrimidine, m. p. 212—214° undepressed in admixture with material made by method (a) (yield, 93·5%). No other substance could be isolated.

4-*Chloro*-2-p-*anisidino*-6-*methylpyrimidine* (XIII; R = OMe).—The above hydroxy compound (15 g.) and phosphoryl chloride (40 c.c.) were refluxed for 2 hours. Unchanged phosphoryl chloride was then removed under reduced pressure and the residue treated with ice. After making alkaline with ammonia the product was filtered off, washed with water, and crystallised from alcohol giving 4-*chloro*-2-p-*anisidino*-6-*methylpyrimidine* (9·05 g.) as colourless blunt-ended needles, m. p. 103—105° (Found: N, 16·5; Cl, 14·3. $C_{12}H_{12}ON_3Cl$ requires N, 16·8; Cl, 14·2%).

2-p-*Anisidino*-4-*β-diethylaminoethylamino*-6-*methylpyrimidine* (XIV; R = OMe, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$).—4-Chloro-2-*p*-anisidino-6-methylpyrimidine (12 g.) and *β*-diethylaminoethylamine (7 g.) were heated at 120—130° for 6 hours. The resulting clear melt was dissolved in warm dilute hydrochloric acid, and the solution filtered and made alkaline with sodium hydroxide. The precipitated oil was taken up in ether and extracted several times with 5% acetic acid. The combined acetic acid extracts were rendered alkaline with sodium hydroxide and extracted with ether. The ether extract was shaken twice with 2N-hydrochloric acid, and the acid extracts evaporated to dryness under reduced pressure at 60—65°. After drying, the residue was crystallised from alcohol. 2-p-*Anisidino*-4-*β-diethylaminoethylamino*-6-*methylpyrimidine dihydrochloride* (2665) (10·25 g.) was thus obtained as colourless thick prisms, m. p. 244° (Found: C, 52·6; H, 7·3; Cl, 17·5. $C_{18}H_{27}ON_5,2HCl,2H_2O$ requires C, 52·6; H, 7·3; Cl, 17·3%). The *dipicrate* prepared from the base with picric acid in methyl alcohol solution formed yellow prisms from *β*-ethoxyethanol–alcohol, m. p. 184—185° (Found: C, 45·9; H, 4·5; N, 19·2. $C_{18}H_{27}ON_5,2C_6H_3O_7N_3$ requires C, 45·7; H, 4·1; N, 19·6%).

2-p-*Chloroanilino*-4-*hydroxy*-6-*methylpyrimidine* (XII; R = Cl).—4-Hydroxy-2-methylthio-6-methylpyrimidine (23·4 g.) and *p*-chloroaniline (47·9 g.) were ground together and the mixture heated at 130—135° in an oil-bath for 24 hours. After cooling, the solid melt was ground and then refluxed with alcohol (240 c.c.), and the insoluble product filtered off and dried (yield, 30·9 g.). 2-p-*Chloroanilino*-4-*hydroxy*-6-*methylpyrimidine* (2792) was very sparingly soluble in the usual organic solvents, but could be recrystallised in small quantities from a large volume of *β*-ethoxyethanol from which it separated in clumps of colourless needles, m. p. 294° (Found: C, 55·6; H, 4·2; N, 17·4. $C_{11}H_{10}ON_3Cl$ requires C, 56·05; H, 4·2; N, 17·8%).

2-o-*Chloroanilino*-4-*hydroxy*-6-*methylpyrimidine* (XVI; R = Cl, R′ = OH), prepared in the same way using *o*-chloroaniline in place of *p*-chloroaniline, crystallised from *β*-ethoxyethanol as colourless elongated prisms, m. p. 244—246° (Found: N, 17·7. $C_{11}H_{10}ON_3Cl$ requires N, 17·8%).

2-m-*Chloroanilino*-4-*hydroxy*-6-*methylpyrimidine* (XV; R = OH), prepared using *m*-chloroaniline, crystallised from *β*-ethoxyethanol as colourless needles, m. p. 227—229° (Found: N, 17·5. $C_{11}H_{10}ON_3Cl$ requires N, 17·8%).

4-*Chloro*-2-p-*chloroanilino*-6-*methylpyrimidine* (XIII; R = Cl).—2-*p*-Chloroanilino-4-hydroxy-6-methylpyrimidine (25 g.) was refluxed with phosphoryl chloride (62·5 c.c.) for 3 hours. After removing the excess of phosphoryl chloride under reduced pressure at 50—60° the residue was treated with ice and water and rendered alkaline with ammonia. The resulting solid was filtered off, washed with water, and purified by crystallisation from alcohol giving 4-*chloro*-2-p-*chloroanilino*-6-*methylpyrimidine* (18·75 g.) as colourless pyramids, m. p. 127—129° (Found: C, 52·2; H, 3·7; Cl, 28·2. $C_{11}H_9N_3Cl_2$ requires C, 52·0; H, 3·5; Cl, 28·0%).

4-*Chloro*-2-o-*chloroanilino*-6-*methylpyrimidine* (XVI; R = R′ = Cl), prepared from 2-*o*-chloroanilino-4-hydroxy-6-methylpyrimidine and phosphoryl chloride, formed colourless needles or tables from alcohol, m. p. 99—100° (Found: N, 16·5; Cl, 28·7. $C_{11}H_9N_3Cl_2$ requires N, 16·5; Cl, 28·0%).

4-*Chloro*-2-m-*chloroanilino*-6-*methylpyrimidine* (XV; R = Cl), prepared from 2-*m*-chloroanilino-4-hydroxy-6-methylpyrimidine, crystallised from alcohol as colourless thick prisms, m. p. 116—118° (Found: N, 16·5; Cl, 28·3. $C_{11}H_9N_3Cl_2$ requires N, 16·5; Cl, 28·0%).

2-p-*Chloroanilino*-4-*β-hydroxyethylamino*-6-*methylpyrimidine* (XIV; R = Cl, R′ = CH_2·CH_2·OH).—4-Chloro-2-*p*-chloroanilino-6-methylpyrimidine (25·4 g.) and β-aminoethyl alcohol (12·2 g.) were heated at 120—130° for 10 hours. The resulting melt was heated with water and the granular product filtered off, ground, and suspended in water. Addition of sodium hydroxide liberated the base which was filtered off, washed with water, and crystallised from methyl alcohol (yield, 25·85 g.). 2-p-*Chloroanilino*-4-*β-hydroxyethylamino*-6-*methylpyrimidine* formed colourless tables, m. p. 157—158° (Found: N, 20·4. $C_{13}H_{15}ON_4Cl$ requires N, 20·1%). The *hydrochloride* (3608) separated from a solution of the base in hot dilute hydrochloric acid, on addition of more hydrochloric acid, as colourless needles, m. p. 218—219° (Found: Cl′, 10·9. $C_{13}H_{15}ON_4Cl$,HCl requires, Cl′, 11·3%).

2-p-*Chloroanilino*-4-*β-chloroethylamino*-6-*methylpyrimidine* (XIV; R = Cl, R′ = CH_2·CH_2Cl).—2-*p*-Chloroanilino-4-β-hydroxyethylamino-6-methylpyrimidine (14 g.) and phosphoryl chloride (42 c.c.) were refluxed for ½ hour. Excess of phosphoryl chloride was then removed under reduced pressure at 55°, and the residue added to ice. The precipitated product was filtered off and purified by dissolving in alcohol, filtering, and adding concentrated hydrochloric acid. 2-p-*Chloroanilino*-4-*β-chloroethylamino*-6-*methylpyrimidine hydrochloride* was thus obtained as colourless flat needles, m. p. 290—291° (Found: N, 16·9; Cl, 33·0. $C_{13}H_{14}N_4Cl_2$,HCl requires N, 16·8; Cl, 32·0%). Attempts to isolate the base in a pure condition failed.

2-p-*Chloroanilino*-4-*β-diethylaminoethylamino*-6-*methylpyrimidine* (XIV; R = Cl, R′ = CH_2·CH_2·NEt_2).—(a) 4-Chloro-2-*p*-chloroanilino-6-methylpyrimidine (16·93 g.) and β-diethylaminoethylamine (9·5 g.) were heated at 120—130°, with stirring, for 6 hours. After cooling, the viscous melt was dissolved in warm dilute hydrochloric acid, and the solution cooled and made alkaline to Clayton yellow by addition of sodium hydroxide. The product was extracted with chloroform and the extract shaken thrice with 5% acetic acid. The acid extracts were combined and made alkaline with sodium hydroxide, and the liberated base was again extracted with chloroform. After drying over potassium carbonate and evaporating the solvent, the residual oil was distilled in a vacuum, b. p. 224—226°/0·03 mm. (yield, 79·7%). The *dipicrate*, prepared in alcoholic solution, crystallised from β-ethoxyethanol as thick yellow prisms, m. p. 219—220° (Found: C, 43·7; H, 4·1; N, 19·0. $C_{17}H_{24}N_5Cl,2C_6H_3O_7N_3$ requires C, 44·0; H, 3·8; N, 19·45%). The *dihydrochloride* (2666) was prepared by dissolving the base in excess of 2N-hydrochloric acid and evaporating the solution to dryness under reduced pressure at 50—60°. The residue was dissolved in alcohol and the solution evaporated to dryness as before. The process was repeated and the residue purified by crystallisation from alcohol or alcohol–ethyl acetate giving colourless needles, readily soluble in water, m. p. 266—267° (Found: C, 50·5; H, 6·5; N, 17·1; Cl, 25·9. $C_{17}H_{24}N_5Cl$,2HCl requires C, 50·2; H, 6·4; N, 17·2; Cl, 26·2%).

(b) A mixture of 2-*p*-chloroanilino-4-β-chloroethylamino-6-methylpyrimidine hydrochloride (11·1 g.) and diethylamine (30 c.c.) was heated in a sealed tube at 140° for 8 hours. After cooling, the contents of the tube were dissolved in dilute hydrochloric acid, and the solution basified and treated as in (a). The resulting oil was distilled in a vacuum and the fraction b. p. 225—230°/0·03 mm. collected. This gave 2-*p*-chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine dipicrate, m. p. 217—219° undepressed by admixture with the dipicrate of the base prepared by method (a).

2-*p*-Chloroanilino-4-γ-diethylaminopropylamino-6-methylpyrimidine (XIV; R = Cl, R′ = $[CH_2]_3$·NEt_2), prepared from 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine (16·94 g.) and γ-diethylaminopropylamine (10·8 g.) (Whitmore *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 725), formed a clear yellowish viscous oil, b. p. 225°/0·4 mm. The *dipicrate*, recrystallised from β-ethoxyethanol, formed yellow prisms, m. p. 225—226° (Found: N, 19·2; Cl, 4·4. $C_{18}H_{26}N_5Cl,2C_6H_3O_7N_3$ requires N, 19·1; Cl, 4·4%). The *dihydrochloride* (3299) crystallised from alcohol as colourless needles, easily soluble in water, m. p. 252—254° (Found: C, 47·2; H, 7·5; N, 15·3; Cl, 22·7. $C_{18}H_{26}N_5Cl,2HCl,2H_2O$ requires C, 47·3; H, 7·0; N, 15·3; Cl, 23·3%).

2-*p*-Choroanilino-4-γ-dimethylaminopropylamino-6-methylpyrimidine (XIV; R = Cl, R′ = $[CH_2]_3$·NMe_2), obtained by condensation of 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine (16·94 g.) and γ-dimethylaminopropylamine * (8·5 g.), formed a faintly yellow viscous oil, b. p. 216—218°/0·18 mm. The *dipicrate* crystallised from β-ethoxyethanol–alcohol as yellow prisms, m. p. 224—225° (Found: C, 43·3; H, 3·6; N, 19·8. $C_{16}H_{22}N_5Cl,2C_6H_3O_7N_3$ requires C, 43·2; H, 3·6; N, 19·8%). The *dihydrochloride* (3711) crystallised from alcohol–ethyl acetate as colourless elongated prisms, m. p. 237—239° (Found: C, 44·7; H, 6·1; N, 16·4; Cl′, 16·6. $C_{16}H_{22}N_5Cl,2HCl,2H_2O$ requires C, 44·8; H, 5·1; N, 16·3; Cl′, 16·6%).

2-p-*Chloroanilino*-4-δ-*diethylaminobutylamino*-6-*methylpyrimidine* (XIV; R = Cl, R′ = $[CH_2]_4$·NEt_2), prepared from 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine (14·0 g.) and δ-diethylaminobutylamine (10 g.) (Utermohlen and Hamilton, *J. Amer. Chem. Soc.*, 1941, **63**, 156), formed a colourless viscous oil, b. p. 225—230°/0·12 mm. (Found: C, 62·4; H, 7·2; N, 19·4. $C_{19}H_{28}N_5Cl$ requires C, 63·1; H, 7·7; N, 19·4%). With picric acid in methanol solution it formed a *dipicrate* which crystallised from β-ethoxyethanol–alcohol as yellow prisms, m. p. 198—199° (Found: C, 45·4; H, 4·0; N, 18·5. $C_{19}H_{28}N_5Cl,2C_6H_3O_7N_3$ requires C, 45·4; H, 4·1; N, 18·8%). The *dihydrochloride* (3338) crystallised from alcohol as colourless needles, m. p. 245—247° (Found: C, 49·5; H, 7·1; N, 15·3; Cl′, 15·5. $C_{19}H_{28}N_5Cl,2HCl,1·5H_2O$ requires C, 49·4; H, 7·15; N, 15·2; Cl′, 15·4%).

2-*p*-Chloroanilino-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (XIV; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2), prepared from 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine (25·4 g.) and δ-diethylamino-α-methylbutylamine (19·75 g.), was a very viscous pale yellow oil, b. p. 210°/0·9 mm. The *dipicrate*, prepared in alcoholic solution, crystallised from alcohol–β-ethoxyethanol as yellow needles, m. p. 168—170° (Found: C, 45·7; H, 4·5; N, 17·8. $C_{20}H_{30}N_5Cl,2C_6H_3O_7N_3$ requires C, 46·1; H, 4·3; N, 18·5%). The *dihydrochloride* (3300), which was readily soluble in water, crystallised from alcohol–ethyl acetate as colourless needles, m. p. 235—237° (Found: C, 49·2, 49·0; H, 8·1, 7·9; N, 14·4; Cl, 21·5. $C_{20}H_{30}N_5Cl,2HCl,2H_2O$ requires C, 49·55; H, 7·4; N, 14·55; Cl, 22·0%).

2-*o*-Chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine (XVI; R = Cl, R′ = NH·$[CH_2]_2$·NEt_2), prepared from 4-chloro-2-*o*-chloroanilino-6-methylpyrimidine and β-diethylaminoethylamine, gave a *dihydrochloride* (3381) which separated from alcohol as colourless needles, m. p. 251—253° (Found: C, 49·5; H, 6·3; N, 16·9; Cl, 26·3. $C_{17}H_{24}N_5Cl,2HCl$ requires C, 50·2; H, 6·4; N, 17·2; Cl, 26·2%).

2-*o*-Chloroanilino-4-γ-diethylaminopropylamino-6-methylpyrimidine (XVI; R = Cl, R′ = NH·$[CH_2]_3$·NEt_2), obtained in a similar manner using γ-diethylaminopropylamine, formed a *dihydrochloride* (3466) which crystallised from alcohol as colourless needles, m. p. 238—239° (Found: C, 46·9; H, 6·9; N, 15·8; Cl, 23·1. $C_{18}H_{26}N_5Cl,2HCl,2H_2O$ requires C, 47·3; H, 7·0; N, 15·3; Cl, 23·3%).

2-m-*Chloroanilino*-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine* (XV; R = NH·$[CH_2]_3$·NEt_2).—The *dihydrochloride* (3554), prepared from 4-chloro-2-*m*-chloroanilino-6-methylpyrimidine and γ-diethylaminopropylamine, was obtained by crystallisation from alcohol as colourless needles, m. p. 215—217° (Found: C, 51·1; H, 6·7; N, 16·5; Cl′, 17·1, 16·9. $C_{18}H_{26}N_5Cl,2HCl$ requires C, 51·4; H, 6·7; N, 16·5; Cl′, 16·9%).

2-o-*Anisidino*-4-*hydroxy*-6-*methylpyrimidine* (XVI; R = OMe, R′ = OH), prepared by heating 4-hydroxy-2-methyl-

* The new aminoalkylamines used in this and subsequent papers of this series will be described in a separate communication.

thio-6-methylpyrimidine with *o*-anisidine as described above for the *p*-compound, crystallised from β-ethoxyethanol as colourless needles, m. p. 245—246° (Found: C, 62·2; H, 5·3. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·6%).

4-*Chloro*-2-o-*anisidino*-6-*methylpyrimidine* (XVI; R = OMe, R′ = Cl), was obtained by refluxing 2-*o*-anisidino-4-hydroxy-6-methylpyrimidine (30·8 g.) with phosphoryl chloride (93·5 c.c.) and, after removing the excess of phosphoryl chloride under reduced pressure, pouring the reaction mixture on ice and making alkaline with ammonia. It crystallised from alcohol as colourless rods, m. p. 104—105° (Found: N, 16·6; Cl, 14·55. $C_{12}H_{12}ON_3Cl$ requires N, 16·8; Cl, 14·55%).

2-o-*Anisidino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (XVI; R = OMe, R′ = NH·$[CH_2]_2$·NEt_2).—The above chloro compound (16·6 g.) and β-diethylaminoethylamine (9·5 g.) condensed together and worked up as before gave the *dihydrochloride* (3382) as colourless needles from alcohol, m. p. 272—273° (Found: C, 53·5; H, 7·1; N, 17·4; Cl, 17·3. $C_{18}H_{27}ON_5$,2HCl requires C, 53·7; H, 7·2; N, 17·4; Cl, 17·7%).

2-*Anilino*-4-*hydroxy*-6-*methylpyrimidine* (XII; R = H).—4-Hydroxy-2-methylthio-6-methylpyrimidine (31·2 g.), aniline (41 g.), and β-ethoxyethanol (100 c.c.) were refluxed in an oil-bath for 30 hours. Methylthiol was evolved. After cooling, the product which had separated was filtered off, washed with alcohol, and dried. Crystallisation from β-ethoxyethanol gave 2-*anilino*-4-*hydroxy*-6-*methylpyrimidine* (20·5 g.) as colourless thick prisms, m. p. 244—246° (Found: C, 65·6; H, 5·5; N, 21·0. $C_{11}H_{11}ON_3$ requires C, 65·7; H, 5·5; N, 20·9%).

4-*Chloro*-2-*anilino*-6-*methylpyrimidine* (XIII; R = H), prepared from the above hydroxy compound and phosphoryl chloride in the manner described previously for similar chloro compounds, crystallised from alcohol as colourless needles, m. p. 92—93° (Found: C, 59·5; H, 4·6; N, 18·6. $C_{11}H_{10}N_3Cl$ requires C, 60·1; H, 4·6; N, 19·1%).

2-*Anilino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (XIV; R = H, R′ = CH_2·CH_2·NEt_2).—4-Chloro-2-anilino-6-methylpyrimidine (16·5 g.) and β-diethylaminoethylamine (9·6 g.) were condensed together and worked up by the usual procedure to give the *dihydrochloride* (18·1 g.) (2725) which crystallised from alcohol as colourless needles, m. p. 264° (decomp.) (Found: C, 52·7; H, 7·6; Cl, 18·7. $C_{17}H_{25}N_5$,2HCl,H_2O requires C, 52·3; H, 7·4; Cl, 18·2%).

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