69. *Synthetic Antimalarials. Part II. 2-Substituted-anilino-4-amino-alkylamino-6-methylpyrimidines.*

By F. H. S. Curd, (Miss) M. I. Davis, and F. L. Rose.

The series of 2-anilino-4-dialkylaminoalkylamino-6-methylpyrimidines carrying substituents in the 2-anilino group, described in Part I (preceding paper), has been extended in a number of directions which have included variation of the dialkylaminoalkylamino group and replacement of the original chlorine and methoxyl substituents in the anilino residue by other groupings.

The importance of substitution in the 4-position of the anilino group is discussed in relation to the hypothesis (Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, in the press) that such compounds, like mepacrine, may owe their activity to an interference with a riboflavin-containing enzyme system essential to the malaria parasite. This hypothetical view of the mode of action of this new type of antimalarial is taken as the basis of further variations in the substitution of the anilino residue which are described.

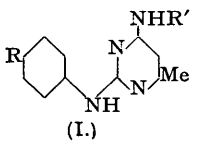
In Part I (preceding paper) the preparation of a number of chlorine and methoxyl substituted anilino-4-dialkylaminoalkylamino-6-methylpyrimidines exhibiting antimalarial activity was described. Highest activity was shown by those compounds in which the substituent occupied the *para*-position of the anilino residue (I; R = Cl or OMe, R′ = dialkylaminoalkyl): transference of the substituent to the *meta*- or *ortho*-positions gave compounds which showed no more than a trace of activity.

Many variations in structure are possible in this type of compound, and this communication deals with further modifications of the substituted anilino and dialkylaminoalkyl residues which were made in the course of a search for compounds of even higher activity. Variations of the substituent in the anilino residue were obviously called for, at least as far as the introduction of those substituents which lead to activity in other antimalarial types.

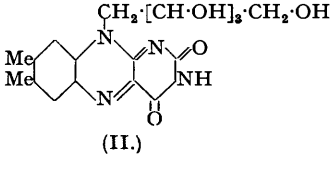
The patent literature (E.PP. 363,392, 437,953, 441,007) indicated that in compounds of the mepacrine type the important substituents for antimalarial activity were halogen, alkyl, alkoxyl, and alkylthio, and the work of Magidson and Grigorowsky (*Ber.*, 1936, **69**, 396), Magidson *et al.* (*J. Microbiol. and Immunobiol.*, 1934, **12**, 1), and Magidson and Trawin (*Ber.*, 1936, **69**, 537) added nitro and cyano groups. All the above substituents have been included in our investigations, and the number has been extended by the addition of phenyl, dimethylamino, and carbomethoxy groups.

It is now generally accepted that the mode of action of drugs of the sulphonamide type is a competition with *p*-aminobenzoic acid which is an essential metabolite of many micro-organisms. It therefore seemed possible that antimalarial drugs might act in a similar way by interference with the utilisation of some growth factor or metabolite essential to the parasites of malaria either by preventing some coenzyme synthesis or by leading to the production of an artefact with consequent disruption of coenzyme function.

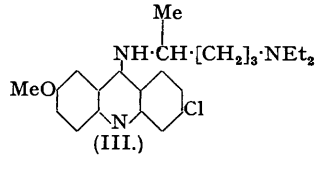
We have pointed out elsewhere (Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, in the press) the formal similarity with riboflavin (II) exhibited, not only by mepacrine (III), but also by compounds of type (I).



(I.)



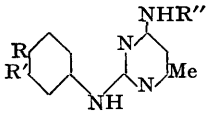
(II.)



(III.)

This suggested that the activity of (I) and (III) might be due to an interference with one or more riboflavin-containing enzyme systems in the malaria parasite. Support has since been lent to this hypothesis by the demonstration (Madinaveitia, *Biochem. J.*, in the press) that the growth-inhibitory action of mepacrine and 2-*p*-chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine (I; R = Cl, R′ = $[CH_2]_2 \cdot NEt_2$) for *Lactobacillus casei* is antagonised by riboflavin.

The apparent necessity for substitution in the *para*-position of the anilino residue indicated by our previous work was difficult to understand on the basis of such a riboflavin antagonism since it might have been anticipated that substitution in the *meta*-position would lead to a similar result and that, in the case of mepacrine, the antagonism might be connected with the correspondence in position either of the chlorine with the 6-methyl group, or of the methoxyl group with the 7-methyl group, of riboflavin, or partly with both, leading to a potentiation of the antagonistic effect. There was, however, the observation of Karrer *et al.* (*Helv. Chim. Acta*, 1935, **18**, 908) that 7-methyl-9-(*d*-1′-ribityl)*iso*alloxazine exhibited vitamin B_2 activity, indicating the importance of the 7-position and therefore probably of the *para*-position in the anilino group of (I) for riboflavin antagonism. It also seemed possible that the antimalarial activity of the 3 : 7-disubstituted acridines carrying an aminoalkylamino group in the 5-position (E.P. 411,132) and of the compounds corresponding to mepacrine but without the 8-substituent (E.P. 441,007) might be connected with this importance of the 7-methyl group in riboflavin. We therefore examined this problem more fully, and, in addition to 2-p-*toluidino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (I; R = Me, R′ = $[CH_2]_2 \cdot NEt_2$), we prepared the corresponding m-*toluidino* (IV; R = H, R′ = Me, R″ = $[CH_2]_2 \cdot NEt_2$) and o-*toluidino* (V; R = Me, R′ = $[CH_2]_2 \cdot NEt_2$)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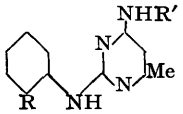
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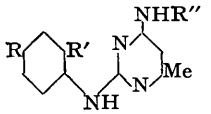
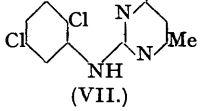
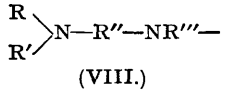

(VI.)

derivatives as showing a closer resemblance to riboflavin. The biological examination of these compounds confirmed, however, that substitution in the *para*-position leads to higher activity than *ortho*- or *meta*-substitution.

At the time this work was carried out the papers of Kuhn, Weygand, and Möller (*Ber.*, 1943, **76**, 1044) on the antiriboflavin activity of 6 : 7-dichloro-9-(*d*-1′-ribityl)*iso*alloxazine and of Emerson and Tishler (*Proc. Soc. Exp. Biol. Med.*, 1944, **55**, 184) on the similar antagonistic effect of *iso*riboflavin [5 : 6-dimethyl-9-(*d*-1′-ribityl)*iso*alloxazine] had not appeared, so there was no guide from work on riboflavin itself to indicate what variations in the substituents of compounds of type (I) might lead to an enhancement of riboflavin antagonism and thus possibly to an increase in antimalarial activity. It did appear, however, that disubstituted compounds of type (IV) which more closely simulate riboflavin might be more effective antimalarial agents, and the following compounds were therefore prepared: 2-(3′ : 4′-*dichloroanilino*)- (IV; R = R′ = Cl, R″ = $[CH_2]_3 \cdot NEt_2$), 2-(3′-*chloro*-4′-*methylanilino*)- (IV; R = Me, R′ = Cl, R″ = $[CH_2]_3 \cdot NEt_2$), and 2-(3′ : 4′-*dimethylanilino*)-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine* (IV; R = R′ = Me, R″ = $[CH_2]_3 \cdot NEt_2$).

Further, it was considered that a combination of *ortho*- and *para*-substitution in the anilino residue (type VI) would also be of interest as providing a type more nearly resembling the closed ring structure of riboflavin. The series of disubstituted anilino-4-γ-diethylaminopropylamino-6-methylpyrimidines was accordingly extended to include 2-(2′ : 4′-*dichloroanilino*)- (VI; R = R′ = Cl, R″ = $[CH_2]_3 \cdot NEt_2$) and 2-(4′-*chloro*-2′-*methylanilino*)-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine* (VI; R = Cl, R′ = Me, R″ = $[CH_2]_3 \cdot NEt_2$). One compound representative of *ortho*- and *meta*-substitution, 2-(2′ : 5′-*dichloroanilino*)-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine* (VII; R = $[CH_2]_3 \cdot NEt_2$), was also made.


(VII.)


(VIII.)

The method of preparation of all the compounds mentioned above was that originally used in Part I (*loc. cit.*). 4-Hydroxy-2-methylthio-6-methylpyrimidine was condensed with the appropriate substituted aniline to give a 2-substituted anilino-4-hydroxy-6-methylpyrimidine (the compounds prepared are listed in Table II), which was then converted into the corresponding 4-chloropyrimidine (see Table III) and this condensed with either β-diethylaminoethylamine (see Table IV) or γ-diethylaminopropylamine (see Table V). These two dialkylaminoalkylamines were selected because they appeared to lead to higher activity in (I; R = Cl) than δ-diethylamino-α-methylbutylamine.

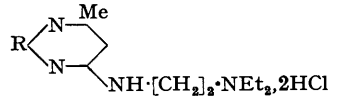
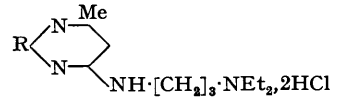
The other aspect of the work now described was concerned with the further variation of the side chain (NHR′) in (I; R = Cl). In other antimalarial types Schulemann (*Proc. Roy. Soc. Med.*, 1931—1932, **25**, Part I, 897) has indicated that the permissible variation is fairly wide, and many of the side-chain types mentioned by Schulemann and in the patent literature have now been introduced into the new pyrimidine

type of antimalarial with the object of defining the limits within which modification can be effected without destroying antimalarial activity. The side-chain residue can be represented by the general formula (VIII), and the variations have included the use of primary (R = R′ = H) and secondary (R = H, R′ = alkyl) terminal amino groups instead of the more conventional tertiary amino group in which various alkyl groups have been tried (R = R′ = Me, Et, Bu$^{\alpha}$; R = Me, R′ = Pr$^{\beta}$). The group NRR′ has also been made a heterocyclic residue such as piperidino and pyrrolidino. The usual alkylene chain R″ has likewise been modified by substitution with alkyl or dialkylaminoalkyl groups, interruption by oxygen (R″ = $[CH_2]_3{\cdot}O{\cdot}[CH_2]_2$) or nitrogen (R″ = $[CH_2]_3{\cdot}NMe{\cdot}[CH_2]_2$), and replacement of all (R″ = C_6H_4) or part of it (R″ = p-$C_6H_4O{\cdot}[CH_2]_2$) by a carbocyclic residue. The usual imino linkage (NR‴; R‴ = H) connecting the side chain to the heterocyclic nucleus has, in addition, been replaced by alkylimino (R‴ = Me) or dialkylaminoalkylimino (R‴ = $[CH_2]_2{\cdot}NEt_2$). The various compounds are listed in Table VI.

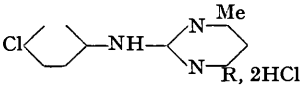
Antimalarial activity was estimated by testing against *P. gallinaceum* in chicks as described by Curd, Davey, and Rose (*Ann. Trop. Med. Parasit.*, in the press), and the method of expressing antimalarial activity is the same as in Part I. The results are given in Table I. Detailed biological results will be published elsewhere.

TABLE I.

Antimalarial Activities.

Ref. No.	Nature of R.	Dose, mg./kg.	Activity.
(*a*) 2-Arylamino-4-β-diethylaminoethylamino-6-methylpyrimidine dihydrochlorides.			
	General formula: 		
3383	4′-Phenetidino-	200	++
3527	4′-Methylthioanilino-	80	+ to ++
		60	+ to ++
3464	4′-Toluidino-	100	++
		80	++
3375	3′-Toluidino-	160	−
3528	2′-Toluidino-	120	+
		80	±
(*b*) 2-Arylamino-4-γ-diethylaminopropylamino-6-methylpyrimidine dihydrochlorides.			
	General formula: 		
3748	4′-Butylanilino-	80	±
3463	4′-Bromoanilino-	100	++
		80	++
		40	+
3830	4′-Nitroanilino-	80	++
		40	+
3905	4′-Cyanoanilino-	80	++
		40	+
3507	4′-Phenetidino-	200	+
		80	−
3693	4′-Dimethylaminoanilino- [1]	80	+
3782	4′-Carbomethoxyanilino-	160	+ to ++
		80	+
3840	4′-Phenylanilino-	200	+ to ++
		80	+
3564	3′ : 4′-Dichloroanilino-	200	+ to ++
		150	+ to ++
		120	+ to ++
		80	±
3668	3′-Chloro-4′-methylanilino-	200	++
		120	+
		80	+
3694	3′ : 4′-Dimethylanilino-	120	+
3621	2′ : 4′-Dichloroanilino-	120	+ to ++
		80	+ to ++
		40	±
3598	4′-Chloro-2′-methylanilino-	80	++
		40	+ to ++
3685	2′ : 5′-Dichloroanilino-	200	−
		120	−
3620	4′-Chloro-2′-methylanilino- [2]	200	++
		120	+
		80	±
		40	−

(*c*) 2-*p*-Chloroanilino-4-alkylamino-6-methylpyrimidine dihydrochlorides.

General formula: 

3906	NH·[CH$_2$]$_2$·NMe$_2$	40	+
		20	±
4413	NH·[CH$_2$]$_2$·N<[CH$_2$]$_3$>CH$_2$	160	++
		80	+
		40	−
4412	NH·[CH$_2$]$_2$·N<[CH$_2$]$_4$>CH$_2$	240	++
		160	++
		80	−
		40	−
3557	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	80	+ to ++
		60	+
4438	NH·CHMe·CH$_2$·N<[CH$_2$]$_4$>CH$_2$	160	+
		80	−
3578	NH·[CH$_2$]$_3$·NBu$^{\alpha}$$_2$	200	++
		80	−
		40	−
3671	NH·[CH$_2$]$_3$·NHBu$^{\alpha}$	80	+ to ++
		40	+
4439	NH·[CH$_2$]$_3$·O·[CH$_2$]$_2$·NEt$_2$	120	+
		40	−
4440	NH·[CH$_2$]$_3$·NMe·[CH$_2$]$_2$·NEt$_2$ [3]	160	+ to ++
		80	+
4414	NMe·[CH$_2$]$_2$·NEt$_2$	160	++
		80	−
4499	N([CH$_2$]$_2$·NEt$_2$)$_2$ [4]	160	±
4498	NH·CH(CH$_2$·NEt$_2$)$_2$ [4]	240	−
		120	−
4667	NH·[CH$_2$]$_3$·NMePr$^{\beta}$	80	+ to ++
		40	+
		20	−
3542	*p*-NH·C$_6$H$_4$·O·[CH$_2$]$_2$·NEt$_2$	80	+ to ++
3654	*p*-NH·C$_6$H$_4$·NMe$_2$	320	±
		120	−
		80	−
4874	NH·[CH$_2$]$_2$·NH$_2$	40	++
		20	+

[1] Trihydrobromide. [2] γ-Dibutylaminopropylamino-derivative. [3] Trihydrochloride. [4] Trihydrobromide.

Experimental.

2-*Substituted-anilino*-4-*hydroxy*-6-*methylpyrimidines*.—Two methods have been employed for the preparation of these compounds which are based on the work described in Part I (*loc. cit.*).

Method A. 4-Hydroxy-2-methylthio-6-methylpyrimidine (0·2 g.-mol.) and the appropriate substituted aniline (0·5 g. mol.) were mixed and heated together at 125—135° for 48 hours under an air condenser with stirring. Methylthiol was evolved. In some cases the mixture set solid during the course of the reaction but in others remained molten throughout, solidifying on cooling. When cold the reaction mixture was ground, refluxed with alcohol (300 c.c.), cooled, and filtered.

Method B. 4-Hydroxy-2-methylthio-6-methylpyrimidine (0·2 g.-mol.) and the substituted aniline (0·25—0·4 g.-mol.) were heated (oil-bath) together in boiling β-ethoxyethanol (200 c.c.) for 48 hours. After cooling, the product was filtered off, washed with alcohol, and dried.

Most of the products obtained by either of the above processes were already virtually pure as judged by m. p. For analysis, the compounds were normally crystallised from β-ethoxyethanol, but alcohol was used for the most soluble compounds (from *p*-phenetidine and *m*-toluidine), and dimethylformamide or nitrobenzene for the least soluble (from 4-aminodiphenyl, methyl 4-aminobenzoate, *p*-cyanoaniline, and *p*-nitroaniline).

The compounds prepared are listed in Table II.

4-*Chloro*-2-*substituted-anilino*-6-*methylpyrimidines*.—The general preparative procedure was as follows: The 2-substituted-anilino-4-hydroxy-6-methylpyrimidine (0·1 g.-mol.) and phosphoryl chloride (0·4 g.-mol.) were refluxed together for 3 hours. After cooling to 50—60° the excess of phosphoryl chloride was removed under reduced pressure at this temperature until the mixture was still just fluid enough to pour. It was then transferred to a mixture of ice and water and left for one hour with occasional stirring. Ammonia was then carefully added, keeping the mixture cool, until alkaline to Brilliant yellow. After stirring for several hours, more ammonia being added if necessary to maintain alkalinity, the mixture was left in the refrigerator overnight. Next day, the solid product was collected, washed with water, dried in a vacuum, and purified by crystallisation, using the solvent indicated in Table III which gives details of the compounds prepared.

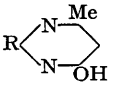
2-*Substituted-anilino*-4-*aminoalkylamino*-6-*methylpyrimidines*.—The following general method of preparation was employed: The chloropyrimidine (0·05 g.-mol.) and the aminoalkylamine (0·05 × 1·25 g.-mol.) were heated together at 120—130° (oil-bath) for 6 hours with stirring. After cooling, the viscous melt was dissolved in warm dilute hydrochloric acid and the solution made strongly alkaline with sodium hydroxide. The liberated product was taken up in ether or chloroform. Usually, this extract was shaken several times with 5% acetic acid, but occasionally it was found advisable to evaporate the solvent and to carry out the extraction procedure on the residue (this was essential with 2-*p*-chloroanilino-4-γ-dibutylaminopropylamino-6-methylpyrimidine, the acetate of which is not appreciably

extracted from chloroform solution by water). The acetic acid extracts were combined and made alkaline with sodium hydroxide, and the liberated base again extracted with ether or chloroform. Evaporation of the dried solution gave the base as a viscous oil which usually crystallised only slowly. Many of the bases were characterised by conversion into their picrates in methanol solution (see Table VII). For biological testing they were converted into their hydrohalic acid salts (usually hydrochlorides) by the following process :

The base was dissolved in excess of 2N-acid, and the solution evaporated to dryness under reduced pressure at 50—60°. The residue was freed from water and excess of acid by repeated evaporation to dryness under reduced pressure with alcohol or alcohol–benzene; it was then crystallised from alcohol or alcohol–ethyl acetate. Tables IV, V, and VI give details of the compounds prepared.

TABLE II.

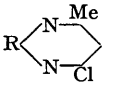
2-*Substituted-anilino*-4-*hydroxy*-6-*methylpyrimidines*.

General formula : 

Nature of R.	Method of preparation.	M. p.	Formula.	Analysis. Found, %.	Analysis. Required, %.
4′-Phenetidino-	A	187—189°	$C_{13}H_{15}O_2N_3$	N, 17·3	N, 17·1
4′-Bromoanilino-	B	284—286	$C_{11}H_{10}ON_3Br$	Br, 30·7	Br, 30·3
4′-Methylthioanilino-	B	210—212	$C_{11}H_{13}ON_3S$	C, 57·6; H, 5·4; N, 17·0	C, 58·3; H, 5·25; N, 17·0
4′-Toluidino-	A	230	$C_{12}H_{13}ON_3$	N, 19·8	N, 19·5
3′-Toluidino-	A	214	$C_{12}H_{13}ON_3$	N, 19·4	N, 19·5
2′-Toluidino-	A	204	$C_{12}H_{13}ON_3$	N, 19·6	N, 19·5
4′-Butylanilino-	B	195—196	$C_{15}H_{19}ON_3$	N, 16·7	N, 16·3
4′-Phenylanilino-	B	258—259	$C_{17}H_{15}ON_3$	N, 15·4	N, 15·2
4′-Dimethylaminoanilino-	B	240—242	$C_{13}H_{16}ON_4$	C, 63·7; H, 6·7	C, 63·9; H, 6·6
4′-Carbomethoxyanilino-	A, B	274—276	$C_{13}H_{13}O_3N_3$	C, 60·3; H, 5·0; N, 16·0	C, 60·2; H, 5·0; N, 16·2
4′-Nitroanilino-	A	>320	$C_{11}H_{10}O_3N_4$	C, 53·8; H, 4·3; N, 23·0	C, 53·2; H, 4·1; N, 22·8
4′-Cyanoanilino-	B	>320	$C_{12}H_{10}ON_4$	C, 63·75; H, 4·5; N, 24·2	C, 63·75; H, 4·45; N, 24·8
3′ : 4′-Dichloroanilino-	B	250—252	$C_{11}H_9ON_3Cl_2$	N, 15·2	N, 15·5
3′-Chloro-4′-methylanilino-	B	252—254	$C_{12}H_{12}ON_3Cl$	N, 16·3	N, 16·8
3′ : 4′-Dimethylanilino-	B	238—239	$C_{13}H_{15}ON_3$	N, 18·2	N, 18·35
2′ : 4′-Dichloroanilino-	A, B	278—280	$C_{11}H_9ON_3Cl_2$	N, 15·0	N, 15·5
4′-Chloro-2′-methylanilino-	B	252—254	$C_{12}H_{12}ON_3Cl$	N, 17·0; Cl, 13·7	N, 16·8; Cl, 14·2
2′ : 5′-Dichloroanilino-	A	250—252	$C_{11}H_9ON_3Cl_2$	C, 49·1; H, 3·3; N, 15·1	C, 48·9; H, 3·3; N, 15·5

TABLE III.

4-*Chloro*-2-*anilino*-6-*methylpyrimidines*.

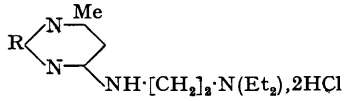
General formula : 

Nature of R.	Crystalline form.	M. p.	Formula.	Analysis. Found, %.	Analysis. Required, %.
4′-Phenetidino-	Colourless tables	116—118°	$C_{13}H_{14}ON_3Cl$	N, 15·9; Cl, 14·3	N, 15·9; Cl, 13·5
4′-Bromoanilino	,, needles	140—141	$C_{11}H_9N_3ClBr$	N, 13·9	N, 14·1
4′-Methylthioanilino-	,, ,,	81—82	$C_{12}H_{12}N_3SCl$	—	—
4′-Toluidino-	,, tables or needles	104—106	$C_{12}H_{12}N_3Cl$	N, 17·3; Cl, 15·9	N, 18·0; Cl, 15·2
3′-Toluidino-	,, tables	101—102	$C_{12}H_{12}N_3Cl$	N, 17·3; Cl, 15·8	N, 18·0; Cl, 15·2
2′-Toluidino-	,, needles	116—118	$C_{12}H_{12}N_3Cl$	N, 17·6; Cl, 15·7	N, 18·0; Cl, 15·2
4′-Butylanilino-	,, plates [1]	51—53	$C_{15}H_{18}N_3Cl$	N, 15·2; Cl, 13·2	N, 15·2; Cl, 12·9
4′-Phenylanilino-	,, ,,	124—125	$C_{17}H_{14}N_3Cl$	N, 14·5	N, 14·2
4′-Dimethylaminoanilino-	,, tables [2]	156—158	$C_{13}H_{15}N_4Cl$	N, 20·8; Cl, 12·7	N, 21·3; Cl, 13·5
4′-Carbomethoxyanilino-	,, prisms [3]	223—225	$C_{13}H_{12}O_2N_3Cl$	C, 56·2; H, 4·4; N, 15·4	C, 56·2; H, 4·3; N, 15·1
4′-Nitroanilino-	Yellow plates [3]	251—252	$C_{11}H_9O_2N_4Cl$	N, 20·4; Cl, 12·9	N, 21·1; Cl, 13·4
4′-Cyanoanilino-	Colourless plates [3]	215—216	$C_{12}H_9N_4Cl$	N, 22·4	N, 22·9
4′-Chloro-2′-methylanilino-	,, needles	107—108	$C_{12}H_{11}N_3Cl_2$	N, 15·5; Cl, 26·5	N, 15·6; Cl, 26·6
3′ : 4′-Dichloroanilino-	,, ,,	134—136	$C_{11}H_8N_3Cl_3$	N, 14·55; Cl, 36·1	N, 14·55; Cl, 36·9
2′ : 4′-Dichloroanilino	,, ,,	120—122	$C_{11}H_8N_3Cl_3$	N, 14·55; Cl, 36·5	N, 14·55; Cl, 36·9
3′ : 4′-Dimethylanilino-	,, rhombic plates	128—129	$C_{13}H_{14}N_3Cl$	N, 17·0	N, 17·0
3′-Chloro-4′-methylanilino-	,, tables or needles	115—117	$C_{12}H_{11}N_3Cl_2$	N, 15·6	N, 15·6
2′ : 5′-Dichloroanilino	,, needles	101	$C_{11}H_8N_3Cl_3$	N, 14·3; Cl, 37·2	N, 14·55; Cl, 36·9

[1] From methyl alcohol–water. [2] From light petroleum (b. p. 100—120°). [3] From β-ethoxyethanol. All others from alcohol.

TABLE IV.

2-Arylamino-4-β-diethylaminoethylamino-6-methylpyrimidine Dihydrochlorides.

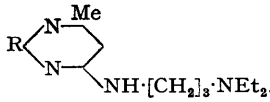
General formula: 

Nature of R.	M. p.	Formula.	Analysis. Found, %. C.	H.	N.	Cl′.	Required, %. C.	H.	N.	Cl′.
4′-Phenetidino-	211—213°	$C_{19}H_{29}ON_5,2HCl,0{\cdot}5H_2O$	54·0	7·5	16·1	16·7	53·65	7·5	16·5	16·7
4′-Methylthioanilino-	232—234	$C_{18}H_{27}N_5S,2HCl,2H_2O$	47·6	7·2	15·5	16·2	47·6	7·3	15·2	15·6
4′-Toluidino-	216—218	$C_{18}H_{27}N_5,2HCl,H_2O$	53·6	7·8	17·4	17·4	53·5	7·7	17·3	17·6
3′-Toluidino-	272—274	$C_{18}H_{27}N_5,2HCl,0{\cdot}5H_2O$	54·3	7·5	17·8	18·4	54·7	7·6	17·7	18·0
2′-Toluidino-	237—238	$C_{18}H_{27}N_5,2HCl,0{\cdot}5H_2O$	55·5	7·8	18·0	18·3	54·7	7·6	17·7	18·0

All these compounds crystallised in colourless needles.

TABLE V.

2-Arylamino-4-γ-diethylaminopropylamino-6-methylpyrimidines (Hydrohalic Acid Salts).

General formula of bases: 

Nature of R.	Formula.	M. p.	Analysis. Found, %. C.	H.	N.	Cl′.	Required, %. C.	H.	N.	Cl′.
4′-Butylanilino-	$C_{22}H_{35}N_5,2HCl,H_2O$	188—190°	57·1	7·7	14·9	15·4	57·4	8·5	15·2	15·4
4′-Bromoanilino-	$C_{18}H_{26}N_5Br,2HCl,2H_2O$	255—257	43·0	6·3	13·8	14·2 (Br, 15·7)	43·1	6·4	14·0	14·2 (Br, 16·0)
4′-Nitroanilino-	$C_{18}H_{26}O_2N_6,2HCl,2H_2O$	226—230	46·8	6·6	18·1	15·7	46·3	6·4	18·0	15·2
4′-Cyanoanilino-	$C_{19}H_{26}N_6,2HCl,3H_2O$	249—251	49·8	7·5	18·4	15·6	49·0	7·3	18·1	15·3
4′-Phenetidino-	$C_{20}H_{31}ON_5,2HCl,H_2O$	253—255	53·6	7·4	15·6	—	53·6	7·4	15·6	—
4′-Dimethylaminoanilino-	$C_{20}H_{32}N_6,3HBr,H_2O$	256—258 (dec.)	39·7	5·9	13·7	38·8 (Br′)	38·9	6·0	13·6	38·9 (Br′)
4′-Carbomethoxyanilino-	$C_{20}H_{29}O_2N_5,2HCl$	263—265 (dec.)	54·0	7·1	15·5	15·8	54·0	7·0	15·75	16·0
4′-Phenylanilino-	$C_{24}H_{31}N_5,2HCl,3H_2O$	244—246	55·6	6·9	13·8	14·3	55·8	7·6	13·6	13·8
3′ : 4′-Dichloroanilino-	$C_{18}H_{25}N_5Cl_2,2HCl,H_2O$	237—239	46·1	6·1	15·2	14·7	45·7	6·1	14·8	15·0
3′-Chloro-4′-methylanilino-	$C_{19}H_{28}N_5Cl,2HCl,H_2O$	230—232	51·0	7·1	15·3	15·6	50·4	7·3	15·5	15·7
3′ : 4′-Dimethylanilino-	$C_{20}H_{31}N_5,2HCl,H_2O$	222—224	56·0	7·7	15·9	16·6	55·55	8·1	16·2	16·4
2′ : 4′-Dichloroanilino- [1]	$C_{18}H_{25}N_5Cl_2,2HCl,2H_2O$	208—210	43·4	6·4	13·7	14·5	44·0	6·3	14·3	14·5
4′-Chloro-2′-methylanilino-	$C_{19}H_{28}N_5Cl,2HCl,H_2O$	150—152	50·0	7·2	15·0	15·4	49·3	6·9	15·1	15·7
2′ : 5′-Dichloroanilino- [2]	$C_{18}H_{25}N_5Cl_2,2HCl,2H_2O$	248—250	44·1	6·3	—	14·6	44·0	6·3	—	14·5
4′-Chloro-2′-methylanilino- [3] *	$C_{23}H_{36}N_5Cl,2HCl$	204—206	55·8	7·5	14·7	14·4	56·3	7·75	14·3	14·5

[1] The base had b. p. 208—210°/0·02 mm. The *dipicrate* crystallised from β-ethoxyethanol in yellow tables, m. p. 210—211° (Found: C, 42·6; H, 3·8; N, 18·2. $C_{18}H_{25}N_5Cl_2,2C_6H_3O_7N_3$ requires C, 42·8; H, 3·7; N, 18·3%).

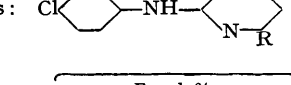
[2] The *base* crystallised as a hydrate from light petroleum (b. p. 100—120°) in colourless cubes, m. p. 98—100° (efferv.) (Found: C, 53·9; H, 6·75; N, 18·0, $C_{18}H_{25}N_5Cl_2,H_2O$ requires C, 54·0; H, 6·75; N, 17·5%).

[3] 4-γ-Dibutylaminopropylamino derivative. The base had b. p. 236°/0·06 mm. The *dipicrate* crystallised from β-ethoxyethanol in yellow laminae, m. p. 161—162° (Found: C, 49·3; H, 5·9; N, 17·3. $C_{23}H_{36}N_5Cl,2C_6H_3O_7N_3$ requires C, 48·8; H, 5·3; N, 16·9%).

* All these compounds crystallised in colourless needles, except the last, which formed irregular colourless tables.

TABLE VI.

2-p-Chloroanilino-4-aminoalkylamino-6-methylpyrimidine Salts.

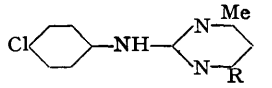
General formula of bases: 

Nature of R.	Formula.	M. p.	Analysis. Found, %. C.	H.	N.	Cl′.	Required, %. C.	H.	N.	Cl′.
$NH{\cdot}[CH_2]_2{\cdot}NMe_2$	$C_{15}H_{26}N_5Cl,2HCl,2H_2O$ [1]	213—215°	43·8	6·0	16·7	16·8	43·4	6·3	16·9	17·2
$NH{\cdot}[CH_2]_2{\cdot}N<[CH_2]_3>CH_2$	$C_{17}H_{22}N_5Cl,2HCl$	280—282	49·7	5·9	17·0	17·4	50·4	5·9	17·3	17·6
$NH{\cdot}[CH_2]_2{\cdot}N<[CH_2]_4>CH_2$	$C_{18}H_{24}N_5Cl,2HCl,H_2O$	290—292	49·5	6·3	16·2	16·1	49·5	5·5	16·0	16·25
$NH{\cdot}[CH_2]_3{\cdot}N<[CH_2]_4>CH_2$	$C_{19}H_{26}N_5Cl,2HCl,2H_2O$	289—292	48·9	7·0	15·2	15·4	48·7	6·8	14·9	15·2
$NH{\cdot}CHMe{\cdot}CH_2{\cdot}N<[CH_2]_4>CH_2$	$C_{19}H_{26}N_5Cl,2HCl,H_2O$	254—256	50·1	6·8	15·2	16·2	50·6	6·7	15·5	16·4
$NH{\cdot}[CH_2]_3{\cdot}NBu_2$ [2]	$C_{22}H_{34}N_5Cl,2HCl,2H_2O$	Indefinite	52·1	7·9	13·7	13·8	51·5	7·8	13·7	13·9
$NH{\cdot}[CH_2]_3{\cdot}NHBu^{\alpha}$	$C_{18}H_{26}N_5Cl,2HCl,H_2O$ [2]	232—235	48·8	7·0	16·4	17·0	49·3	6·8	16·0	16·2
$NH{\cdot}[CH_2]_3{\cdot}O{\cdot}[CH_2]_2{\cdot}NEt_2$	$C_{20}H_{30}ON_5Cl,2HCl,H_2O$ [2]	192—193	49·6	6·9	14·8	15·3	49·7	7·05	14·5	14·7
$NH{\cdot}[CH_2]_3{\cdot}NMe{\cdot}[CH_2]_2{\cdot}NEt_2$	$C_{21}H_{32}N_5Cl,3HCl,2H_2O$	234—236 (dec.)	45·8	6·7	15·8	20·4	45·8	7·8	15·3	19·4
$NMe{\cdot}[CH_2]_2{\cdot}NEt_2$	$C_{18}H_{26}N_5Cl,2HCl$	257—258 (dec.)	50·7	6·5	16·0	17·2	51·4	6·7	16·7	16·9
$N(CH_2{\cdot}CH_2{\cdot}NEt_2)_2$	$C_{23}H_{37}N_5Cl,3HI,H_2O$	241—243 (dec.)	33·4	5·0	10·3	46·1 (I′)	33·1	5·0	10·1	46·0 (I′)
$NH{\cdot}CH(CH_2{\cdot}NEt_2)_2$	$C_{22}H_{35}N_5Cl,3HI,H_2O$	240—241 (dec.)	31·7	5·4	10·2	46·9 (I′)	32·2	4·8	10·2	47·0 (I′)
$NH{\cdot}[CH_2]_3{\cdot}NMePr^{\beta}$	$C_{18}H_{26}N_5Cl,2HCl,2H_2O$	251—252	47·5	6·4	15·35	15·7	47·3	7·0	15·35	15·6

[1] Colourless rods. [2] Colourless prisms. All others, colourless needles.

TABLE VII.

Picrates of 2-p-*Chloroanilino*-4-*aminoalkylamino*-6-*methylpyrimidines.*

General formula of bases: 

Nature of R.	Formula.	Description.	M. p.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
NH·$[CH_2]_2$·NMe_2	$C_{15}H_{29}N_5Cl,2C_6H_3O_7N_3$	Thick yellow prisms [1]	197—199°	42·7	3·6	20·0	42·4	3·4	20·2
NH·$[CH_2]_2$·N<$[CH_2]_2$>CH_2	$C_{17}H_{27}N_5Cl,2C_6H_3O_7N_3$	Yellow microcrystals [1]	189—192	44·3	3·6	19·5	44·1	3·6	19·5
NH·$[CH_2]_2$·N<$[CH_2]_4$>CH_2	$C_{18}H_{29}N_5Cl,2C_6H_3O_7N_3$	Yellow laminæ	230—231	45·3	3·7	18·6	44·8	3·7	19·2
NH·$[CH_2]_3$·N<$[CH_2]_4$>CH_2	$C_{19}H_{29}N_5Cl,2C_6H_3O_7N_3$	Yellow needles	215—216	45·6	4·2	18·5	45·5	3·9	18·8
NH·CHMe·CH_2·N<$[CH_2]_4$>CH_2	$C_{19}H_{29}N_5Cl,2C_6H_3O_7N_3$	Yellow plates	222—223	45·8	3·9	18·3	45·5	3·9	18·8
NH·$[CH_2]_3$·NBu_2^n	$C_{22}H_{35}N_5Cl,2C_6H_3O_7N_3$	Yellow tables [1]	147—149	46·5	4·7	17·4	47·4	4·6	17·9
NH·$[CH_2]_3$·$NHBu^n$	$C_{18}H_{29}N_5Cl,2C_6H_3O_7N_3$	Yellow laminæ [1]	182—183	44·7	4·0	18·8	44·7	4·0	19·1
NH·$[CH_2]_3$·O·$[CH_2]_2$·NEt_2	$C_{29}H_{39}ON_5Cl,2C_6H_3O_7N_3$	Yellow prisms [1]	142—144	44·9	4·2	17·9	45·2	4·2	18·1
NH·$[CH_2]_3$·NMe·$[CH_2]_2$·NEt_2	$C_{21}H_{39}N_6Cl,3C_6H_3O_7N_3$	Yellow microcrystals [1]	206—208	42·6	3·8	19·1	42·9	3·85	19·3
NMe·$[CH_2]_2$·NEt_2	$C_{18}H_{26}N_5Cl,2C_6H_3O_7N_3$	Yellow prisms	204—206	43·9	4·0	18·8	44·7	4·0	19·1
N(CH_2·CH_2·NEt_2)$_2$	$C_{29}H_{37}N_6Cl,3C_6H_3O_7N_3$	Yellow plates	192—194	44·5	4·4	18·6	44·0	4·1	18·8
NH·CH(CH_2·NEt_2)$_2$	$C_{22}H_{35}N_6Cl,3C_6H_3O_7N_3$	Yellow plates	181—183	43·7	4·6	18·2	43·4	4·0	19·0
NH·$[CH_2]_3$·$NMePr^\beta$	$C_{18}H_{26}N_5Cl,2C_6H_3O_7N_3$	Yellow prisms	217—219	44·8	4·0	18·5	44·7	4·0	19·1

[1] From β-ethoxyethanol-alcohol. All others from β-ethoxyethanol.

2-p-*Chloroanilino*-4-p-*β-diethylaminoethoxyphenylamino*-6-*methylpyrimidine* (I; R = Cl, R′ = C_6H_4·O·$[CH_2]_2$·NEt_2).—4-Chloro-2-*p*-chloroanilino-6-methylpyrimidine (8·45 g.) and *β-p*-aminophenoxyethyldiethylamine (8·75 g.) were heated together at 125—135° with stirring for 8 hours. The resulting melt was dissolved in hot dilute hydrochloric acid and the solution rendered alkaline with sodium hydroxide without previous cooling. The product separated as an oil which soon solidified. It was collected, dissolved in 5% acetic acid, and the solution filtered from a little insoluble matter and made alkaline with sodium hydroxide. The liberated base was extracted with chloroform, and the extract dried over potassium carbonate and evaporated. Crystallisation of the residue from alcohol gave 2-p-*chloroanilino*-4-(p-*β-diethylaminoethoxyphenylamino*)-6-*methylpyrimidine* as colourless thick prisms, m. p. 150—152° (Found: C, 65·4; H, 6·7; N, 16·0. $C_{23}H_{28}ON_5Cl$ requires C, 64·9; H, 6·6; N, 16·45%).

2-p-*Chloroanilino*-4-p-*dimethylaminophenylamino*-6-*methylpyrimidine* (I; R = Cl, R′ = C_6H_4·NMe_2).—A mixture of 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine (12·7 g) and *p*-aminodimethylaniline (8·5 g.) was heated at 120—130° for 6 hours. The cooled melt was ground and dissolved in dilute hydrochloric acid, and the solution made alkaline with sodium hydroxide. The precipitated product was filtered off, washed with water, and crystallised from alcohol to yield colourless flat needles, m. p. 171° (Found: C, 65·1; H, 5·9; N, 19·8. $C_{19}H_{20}N_5Cl$ requires C, 64·5; H, 5·7; N, 19·8%).

2-p-*Chloroanilino*-4-*β-aminoethylamino*-6-*methylpyrimidine* (I; R = Cl, R′ = $[CH_2]_2$·NH_2).—4-Chloro-2-*p*-chloroanilino-6-methylpyrimidine (12·7 g.) and ethylenediamine (28 g. of 67%) were heated together on the steam-bath for 3 hours. Dilute hydrochloric acid was then added and the heating continued until no oil remained. Addition of sodium hydroxide to the resulting suspension precipitated the base as an oil which rapidly crystallised. It was filtered off, dried, and crystallised from ethyl acetate to yield colourless needles, m. p. 134—135° (Found: C, 56·0; H, 5·8; Cl, 12·5. $C_{13}H_{16}N_5Cl$ requires C, 56·2; H, 5·8; Cl, 12·8%).

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