74. *Synthetic Antimalarials. Part VII. 2-Arylamino-4-dialkylaminoalkylamino-pyrimidines. Variation of Substituents in the 5- and the 6-Position.*

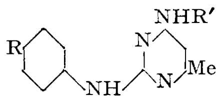
By F. H. S. Curd, (Miss) D. N. Richardson, and F. L. Rose.

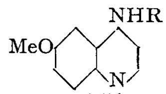
The studies of 2-arylamino-4-aminoalkylamino-6-methylpyrimidines as antimalarials (Curd and Rose, this vol., p. 343; Curd, Davis, and Rose, *ibid.*, p. 351) have been extended to compounds having (*a*) no substituent in the 6-position, (*b*) a 6-phenyl group, and (*c*) various substituents in the 5-position (with and without a 6-methyl group).

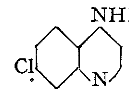
The formal similarity of compounds of type (I) to riboflavin (see previous papers) has been further explored and an attempt has been made to increase their activity by the synthesis of structures capable not only of riboflavin antagonism but also possibly of interference with nucleoside synthesis on the basis of the hypothesis (Part III, Hull, Lovell, Openshaw, Payman, and Todd, this vol., p. 357) that pyrimidine derivatives bearing a substituent in position 5 and an aminoalkylamino group in position 4 might be capable of functioning in this way.

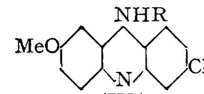
In our initial study of 2-arylamino-4-dialkylaminoalkylamino-6-methylpyrimidines (I; R = Cl, OMe, R′ = NH·alkylene·N(alkyl)$_2$) as antimalarials (Part I, this vol., p. 343) and the later more detailed examination of the effect of different substituents in the arylamino group and of variations in the dialkylaminoalkylamino residue (Part II, this vol., p. 351; Part V, *ibid.*, p. 366) the 6-methyl group was invariably present. The original reason for this was that such compounds were more accessible than those unsubstituted in the 6-position, and not because the 6-methyl group was thought to have any chemotherapeutic significance.

It has been suggested (Part V, *loc. cit.*) that quinoline derivatives of types (II and III; R = dialkylamino-alkyl) may, because of their relationship to mepacrine (IV; R = $CHMe\cdot[CH_2]_3\cdot NEt_2$), act in a similar manner to this drug and therefore to the compounds of type (I), by interference with a riboflavin-containing enzyme important for the survival of the malaria parasite. The introduction of a methyl group into the 2-position of compounds of type (II) appears to have a dystherapeutic effect (Magidson and Rubtsov, *J. Gen. Chem. Russ.*, 1937, **7**, 1896; Krichevski *et al.*, *J. Microbiol. Epidemiol. and Immunobiol. U.S.S.R.*, 1935, **14**, 642). According to D.R.P. 683,692 the same is true of compounds of type (III), and by analogy it seemed possible that removal

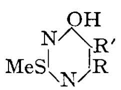

(I.)

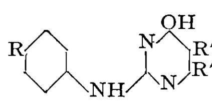

(II.)

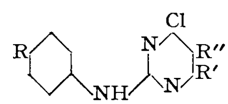

(III.)

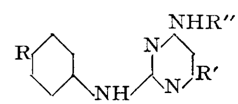

(IV.)

of the 6-methyl group in type (I) might lead to increased antimalarial activity. In order to investigate this point we prepared 2-p-*chloroanilino*-4-β-*diethylaminoethylaminopyrimidine* (VIII; R = Cl, R′ = H, R″ = $[CH_2]_2\cdot NEt_2$) and the corresponding *diethylaminopropylamino* derivative (VIII; R = Cl, R′ = H, R″ = $[CH_2]_3\cdot NEt_2$) by condensing *p*-chloroaniline with 4-hydroxy-2-methylthiopyrimidine (V; R = R′ = H) (Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 478) to give 2-p-*chloroanilino*-4-*hydroxypyrimidine* (VI; R = Cl, R′ = R″ = H) followed by conversion, with phosphoryl chloride, into the *chloropyrimidine* (VII; R = Cl, R′ = R″ = H) and condensation of this with β-diethylaminoethylamine and γ-diethylaminopropylamine respectively. The antimalarial activity of these compounds was much lower than that of the corresponding 6-methyl derivatives. Similar low antimalarial activity was found with 2-p-*toluidino*-4-β-*diethylaminoethyl-aminopyrimidine* (VIII; R = Me, R′ = H, R″ = $[CH_2]_2\cdot NEt_2$).


(V.)

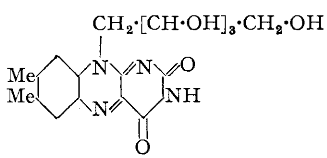

(VI.)

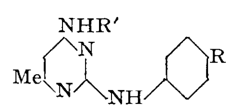

(VII.)


(VIII.)

The importance of the 6-methyl group in (I; R = Cl, R′ = dialkylaminoalkyl) having been demonstrated we were led to examine the effect of replacing the 6-methyl group by a variety of other groups. This will be dealt with more fully in a later communication, but we record here the synthesis of 2-p-*chloroanilino*-4-β-*diethylaminoethylamino*-6-*phenylpyrimidine* (VIII; R = Cl, R′ = Ph, R″ = $[CH_2]_2\cdot NEt_2$) from 4-hydroxy-2-methylthio-6-phenylpyrimidine (V; R = Ph, R′ = H) *via* (VI; R = Cl, R′ = Ph, R″ = H) and the *chloro-pyrimidine* (VII; R = Cl, R′ = Ph, R″ = H). The product was practically devoid of antimalarial activity.

Previously, in considering the formal resemblance of compounds of type (I) to riboflavin (IX), it has been supposed that the pyrimidine ring of (I) corresponds to the same ring of the vitamin, but it seemed possible that the observed antagonism between (I; R = Cl, R′ = $[CH_2]_2\cdot NEt_2$) and (IX) (Madinaveitia, *Biochem. J.*, in the press) might be accounted for by a correspondence of the pyrimidine ring of the former to the benzene ring of riboflavin thus correlating the 6-methyl group of (I) to the 6-methyl group of the vitamin. This is illustrated in (Ia).

(IX.)



(Ia.)

On this basis the introduction of an additional methyl group into the 5-position of the pyrimidine ring of (I) to correspond to the 7-methyl group of riboflavin appeared to be of interest, but there were other reasons for a detailed study of the effect of introducing additional substituents into this position in (I).

An investigation of alkylpyrimidines carrying aminoalkylamino groups uncomplicated by anilino groups, carried out at Manchester University under Professor Todd and reported in Part III (this vol., p. 357), led to the discovery that 2-amino-4-aminoalkylamino-6-methylpyrimidines of type (X), corresponding to the anilino derivatives of type (I), were without antimalarial activity at tolerated doses, but that the introduction of alkyl substituents into the 5-position of the pyrimidine ring to give (XI; R = dialkylaminoalkyl, R′ = alkyl) restored activity.

This dissimilarity between compounds of type (X) and type (I) and the fact that no antagonism could be demonstrated between (XI; R = $CHMe\cdot[CH_2]_3\cdot NEt_2$, R′ = Me) and riboflavin using *Lactobacillus casei* suggested a mode of action for compounds of type (XI) different from that which is responsible for the activity of compounds of type (I), and the speculative hypothesis was advanced that compounds of the former type might be capable of interference with either the synthesis or the function of purine nucleosides, particularly those, such as adenosine, which are widely occurring coenzyme constituents.

If this hypothesis is correct then it seemed possible that the introduction of a substituent into the 5-position of the pyrimidine ring of compounds of type (I) might cause a potentiation of activity. Such compounds

TABLE I.

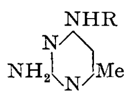
Antimalarial Activities.

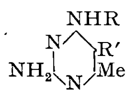
The antimalarial activities were estimated using chicks infected with *P. gallinaceum.* For the significance of the symbols used to express activity reference should be made to Part I.

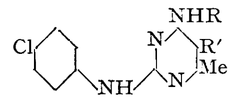
Ref. No.	Substance.	Dose, mg./kg.	Activity.
3780	2-*p*-Chloroanilino-4-γ-diethylaminopropylaminopyrimidine	160	+
		80	−
3839	2-*p*-Chloroanilino-4-β-diethylaminoethylaminopyrimidine	160	+ to ++
		80	−
3834	2-*p*-Toluidino-4-β-diethylaminoethylaminopyrimidine	120	±
		80	±
4145	2-*p*-Chloroanilino-4-β-diethylaminoethylamino-6-phenylpyrimidine	160	±
		80	−
3687	2-*p*-Chloroanilino-4-γ-diethylaminopropylamino-5 : 6-dimethylpyrimidine	160	++
		80	++
		40	+ to ++
3903	2-*p*-Chloroanilino-4-β-diethylaminoethylamino-5 : 6-dimethylpyrimidine	40	+
		20	±
4410	2-*p*-Chloroanilino-4-γ-dimethylaminopropylamino-5 : 6-dimethylpyrimidine	40	++
		20	+
4065	2-*p*-Chloroanilino-4-β-diethylaminoethylamino-6-methyl-5-ethylpyrimidine	120	+ to ++
		80	+
		40	±
4119	2-*p*-Chloroanilino-4-β-dimethylaminoethylamino-6-methyl-5-ethylpyrimidine	80	+
		40	−
4120	2-*p*-Chloroanilino-4-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine	80	+
		40	−
4118	2-*p*-Chloroanilino-4-γ-dimethylaminopropylamino-6-methyl-5-ethyl-pyrimidine	80	++
		40	+
4396	2-*p*-Chloroanilino-4-δ-diethylamino-α-methylbutylamino-6-methyl-5-ethyl-pyrimidine	160	+
		120	−
		80	−
4209	2-*p*-Chloroanilino-4-β-diethylaminoethylamino-5-benzyl-6-methyl-pyrimidine	160	+ to ++
		40	+
4231	2-*p*-Chloroanilino-4-γ-diethylaminopropylamino-5-benzyl-6-methyl-pyrimidine	160	+ to ++
		80	−
4288	2-*p*-Chloroanilino-4-γ-dimethylaminopropylamino-5-benzyl-6-methyl-pyrimidine	160	+
		80	±
4253	2-*p*-Chloroanilino-4-δ-diethylamino-α-methylbutylamino-5-benzyl-6-methyl-pyrimidine	160	−
		80	−
3563	5-Bromo-2-*p*-chloroanilino-4-γ-diethylaminopropylamino-6-methyl-pyrimidine	400	+
		80	−
4343	2-*p*-Chloroanilino-4-β-diethylaminoethylamino-5 : 6-*cyclo*hexenopyrimidine	200	++
		120	+
		80	+
		40	−
4356	2-*p*-Chloroanilino-4-γ-diethylaminopropylamino-5 : 6-*cyclo*hexeno-pyrimidine	80	+ to ++
		40	+
4355	2-*p*-Chloroanilino-4-γ-dimethylaminopropylamino-5 : 6-*cyclo*hexeno-pyrimidine	80	++
		40	++
		20	+ to ++
		10	+
4557	2-*p*-Chloroanilino-4-γ-dimethylaminopropylamino-5 : 6-*cyclo*penteno-pyrimidine	80	+ to ++
		40	−
3815	2-*p*-Chloroanilino-4-β-diethylaminoethylamino-5-methylpyrimidine	80	−
		40	−
4146	2-*p*-Chloroanilino-4-β-diethylaminoethylamino-5-phenylpyrimidine	160	±
		80	−
4208	2-*p*-Chloroanilino-4-γ-diethylaminopropylamino-5-phenylpyrimidine	80	−
		40	−
4064	2-*p*-Anisidino-4-β-diethylaminoethylamino-5-phenylpyrimidine	160	−
		80	−
4260	2-*p*-Chloroanilino-4-β-diethylaminoethylamino-5-phenoxypyrimidine	160	±
		80	−
		40	−
2666	2-*p*-Chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine	80	++
		40	+
3711	2-*p*-Chloroanilino-4-γ-dimethylaminopropylamino-6-methylpyrimidine	40	++
		20	+

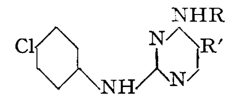
should still retain the property of acting as riboflavin antagonists and if they were capable also of purine nucleoside antagonism they might be expected to possess a greater activity against an enzyme system of which riboflavin-adenosine-dinucleotide is a constituent than a compound capable only of interference with either the riboflavin or the adenosine portion. It also appeared possible that a compound of type (XII) might have a wider range of antagonistic activity and be capable of interference not only with riboflavin-containing enzymes but also with other enzyme systems having a purine nucleoside as a coenzyme constituent.

A series of compounds of type (XII) has therefore been prepared, and the following have been introduced as substituents into the 5-position: methyl, ethyl, benzyl, bromine. Disubstitution in the 5- and the 6-position has also taken the form of an additional 5- or 6-membered *cyclo*penteno- or *cyclo*hexeno-ring. In nearly every case more than one dialkylaminoalkyl group has been tried. The compounds prepared are listed in Table I, which gives an indication of the antimalarial activities. For comparison the activities of two compounds of type (I) are included. Full biological details will be published and discussed in detail elsewhere, but no compound of type (XII) has shown a significantly greater activity than the corresponding compound of type (I) without the 5-substituent.


(X.)


(XI.)


(XII.)


(XIII.)

It then occurred to us that an investigation of compounds of type (XIII; R′ = alkyl) might give some information on the mode of action of type (XII). It has been mentioned above that compounds of type (VIII; R′ = H) are much less active than those of type (VIII; R′ = Me). If then the introduction of a substituent into position 5 of (VIII; R = H) to give (XIII) conferred on these compounds the power to act in the same manner as those of type (XI) it might be anticipated that in type (XIII; R′ = alkyl) the activity might be largely restored as compared with (VIII; R = H). 2-p-*Chloroanilino*-4-β-*diethylaminoethylamino*-5-*methylpyrimidine* (XIII; R = $[CH_2]_2$·NEt_2, R′ = Me) was therefore prepared but had no activity. Low activity was also characteristic of several other compounds of this type, but with different substituents in the 5-position, which were prepared: 2-p-*chloroanilino*-4-β-*diethylaminoethylamino*-5-*phenylpyrimidine* (XIII; R = $[CH_2]_2$·NEt_2, R′ = Ph), the corresponding p-*anisidino*-derivative, 2-p-*chloroanilino*-4-γ-*diethylaminopropylamino*-5-*phenylpyrimidine* (XIII; R = $[CH_2]_3$·NEt_2, R′ = Ph), and 2-p-*chloroanilino*-4-β-*diethylaminoethylamino*-5-*phenoxypyrimidine* (XIII; R = $[CH_2]_2$·NEt_2, R′ = OPh).

Compounds of types (XII) and (XIII) were made by the now well established method from a 4-hydroxy-2-alkylthiopyrimidine (V) appropriately substituted in the 5- and 6-positions through the intermediate stages (VI) and (VII). The majority of the 4-hydroxy-2-alkylthiopyrimidines of type (V) used were known compounds but a few are described now for the first time. 5-*Bromo*-4-*hydroxy*-2-*methylthio*-6-*methylpyrimidine* was prepared by bromination of 4-hydroxy-2-methylthio-6-methylpyrimidine in acetic acid. 4-*Hydroxy*-2-*methylthio*-5 : 6-cyclo*pentenopyrimidine* and 4-*hydroxy*-2-*methylthio*-5 : 6-cyclo*hexenopyrimidine* were prepared by condensation of ethyl *cyclo*pentanone-2-carboxylate and ethyl *cyclo*hexanone-2-carboxylate respectively with *S*-methyl*iso*thiourea in an aqueous medium. The yields were low owing to side reactions the products of which were not investigated, but in the latter case the yield was considerably improved by condensing the ethyl *cyclo*hexanone-2-carboxylate with thiourea and methylating the resulting 4-*hydroxy*-2-*thiol* 5 : 6-cyclo*hexenopyrimidine* with methyl sulphate and alkali.

Experimental.

2-p-*Chloroanilino*-4-*hydroxypyrimidine* (VI; R = Cl, R′ = R″ = H).—4-Hydroxy-2-methylthiopyrimidine (Wheeler and Merriam, *loc. cit.*) (18 g.), *p*-chloroaniline (32 g.), and β-ethoxyethanol (50 c.c.) were refluxed with stirring for 26 hours. The solid material which separated was filtered off after cooling, washed with hot alcohol (100 c.c.), and dried (yield, 21·5 g.). Crystallisation from acetic acid gave 2-p-*chloroanilino*-4-*hydroxypyrimidine* as thin colourless prisms, m. p. 242—244° (Found: N, 19·0. $C_{10}H_8ON_3Cl$ requires N, 19·0%).

4-*Chloro*-2-p-*chloroanilinopyrimidine* (VII; R = Cl, R′ = R″ = H).—2-*p*-Chloroanilino-4-hydroxypyrimidine (21·5 g.) and phosphoryl chloride (55 c.c.) were refluxed for 15 minutes. The excess of phosphoryl chloride was removed under reduced pressure and the solid residue added to ice. The resulting suspension was made alkaline with ammonia and, after stirring for 1 hour, the crude *product* was collected and washed with water. It crystallised from alcohol in clusters of colourless prisms, m. p. 124° (yield, 16·0 g.) (Found: C, 50·2; H, 2·6; N, 17·0; Cl, 29·4. $C_{10}H_7N_3Cl_2$ requires C, 50·0; H, 2·9; N, 17·5; Cl, 29·6%).

2-p-*Chloroanilino*-4-*hydroxy*-6-*phenylpyrimidine* (VI; R = Cl, R′ = Ph, R″ = H).—4-Hydroxy-2-methylthio-6-phenylpyrimidine (Wheeler and Merriam, *loc. cit.*) (8·2 g.) and *p*-chloroaniline (12 g.) were stirred and heated at 130—140° for 6 hours. The cooled melt was ground and then refluxed with alcohol (75 c.c.) for 1½ hours. The *product* was filtered off, washed with alcohol, and dried (yield, 9·7 g.). It crystallised from β-ethoxyethanol as colourless needles, m. p. 312—313° (Found: C, 64·1; H, 4·0; N, 14·0. $C_{16}H_{12}ON_3Cl$ requires C, 64·5; H, 4·0; N, 14·1%).

4-*Chloro*-2-p-*chloroanilino*-6-*phenylpyrimidine* (VII; R = Cl, R′ = Ph, R″ = H).—The above hydroxy compound (9·3 g.) and phosphoryl chloride (30 c.c.) were refluxed for 1½ hours. After removing the excess of phosphoryl chloride under reduced pressure the residue was added to crushed ice and made alkaline with ammonia. After standing for 1 hour the crude product was filtered off, washed with water, and crystallised from alcohol, giving 4-*chloro*-2-p-*chloroanilino*-6-*phenylpyrimidine* as colourless prisms, m. p. 166—168° (yield, 6·1 g.) (Found: N, 13·5; Cl, 22·3. $C_{16}H_{11}N_3Cl_2$ requires N, 13·3; Cl, 22·5%).

2-p-*Chloroanilino*-4-*hydroxy*-5 : 6-*dimethylpyrimidine* (VI; R = Cl, R′ = R″ = Me).—4-Hydroxy-2-ethylthio-5 : 6-dimethylpyrimidine (Wheeler and Merriam, *loc. cit.*) (15 g.) and *p*-chloroaniline (26 g.) were heated at 130—140° for 9 hours with stirring. The cooled and ground reaction mixture was refluxed with alcohol (150 c.c.) for 1 hour and filtered, and the undissolved residue washed with alcohol and dried (yield, 20·85 g.). When purified by crystallisation from aqueous acetic acid the *compound* had m. p. 270—272° (Found: C, 57·8; H, 5·2; N, 16·5. $C_{12}H_{12}ON_3Cl$ requires C, 57·7; H, 4·8; N, 16·9%).

4-*Chloro*-2-p-*chloroanilino*-5 : 6-*dimethylpyrimidine* (VII; R = Cl, R′ = R″ = Me).—2-*p*-Chloroanilino-4-hydroxy-5 : 6-dimethylpyrimidine (20 g.) and phosphoryl chloride (60 c.c.) were refluxed for 1½ hours and the reaction mixture worked up as in the case of previous chloropyrimidines. Purified by crystallisation from alcohol the *product* formed colourless prisms, m. p. 161—162° (yield, 11·4 g.) (Found : C, 53·2; H, 4·1; N, 15·5. $C_{12}H_{11}N_3Cl_2$ requires C, 53·7; H, 4·1; N, 15·7%).

2-p-*Chloroanilino*-4-*hydroxy*-6-*methyl*-5-*ethylpyrimidine* (VI; R = Cl, R′ = Me, R″ = Et).—Prepared from 4-hydroxy-2-methylthio-6-methyl-5-ethylpyrimidine (*idem, ibid.*) (18·4 g.) and *p*-chloroaniline (32 g.) exactly as described above for the corresponding 5-methyl compound, the *compound* formed clusters of colourless needles from β-ethoxyethanol, m. p. 246—247° (Found : C, 59·1; H, 5·3; N, 15·9. $C_{13}H_{14}ON_3Cl$ requires C, 59·2; H, 5·3; N, 15·9%) (yield, 24·95 g.).

4-*Chloro*-2-p-*chloroanilino*-6-*methyl*-5-*ethylpyrimidine* (VII; R = Cl, R′ = Me, R″ = Et).—2-*p*-Chloroanilino-4-hydroxy-6-methyl-5-ethylpyrimidine (13·05 g.) and phosphoryl chloride (40 c.c.) were refluxed for 1¼ hours and the reaction mixture worked up in the usual way. The *chloropyrimidine* crystallised from alcohol as stout colourless needles, m. p. 128—130° (yield, 11·4 g.) (Found : N, 14·9; Cl, 25·3. $C_{13}H_{13}N_3Cl_2$ requires N, 14·9; Cl, 25·2%).

2-p-*Chloroanilino*-4-*hydroxy*-5-*benzyl*-6-*methylpyrimidine* (VI; R = Cl, R′ = Me, R″ = CH_2Ph).—4-Hydroxy-2-ethylthio-5-benzyl-6-methylpyrimidine (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 101) (13·08 g.) and *p*-chloroaniline (17·5 g.) heated at 130—140° for 6 hours and worked up as described above for this type of compound gave the *hydroxypyrimidine* (yield, 15·55 g.) which crystallised from β-ethoxyethanol as colourless needles, m. p. 258—260° (Found : C, 65·8; H, 4·9; N, 12·9. $C_{18}H_{16}ON_3Cl$ requires C, 66·4; H, 4·9; N, 12·9%).

4-*Chloro*-2-p-*chloroanilino*-5-*benzyl*-6-*methylpyrimidine* (VII; R = Cl, R′ = Me, R″ = CH_2Ph), prepared from the above hydroxy compound (29·55 g.) and phosphoryl chloride (90 c.c.), crystallised from alcohol as colourless tables, m. p. 124—125° (yield, 25·5 g.) (Found : N, 12·3; Cl, 20·5. $C_{18}H_{15}N_3Cl_2$ requires N, 12·2; Cl 20·6%).

5-*Bromo*-4-*hydroxy*-2-*methylthio*-6-*methylpyrimidine* (V; R = Me, R′ = Br).—4-Hydroxy-2-methylthio-6-methylpyrimidine (45 g.) was dissolved in acetic acid (1,500 c.c.) and bromine (54 g.) added gradually with stirring at room temperature. The precipitate was collected and washed with water. It was then stirred with dilute ammonia, filtered off, and purified by crystallisation from β-ethoxyethanol from which the *compound* separated as colourless thick prisms, m. p. 254—256° (decomp.) (yield, 41 g.) (Found : N, 11·8; Br, 34·5. $C_6H_7ON_2BrS$ requires N, 11·9; Br, 34·0%).

5-*Bromo*-2-p-*chloroanilino*-4-*hydroxy*-6-*methylpyrimidine* (VI; R = Cl; R′ = Me; R″ = Br).—5-Bromo-4-hydroxy-2-methylthio-6-methylpyrimidine (11·75 g.), *p*-chloroaniline (12·75 g.), and β-ethoxyethanol (25 c.c.) were stirred and heated at 120—130° for 26 hours. The *product* was filtered off, washed well with alcohol, and dried (yield, 11·75 g.). It crystallised from dimethylformamide–water in colourless blunt-ended needles, m. p. 267—269° (decomp.) (Found : C, 42·5; H, 3·2; N, 13·6. $C_{11}H_9ON_3ClBr$ requires C, 42·0; H, 2·9; N, 13·4%).

4-*Chloro*-5-*bromo*-2-p-*chloroanilino*-6-*methylpyrimidine* (VII; R = Cl, R′ = Me, R″ = Br).—The above hydroxypyrimidine (20 g.) and phosphoryl chloride (45 c.c.) were refluxed for 3 hours. Excess of phosphoryl chloride was then removed under reduced pressure and the residue added to ice with stirring. After making alkaline with ammonia, the chloro compound was extracted with ether, and the extract dried and evaporated. Crystallisation of the residue from alcohol gave the *chloropyrimidine* as practically colourless prisms, m. p. 176—178° (Found : N, 12·5; 1 mg. = 1·376 mg. Ag halides. $C_{11}H_8N_3Cl_2Br$ requires N, 12·6%; 1 mg. = 1·426 mg. Ag halides).

4-*Hydroxy*-2-*methylthio*-5 : 6-cyclo*hexenopyrimidine*.—(a) Ethyl *cyclo*hexanone-2-carboxylate (29 g.) was added to a solution of *S*-methyl*iso*thiourea sulphate (24 g.) in water (150 c.c.) containing potassium hydroxide (12 g.). The ester dissolved immediately and a solid was precipitated. After standing overnight this was filtered off and washed with water. It was then dissolved in sodium hydroxide solution, and the solution treated with charcoal, filtered, and acidified with acetic acid. The dried precipitate was crystallised first from β-ethoxyethanol and then from alcohol, giving 4-*hydroxy*-2-*methylthio*-5 : 6-cyclo*hexenopyrimidine* as colourless needles, m. p. 220—222° (yield, 4·7 g.) (Found : C, 55·3; H, 5·8; N, 14·0. $C_9H_{12}ON_2S$ requires C, 55·1; H, 6·1; N, 14·3%).

(b) Thiourea (16 g.) and ethyl *cyclo*hexanone-2-carboxylate (34 g.) were added to a solution of sodium (12 g.) in methanol (300 c.c.) and refluxed for 5½ hours. The mixture was then evaporated to dryness under reduced pressure, and the residue dissolved in water, treated with decolourising charcoal, and filtered. The filtrate was acidified with acetic acid and the precipitated product collected, washed with water, and dried. Crystallisation from β-ethoxyethanol gave 4-*hydroxy*-2-*thiol*-5 : 6-cyclo*hexenopyrimidine* as colourless flat prisms, m. p. 314—320° (decomp.) (yield, 20·8 g.) (Found : C, 52·8; H, 5·2; N, 15·4. $C_8H_{10}ON_2S$ requires C, 52·75; H, 5·5; N, 15·4%).

4-Hydroxy-2-thiol-5 : 6-*cyclo*hexenopyrimidine (18·2 g.) was dissolved in 10% potassium hydroxide solution (50 c.c.) and methyl sulphate (15 g.) added to the solution in small portions, with shaking. The precipitate was filtered off, washed with water, and dried. Crystallisation from alcohol gave 4-hydroxy-2-methylthio-5 : 6-*cyclo*hexenopyrimidine, m. p. 220—222° undepressed in admixture with material made by method (a) (yield, 11·15 g.).

2-p-*Chloroanilino*-4-*hydroxy*-5 : 6-cyclo*hexenopyrimidine*.—4-Hydroxy-2-methylthio-5 : 6-*cyclo*hexenopyrimidine (14·8 g.) and *p*-chloroaniline (24 g.) were heated at 130—140° for 6 hours with stirring in the initial stages. Methylthiol was evolved and a homogeneous melt formed which gradually solidified. After cooling this was ground and refluxed with alcohol (200 c.c.) for 1½ hours. The mixture was then cooled, filtered, and the residue washed with alcohol and dried (yield, 19·4 g.). The *compound* separated from β-ethoxyethanol as clusters of colourless prisms, m. p. 284—287° with previous darkening (Found : C, 60·6; H, 5·0; N, 15·1. $C_{14}H_{14}ON_3Cl$ requires C, 61·0; H, 5·1; N, 15·2%).

4-*Chloro*-2-p-*chloroanilino*-5 : 6-cyclo*hexenopyrimidine*.—The above hydroxy compound (18·4 g.) and phosphoryl chloride (56 c.c.) were refluxed for 1½ hours and the reaction mixture worked up as in the case of previous chloropyrimidines. The *product* separated from alcohol as colourless plates, m. p. 137—138° (yield, 13·84 g.) (Found : N, 14·5; Cl, 24·1. $C_{14}H_{13}N_3Cl_2$ requires N, 14·3; Cl, 24·2%).

4-*Hydroxy*-2-*methylthio*-5 : 6-cyclo*pentenopyrimidine*.—*S*-Methyl*iso*thiourea sulphate (33 g.) and ethyl *cyclo*pentanone-2-carboxylate (40 g.) were added to a solution of potassium hydroxide (15 g.) in water (100 c.c.). The ester quickly dissolved and the mixture was left for 2 days. The solid material was then collected and dissolved in sodium hydroxide solution, and the solution treated with charcoal. After filtration the solution was acidified with acetic acid and the precipitate filtered off, washed with water, and dried. Crystallisation from β-ethoxyethanol gave 4-*hydroxy*-2-*methylthio*-5 : 6-cyclo*pentenopyrimidine* (3·5 g.) as colourless prisms, m. p. 270—272° (Found : C, 52·6; H, 5·2; N, 15·3. $C_8H_{10}ON_2S$ requires C, 52·8; H, 5·5; N, 15·4%).

2-p-*Chloroanilino*-4-*hydroxy*-5 : 6-cyclo*pentenopyrimidine*.—4-Hydroxy-2-methylthio-5 : 6-*cyclo*pentenopyrimidine (6 g.) and *p*-chloroaniline (11 g.) were intimately mixed and heated at 130—140° for 24 hours. The product was powdered, boiled with alcohol (100 c.c.) for 3 hours, and filtered. The insoluble material was crystallised from β-ethoxyethanol–water giving the *hydroxypyrimidine* as colourless needles, m. p. 244—246° with previous darkening (yield, 6·35 g.) (Found : C, 60·1; H, 4·7; N, 15·7. $C_{13}H_{12}ON_3Cl$ requires C, 59·7; H, 4·6; N, 16·1%).

4-*Chloro*-2-p-*chloroanilino*-5 : 6-cyclo*pentenopyrimidine*, prepared from the above hydroxy compound (5·8 g.) and phosphoryl chloride (18 c.c.), crystallised from alcohol as colourless laminæ, m. p. 151—152° (yield, 3·95 g.) (Found : N, 14·7; Cl, 25·2. $C_{13}H_{11}N_3Cl_2$ requires N, 15·0; Cl, 25·4%).

2-p-*Chloroanilino*-4-*hydroxy*-5-*methylpyrimidine* (VI; R = Cl, R′ = H, R″ = Me).—4-Hydroxy-2-methylthio-5-

TABLE II.

2-p-*Chloroanilino-4-dialkylaminoalkylaminopyrimidines. Variation of the Substitutents in the 5- and the 6-Position.*

Substituent at— 5.	6.	4.	Derivative.	M. p.	Formula.	Analysis. Found, % C.	H.	N.	Cl′.	Required, % C.	H.	N.	Cl′.
H	H	NH·[CH₂]₂·NEt₂	—	71—72°	$C_{16}H_{23}N_5Cl$	60·0	6·8	22·0	—	60·1	6·9	21·9	—
			Dihydrochloride	237—238	$C_{16}H_{22}N_5Cl,2HCl,1·5H_2O$	45·6	7·4	16·1	17·2	45·8	6·4	16·7	16·9
H	H	NH·[CH₂]₃·NEt₂	—	Oil									
			Dipicrate	218—220	$C_{17}H_{24}N_5Cl,2C_6H_3O_7N_3$	44·1	3·8	18·8	—	44·0	3·8	19·5	—
			Dihydrochloride	208—210	$C_{17}H_{24}N_5Cl,2HCl,2H_2O$	46·1	6·7	15·8	16·7	46·1	6·8	15·8	16·05
H	Ph	NH·[CH₂]₂·NEt₂	—	Oil									
			Dihydrochloride	277—279	$C_{22}H_{26}N_5Cl,2HCl$	56·0	5·6	15·2	15·2	56·3	6·0	14·9	15·15
Me	Me	NH·[CH₂]₂·NEt₂	—	100—102	$C_{18}H_{26}N_5Cl$	62·0	7·6	20·4	—	62·2	7·5	20·1	—
			Dihydrochloride	270—272	$C_{18}H_{26}N_5Cl,2HCl,H_2O$	49·1	6·8	16·0	16·0	49·3	6·8	16·0	16·2
Me	Me	NH·[CH₂]₃·NEt₂	—	104—106	$C_{19}H_{28}N_5Cl$	63·7	8·1	19·3	—	63·1	7·7	19·4	—
			Dihydrochloride	277—279 (decomp.)	$C_{19}H_{28}N_5Cl,2HCl,H_2O$	49·8	7·0	15·1	—	50·4	7·1	15·5	—
Me	Me	NH·[CH₂]₃·NMe₂	—	116—118	$C_{17}H_{24}N_5Cl$	60·9	7·0	20·6	—	61·2	7·2	21·0	—
			Dihydrochloride	238—240	$C_{17}H_{24}N_5Cl,2HCl,H_2O$	47·8	6·4	16·2	16·9	48·1	6·6	16·5	16·7
Et	Me	NH·[CH₂]₂·NEt₂	—	92—94	$C_{19}H_{28}N_5Cl$	63·3	7·7	19·2	—	63·1	7·7	19·4	—
			Dihydrochloride	258—260	$C_{19}H_{28}N_5Cl,2HCl,0·5H_2O$	51·2	6·9	15·8	15·8	51·4	7·0	15·8	16·05
Et	Me	NH·[CH₂]₂·NMe₂	—	115—116	$C_{17}H_{24}N_5Cl$	60·6	7·1	20·4	—	61·2	7·2	21·0	—
			Dihydrochloride	262	$C_{17}H_{24}N_5Cl,2HCl,H_2O$	47·9	6·6	16·6	16·5	48·1	6·6	16·5	16·75
Et	Me	NH·[CH₂]₃·NEt₂	—	108—109	$C_{20}H_{30}N_5Cl$	63·7	7·7	18·3	—	63·9	8·0	18·6	—
			Dihydrochloride	272—274	$C_{20}H_{30}N_5Cl,2HCl,H_2O$	51·3	7·3	15·0	14·7	51·4	7·3	15·0	15·2
Et	Me	NH·[CH₂]₃·NMe₂	—	126—128	$C_{18}H_{26}N_5Cl$	62·6	7·5	19·7	—	62·2	7·5	20·1	—
			Dihydrochloride	244—246	$C_{18}H_{26}N_5Cl,2HCl,1·5H_2O$	48·1	6·7	15·0	16·1	48·3	6·9	15·6	15·9
Et	Me	NH·CHMe·[CH₂]₃·NEt₂	—	Oil									
			Dihydrochloride	231—233	$C_{22}H_{34}N_5Cl,2HCl,1·5H_2O$	52·8	7·7	14·0	14·3	52·4	7·7	13·9	14·1
CH₂·Ph	Me	NH·[CH₂]₂·NEt₂	—	114—115	$C_{24}H_{30}N_5Cl$	67·8	6·9	16·4	—	68·0	7·1	16·5	—
			Dihydrochloride	255—256	$C_{24}H_{30}N_5Cl,2HCl,0·5H_2O$	56·8	6·3	14·0	14·0	57·0	6·5	13·8	14·0
CH₂·Ph	Me	NH·[CH₂]₃·NEt₂	—	104—105	$C_{25}H_{32}N_5Cl$	68·7	7·2	16·6	—	68·6	7·3	16·0	—
			Dihydrochloride	274—276 (decomp.)	$C_{25}H_{32}N_5Cl,2HCl$	58·6	6·5	13·4	13·7	58·8	6·7	13·7	13·9
CH₂·Ph	Me	NH·[CH₂]₃·NMe₂	—	112—114	$C_{23}H_{28}N_5Cl$	67·4	6·7	17·0	—	67·4	6·8	17·1	—
			Dihydrochloride	254—256	$C_{23}H_{28}N_5Cl,2HCl,H_2O$	55·2	5·9	14·1	14·3	55·1	6·4	14·0	14·2
CH₂·Ph	Me	NH·CHMe·[CH₂]₃·NEt₂	—	Oil									
			Dihydrochloride	242—244	$C_{27}H_{38}N_5Cl,2HCl,0·5H_2O$	59·5	6·7	13·2	13·2	59·2	7·1	12·8	13·0
Br	Me	NH·[CH₂]₃·NEt₂	—	94—96	$C_{18}H_{25}N_5ClBr$	50·1	5·9	16·0	—	50·6	5·9	16·4	—
			Dihydrochloride	238—240	$C_{18}H_{25}N_5ClBr,2HCl,0·5H_2O$	42·8	6·0	13·7	13·4	42·5	5·5	13·8	14·0
5 : 6-*cyclo*Hexeno		NH·[CH₂]₂·NEt₂	—	132—134	$C_{20}H_{28}N_5Cl$	64·3	7·0	18·3	—	64·3	7·5	18·7	—
			Dihydrochloride	224—226	$C_{20}H_{28}N_5Cl,2HCl,2H_2O$	49·4	6·8	14·8	14·5	49·7	7·0	14·5	14·7
5 : 6-*cyclo*Hexeno		NH·[CH₂]₃·NEt₂	—	138—140	$C_{21}H_{30}N_5Cl$	65·1	7·7	18·4	—	65·0	7·7	18·1	—
			Dihydrochloride	202—204	$C_{21}H_{30}N_5Cl,2HCl,1·5H_2O$	51·3	6·8	14·7	14·7	51·7	7·2	14·4	14·6
: 6-*cyclo*Hexeno		NH·[CH₂]₃·NMe₂	—	125—127	$C_{19}H_{26}N_5Cl$	63·6	7·1	19·5	—	63·4	7·2	19·5	—
			Dihydrochloride	290 (decomp.)	$C_{19}H_{26}N_5Cl,2HCl$	53·3	6·3	16·1	16·4	52·7	6·5	16·2	16·4
5 : 6-*cyclo*Penteno		NH·[CH₂]₃·NMe₂	—	142—144	$C_{18}H_{24}N_5Cl$	62·8	7·4	20·8	—	62·5	6·9	20·3	—
Me	H	NH·[CH₂]₂·NEt₂	—	106—108	$C_{17}H_{24}N_5Cl$	61·4	7·4	21·0	—	61·2	7·2	21·0	—
			Dihydrochloride	269 (decomp.)	$C_{17}H_{24}N_5Cl,2HCl$	50·0	6·5	17·2	17·0	50·2	6·4	17·2	17·5
Ph	H	NH·[CH₂]₂·NEt₂	—	152—153	$C_{22}H_{26}N_5Cl$	67·1	6·4	17·3	—	66·8	6·6	17·7	—
			Dihydrochloride	264—266	$C_{22}H_{26}N_5Cl,2HCl$	56·6	6·0	14·8	15·2	56·35	6·0	14·9	15·2
Ph	H	NH·[CH₂]₃·NEt₂	—	155—156	$C_{23}H_{28}N_5Cl$	67·0	6·5	16·9	—	67·4	6·8	17·1	—
			Dihydrochloride	264—266	$C_{23}H_{28}N_5Cl,2HCl$	56·7	6·3	14·4	14·8	57·2	6·2	14·5	14·7
OPh	H	NH·[CH₂]₂·NEt₂	—	84—85	$C_{22}H_{26}ON_5Cl$	64·2	6·2	17·0	—	64·2	6·3	17·0	—

methylpyrimidine (Wheeler and Merriam, *loc. cit.*) (20·8 g.) and *p*-chloroaniline (34 g.) were boiled in β-ethoxyethanol (50 c.c.) for 48 hours and the mixture worked up as described above for 2-*p*-chloroanilino-4-hydroxypyrimidine. The *compound* crystallised from acetic acid as colourless thin plates, m. p. 266—267° (yield, 26 g.) (Found: C, 55·6; H, 4·5; N, 17·7. $C_{11}H_{10}ON_3Cl$ requires C, 56·05; H, 4·2; N, 17·8%).

4-*Chloro*-2-p-*chloroanilino*-5-*methylpyrimidine* (VII; R = Cl, R′ = H, R″ = Me), prepared by refluxing 2-*p*-chloroanilino-4-hydroxy-5-methylpyrimidine (21 g.) and phosphoryl chloride (63 c.c.) for ½ hour and working up in the usual way, crystallised from β-ethoxyethanol as colourless prisms, m. p. 158—159° (yield, 13·9 g.) (Found: N, 16·0; Cl, 28·4. $C_{11}H_9N_3Cl_2$ requires N, 16·5; Cl, 28·0%).

2-p-*Chloroanilino*-4-*hydroxy*-5-*phenylpyrimidine* (VI; R = Cl, R′ = H, R″ = Ph).—4-Hydroxy-2-ethylthio-5-phenylpyrimidine (Wheeler and Bristol, *Amer. Chem. J.*, 1905, **33**, 460) (19·44 g.) and *p*-chloroaniline (29·9 g.) were heated at 130—140° for 6 hours, with stirring until the melt solidified. When cold, it was ground, refluxed with alcohol (150 c.c.) for 1½ hours, and filtered off. The *compound* was practically insoluble in all the usual organic solvents and was purified by dissolution in sodium hydroxide solution and reprecipitation with acetic acid followed by boiling with β-ethoxyethanol. It then had m. p. 328—330° (Found: C, 64·0; H, 4·1; N, 14·6. $C_{16}H_{12}ON_3Cl$ requires C, 64·5; H, 4·0; N, 14·1%).

4-*Chloro*-2-p-*chloroanilino*-5-*phenylpyrimidine* (VII; R = Cl, R′ = H, R″ = Ph), prepared by the action of phosphoryl chloride (60 c.c.) on the preceding hydroxy compound (20 g.) for ½ hour followed by working up in the usual way, crystallised from alcohol as colourless elongated prisms, m. p. 133—134° (yield, 15·35 g.) (Found: N, 13·1; Cl, 22·1. $C_{16}H_{11}N_3Cl_2$ requires N, 13·3; Cl, 22·5%).

2-p-*Anisidino*-4-*hydroxy*-5-*phenylpyrimidine* (VI; R = OMe, R′ = H, R″ = Ph).—4-Hydroxy-2-ethylthio-5-phenylpyrimidine (17·4 g.) and *p*-anisidine (18·45 g.) were boiled in β-ethoxyethanol (50 c.c.) for 21 hours. After cooling, the crystalline *product* was filtered off, washed well with hot alcohol, and dried (yield, 19·1 g.). It separated from acetic acid as colourless laminæ, m. p. 271—272° (Found: C, 69·3; H, 5·0; N, 14·5. $C_{17}H_{15}O_2N_3$ requires C, 69·6; H, 5·1; N, 14·3%).

4-*Chloro*-2-p-*anisidino*-5-*phenylpyrimidine* (VII; R = OMe, R′ = H, R″ = Ph), from 2-*p*-anisidino-4-hydroxy-5-phenylpyrimidine (17·15 g.) with phosphoryl chloride (45 c.c.), crystallised from alcohol as colourless needles, m. p. 152° (yield, 11·65 g.) (Found: N, 13·4; Cl, 11·4. $C_{17}H_{14}ON_3Cl$ requires N, 13·5; Cl, 11·4%).

2-p-*Chloroanilino*-4-*hydroxy*-5-*phenoxypyrimidine* (VI; R = Cl, R′ = H, R″ = OPh).—4-Hydroxy-2-ethylthio-5-phenoxypyrimidine (Johnson and Heyl, *Amer. Chem. J.*, 1907, **37**, 628) (11·6 g.) and *p*-chloroaniline (16 g.) were heated at 130—140° for 28 hours. The residue (solid when cold) was worked up as before giving the *hydroxypyrimidine* which, after crystallisation from β-ethoxyethanol, had m. p. 240—242° (yield, 14·3 g.) (Found: C, 60·9; H, 3·8; N, 13·1. $C_{16}H_{12}O_2N_3Cl$ requires C, 61·2; H, 3·8; N, 13·4%).

4-*Chloro*-2-p-*chloroanilino*-5-*phenoxypyrimidine* (VII; R = Cl, R′ = H, R″ = OPh).—2-*p*-Chloroanilino-4-hydroxy-5-phenoxypyrimidine (9·45 g.) and phosphoryl chloride (30 c.c.) were refluxed for 30 minutes. The resulting clear solution was poured on ice and the mixture made alkaline with ammonia. After stirring for 2½ hours the supernatant liquid was decanted. The oily residue was dissolved in alcohol, the solution made alkaline with ammonia and poured into water, and the precipitate collected. The *compound* crystallised from aqueous alcohol as colourless prisms, m. p. 112—113° (yield, 5·3 g.) (Found: C, 58·1; H, 3·7; N, 12·6. $C_{16}H_{11}ON_3Cl_2$ requires C, 57·8; H, 3·3; N, 12·65%).

4-*Dialkylaminoalkylaminopyrimidines*.—The chloropyrimidine and the dialkylaminoalkylamine (1·25 mols.) were heated at 125—135° for 8 hours with stirring. The resulting melt was dissolved in hot dilute hydrochloric acid and the solution made alkaline with sodium hydroxide. The base was then extracted with ether or chloroform and the extract shaken several times with 5% acetic acid. Alternatively, the solvent was removed by distillation and the residue extracted with 5% acetic acid. The base was liberated from the combined acetic acid extracts by the addition of sodium hydroxide and again taken into ether or chloroform. Evaporation of the dried solution left the base as a solid, or as an oil which usually crystallised when triturated with light petroleum (b. p. 40—60°). The substances which could not be obtained crystalline in this way, notably those containing the δ-diethylamino-α-methylbutyl side chain, were converted into their dihydrochlorides. The solid bases were purified by crystallisation from light petroleum. For biological testing the dihydrochlorides were usually prepared by dissolving the bases in hot 2N-hydrochloric acid and allowing the solution to cool, whereupon the salt normally crystallised out and was collected and dried. If the hydrochloride failed to separate on cooling the solution was evaporated to dryness under reduced pressure at 50—60° and the evaporation repeated with alcohol or alcohol–benzene to remove water and adhering hydrochloric acid; it was then purified by crystallisation from alcohol, alcohol–ethyl acetate, or alcohol–acetone.

In addition to the substances contained in Table II the following were prepared by the same general method:

2-*p*-Toluidino-4-β-diethylaminoethylaminopyrimidine, prepared from 4-chloro-2-*p*-toluidinopyrimidine (Johnson and Storey, *Amer. Chem. J.*, 1908, **40**, 143) and β-diethylaminoethylamine, gave a *dihydrochloride* which crystallised from alcohol-acetone as colourless prisms, m. p. 220—221° (Found: C, 52·1; H, 7·3; N, 17·5; Cl′, 18·3. $C_{17}H_{25}N_5,2HCl,H_2O$ requires C, 52·3; H, 7·4; N, 17·9; Cl′, 18·2%).

2-p-*Anisidino*-4-β-*diethylaminoethylamino*-5-*phenylpyrimidine*, crystallised from light petroleum (b. p. 100—120°) in clusters of colourless prisms, m. p. 158—159° (Found: C, 70·2; H, 7·4; N, 18·0. $C_{23}H_{29}ON_5$ requires C, 70·6; H, 7·4; N, 17·9%). The *dihydrochloride* separated from alcohol–ethyl acetate as crystals, m. p. 209—211° (Found: C, 56·4; H, 6·2; N, 14·5; Cl′, 15·3. $C_{23}H_{29}ON_5,2HCl,1{\cdot}5H_2O$ requires C, 56·2; H, 6·9; N, 14·3; Cl′, 14·5%).

Imperial Chemical Industries, Limited,
Research Laboratories, Blackley, Manchester, 9.

[*Received, October 17th, 1945.*]