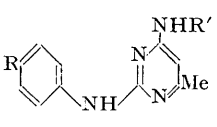
## 119. *Synthetic Antimalarials. Part XXIII. 2-Arylguanidino-4-aminoalkylaminopyrimidines. Further Variations.*

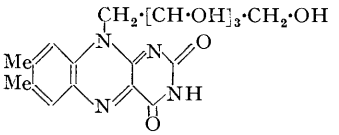
By W. H. Cliffe, F. H. S. Curd, F. L. Rose, and (Miss) M. Scott.

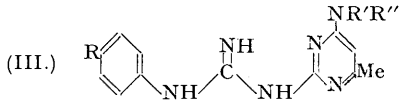
Curd and Rose (Part IV, *J.*, 1946, 362) described a series of 2-phenylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines, many of which showed antimalarial activity when tested against *P. gallinaceum* in chicks. The present work concerns further syntheses of the same type with variations of the substituent in the aryl group and the complexity of the basic side chain, and introduction of substituents into position 5 of the pyrimidine ring as well as different groups in position 6. No notable increase in therapeutic activity is recorded.

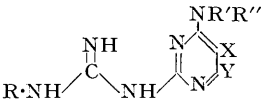
Anilinopyrimidines of type (I; R = Cl, R′ = dialkylaminoalkyl) have been widely varied in attempts to enhance the antimalarial activity exhibited by some members of the series (Part I, *J.*, 1946, **343**; Part II, *ibid.*, p. **351**; Part V, *ibid.*, p. **366**; Part VII, *ibid.*, p. **378**). These variations have included not only a routine investigation of the influence of changing the nature and position of the aromatic subsitiuent and the size of the basic side-chain group, but have sought also to promote increased therapeutic activity by effecting such substitution in the benzene and pyrimidine rings (mainly appropriately placed methyl groups) as would give the drug molecule a closer structural resemblance to riboflavin (II), in view of the possible parallelism between antimalarial activity and the antagonism exhibited by type (I) for this

factor, with respect to the growth of *Lactobacillus casei* (Madinaveitia, *Biochem. J.*, **1946**, **40**, 373).




In Part IV (*ibid.*, p. 362) a major modification of (I) was described in which the anilino-group was replaced by the phenylguanidino-residue giving (III). This led to substances of appreciably enhanced activity against experimental malarial infections and the selection of (III; R = Cl, R′ = H, R″ = $[CH_2]_2$·$NEt_2$) for clinical investigation in man (Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, **1945**, **39**, 139). The preparation of a limited number of chemical variants was described in Part IV, but the clinical efficacy of this type called for a more complete study of the effect of changes in molecular detail along the lines followed for the earlier type (I). The chief modifications were as follows :

(a) *Variations in the side chains* R′,R″. Dialkylaminoalkyl groups of varying complexity have been introduced into the molecule, including γ-dimethylaminopropyl which led to high activity when incorporated in the anilinopyrimidines (type I) (see Part I), others in which ether, thioether, amino- and phenyl groupings were interposed, and in addition bis(dialkylamino)-alkyl groups. The NR′R″ (III) group has also been derived from secondary amines such as ethyl-β-diethylaminoethylamine and diethylamine. The use of simple amine residues such as the latter was considered justifiable since it was thought that omission of the basic centre in the alkyl side chain would be balanced in part by the increased basicity of type (III), as compared with type (I), owing to the presence in the molecule of the guanidine group. The two general methods described in Part (IV) for the preparation of 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine were used throughout for the introduction of the group NR′R″, namely, reaction between the 4-chloropyrimidine and the appropriate amine, either in acetic acid at temperatures up to 130°, or under reflux in a mixture of chlorobenzene and dilute sodium hydroxide. In general, the latter method gave the better yields. A single preparation of a related substance, in which NR′R″ was replaced by the methyl group giving 2-p-*chlorophenylguanidino*-4 : 6-*dimethylpyrimidine* (III; R = Cl, NR′R″ = Me), was made by reaction of *p*-chlorophenyldiguanide with acetylacetone in acetic acid in the presence of anhydrous sodium acetate. It was assumed that, by analogy with the β-keto-ester reaction, condensation occurred between the diketone and the terminal pair of nitrogen atoms of the diguanide.

(b) *Variation of the substituents in the phenyl group.* This aspect of the investigation has followed closely the variations made in type (I) and described in Parts I and II, thus enabling comparisons to be made of the effect on antimalarial activity of similar substitution in both types (I) and (III). An attempt was made to introduce the sulphonamide grouping into the molecule, not on account of its significance in the sulphanilamide type of drug, but because the inductive effect of such a grouping was in the same sense as that of cyano-, nitro-, and halogeno- which had earlier been shown to promote positive antimalarial activity. The requisite synthesis was successful up to the preparation of 4-*hydroxy*-2-p-*sulphonamidophenylguanidino*-6-*methylpyrimidine*, but the isolation of the corresponding 4-chloropyrimidine in a pure form was not achieved and reaction of this crude intermediate with β-diethylaminoethylamine gave intractable products. Synthesis of the related 2-*p*-sulphondimethylamidophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine was, however, successful at all stages, and failure with the unsubstituted sulphonamido-compound can probably be attributed to the presence in the latter of easily replaceable hydrogen atoms which result in self-condensation at the chloropyrimidine stage. A sulphone group was also introduced into type (III) by the preparation of 2-p-*methylsulphonylphenylguanidino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (III, R = $SO_2$·Me, R′ = H, R″ = $[CH_2]_2$·$NEt_2$).

The observation by Madinaveitia (*loc. cit.*) that (III; R = Cl, R′ = H, R″ = $[CH_2]_2$·$NEt_2$), like type (I), behaved as a riboflavin antagonist with respect to the growth of *L. casei*, suggested that substitution of methyl groups in positions 3 and 4 of the benzene ring (corresponding to the 5 : 6-dimethylbenz-portion of riboflavin) would be of interest, and accordingly

2-(4′-o-*xylyl*)*guanidino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (IV; R = 3 : 4-$C_6H_3Me_2$, R′ = H, R″ = $[CH_2]_2$·$NEt_2$, X = H, Y = Me) was prepared.

The synthesis of substances of type (III), variously substituted in the aromatic ring, followed closely the two methods used in Part IV, namely the preparation of the required hydroxypyrimidines by interaction of ethyl acetoacetate with the aryldiguanide, or of the arylamine hydrochloride with 2-cyanoamino-4-hydroxy-6-methylpyrimidine, followed by conversion with phosphoryl chloride into the chloropyrimidine, which was then caused to react by one or other of the methods indicated above with the side-chain amine.

(c) *Variation of the substituents in the* 5 *and* 6 *position of the pyrimidine ring.* Here again the modifications made in type (I) drugs and described in Part VII (*loc. cit.*) have been applied to type (III), and mainly concern the introduction of alkyl substituents into position 5 (IV; Y = Me, X = alkyl), the substitution of hydrogen or phenyl for the 6-methyl group (IV;

TABLE I.

*Antimalarial Activities.*

The antimalarial activities were estimated by our colleague Dr. D. G. Davey using chicks infected with *P. gallinaceum*. The meaning of the symbols used to express activity is given in Part I.

| Ref. no. | Substance. | Dose, mg./kg. | Activity. |
|---|---|---|---|
| 4595 | 2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylamino-5 : 6-dimethylpyrimidine | 40 | — |
| 4726 | 2-*p*-Chlorophenylguanidino-4-γ-diethylaminopropylamino-5 : 6-dimethylpyrimidine | 120 | ++ |
| | | 40 | + |
| 4725 | 2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylamino-6-methyl-5-ethylpyrimidine | 240 | — |
| 4851 | 2-*p*-Chlorophenylguanidino-4-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine | 80 | + |
| 4852 | 2-*p*-Chlorophenylguanidino-4-γ-diethylaminopropylamino-6-methyl-5-*n*-propylpyrimidine | 120 | + |
| 4724 | 2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylamino-6-methyl-5-*n*-butylpyrimidine | 120 | + |
| | | 80 | — |
| 4855 | 2-*p*-Chlorophenylguanidino-4-γ-diethylaminopropylamino-6-methyl-5-*n*-butylpyrimidine | 120 | + |
| 4853 | 2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylamino-6-methyl-5-*iso*amylpyrimidine | 80 | — |
| 4854 | 2-*p*-Chlorophenylguanidino-4-γ-diethylaminopropylamino-6-methyl-5-*iso*amylpyrimidine | 80 | — |
| 4596 | 2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylaminopyrimidine | 80 | + |
| 5119 | 2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylamino-6-phenylpyrimidine | 80 | — |
| 4212 | 2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylamino-5 : 6-*cyclo*pentenopyrimidine | 160 | + |
| | | 80 | — |
| 4289 | 2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylamino-5 : 6-*cyclo*hexenopyrimidine | 160 | + |
| | | 80 | — |
| 3924 | 2-*p*-Diphenylylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine | 120 | + |
| | | 80 | — |
| 3965 | 2-*p*-Dimethylaminophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine | 160 | — |
| 3951 | 2-*p*-Sulphondimethylamidophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine | 200 | — |
| 3999 | 2-(2′ : 5′-Dichlorophenyl)guanidino-4-β-diethylaminoethylamino-6-methylpyrimidine | 120 | + |
| 4019 | 2-(5′-Chloro-2′-methoxyphenyl)guanidino-4-β-diethylaminoethylamino-6-methylpyrimidine | 200 | + |
| 4060 | 2-*p*-Methylthiophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine | 200 | ++ |
| | | 120 | + |
| 4328 | 2-(3′ : 5′-Dichlorophenyl)guanidino-4-β-diethylaminoethylamino-6-methylpyrimidine | 160 | ++ |
| | | 80 | ++ |
| 3553 | 2-*p*-Tolylguanidino-γ-diethylaminopropylamino-6-methylpyrimidine | 160 | + |
| 3796 | 2-*m*-Tolylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine | 160 | + |
| 3803 | 2-*o*-Tolylguanidino-4-γ-diethylaminopropylamino-6-methylpyrimidine | 160 | + |
| | | 80 | — |
| 3950 | 2-*p*-Methylsulphonylphenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine | 200 | + |
| | | 40 | — |
| 3974 | 2-(5′-Chloro-*o*-tolyl)guanidino-4-β-diethylaminoethylamino-6-methylpyrimidine | 80 | + |
| | | 40 | — |
| 3746 | 2-(4′-*o*-Xylyl)guanidino-4-β-diethylaminoethylamino-6-methylpyrimidine | 200 | + |
| 3600 | 2-β-Naphthylguanidino-4-γ-diethylaminopropylamino-6-methylpyrimidine | 160 | + |

TABLE I—*continued.*

| Ref. no. | Substance. | Dose, mg./kg. | Activity. |
|---|---|---|---|
| 3877 | 2-Phenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine | 160 | + |
| 4378 | 2-*p*-Chlorophenylguanidino-4-diethylamino-6-methylpyrimidine | 80 | ± |
| 4386 | 2-*p*-Chlorophenylguanidino-4-methyl*iso*propylamino-6-methylpyrimidine | 120 | + |
| 3765 | 2-*p*-Chlorophenylguanidino-4-piperidino-6-methylpyrimidine | 160 | + |
| 3741 | 2-*p*-Chlorophenylguanidino-4-γ-dimethylaminopropylamino-6-methylpyrimidine | 160 | + |
| 4384 | 2-*p*-Chlorophenylguanidino-4-β-pyrrolidinoethylamino-6-methylpyrimidine | 40 | + |
| 4379 | 2-*p*-Chlorophenylguanidino-4-ethyl-β-diethylaminoethylamino-6-methylpyrimidine | 40 | + |
| 4327 | 2-*p*-Chlorophenylguanidino-4-γ-*n*-butylaminopropylamino-6-methylpyrimidine | 400<br>120 | +<br>— |
| 4096 | 2-*p*-Chlorophenylguanidino-4-methyl-β-diethylaminoethylamino-6-methylpyrimidine | 160 | + |
| 3672 | 2-*p*-Chlorophenylguanidino-4-γ-diethylaminoproyplamino-6-methylpyrimidine | 200<br>80 | +<br>— |
| 4110 | 2-*p*-Chlorophenylguanidino-4-γ-*n*-dibutylaminopropylamino-6-methylpyrimidine | 80 | + |
| 4261 | 2-*p*-Chlorophenylguanidino-4-β-piperidino-α-methylethylamino-6-methylpyrimidine | 80<br>40 | ++<br>+ |
| 4250 | 2-*p*-Chlorophenylguanidino-4-*p*-(β-diethylaminoethylthio)phenylamino-6-methylpyrimidine | 160 | + |
| 4392 | 2-*p*-Chlorophenylguanidino-4-γ-(β′-diethylaminoethoxy)propylamino-6-methylpyrimidine | 120 | + |
| 4403 | 2-*p*-Chlorophenylguanidino-4-γ-methyl-β′-diethylaminoethylaminopropylamino-6-methylpyrimidine | 240<br>120 | +<br>— |
| 4411 | 2-*p*-Chlorophenylguanidino-4-ββ′-bis(diethylamino)*iso*propylamino-6-methylpyrimidine | 160<br>80 | +<br>— |
| 4514 | 2-*p*-Chlorophenylguanidino-4-bis-(β-diethylaminoethyl)amino-6-methylpyrimidine | 320<br>160 | +<br>— |
| 4380 | 2-*p*-Chlorophenylguanidino-4 : 6-dimethylpyrimidine | 160 | ++ |

X = H, Y = H or Ph), and the formation of a *cyclo*penteno- or *cyclo*hexeno-ring across positions 5 and 6 (IV; X and Y = $[CH_2]_3$ or $[CH_2]_4$). In the last process, the product is a 5 : 6 : 7 : 8-tetrahydroquinazoline derivative and therefore related to the active 2-*p*-chloroanilino-4-substituted-aminoquinazolines described in Part XIV (*J.*, 1947, 775). Preparation of many of the intermediate 4-hydroxy-2-*p*-chlorophenylguanidinopyrimidines has been through both the diguanide and the 2-cyanoaminopyrimidine routes. In general, the latter method has given the more satisfactory result, both as regards purity of the crude condensation product and yield. A notable difference in yield was observed in the production of the cyanoaminopyrimidine intermediates from ethyl *cyclo*pentanone- and *cyclo*hexanone-2-carboxylate, the latter reacting much more easily and efficiently with dicyandiamide in the presence of sodium methoxide. The reduced yields observed when the aryldiguanides were employed were due to the formation of by-products, probably 1 : 3 : 5-triazines (cf. Part IV), which, however, were not further investigated.

## EXPERIMENTAL.

2-p-*Chlorophenylguanidino*-4-β-*diethylaminoethylamino*-5 : 6-*dimethylpyrimidine* (IV; R = *p*-$C_6H_4Cl$, R′ = H, R″ = $[CH_2]_2$·$NEt_2$, X = Y = Me) (4595).—(a) 4-H*ydroxy*-2-p-*chlorophenylguanidino*-5 : 6-*dimethylpyrimidine* was precipitated (yield, 57 g.) when a solution from *p*-chlorophenyldiguanide (62 g.), 11N-sodium hydroxide (33 c.c.), and methanol (200 c.c.) was stirred for 70 hours with ethyl α-methylacetoacetate at 20°. A single extraction with hot dilute acetic acid and lixiviation with hot ethanol left a crystalline solid, m. p. 263° (decomp.) (Found: C, 52·6; H, 4·65; N, 23·95; Cl, 11·7. $C_{13}H_{14}ON_5Cl$ requires C, 53·5; H, 4·8; N, 24·0; Cl, 12·2%). The same hydroxypyrimidine (m. p. and mixed m. p.) was also obtained by refluxing for 17 hours *p*-chloroaniline (8·7 g.), β-ethoxyethanol (70 c.c.), 10N-hydrochloric acid (6·7 c.c.), water (17 c.c.), and the 2-cyanoamino-4-hydroxy-5 : 6-dimethylpyrimidine [m. p. 281° (decomp.), 10·9 g.] prepared by refluxing for 2 hours a mixture of ethyl α-methylacetoacetate (14·4 g.), dicyandiamide (8·4 g.), and sodium (2·3 g.) dissolved in ethanol (65 c.c.).

(b) 4-*Chloro*-2-p-*chlorophenylguanidino*-5 : 6-*dimethylpyrimidine* was obtained by stirring for 1½ hours at 78—84° a mixture of the above crude hydroxypyrimidine (52·5 g.), phosphoryl chloride (18 c.c.), and chlorobenzene (77 c.c.), and adding it to crushed ice and water (360 c.c.) and 11N-sodium hydroxide (94 c.c.). After being collected, washed with water and dried in a vacuum (yield, 52·7 g.) it had m. p. 179—181°. Rapid crystallisation of a little from ethanol gave colourless needles, m. p. 188° (Found: C, 50·05; H, 3·9; N, 22·3; Cl, 22·3. $C_{13}H_{13}N_5Cl_2$ requires C, 50·3; H, 4·1; N, 22·6; Cl, 22·9%).

(c) The crude chloropyrimidine (38 g.), β-diethylaminoethylamine (17·7 g.), chlorobenzene (108 c.c.), and 2·5N-sodium hydroxide (166 c.c.) were refluxed for 2 hours. The chlorobenzene was distilled off in

steam. The residual solid, dissolved at 60° in water (1 l.) and acetic acid (25 c.c.), treated with charcoal, and reprecipitated with sodium hydroxide, gave crude 2-p-*chlorophenylguanidine*-4-β-*diethylamino*-*ethylamino*-5 : 6-*dimethylpyrimidine* (39·9 g.), m. p. 70—90°. After crystallisation from light petroleum (b. p. 100—120°) it had m. p. 113°, and it was then converted into the colourless crystalline *dihydrochloride*, m. p. 181—183°, by adding N-hydrochloric acid (2 equivs.) to a solution in acetone (Found: C, 45·3; H, 6·8; N, 19·7. $C_{19}H_{28}N_7Cl,2HCl,2H_2O$ requires C, 45·8, H, 7·0; N, 19·7%). Treatment of an aqueous solution with sodium hydroxide gave the base, m. p. 121—122°, after crystallisation twice from ligroin (Found: N, 25·0. $C_{19}H_{28}N_7Cl$ requires N, 25·1%).

2-p-*Chlorophenylguanidino*-4-γ-*diethylaminopropylamino*-5 : 6-*dimethylpyrimidine* (IV; R = *p*-$C_6H_4Cl$, R′ = H, R″ = $[CH_2]_3$·$NEt_2$, X = Y = Me) (4726).—Similarly prepared using γ-diethylaminopropylamine, this *base* formed crystals from ligroin, m. p. 112—113° (Found: C, 59·1; H, 7·2; N, 24·2; Cl, 9·1. $C_{20}H_{30}N_7Cl$ requires C, 59·4; H, 7·4; N, 24·2; Cl, 8·8%).

2-p-*Chlorophenylguanidino*-4-β-*diethylaminoethylamino*-6-*methyl*-5-*ethylpyrimidine* (IV; R = *p*-$C_6H_4Cl$, R′ = H, R″ = $[CH_2]_2$·$NEt_2$, X = Et, Y = Me) (4725).—Similarly prepared from 4-chloro-2-*p*-chlorophenylguanidino-6-methyl-5-ethylpyrimidine (m. p. 194—196° from methanol, 19·6 g.), β-diethylaminoethylamine (9·8 g.), chlorobenzene (53 c.c.), and 2·5N-sodium hydroxide (82 c.c.), refluxed for 5 hours, this *base* had m. p. 135—137° (yield, 15·3 g.) from ligroin (Found: C, 59·0; H, 7·2; N, 23·5. $C_{20}H_{30}N_7Cl$ requires C, 59·4; H, 7·4; N, 24·2%). The intermediate 4-hydroxy-2-*p*-chlorophenylguanidino-6-methyl-5-ethylpyrimidine, m. p. 259—261°, was formed in only low yield from *p*-chlorophenyldiguanide and ethyl α-ethylacetoacetate. Higher overall yields were obtained by interaction of *p*-chloroaniline, as for 4595, with 2-cyanoamino-4-hydroxy-6-methyl-5-ethylpyrimidine [m. p. 261° (decomp.)].

2-p-*Chlorophenylguanidino*-4-γ-*diethylaminopropylamino*-6-*methyl*-5-*ethylpyrimidine* (IV; R=*p*-$C_6H_4Cl$, R′ = H, R″ = $[CH_2]_3$·$NEt_2$, X = Et, Y = Me) (4851).—Similarly prepared using γ-diethylaminopropylamine, this *base* had m. p. 116—118° from ligroin (Found C, 61·1; H, 7·9; N, 23·5. $C_{21}H_{32}N_7Cl$ requires C, 60·4; H, 7·7; N, 24·45%).

2-p-*Chlorophenylguanidino*-4-γ-*diethylaminopropylamino*-6-*methyl*-5-n-*propylpyrimidine* (IV; R = *p*-$C_6H_4Cl$, R′ = H, R″ = $[CH_2]_3$·$NEt_2$, X = $Pr^a$, Y = Me) (4852).—Similarly prepared from 4-*chloro*-2-p-*chlorophenylguanidino*-6-*methyl*-5-n-*propylpyrimidine* (m. p. 201—202° from methanol) (Found: C, 53·6; H, 4·95; N, 20·2; Cl, 20·6. $C_{15}H_{17}N_5Cl_2$ requires C, 53·25; H, 5·05; N, 20·7; Cl, 21·0%) and γ-diethylaminopropylamine, this gave a *dihydrochloride* from acetone, m. p. 114—116° (Found: C, 46·15; H, 7·3; N, 16·9; Cl′, 11·8. $C_{22}H_{34}N_7Cl,2HCl,3H_2O$ requires C, 45·8; H, 7·6; N, 16·9; Cl′, 12·3%). The intermediate 4-hydroxy-2-*p*-chlorophenylguanidino-6-methyl-5-*n*-propylpyrimidine had m. p. 242° from methanol and was prepared both by the diguanide route and from 2-cyanoamino-4-hydroxy-6-methyl-5-*n*-propylpyrimidine (m. p. 233—234° from water).

2-p-*Chlorophenylguanidino*-4-β-*diethylaminoethylamino*-6-*methyl*-5-n-*butylpyrimidine* (IV; R = *p*-$C_6H_4Cl$, R′ = H, R″ = $[CH_2]_2$·$NEt_2$, X = $Bu^a$, Y = Me) (4724).—Similarly prepared and converted into the dihydrochloride and thence into the *base*, which had m. p. 108—109° from ligroin (Found: C, 60·85; H, 7·6; N, 22·5. $C_{22}H_{34}N_7Cl$ requires C, 61·1; H, 7·8; N, 22·7%). The intermediate chloropyrimidine formed colourless needles from methanol, m. p. 194°, and the corresponding hydroxypyrimidine had m. p. 228—229° from ethanol.

2-p-*Chlorophenylguanidino*-4-γ-*diethylaminopropylamino*-6-*methyl*-5-n-*butylpyrimidine* (IV; R = *p*-$C_6H_4Cl$, R′ = H, R″ = $[CH_2]_3$·$NEt_2$, X = $Bu^a$, Y = Me) (4855).—Similarly prepared, this formed a *dihydrochloride* from acetone, m. p. 113—115° (Found: C, 48·2; H, 7·25; N, 16·15; Cl′, 12·5. $C_{23}H_{36}N_7Cl,2HCl,3H_2O$ requires C, 48·2; H, 7·7; N, 17·1; Cl′, 12·4%).

2-p-*Chlorophenylguanidino*-4-β-*diethylaminoethylamino*-6-*methyl*-5-iso*amylpyrimidine* (IV; R = *p*-$C_6H_4Cl$, R′ = H, R″ = $[CH_2]_2$·$NEt_2$, X = $Am^\beta$, Y = Me) (4853).—Similarly prepared from 4-chloro-2-*p*-chlorophenylguanidino-6-methyl-5-*iso*amylpyrimidine (m. p. 202° from methanol), this *base* formed colourless crystals from ligroin, m. p. 119—120° (Found: C, 62·35; H, 8·05; N, 22·35. $C_{23}H_{36}N_7Cl$ requires C, 61·95; H, 8·1; N, 22·0%). The intermediate hydroxypyrimidine (from *p*-chlorophenyldiguanide and ethyl *iso*amylacetoacetate, or from *p*-chloroaniline hydrochloride and 2-cyanoamino-4-hydroxy-6-methyl-5-*iso*amylpyrimidine, m. p. 248—250° from methanol) had m. p. 238° from methanol.

2-p-*Chlorophenylguanidino*-4-γ-*diethylaminopropylamino*-6-*methyl*-5-iso*amylpyrimidine* (IV; R = *p*-$C_6H_4Cl$, R′ = H, R″ = $[CH_2]_3$·$NEt_2$, X = $Am^\beta$, Y = Me) (4854).—Similarly prepared using γ-diethylaminopropylamine and purified as the *dihydrochloride* which had m. p. 139—141° from acetone (Found: C, 48·65; H, 7·55; N, 16·95; Cl′, 12·5. $C_{24}H_{38}N_7Cl,2HCl,3H_2O$ requires C, 49·1; H, 7·8; N, 16·7; Cl′, 12·1%).

2-p-*Chlorophenylguanidino*-4-β-*diethylaminoethylaminopyrimidine* (IV; R = *p*-$C_6H_4Cl$, R′ = H, R″ = $[CH_2]_2$·$NEt_2$, X = Y = H) (4596).—Similarly prepared from 4-chloro-2-*p*-chlorophenylguanidinopyrimidine (m. p. 156—158° from methanol), this *base* formed colourless needles from toluene, m. p. 191·5—192·5° (Found: C, 56·7; H, 6·4; N, 26·25. $C_{17}H_{24}N_7Cl$ requires C, 56·4; H, 6·6; N, 27·1%). The intermediate hydroxypyrimidine (from *p*-chlorophenyldiguanide and ethyl formylacetate, or from *p*-chloroaniline hydrochloride and 2-cyanoamino-4-hydroxypyrimidine, m. p. >310°) had m. p. 257°.

2-p-*Chlorophenylguanidino*-4-β-*diethylaminoethylamino*-6-*phenylpyrimidine* (IV; R = *p*-$C_6H_4Cl$, R′ = H, R″ = $[CH_2]_2$·$NEt_2$, X = H, Y = Ph) (5119).—*p*-Chlorophenyldiguanide (17·8 g.), ethyl benzoylacetate (15 c.c.), and ethanol (40 c.c.) were refluxed for 7 hours. The precipitate after extraction with hot methanol gave colourless prisms (3 g.) from nitrobenzene of 2-p-*chlorophenylguanidino*-4-*hydroxy*-6-*phenylpyrimidine*, m. p. 254° (Found: C, 58·9; H, 4·4; N, 20·25. $C_{17}H_{14}ON_5Cl$ requires C, 60·0; H, 4·1; N, 20·6%). Treatment with phosphoryl chloride gave the corresponding chloropyrimidine. 2-p-*Chlorophenylguanidino*-4-β-*diethylaminoethylamino*-6-*phenylpyrimidine* from the latter and β-diethylaminoethylamine formed colourless needles from light petroleum (b. p. 100—120°), m. p. 166—167° (Found: N, 22·15. $C_{23}H_{28}N_7Cl$ requires N, 22·4%).

2-p-*Chlorophenylguanidino*-4-β-*diethylaminoethylamino*-5 : 6-cyclo*pentenopyrimidine* (IV: R = *p*-$C_6H_4$·Cl, R′ = H, R″ = $[CH_2]_2$·$NEt_2$, XY = $[CH_2]_3$) (4212).—(a) 2-*Cyanoamino*-4-*hydroxy*-5 : 6-cyclo*pentenopyrimidine* prepared by refluxing for 9 hours a mixture of ethyl *cyclo*pentanone-2-carboxylate

(15·6 g.), dicyandiamide (8·4 g.), and sodium (2·3 g.) in methanol (40 c.c.), and then acidifying with acetic acid, formed a colourless solid sparingly soluble in solvents, which when reprecipitated from solution in dilute sodium hydroxide (yield 4·5 g.) darkened and sintered at 240°, finally decomposing at 275° (Found : N, 31·0. $C_8H_8ON_4$ requires N, 31·75%).

(b) 4-*Hydroxy*-2-p-*chlorophenylguanidino*-5 : 6-cyclo*pentenopyrimidine* prepared by refluxing the above 2-cyanoaminopyrimidine (10·6 g.), *p*-chloroaniline (15·4 g.), β-ethoxyethanol (50 c.c.), and 4N-hydrochloric acid (15 c.c.), and purified by adding ammonia to a solution of the crude product in methanol and excess of hydrochloric acid (yield, 6·7 g.), gave colourless needles from β-ethoxyethanol, m. p. 257—258° (Found : C, 55·35; H, 5·35. $C_{14}H_{14}ON_5Cl$ requires C, 55·3; H, 4·6%).

(c) The above hydroxypyrimidine (6·5 g.) and phosphoryl chloride (14 c.c.) were heated for ½ hour at 100° and added to crushed ice and excess of ammonia. An extract of the wet precipitate in water (100 c.c.) and acetic acid (10 c.c.) at 60° gave on cooling and being made alkaline the crude chloropyrimidine (1·8 g., m. p. 162—165°) which after drying in a vacuum over sodium hydroxide was heated for 1½ hours at 95—100° with β-diethylaminoethylamine (0·8 g.) and acetic acid (1 c.c.). Addition of water, filtration, and basification with sodium hydroxide gave 2-p-*chlorophenylguanidino*-4-β-*diethylaminoethylamino*-5 : 6-cyclo*pentenopyrimidine* which formed colourless needles (0·9 g.), m. p. 98—102° from light petroleum (b. p. 100—120°) (Found : C, 60·6; H, 7·1; N, 23·4. $C_{20}H_{28}N_7Cl$ requires C, 59·7; H, 7·0; N, 24·4%).

2 - p - *Chlorophenylguanidino* - 4 - β - *diethylaminoethylamino* - 5 : 6 - cyclo*hexenopyrimidine* (IV; R = *p*-$C_6H_4Cl$, R′ = H, R″ = $[CH_2]_2$·$NEt_2$, XY = $[CH_2]_4$) (4289).—(a) 2-*Cyanoamino*-4-*hydroxy*-5 : 6-cyclo*hexenopyrimidine* was obtained crude [m. p. 277° (decomp.)] in good yield (49 g.) by heating under reflux ethyl *cyclo*hexanone-2-carboxylate (51 g.), dicyandiamide (25·2 g.), and sodium (6·9 g.) dissolved in methanol (120 c.c.), and cooling and washing the precipitate, after filtration, with warm very dilute acetic acid. It formed colourless needles from much β-ethoxyethanol, m. p. 278° (decomp.). (Found : C, 56·8; H, 5·3; N, 29·5. $C_9H_{10}ON_4$ requires C, 57·8; H, 5·3; N, 29·1%).

(b) The above cyanoamino-compound (19 g.), refluxed for 3 hours with *p*-chloroaniline (12·8 g.), β-ethoxyethanol (100 c.c.), and 4N-hydrochloric acid (24 c.c.), and worked up as for the *cyclo*penteno-homologue, gave crude 4-*hydroxy*-2-p-*chlorophenylguanidino*-5 : 6-cyclo*hexenopyrimidine* (24·3 g., m. p. 255—257°) which formed colourless needles from β-ethoxyethanol, m. p. 260—261° (Found : C, 56·6; H, 4·9. $C_{15}H_{16}ON_5Cl$ requires C, 56·8; H, 5·25%).

(c) 4-*Chloro*-2-p-*chlorophenylguanidino*-5 : 6-cyclo*hexenopyrimidine*, prepared as for the corresponding *cyclo*penteno-derivative, formed prisms from toluene, m. p. 173—175° (Found : N, 20·6. $C_{15}H_{15}N_5Cl_2$ requires N, 20·8%).

(d) The chloropyrimidine (3·4 g.), β-diethylaminoethylamine (1·45 g.), and acetic acid (1·5 c.c.), heated for 1 hour at 100°, gave 2-p-*chlorophenylguanidino*-4-β-*diethylaminoethylamino*-5 : 6-cyclo*hexenopyrimidine* (1·7 g.) which formed colourless needles from light petroleum (b. p. 100—120°), m. p. 159—160° (Found : C, 62·2; H, 7·4; N, 22·8. $C_{21}H_{30}N_7Cl$ requires C, 62·0; H, 7·2; N, 23·5%).

4-*Hydroxy*-2-*substituted-arylguanidino*-6-*methylpyrimidines*.—(*a*) The following were made by interaction of the appropriate *base* with 2-cyanoamino-4-hydroxy-6-methylpyrimidine (method as described above for 4-hydroxy-2-*p*-chlorophenylguanidino-5 : 6-dimethylpyrimidine). 4-*Hydroxy*-2-p-*diphenylylguanidino*-6-*methylpyrimidine* from *p*-aminodiphenyl (16·9 g.) and the cyanoaminopyrimidine (15 g.) (yield of crude product, 12 g.); colourless prisms from benzene, m. p. 261° (Found : C, 70·7; H, 5·9; N, 19·15. $C_{18}H_{17}ON_5,\frac{1}{2}C_6H_6$ requires C, 70·4; H, 5·5; N, 19·55%). 4-*Hydroxy*-2-p-*dimethylaminophenylguanidino*-6-*methylpyrimidine* from *p*-aminodimethylaniline (22 g.) and the cyanoaminopyrimidine (25 g.) (yield of crude product, 28·3 g.); colourless prisms from *o*-dichlorobenzene, m. p. 257—258° (Found : C, 58·7; H, 6·3. $C_{14}H_{18}ON_6$ requires C, 57·7; H, 5·95%). 4-*Hydroxy*-2-p-*sulphondimethylaminophenylguanidino*-6-*methylpyrimidine* from sulphanildimethylamide (14 g.) and the cyanoaminopyrimidine (10·5 g.) (yield of crude product, 8·5 g.); crystals from nitrobenzene, m. p. 259—261° (Found : N, 24·15. $C_{14}H_{18}O_3N_6S$ requires N, 24·0%). 4-*Hydroxy*-2-p-*sulphonamidophenylguanidino*-6-*methylpyrimidine* from sulphanilamide (17·2 g.) and the cyanoaminopyrimidine (15 g.) (yield of crude product, 16·5 g.); insoluble in common organic solvents, and purified by precipitation with ammonia from an aqueous solution of the hydrochloride, m. p. 266—269° (Found : C, 44·8; H, 4·5; N, 25·2. $C_{12}H_{14}O_3N_6S$ requires C, 44·7; H, 4·35; N, 26·1%). 4-*Hydroxy*-2-(2′ : 5′-*dichlorophenyl*)-*guanidino*-6-*methylpyrimidine* from 2 : 5-dichloroaniline (16·2 g.) and the cyanoaminopyrimidine (15 g.) (yield of crude product, 8 g.); purified by addition of dilute ammonia to a solution of the hydrochloride in aqueous β-ethoxyethanol, m. p. 263—266° (Found : C, 45·4; H, 3·6; N, 22·0. $C_{12}H_{11}ON_5Cl_2$ requires C, 46·15; H, 3·5; N, 22·3%). 4-*Hydroxy*-2-(5′-*chloro*-2′-*methoxyphenyl*)*guanidino*-6-*methylpyrimidine*, similarly prepared from 5-chloro-2-methoxyaniline and purified, m. p. 249—250° (Found : N, 22·7. $C_{13}H_{14}O_2N_5Cl$ requires N, 22·75%).

(*b*) The following were made by reaction of the appropriate diguanide with ethylacetoacetate (method as described above for 4-hydroxy-2-*p*-chlorophenylguanidino-5 : 6-dimethylpyrimidine) : 4-*Hydroxy*-2-p-*methylthiophenylguanidino*-6-*methylpyrimidine* from *p*-methylthiophenyldiguanide hydrochloride (18 g.), ethyl acetoacetate (18 c.c.), ethanol (75 c.c.) and 11N-sodium hydroxide (9·7 c.c.), kept for 15 hours (yield of crude product, 16·1 g.); recrystallised from *o*-dichlorobenzene, m. p. 250—252° (Found : C, 53·0; H, 5·3; N, 24·2. $C_{13}H_{15}ON_5S$ requires C, 53·9; H, 5·2; N, 23·4%). 4-*Hydroxy*-2-(3′ : 5′-*dichlorophenyl*)*guanidino*-4-*methylpyrimidine* from 3 : 5-dichlorophenyldiguanide hydrochloride (18·5 g.), ethyl acetoacetate (17 c.c.), ethanol (60 c.c.), and 11N-sodium hydroxide (9·1 c.c.), kept for 16 hours (yield of crude product, 18·75 g.); colourless needles from *o*-dichlorobenzene, m. p. 270—272° (Found : C, 46·15; H, 3·35; N, 22·55. $C_{12}H_{11}ON_5Cl_2$ requires C, 46·2; H, 3·5; N, 22·4%). 4-Hydroxy-2-*p*-tolyl (m. p. 262—264°), -*m*-tolyl (m. p. 241—243°), -*o*-tolyl (m. p. 247—248°), -*p*-methylsulphonylphenyl (m. p. 281°), -5′-chloro-*o*-tolyl (m. p. 252—255°), -4′-*o*-xylyl (m. p. 246—248°), and -β-naphthyl (m. p. 230°)-guanidino-6-methylpyrimidines were made similarly but not obtained analytically pure before proceeding to the next stage.

2-*Substituted-aryl*-4-β-*diethylaminoethyl-* (*or* γ-*diethylaminopropyl-*)*amino*-6-*methylpyrimidines* (IV; X = H, Y = Me).—Conversion of the above 4-hydroxypyrimidines into the corresponding

TABLE II.

*2-Substituted-arylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines.*

| No. | 2-Aryl group. | 4-Dialkylaminoalkylamino-group. | Solvent. | M. p. | Formula. | Analysis: Found, %. C. | H. | N. | Required, %. C. | H. | N. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3924 | *p*-$C_6H_4{\cdot}C_6H_5$ | NH·$[CH_2]_2$·$NEt_2$ | Aqueous ethanol | 161—163° | $C_{24}H_{31}N_7$ | 68·7 | 6·75 | 23·35 | 69·1 | 7·4 | 23·5 |
| 3965 | *p*-$C_6H_4{\cdot}NMe_2$ | NH·$[CH_2]_2$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 183·5—184·5 | $C_{20}H_{32}N_8$ | 62·3 | 8·25 | 28·75 | 62·5 | 8·3 | 29·2 |
| 3951 | *p*-$C_6H_4{\cdot}SO_2{\cdot}NMe_2$ | NH·$[CH_2]_2$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 149—150 | $C_{20}H_{32}O_2N_8S$ | 53·8 | 7·65 | 24·8 | 53·6 | 7·15 | 24·8 |
| 3999 | 2 : 5-$C_6H_3Cl_2$ | NH·$[CH_2]_2$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 133·5—134·5 | $C_{18}H_{25}N_7Cl_2$ | 53·05 | 6·3 | 23·7 | 52·7 | 6·1 | 23·9 |
| 4019 | 3-6-$C_6H_3Cl$(OMe) | NH·$[CH_2]_2$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 145—147 | $C_{19}H_{28}ON_7Cl$ | 56·35 | 7·1 | 23·7 | 56·25 | 6·9 | 24·15 |
| 4060 | *p*-$C_6H_4{\cdot}SMe$ | NH·$[CH_2]_2$·$NEt_2$ | Toluene | 155—157 | $C_{19}H_{29}N_7S$ | 58·6 | 7·75 | 24·7 | 58·9 | 7·5 | 25·3 |
| 4328 | 3 : 5-$C_6H_3Cl_2$ | NH·$[CH_2]_2$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 158—159 | $C_{18}H_{25}N_7Cl_2$ | 53·1 | 6·2 | 23·85 | 52·7 | 6·1 | 23·9 |
| 3553 | *p*-$C_6H_4Me$ | NH·$[CH_2]_3$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 137 | $C_{20}H_{31}N_7$ | — | — | 26·2 | — | — | 26·5 |
| 3796 | *m*-$C_6H_4Me$ | NH·$[CH_2]_2$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 134—135 | $C_{19}H_{29}N_7$ | 64·05 | 7·85 | 27·85 | 64·2 | 8·15 | 27·6 |
| 3803 | *o*-$C_6H_4Me$ | NH·$[CH_2]_3$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 133—133·5 | $C_{20}H_{31}N_7$ | 65·0 | 8·0 | 26·3 | 64·9 | 8·4 | 26·5 |
| 3950 | *p*-$C_6H_4{\cdot}SO_2Me$ | NH·$[CH_2]_2$·$NEt_2$ | Toluene | 152—154 | $C_{19}H_{29}O_2N_7S$ | 54·4 | 7·6 | 22·6 | 54·4 | 6·9 | 23·4 |
| 3974 | 4-6-$C_6H_3Cl$(Me) | NH·$[CH_2]_2$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 138—139 | $C_{19}H_{28}N_7Cl$ | 58·05 | 7·15 | 24·8 | 58·45 | 7·2 | 25·1 |
| 3746 | 3 : 4-$C_6H_3Me_2$ | NH·$[CH_2]_2$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 144—145 | $C_{20}H_{31}N_7$ | 64·9 | 8·0 | 25·9 | 64·9 | 8·4 | 26·5 |
| 3600 | $\beta$-$C_{10}H_7$ | NH·$[CH_2]_3$·$NEt_2$ | Water (as hydrochloride) | 102—106 | $C_{23}H_{31}N_7$,2HCl,2$H_2O$ | 53·1 | 7·2 | 19·2 | 53·7 | 6·8 | 19·0 |
| 3877 | $C_6H_5$ | NH·$[CH_2]_2$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 122—122·5 | $C_{18}H_{27}N_7$,$H_2O$ | 63·65 | 8·0 | 27·95 | 63·2 | 8·0 | 27·95 |

TABLE III.

*2-p-Chlorophenylguanidino-4-substituted-amino-6-methylpyrimidines.*

| No. | 4-Substituted-amino-group. | Solvent. | M. p. | Formula. | Analysis. Found, %. C. | H. | N. | Required, %. C. | H. | N. |
|---|---|---|---|---|---|---|---|---|---|---|
| 4378 | $NEt_2$ | Light petroleum (b. p. 100—120°) | 152—153·5° | $C_{16}H_{21}N_6Cl$ | 57·1 | 5·9 | 24·55 | 57·75 | 6·3 | 25·25 |
| 4386 | NMePr$^\beta$ | Toluene | 186—187·5 | $C_{16}H_{21}N_6Cl$ | 57·3 | 6·2 | 24·65 | 57·75 | 6·3 | 25·25 |
| 3765 | $NC_5H_{10}$ | Butanol (hydrochloride) | 253—254 | $C_{17}H_{21}N_6Cl$,HCl | 53·35 | 6·0 | 21·8 | 53·5 | 5·8 | 22·1 |
| 3741 | NH·$[CH_2]_3$·$NMe_2$ | Toluene | 182—184 | $C_{17}H_{24}N_7Cl$ | 55·6 | 6·4 | 25·6 | 56·35 | 6·6 | 27·05 |
| 4384 | NH·$[CH_2]_2$·$NC_4H_8$ | Toluene | 184—185 | $C_{18}H_{24}N_7Cl$ | 57·9 | 6·25 | 25·9 | 57·85 | 6·45 | 26·25 |
| 4379 | NEt·$[CH_2]_2$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 102—103 | $C_{20}H_{30}N_7Cl$ | 59·5 | 7·65 | (Cl, 9·0) | 59·45 | 7·45 | (Cl, 8·8) |
| 4327 | NH·$[CH_2]_3$·NHBu[a] | Light petroleum (b. p. 100—120°) | 136—138 | $C_{19}H_{28}N_7Cl$ | 59·2 | 6·85 | 24·8 | 58·5 | 7·2 | 25·15 |
| 4096 | NMe·$[CH_2]_2$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 108—109 | $C_{19}H_{28}N_7Cl$ | 58·05 | 6·7 | 25·3 | 58·5 | 7·2 | 25·15 |
| 3672 | NH·$[CH_2]_3$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 144·5—145 | $C_{19}H_{28}N_7Cl$ | 58·85 | 7·35 | 24·9 | 58·5 | 7·2 | 25·15 |
| 4110 | NH·$[CH_2]_3$·$NBu_2$[a] | Acetone | 93— 94 | $C_{23}H_{36}N_7Cl$ | 61·95 | 7·5 | 21·75 | 61·95 | 8·1 | 21·9 |
| 4261 | NH·CHMe·$CH_2{\cdot}NC_5H_{10}$ | Light petroleum (b. p. 100—120°) | 143—144 | $C_{20}H_{28}N_7Cl$ | 60·05 | 6·55 | 23·9 | 59·7 | 6·95 | 24·4 |
| 4250 | *p*-NH·$C_6H_4{\cdot}S{\cdot}[CH_2]_2{\cdot}NEt_2$ | Light petroleum (b. p. 100—120°) | 146—147 | $C_{24}H_{30}N_7SCl$ | 59·45 | 6·1 | 19·55 | 59·4 | 6·2 | 20·2 |
| 4392 | NH·$[CH_2]_3$·O·$[CH_2]_2$·$NEt_2$ | Light petroleum (b. p. 100—120°) | 123—124 | $C_{21}H_{32}ON_7Cl$ | 57·55 | 6·9 | 22·7 | 58·1 | 7·4 | 22·6 |
| 4403 | NH·$[CH_2]_3$·NMe·$[CH_2]_2$·$NEt_2$ | Toluene | 119—120 | $C_{22}H_{35}N_8Cl$ | 59·1 | 7·75 | 24·25 | 59·05 | 7·85 | 25·05 |
| 4411 | NH·$CH(CH_2{\cdot}NEt_2)_2$ | Light petroleum (b. p. 100—120°) | 111—113 | $C_{23}H_{37}N_8Cl$ | 60·1 | 7·6 | 23·9 | 59·95 | 8·05 | 24·3 |
| 4514 | $N([CH_2]_2{\cdot}NEt_2)_2$ | Water (trihydriodide) | 158—162 | $C_{24}H_{39}N_8Cl$,3HI | 33·3 | 5·15 | 12·65 | 33·65 | 4·6 | 13·05 |

4-chloropyrimidines and interaction of the latter with either β-diethylaminoethylamine or γ-diethylaminopropylamine was by the method described above for 4212. The substances so prepared are contained in Table II. In addition a related substance, 2-p-*aminophenylguanidino*-4-*β-diethylaminoethylamino*-6-*methylpyrimidine* (III, R = $NH_2$, R′ = H, R″ = $[CH_2]_2{\cdot}NEt_2$) (3819) was prepared by reduction of the corresponding nitro-derivative (Curd and Rose, *J.*, 1946, 366) with hydrogen and Raney nickel at ordinary temperature and pressure. It formed colourless needles from light petroleum (b. p. 100—120°), m. p. 143—145° (Found : N, 30·05. $C_{18}H_{28}N_8,H_2O$ requires N, 30·4%).

2-p-*Chlorophenylguanidino*-4-*substituted-amino*-6-*methylpyrimidines* (III; R = Cl).—These compounds, prepared by interaction of 4-chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine (see Part IV) with the appropriate amines, either in acetic acid or chlorobenzene in the presence of dilute sodium hydroxide, are listed in Table III.

2-p-*Chlorophenylguanidino*-4 : 6-*dimethylpyrimidine* (4380).—*p*-Chlorophenyldiguanide hydrochloride (12·5 g.), acetylacetone (6 g.), anhydrous sodium acetate (8·2 g.), and acetic acid (100 c.c.) were refluxed for 2 hours, added to water (400 c.c.), and made alkaline with sodium hydroxide. The solid was collected, reprecipitated from solution in dilute hydrochloric acid with ammonia, and crystallised from aqueous dioxan. It formed colourless needles, m. p. 204—205° (Found : Cl, 12·3. $C_{13}H_{14}N_5Cl,H_2O$ requires Cl, 12·4%).

IMPERIAL CHEMICAL INDUSTRIES LTD., RESEARCH LABORATORIES,
BLACKLEY, MANCHESTER, 9.

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