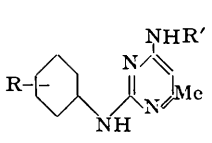
71. *Synthetic Antimalarials. Part IV. 2-Phenylguanidino-4-aminoalkylamino-6-methylpyrimidines.*

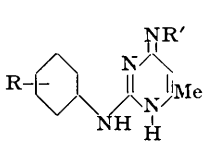
By F. H. S. Curd and F. L. Rose.

The series of 2-anilino-4-dialkylaminoalkylamino-6-methylpyrimidines carrying substituents in the 2-anilino group, described in Part I (this vol., p. 343), has been extended to the 2-phenylguanidino derivatives. The new compounds, like those of the earlier paper, function as riboflavin antagonists. Several are potent antimalarial agents.

In Part I (*loc. cit.*) we recorded the development of a new class of antimalarial drug based on pyrimidine. The most active compounds were of type (I; R = Cl or OMe, R′ = alkylene·N(alkyl)$_2$). The therapeutic activity of these compounds was thought to be associated with a tautomeric possibility (I) $\rightleftharpoons$ (II) similar to that suggested by Schönhöfer for mepacrine (III) (*Z. physiol. Chem.*, 1942, **274**, 1), and to the ability of these substances to function as antagonists of the growth factor riboflavin (Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, in the press). This antagonism was attributed to the formal resemblance of (I) and (III), when formulated as planar molecules, to the structure of riboflavin (IV). It was apparent that the tautomerism (I) $\rightleftharpoons$ (II) would be largely independent of the nature of the amino substituent in the 2-position of the pyrimidine ring,

thus allowing considerable scope for variation with the possibility that active compounds might still result. We were at that time interested in aryldiguanides in another connection, and it occurred to us that a diguanide such as (V) might give rise to compounds of type (VI) having similar tautomeric potentialities to (I) and still possessing, when formulated as a planar molecule, some slight structural resemblance to riboflavin. Aryldiguanides are known compounds and are most readily prepared in the form of their salts by the interaction of arylamine salts with dicyandiamide (Smolka and Friedreich, *Monatsh.*, 1888, **9**, 230; Cohn, *J. pr. Chem.*,


(I.)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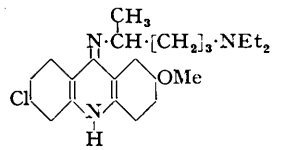
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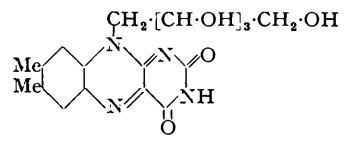
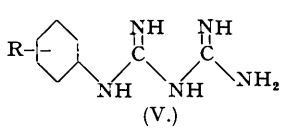

(IV.)

1911, **84**, 394). The necessary precursor of (VI) would be the hydroxypyrimidine (VII) which, by analogy with the reaction between *p*-methoxyphenylguanidine and ethyl acetoacetate described by Curd and Rose (*loc. cit.*), might be expected to result from the reaction of the latter with (V). It was anticipated, however, that a mixture of isomers would be obtained since nitrogen atoms other than the terminal pair might be involved in the condensation, resulting, for example, in (VIII). Further, it has been shown that ethyl formate reacts with diguanide to give 2 : 4-diamino-1 : 3 : 5-triazine (Rackmann, *Annalen*, 1910, **376**, 167) and with phenyl-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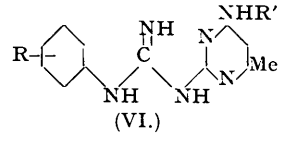
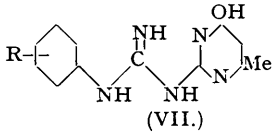

(VI.)

diguanide to give compounds believed to be triazines (Wagner, *J. Org. Chem.*, 1940, **5**, 140), so that with ethyl acetoacetate compounds of type (IX) might also be formed. The reactions were carried out either between the aryldiguanide and the β-keto ester in ethyl alcohol in the presence of sodium hydroxide or sodium ethoxide, or starting with the diguanide hydrochloride and using an additional molar quantity of alkali or alkoxide. Under these conditions, and dependent upon reaction temperature, two substances have been obtained from the reaction with *p*-chlorophenyldiguanide. The compound tentatively formulated as (VII; R = *p*-Cl) con-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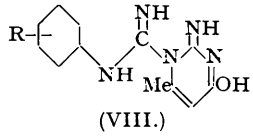
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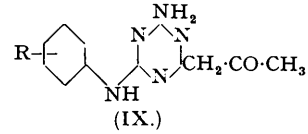
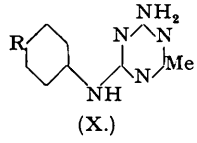

(IX.)

stituted 80% or more of the reaction mixture, but a substance of the same empirical formula as (IX; R = *p*-Cl) was also isolated in small yield. Dr. A. G. Murray and Mr. R. S. Neal working in these laboratories have examined this reaction in some detail and have found that this second compound is decomposed by hot dilute sodium hydroxide giving a compound analysing as (X; R = Cl) and identical with the product obtained by acetylation of (V; R = *p*-Cl); its feeble basicity and solubility properties suggest that it has the triazine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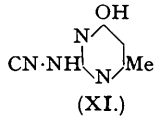
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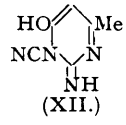
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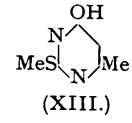
(XIII.)

structure formulated. Compounds of the type (VII; R = *p*-Cl, F, NO_2) have also been made by interaction of the appropriate aniline hydrochloride with the condensation product of dicyandiamide and ethyl acetoacetate to which structure (XI) has been attributed (Pohl, *J. pr. Chem.*, 1908, **77**, 542). The isomeric structure (XII), which with $R{\cdot}C_6H_4{\cdot}NH_2$ would give (VIII), was, however, not excluded. More recently the structure of (VII; R = *p*-Cl) has been established by an unequivocal synthesis from *p*-chlorophenylguanidine and (XIII), the reaction product of *S*-methyl*iso*thiourea and ethyl acetoacetate. Details will be given in a later communication.

The hydroxyl group of compounds of type (VII) was readily replaced by chlorine by treatment with phosphoryl chloride. The resultant chloropyrimidines were labile compounds of high m. p. and low solubility and were not all obtained analytically pure before reaction with dialkylaminoalkylamines to give substances of type (VI). They were, however, more stable under alkaline than acid conditions, and highest yields of the amino compounds were obtained when the reaction was effected by heating the components together in the presence of dilute sodium hydroxide and a solvent such as chlorobenzene. The reaction was also accomplished by fusing the components either alone or with addition of a little acetic acid, but gummy by-products were invariably produced, particularly if the temperature exceeded 130°.

The first preparation in the series was 2-p-*chlorophenylguanidino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (VI; R = *p*-Cl, R′ = $CH_2 \cdot CH_2 \cdot NEt_2$); this was found to have high antimalarial activity against *P. gallinaceum* in chicks (method described by Curd, Davey, and Rose, *loc. cit.*). Futher structural variations were made to ascertain how far activity was dependent upon the substituent in the aniline residue and the nature of the basic side chain. In all, some fifty compounds have been made, but in this communication we record the results with a limited number of the earliest preparations. The remainder will be discussed in a later paper of this series.

Antimalarial Activities.

The activity at various doses is expressed as in Part I. The drugs were administered orally.

	Formula of Base (VI).		Dose,	
Ref. No.	R.	R′.	mg./kg.	Activity.
3688	H	$CH_2 \cdot CH_2 \cdot CH_2 \cdot NEt_2$	300	+
3349	*p*-Cl	$CH_2 \cdot CH_2 \cdot NEt_2$	40	++
			20	+
3916	*p*-Cl	$CH_2 \cdot CH_2 \cdot CH_2 \cdot NC_5H_{10}$	160	+
3907	*p*-Cl	$CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NEt_2$	200	+
3833	*m*-Cl	$CH_2 \cdot CH_2 \cdot NEt_2$	80	+
3836	*o*-Cl	$CH_2 \cdot CH_2 \cdot NEt_2$	160	+
4510	*p*-F	$CH_2 \cdot CH_2 \cdot NEt_2$	40	++
			20	+
3779	*p*-Br	$CH_2 \cdot CH_2 \cdot NEt_2$	50	+
3831	*p*-I	$CH_2 \cdot CH_2 \cdot NEt_2$	40	+
3822	*p*-CN	$CH_2 \cdot CH_2 \cdot NEt_2$	40	++
			20	+
3747	*p*-NO_2	$CH_2 \cdot CH_2 \cdot NEt_2$	40	++
			20	+
3742	*p*-MeO	$CH_2 \cdot CH_2 \cdot NEt_2$	200	—

One of the most active compounds (3349) was examined by Dr. Madinaveitia and found to antagonise riboflavin with respect to the growth of *Lactobacillus casei* so the mode of action of this type of drug was probably related to that of the allied *p*-chloroanilino compounds recorded in Part I.

Experimental.

p-*Chlorophenyldiguanide* (V; R = *p*-Cl).—*p*-Chloroaniline hydrochloride (170 g.) and dicyandiamide (84 g.) were refluxed together in water (400 c.c.) for 1 hour. The diguanide salt separated out. The suspension was cooled and filtered. Recrystallisation of the solid from water gave p-*chlorophenyldiguanide hydrochloride* as colourless plates (120 g.), m. p. 253—254° (Found: N, 27·9. $C_8H_{10}N_5Cl,HCl$ requires N, 28·2%). The free *base* was obtained by adding excess sodium hydroxide to a solution of the hydrochloride in water at 90°. The oil which formed solidified on cooling and crystallised from water as colourless prisms, m. p. 94—95° (Found: Cl, 15·25. $C_8H_{10}N_5Cl,H_2O$ requires Cl, 15·45%).

4-*Hydroxy*-2-p-*chlorophenylguanidino*-6-*methylpyrimidine* (VII; R = *p*-Cl).—(a) *p*-Chlorophenyldiguanide hydrochloride (160 g.) was stirred in a mixture of ethyl alcohol (400 c.c.), water (60 c.c.), and sodium hydroxide (40 g.) at 40° until dissolved. Ethyl acetoacetate (192 c.c.) was added and the mixture left at room temperature for 20 hours. The precipitate was filtered off, washed with a little alcohol, then well with water, and dried. The crude solid (138 g.) was boiled in methyl alcohol (300 c.c.) for several minutes, cooled a little, and filtered. The insoluble residue (122 g.) melted at 288—289° and was pure 4-*hydroxy*-2-p-*chlorophenylguanidino*-6-*methylpyrimidine* (Found: C, 52·0; H, 4·05; N, 24·8. $C_{12}H_{12}ON_5Cl$ requires C, 52·0; H, 4·3; N, 25·2%). Recrystallisation from nitrobenzene gave colourless needles, m. p. 288—289°.

The methyl alcohol extract was diluted with water and the precipitate collected and recrystallised from a smaller volume of methyl alcohol. The colourless crystalline solid, m. p. 162—164°, was considered to be 2-*amino*-4-p-*chlorophenylamino*-6-*acetonyl*-1 : 3 : 5-*triazine* (IX; R = *p*-Cl) (Found: C, 52·35; H, 4·8; N, 25·0; Cl, 12·5. $C_{12}H_{12}ON_5Cl$ requires C, 52·0; H, 4·3; N, 25·2; Cl, 12·8%). A solution in dilute sodium hydroxide gave, on heating, a compound, m. p. 195—196°. An identical compound (no depression of m. p.) was obtained by cautiously adding acetic anhydride (4 c.c.) to a solution of 4-chlorophenyldiguanide hydrochloride (4·6 g.) in dioxan (10 c.c.), water (10 c.c.), and sodium hydroxide (10 g.), stirred at 40—50°, and after 30 minutes adding water (70 c.c.) and recrystallising the dried and washed precipitate from *n*-butyl alcohol. 2-*Amino*-4-p-*chlorophenylamino*-6-*methyl*-1 : 3 : 5-*triazine* (X; R = Cl) was thus obtained as colourless needles, m. p. 195—196° (Found: C, 50·6; H, 3·8; N, 29·25. $C_{10}H_{10}N_5Cl$ requires C, 50·95; H, 4·25; N, 29·6%).

(b) 2-Cyanoamino-4-hydroxy-6-methylpyrimidine (5·6 g.; Pohl, *loc. cit.*), and *p*-chloroaniline (5·6 g.) were refluxed for 10 hours in a mixture of β-ethoxyethanol (60 c.c.) and 2N-hydrochloric acid (50 c.c.). The resultant solution was made alkaline with concentrated sodium hydroxide solution while still hot, and diluted with cold water (400 c.c.). The crystalline precipitate of crude (VII; R = *p*-Cl) was collected and purified through conversion into the hydrochloride. For this purpose the solid was dissolved in water (200 c.c.) and concentrated hydrochloric acid (10 c.c.) at 40°, and filtered from insoluble impurity. More hydrochloric acid (100 c.c.) was added to the filtrate, and the precipitated hydrochloride filtered off. This was converted to the free base by dissolving in water (100 c.c.) at 60° and adding dilute ammonia until just alkaline. The precipitate was collected, washed, and dried (3·8 g.), and recrystallised from nitrobenzene, m. p. 288—289° (no depression with material made as in (a)).

4-*Chloro*-2-p-*chlorophenylguanidino*-6-*methylpyrimidine*.—4-Hydroxy-2-*p*-chlorophenylguanidino-6-methylpyrimidine (150 g.) was refluxed with phosphoryl chloride (300 c.c.) for 30 minutes. The hot reaction mixture was cautiously added to crushed ice and water (3 kg.) containing dissolved sodium hydroxide (600 g.). The precipitate was filtered off, washed with water, and dried in a vacuum over solid potassium hydroxide (yield, 142 g.). It was not convenient, necessary, or even possible without considerable decomposition, to purify the entire yield. A small quantity was therefore crystallised rapidly from acetone. 4-*Chloro*-2-p-*chlorophenylguanidino*-6-*methylpyrimidine* was then obtained as colourless silky needles, m. p. 180° (Found: C, 48·1; H, 3·4; N, 23·25. $C_{12}H_{11}N_5Cl_2$ requires C, 48·65; H, 3·7; N,

23·6%). Omission of the sodium hydroxide from the above ice-water mixture gave the 4-chloropyrimidine as the unstable hydrochloride. This recrystallised from water in colourless needles, carrying water of crystallisation, which melted indefinitely dependent upon rate of heating. The crude chloropyrimidine hydrochloride, after drying in a vacuum over potassium hydroxide, was used successfully for reaction with dialkylaminoalkylamines.

2-p-*Chlorophenylguanidino*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* (VI; R = *p*-Cl, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$).—(a) 4-Chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine hydrochloride (crude dried reaction product, 135 g.), *β*-diethylaminoethylamine (59 g.), and acetic acid (55 c.c.) were heated together for 30 minutes in an oil-bath at 120—130°. The hot reaction melt was added to cold water (1 l.), stirred with decolourising charcoal, and filtered. The filtrate was made alkaline with sodium hydroxide. The sticky precipitate solidified on warming to 60—70° and was filtered off and dried (yield, 106 g.); 60 g. were crystallised from light petroleum (b. p. 100—120°) to give colourless needles (35 g.) of 2-p-*chlorophenylguanidino*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine*, m. p. 154—155° (Found: C, 57·4; H, 6·65; N, 25·8. $C_{18}H_{26}N_7Cl$ requires C, 57·5; H, 6·9; N, 26·1%).

(b) 4-Chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine (3·3 g.; crystalline base), *β*-diethylaminoethylamine (1·9 g.), chlorobenzene (10 c.c.), sodium hydroxide (1·6 g.), and water (10 c.c.) were refluxed with stirring for ½ hour. The chlorobenzene was distilled off in steam and the residual solid collected. This crude product was purified by dissolving in dilute acetic acid and reprecipitating, after filtration, with sodium hydroxide. The base was filtered off and dried (yield, 3·7 g.), m. p. 154—154·5°, undepressed in admixture with crystalline material made by method (a). 2-p-*Chlorophenylguanidino*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine dihydrochloride* (3349) was obtained as colourless prisms, m. p. 142—144°, by dissolving the base (69·6 g.) in 2N-hydrochloric acid (179 c.c.) and adding acetone (750 c.c.) (Found: Cl′, 15·1. $C_{18}H_{26}N_7Cl,2HCl,H_2O$ requires Cl′, 15·2%).

2-p-*Chlorophenylguanidino*-4-*γ*-*diethylaminopropylamino*-6-*methylpyrimidine* (VI; R = *p*-Cl, R′ = $CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2$) (3907), prepared by method (a) above by interaction of *γ*-diethylaminopropylamine (10·6 g.) and the chloropyrimidine (pure crystalline base, 14·8 g.), formed colourless needles from light petroleum (b. p. 80—100°) (Found: C, 59·65; H, 7·65; N, 24·1. $C_{19}H_{28}N_7Cl$ requires C, 59·4; H, 7·4; N, 24·3%).

2-p-*Chlorophenylguanidino*-4-*β*-*piperidinoethylamino*-6-*methylpyrimidine* (VI; R = *p*-Cl, R′ = $CH_2{\cdot}CH_2{\cdot}N{<}[CH_2]_4{>}CH_2$) (3916), prepared analogously from *β*-piperidinoethylamine (10·7 g.) and the chloropyrimidine (pure crystalline base, 14·8 g.), formed colourless prisms from *n*-butyl alcohol, m. p. 192° (Found: C, 59·6; H, 6·55; N, 24·0. $C_{20}H_{28}N_7Cl$ requires C, 59·8; H, 7·0; N, 24·4%).

4-*Hydroxy*-2-p-*fluorophenylguanidino*-6-*methylpyrimidine* (VII; R = *p*-F), obtained as for the *p*-chlorophenyl derivative (method (b)) by refluxing for 22 hours a mixture of *p*-fluoroaniline hydrochloride (12 g.), 2-cyanoamino-4-hydroxy-6-methylpyrimidine (12·5 g.), *β*-ethoxyethanol (60 c.c.), and water (20 c.c.), crystallised from nitrobenzene as colourless needles, m. p. 258—260° (Found: C, 54·95; H, 5·0; N, 26·0. $C_{12}H_{12}ON_5F$ requires C, 55·2; H, 4·6; N, 26·8%).

4-*Hydroxy*-2-p-*nitrophenylguanidino*-6-*methylpyrimidine* (VII; R = *p*-NO_2) was prepared similarly by refluxing for 5 hours a mixture of *p*-nitroaniline (27·4 g.), 2-cyanoamino-4-hydroxy-6-methylpyrimidine (30 g.), *β*-ethoxyethanol (150 c.c.), concentrated hydrochloric acid (17·4 c.c.), and water (20 c.c.) (yield of crude product, 42 g.), m. p. 260—262°. It crystallised from nitrobenzene as yellow needles, m. p. 279—281° (Found: C, 49·5; H, 4·2; N, 28·7. $C_{12}H_{12}O_3N_6$ requires C, 50·0; H, 4·2; N, 29·2%). A solution in hot dilute sodium hydroxide gave golden yellow needles of a sodium salt on cooling.

Substituted Phenyldiguanides (V).—The following diguanides were made as intermediates for the preparation of the corresponding 4-hydroxy-2-substitued-phenylguanidino-6-methylpyrimidines:

o-*Chlorophenyldiguanide hydrochloride* (V; R = *o*-Cl), prepared as for (V, R = *p*-Cl) by refluxing for 1½ hours *o*-chloroaniline (32 g.), dicyandiamide (21 g.), concentrated hydrochloric acid (22 c.c.), and water (150 c.c.). Colourless needles from water, m. p. 239° (yield, 37 g.) (Found: N, 27·85. $C_8H_{10}N_5Cl,HCl$ requires N, 28·2%). m-*Chlorophenyldiguanide hydrochloride* (V; R = *m*-Cl), prepared similarly from *m*-chloroaniline hydrochloride (46 g.), dicyandiamide (23 g.) and water (70 c.c.). Colourless prisms from water, m. p. 208° (yield, 21 g.) (Found: N, 27·7. $C_8H_{10}N_5Cl,HCl$ requires N, 28·2%). p-*Bromophenyldiguanide hydrochloride* (V; R = *p*-Br), prepared similarly from *p*-bromoaniline hydrochloride (31·4 g.), dicyandiamide (12·7 g.), and water (50 c.c.), refluxed for 15 minutes and recrystallised from water, m. p. 242—244° (yield, 25·3 g.) (Found: N, 23·65. $C_8H_{10}N_5Br,HCl$ requires N, 23·9%). p-*Iodophenyldiguanide hydrochloride* (V; R = *p*-I), prepared similarly from *p*-iodoaniline (21·5 g.), dicyandiamide (8·4 g.), concentrated hydrochloric acid (8·8 c.c.), and water (70 c.c.) by refluxing for 1 hour. Colourless prisms from water, m. p. 234° (yield, 19 g.) (Found: N, 19·65. $C_8H_{10}N_5I,HCl,H_2O$ requires N, 19·6%). p-*Cyanophenyldiguanide hydrochloride* (V; R = *p*-CN), prepared from *p*-aminobenzonitrile (11·8 g.), dicyandiamide (8·4 g.), concentrated hydrochloric acid (8·8 c.c.), and water (70 c.c.) refluxed for 15 minutes. Colourless crystals from water, m. p. 284—286° (yield, 10·8 g.) (Found: N, 34·8. $C_9H_{10}N_6,HCl$ requires N, 35·2%).

p-*Nitrophenyldiguanide* (V; R = *p*-NO_2) required slightly modified reaction conditions. *p*-Nitroaniline (8·4 g.) was dissolved in hot water (20 c.c.) and concentrated hydrochloric acid (8·8 c.c.). Dicyandiamide (14 g.) was added and the mixture was refluxed for 15 minutes. The crystalline precipitate formed on cooling contained unreacted *p*-nitroaniline hydrochloride. The suspension was diluted with water, re-heated to give complete solution, and poured into excess dilute sodium hydroxide. The yellow precipitate was filtered off, dried at 100°, then stirred with toluene (120 c.c.) at 50°. Unchanged *p*-nitroaniline dissolved, leaving *p*-nitrophenyldiguanide. This was collected and crystallised from ethyl alcohol, being thus obtained as golden yellow needles, m. p. 177—179° (yield, 3·2 g.) (Found: C, 40·0; H, 5·0; N, 34·35. $C_8H_{10}O_2N_6,H_2O$ requires C, 40·0; H, 5·0; N, 35·0%).

4-*Hydroxy*-2-*substituted*-*phenylguanidino*-6-*methylpyrimidines* (VII).—The following were made by reaction of the appropriate diguanides with ethyl acetoacetate [method (a) described above for (VII; R = *p*-Cl)]:

4-*Hydroxy*-2-*phenylguanidino*-6-*methylpyrimidine* (VII; R = H), from phenyldiguanide hydrochloride (55 g.; Cohn, *J. pr. Chem.*, 1911, **84**, 394), ethyl acetoacetate (80 c.c.), ethyl alcohol (150 c.c.), and sodium hydroxide solution (40 c.c., 40%) (yield of crude product, 39 g.). Colourless needles from nitrobenzene, m. p. 244—246° (Found: N, 28·55. $C_{12}H_{13}ON_5$ requires N, 28·8%). 4-*Hydroxy*-2-m-*chlorophenylguanidino*-6-*methylpyrimidine* (VII; R = *m*-Cl), from *m*-chlorophenyldiguanide hydrochloride (20 g.), ethyl acetoacetate (29 c.c.), ethyl alcohol (70 c.c.), and sodium hydroxide solution (15·6 c.c., 40%) (yield of crude product, 18 g.). Colourless needles from nitrobenzene, m. p. 239° (Found: N, 24·55. $C_{12}H_{12}ON_5Cl$ requires N, 25·2%). 4-*Hydroxy*-2-o-*chlorophenylguanidino*-6-*methylpyrimidine* (VII; R = *o*-Cl), from *o*-chlorophenyldiguanide hydrochloride using the same quantities as for the *m*-chloro derivative (yield of crude product, 20 g.). Colourless crystals from nitrobenzene, m. p. 252—254° (Found: N, 24·35. $C_{12}H_{12}ON_5Cl$ requires N, 25·2%). 4-*Hydroxy*-2-p-*bromophenylguanidino*-6-*methylpyrimidine* (VII; R = *p*-Br), similarly prepared from *p*-bromophenyldiguanide hydrochloride (25·3 g.) (yield of crude product 24·2 g.). Needles from nitrobenzene, m. p. 252—254° (Found: N, 21·4. $C_{12}H_{12}ON_5Br$ requires N, 21·75%). 4-*Hydroxy*-2-p-*iodophenylguanidino*-6-*methylpyrimidine* (VII; R = *p*-I), similarly prepared from *p*-iodophenyldiguanide hydrochloride (19 g.) (yield of crude product 17 g.). Pale yellow needles from nitrobenzene, m. p. 275—280° (Found: N, 18·15. $C_{12}H_{12}ON_5I$ requires N, 18·9%). 4-*Hydroxy*-2-p-*cyanophenylguanidino*-6-*methylpyrimidine* (VII; R = *p*-CN), similarly prepared from *p*-cyanophenyl-

diguanide hydrochloride (10·7 g.). Colourless prisms from nitrobenzene, m. p. 278° (Found: N, 31·1. $C_{13}H_{13}ON_6$ requires N, 31·3%).

4-Hydroxy-2-p-nitrophenylguanidino-6-methylpyrimidine (VII; R = *p*-NO_2). *p*-Nitrophenyldiguanide (9 g.), ethyl acetoacetate (11·4 g.), sodium methoxide (2·6 g.), and methyl alcohol (60 c.c.) were refluxed for 15 hours. The mixture was cooled and the crude hydroxypyrimidine which precipitated was purified by dissolving in hot dilute sodium hydroxide, reprecipitating with dilute acetic acid and recrystallising from nitrobenzene. Yellow needles, m. p. 279—281°, undepressed in admixture with material made as described above from 2-cyanoamino-4-hydroxy-6-methylpyrimidine and *p*-nitroaniline (p. 365).

4-Hydroxy-2-p-anisylguanidino-6-methylpyrimidine (VII; R = *p*-OMe), prepared from *p*-anisyldiguanide hydrochloride (10·1 g.), ethyl acetoacetate (11 c.c.), ethyl alcohol (20 c.c.), and sodium hydroxide solution (3·6 c.c., 40%), left at room temperature for 4 days. The reaction product was recrystallised from β-ethoxyethanol. Colourless prisms, m. p. 253° (Found: N, 25·2. $C_{13}H_{13}O_2N_5$ requires N, 25·6%).

2-Substituted-phenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidines (VI).—The 4-hydroxypyrimidine derivatives described above were converted, by the methods already indicated, successively into the corresponding 4-chloro- and 4-β-diethylaminoethylamino-pyrimidines. The chloropyrimidines were isolated from the phosphoryl chloride reaction mixture either as free bases by adding to ice and sodium hydroxide, or as hydrochlorides by adding to ice alone. The crude 4-chloropyrimidines were not characterised, but, after drying in a vacuum over potassium hydroxide, were caused to react with β-diethylaminoethylamine by method (a) described above for (VI; R = *p*-Cl, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$). In one instance, *viz.*, (VI; R = *p*-F, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$), method (b) was employed.

2-Phenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine (VI; R = H, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$) (3688). The 4-chloropyrimidine hydrochloride (17·8 g.; crude reaction product from (VII; R = H, 39 g.) and phosphoryl chloride (78 c.c.)) were heated with β-diethylaminoethylamine (10·6 c.c.) in acetic acid (10 c.c.) for 1 hour in an oil-bath at 130°. The reaction mixture was worked up as indicated earlier and the base recrystallised from light petroleum (b. p. 100—120°). Colourless flat needles, m. p. 127—128° (Found: C, 63·95; H, 7·95; N, 27·4. $C_{19}H_{29}N_7$ requires C, 64·3; H, 8·2; N, 27·6%). The 2-m-*chlorophenyl* compound (VI; R = *m*-Cl, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$) (3833), analogously prepared from the corresponding 4-chloropyrimidine hydrochloride (17 g.; crude reaction product), β-diethylaminoethylamine (9 g.), and acetic acid (9 c.c.), crystallised from light petroleum (b. p. 100—120°), after drying the hot solution over potassium hydroxide, as colourless needles, m. p. 149° (Found: C, 57·3; H, 6·7; N, 25·65. $C_{18}H_{26}N_7Cl$ requires C, 57·5; H, 6·9; N, 26·1%). The 2-o-*chlorophenyl* compound (VI; R = *o*-Cl, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$) (3836), from the corresponding 4-chloropyrimidine hydrochloride (15 g.; crude reaction product), β-diethylaminoethylamine (7·9 c.c.), and acetic acid (7 c.c.), crystallised from light petroleum as colourless prisms, m. p. 130° (Found: C, 57·1; H, 6·8; N, 25·45. $C_{18}H_{26}N_7Cl$ requires C, 57·5; H, 6·9; N, 26·1%). The 2-p-*fluorophenyl* compound (VI; R = *p*-F, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$) (4510), from the corresponding 4-chloropyrimidine base (4·5 g.; crude reaction product), β-diethylaminoethylamine (3·8 g.), chlorobenzene (35 c.c.), sodium hydroxide solution (5 c.c., 40%), and water (35 c.c.) by refluxing for 2 hours, crystallised from light petroleum (b. p. 100—120°) as colourless needles, m. p. 163—164° (Found: C, 57·8; H, 7·05; N, 26·05. $C_{18}H_{26}N_7F,H_2O$ requires C, 57·3; H, 7·4; N, 26·0%). The 2-p-*bromophenyl* compound (VI; R = *p*-Br, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$) (3779), from the corresponding 4-chloropyrimidine hydrochloride (28·4 g.; crude reaction product), β-diethylaminoethylamine (10·5 g.), and acetic acid (9 c.c.), heated for 30 mins. in an oil-bath at 95—100°, crystallised from light petroleum (b. p. 100—120°) as colourless prisms, m. p. 154—155° (Found: C, 50·95; H, 5·8; N, 22·7. $C_{18}H_{26}N_7Br$ requires C, 51·4; H, 6·2; N, 23·3%). The 2-p-*iodophenyl* compound (VI; R = *p*-I, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$) (3831), from the corresponding 4-chloropyrimidine hydrochloride (18 g.; crude reaction product), β-diethylaminoethylamine (7·4 g.), and acetic acid (7 c.c.) heated for 1 hour at 100°, crystallised from acetone as colourless prisms, m. p. 157—159° (Found: N, 20·7. $C_{18}H_{26}N_7I$ requires N, 21·0%). The 2-p-*cyanophenyl* compound (VI; R = *p*-CN, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$) (3822), from the corresponding 4-chloropyrimidine hydrochloride (7·6 g.; crude reaction product), β-diethylaminoethylamine (3·3 g.), and acetic acid (3 c.c.) heated for 1 hour at 100°, crystallised from *n*-butyl alcohol as colourless prisms, m. p. 220—221° (Found: C, 61·9; H, 7·25; N, 29·8. $C_{19}H_{26}N_8$ requires C, 62·0; H, 7·1; N, 30·6%). The 2-p-*nitrophenyl* compound (VI; R = *p*-NO_2, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$) (3747), from the corresponding 4-chloropyrimidine hydrochloride (5·1 g.; crude reaction product), β-diethylaminoethylamine (2·3 g.), and acetic acid (2 c.c.) heated 1 hour at 100°, crystallised from *n*-propyl alcohol as colourless needles, m. p. 214—215° (yield, 2·2 g.) (Found: C, 55·4; H, 6·2; N, 28·45. $C_{18}H_{26}O_2N_8$ requires C, 55·8; H, 6·6; N, 29·0%). The 2-p-*anisyl* compound (VI; R = *p*-OMe, R′ = $CH_2{\cdot}CH_2{\cdot}NEt_2$) (3742), from the corresponding 4-chloropyrimidine hydrochloride (16·4 g.; crude reaction product), β-diethylaminoethylamine (7 g.), and acetic acid (6 c.c.) heated for 15 mins. in an oil-bath at 120—130°, crystallised from toluene as colourless prisms, m. p. 185—186° (yield, 6 g.) (Found: C, 61·7; H, 7·4; N, 26·15. $C_{19}H_{29}ON_7$ requires C, 61·4; H, 7·8; N, 26·4%).

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