121. *Synthetic Antimalarials. Part XXV. Some 4-Arylguanidino-2- and -6-dialkylaminoalkylaminopyrimidines.*

By A. F. Crowther, F. H. S. Curd, and F. L. Rose.

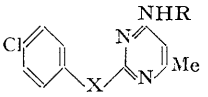
The presumed constitution (Part IV, *J.*, 1946, 362) of the main product of condensation of an aryldiguanide with ethyl acetoacetate has been unequivocally proved to be that of a 2-arylguanidino-4-hydroxy-6-methylpyrimidine by the synthesis, in two cases, of the same compounds from the appropriate arylguanidine and 4-hydroxy-2-methylthio-6-methylpyrimidine.

The study of 2-arylguanidino-4-aminoalkylamino-6-methylpyrimidines, for which these 2-arylguanidino-4-hydroxy-6-methylpyrimidines served as intermediates (Part IV, *loc. cit.*; Part XXIII, this vol., p. 574), has been extended, in the present paper, to include the isomeric 4-arylguanidino-2-dialkylaminoalkylamino-6-methyl- and 4-arylguanidino-6-dialkylaminoalkylamino-2-methyl-pyrimidines. The preferred method of synthesis of these new types involves condensation of an aryl *iso*thiocyanate with 4-amino-2-dialkylaminoalkylamino-6-methylpyrimidines and 4-amino-6-dialkylaminoalkylamino-2-methylpyrimidines respectively, followed by conversion of the resulting arylthioureido-dialkylaminoalkylamino-methylpyrimidines into the corresponding guanidino-compounds by the action of ammonia and a desulphurising agent.

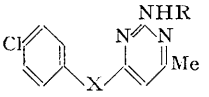
This type of synthesis has also enabled the preparation of 2-arylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines in which the guanidino-linkage carries an additional alkyl group.

Antimalarial activity is exhibited by all the new types now described.

In this paper we propose to give an account of further arylguanidino-aminoalkylaminopyrimidines which we have investigated following the demonstration of antimalarial activity in compounds of type [I; X = NH·C(:NH)·NH, R = dialkylaminoalkyl] (Part IV, *J.*, 1946, 362) not only against avian malaria but also against human malaria (Adams and Sanderson, *Ann. Trop. Med. Parasit.*, 1945, **39**, 165, 169, 173, 180). Because of the activity of types (I and II; X = NH, R = dialkylaminoalkyl) (*J.*, 1946, 343, 370) which are isomeric, our first objective was the preparation of substances of type [II; X = NH·C(:NH)·NH,



(I.)



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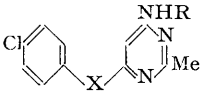
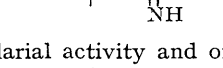


(III.)

R = dialkylaminoalkyl] similarly related to type [I; X = NH·C(:NH)·NH]: later, substances of type [III; X = NH·C(:NH)·NH, R = dialkylaminoalkyl] were also prepared. The anilino-compounds (III; X = NH) described in Parts VIII (*J.*, 1946, 713) and XXI (*J.*, 1947, 1354) are without activity, and this has been tentatively related to the interdependence of the two amidine systems which does not allow a conjugated path to be traced between the aryl and dialkylaminoalkyl groups *via* alternate carbon and nitrogen atoms in any of the polarised or tautomeric forms of the molecule. Similar considerations apply to [III;

X = NH·C(:NH)·NH] although the incorporation of an additional amidine unit in the bridge between the aryl and pyrimidine nuclei provides in a different manner the system



thought to be essential for antimalarial activity and on which the highly active diguanides described in Part X (*J.*, 1946, 729) were based.

The method of preparation utilised for compounds of type [I; X = NH·C(:NH)·NH] (Part IV, *loc. cit.*) could not be used for the isomeric types [II and III; X = NH·C(:NH)·NH], and different methods of synthesis had to be sought.

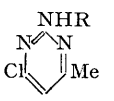
In Part VI (*J.*, 1946, 370) the preparation of compounds of type (II; X = NH) by condensation of a 4-chloro-2-dialkylaminoalkylamino-6-methylpyrimidine (IV) with an arylamine was described, and in Part XV (*J.*, 1947, 783) a similar method was applied to compounds of type (I; X = NH). The condensation of 2-chloro-4-β-diethylaminoethylamino-6-methylpyrimidine (V; R = $[CH_2]_2$·NEt_2) and *p*-chlorophenylguanidine (conveniently prepared by interaction of benzoylcyanamide and *p*-chloroaniline hydrochloride followed by hydrolysis of the resulting benzoyl-*p*-chlorophenylguanidine) was therefore tried. Heated together at 110—120° for 18 hours, these compounds reacted to give 2-*p*-chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine (I; X = NH, R = $[CH_2]_2$·NEt_2) and not the expected 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine {I; X = NH·C(:NH)·NH, R = $[CH_2]_2$·NEt_2}. The reaction between 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (IV; R = $[CH_2]_2$·NEt_2) and *p*-chlorophenylguanidine, which was examined more extensively, proceeded similarly and gave 4-*p*-chloroanilino-2-β-diethylaminoethylamino-6-methylpyrimidine (II; X = NH, R = $[CH_2]_2$·NEt_2). One possible explanation of these unexpected results is that the chloropyrimidines condensed with *p*-chlorophenylguanidine on the nitrogen atom carrying the aryl group to give, in the latter case, the compound (VI; R = NH·$[CH_2]_2$·NEt_2) which was then degraded to give (II; X = NH, R = $[CH_2]_2$·NEt_2). However, the possibility cannot be excluded that, under the reaction conditions, the *p*-chlorophenylguanidine decomposed to give *p*-chloroaniline before condensation. N-p-*Chlorophenyl*-S-*methyl*isothiourea also reacted with (IV; R = $[CH_2]_2$·NEt_2) to give 4-*p*-chloroanilino-2-β-diethylaminoethylamino-6-methylpyrimidine as the sole product.

Another synthetic approach to compounds of type [II; X = NH·C(:NH)·NH, R = dialkylaminoalkyl] involving the use of *p*-chlorophenylguanidine was then made in the following way. 2-Hydroxy-4-methylthio-6-methylpyrimidine (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 431) reacted with *p*-chlorophenylguanidine in boiling *o*-dichlorobenzene to give a product from which 4-*p*-chlorophenylguanidino-2-hydroxy-6-methylpyrimidine [VII; X = NH·C(:NH)·NH, R = OH] was isolated as its *hydrochloride* by extraction with hot dilute hydrochloric acid. For continuation of the synthesis the total acid extract was made alkaline with ammonia and the precipitated product dried and treated with phosphoryl chloride. The resulting chloropyrimidine [VII; X = NH·C(:NH)·NH, R = Cl], without being characterised, was condensed with β-diethylaminoethylamine, γ diethylaminopropylamine, and γ-di-*n*-butylaminopropylamine, by heating either in excess of the aliphatic amine, or in chlorobenzene in presence of aqueous sodium hydroxide, to give poor yields of compounds of type [II; X = NH·C(:NH)·NH] where R = $[CH_2]_2$·NEt_2, $[CH_2]_3$·NEt_2, and $[CH_2]_3$·NBu^{α}_2 respectively. In each case a by-product was isolated which was insoluble in dilute acetic acid and on retreatment with phosphoryl chloride followed by condensation of the product with γ-dimethylaminopropylamine gave 4-*p*-chloroanilino-2-γ-dimethylaminopropylamino-6-methylpyrimidine (II; X = NH, R = $[CH_2]_3$·NMe_2) (cf. Part VI, *loc. cit.*). Again two possible explanations presented themselves. Either the reaction of *p*-chlorophenylguanidine with 2-hydroxy-4-methylthio-6-methylpyrimidine followed two courses, and in addition to the formation of [VII; X = NH·C(:NH)·NH, R = OH] some reaction took place on the nitrogen atom of *p*-chlorophenylguanidine already substituted, to give (VI; R = OH) which then decomposed to give (VII; X = NH, R = OH) and acted as the source of 4-*p*-chloroanilino-2-γ-dimethylaminopropylamino-6-methylpyrimidine in the subsequent transformations; or the *p*-chlorophenylguanidine suffered degradation to *p*-chloroaniline under the conditions of the initial reaction, and the *p*-chloroaniline then reacted with 2-hydroxy-4-methylthio-6-methylpyrimidine to give (VII; X = NH, R = OH). The second explanation seems more likely since it was subsequently demonstrated that *p*-chlorophenylguanidine actually affords some *p*-chloroaniline when heated in boiling *o*-dichlorobenzene for several hours.

Analogous results were obtained in the condensation of *p*-chlorophenylguanidine and

4-hydroxy-2-methylthio-6-methylpyrimidine. When fused together at 160—170° a product was obtained from which it was possible to isolate 4-hydroxy-2-*p*-chlorophenylguanidino-6-methylpyrimidine [VIII; X = NH·C(:NH)·NH, R = Cl, R′ = OH], but when the crude product from a condensation in boiling *o*-dichlorobenzene was treated with phosphoryl chloride a mixture of chloro-compounds resulted, from which 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine (VIII; X = NH, R = R′ = Cl) was separated in addition to 4-chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine [VIII; X = NH·C(:NH)·NH, R = R′ = Cl]. Similarly, *p*-anisylguanidine and 4-hydroxy-2-methylthio-6-methylpyrimidine gave 4-hydroxy-2-*p*-anisylguanidino-6-methylpyrimidine [VIII; X = NH·C(:NH)·NH, R = OMe, R′ = OH], identical with that prepared from *p*-anisyldiguanide and ethyl acetoacetate (Part IV, *loc. cit.*).

The identity of the 4-hydroxy-2-*p*-chlorophenylguanidino-6-methylpyrimidine, arising from condensation of *p*-chlorophenylguanidine with 4-hydroxy-2-methylthio-6-methylpyrimidine, with the main product obtained from the reaction of *p*-chlorophenyldiguanide and ethyl acetoacetate (see Part IV) conclusively proves the constitution of the latter, and hence of the compounds of type [I; X = NH·C(:NH)·NH, R = dialkylaminoalkyl] described in Part IV. The only alternative structure which the former might have is (IX), but such a structure could not possibly result from the condensation of *p*-chlorophenyldiguanide and ethyl acetoacetate. The constitution of the product of interaction of dicyandiamide and ethyl acetoacetate as 2-cyanoamino-4-hydroxy-6-methylpyrimidine (Pohl, *J. pr. Chem.*, 1908, **77**, 542) is also thereby rigidly established, since this compound (X; R = CN) not only condenses with arylamines to give 4-hydroxy-2-arylguanidino-6-methylpyrimidines (see Part IV), but reacts with ammonia to give 4-hydroxy-2-guanidino-6-methylpyrimidine [X; R = C(:NH)·NH_2] which also condenses with *p*-chloroaniline hydrochloride to give [VIII; X = NH·C(:NH)·NH, R = Cl, R′ = OH].



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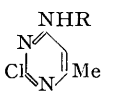

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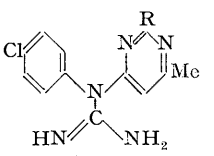

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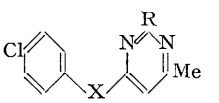

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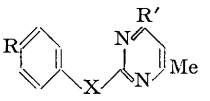

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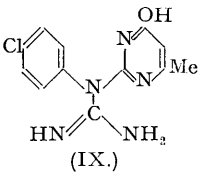

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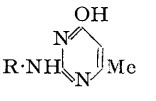

(X.)

A more convenient method of synthesis of compounds of type [II; X = NH·C(:NH)·NH, R = dialkylaminoalkyl] than that outlined above was provided by a series of reactions analogous to that described in the previous paper for the preparation of 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine. 4-Amino-2-β-diethylaminoethylamino-6-methylpyrimidine, prepared by the method of Hull, Lovell, Openshaw, and Todd (Part XI, *J.*, 1947, 41) or by the interaction of 2-chloro-4-amino-6-methylpyrimidine (V; R = H) with β-diethylaminoethylamine, reacted with *p*-chlorophenyl *iso*thiocyanate to give 4-p-*chlorophenylthioureido*-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (II; X = NH·CS·NH, R = $[CH_2]_2$·NEt_2) which was then converted by the action of alcoholic ammonia in the presence of copper sulphate into {II; X = NH·C(:NH)·NH, R = $[CH_2]_2$·NEt_2} identical with the product made by the original route. An attempt to prepare {II; X = NH·C(:NH)·NH, R = CHMe·$[CH_2]_3$·NEt_2} by the same method was abandoned, since the intermediate product from condensing 4-*amino*-2-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine* with *p*-chlorophenyl *iso*thiocyanate could not be obtained crystalline.

Two compounds of the isomeric series were prepared: 4-p-*chlorophenylguanidino*-6-β-*diethylaminoethylamino*-2-*methylpyrimidine* {III; X = NH·C(:NH)·NH, R = $[CH_2]_2$·NEt_2} and 4-p-*chlorophenylguanidino*-6-γ-*diethylaminopropylamino*-2-*methylpyrimidine* {III; X = NH·C(:NH)·NH, R = $[CH_2]_3$·NEt_2}, both from the corresponding *thioureas* (III; X = NH·CS·NH, R = $[CH_2]_2$·NEt_2) and (III; X = NH·CS·NH, R = $[CH_2]_3$·NEt_2), by interaction with methanolic ammonia in presence of mercuric oxide. The thioureas resulted from the condensation of *p*-chlorophenyl *iso*thiocyanate with 4-amino-6-β-diethylaminoethylamino- and 4-amino-6-γ-diethylaminopropylamino-2-methylpyrimidine, respectively.

The preparation of 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine from the corresponding thioureido-compound (I; X = NH·CS·NH, R = $[CH_2]_2$·NEt_2) (preceding paper), and the work on the isomeric types now described, suggested a convenient and unambiguous method of synthesis for compounds of type [I; X = NH·C(:NAlkyl)·NH]. For this purpose, 2-*p*-chlorophenylthioureido-4-β-diethylaminoethylamino-6-methylpyrimidine was brought into reaction with methylamine in presence of mercuric oxide to give 2-N^1-p-*chlorophenyl*-N^2-*methylguanidino*-N^3-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* {I; X = NH·C(:NMe)·NH, R = $[CH_2]_2$·NEt_2}. In a similar manner ethylamine gave 2-N^1-p-*chlorophenyl*-N^2-*ethylguanidino*-N^3-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* {I; X = NH·C(:NEt)·NH, R = $[CH_2]_2$·NEt_2} and *n*-butylamine gave 2-N^1-p-*chlorophenyl*-N^2-n-*butylguanidino*-N^3-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (*dihydrochloride*) {I; X = NH·C(:NBu^a)·NH, R = $[CH_2]_2$·NEt_2}. The same method was also applied to the preparation of 2-*N*^{1}-*p*-chlorophenyl-*N*^{2}-methylguanidino-*N*^{3}-4-γ-diethylaminopropylamino-6-methylpyrimidine (*trihydrochloride*) {I; X = NH·C(:NMe)·NH, R = $[CH_2]_3$·NEt_2}.

Antimalarial Activities.

The antimalarial activities were estimated against *P. gallinaceum* in chicks by Dr. D. G. Davey, using a method previously described (*Ann. Trop. Med. Parasit.*, 1945, **39**, 139; 1946, **40**, 52). In the summarised results given below activities are expressed in the same way as in Part I (*J.*, 1946, 343).

Ref. no.	Compound.	Dose mg./kg.	Activity.
4924	4-*p*-Chlorophenylguanidino-2-*β*-diethylaminoethylamino-6-methylpyrimidine	40	+ to ++
4985	4-*p*-Chlorophenylguanidino-2-γ-diethylaminopropylamino-6-methylpyrimidine	80	+
		20	—
4986	4-*p*-Chlorophenylguanidino-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine	80	+ to ++
		40	+
		20	±
5227	4-*p*-Chlorophenylthioureido-6-*β*-diethylaminoethylamino-2-methylpyrimidine	160	Toxic
		80	—
5236	4-*p*-Chlorophenylguanidino-6-*β*-diethylaminoethylamino-2-methylpyrimidine	80	+
		40	±
5218	4-*p*-Chlorophenylthioureido-6-γ-diethylaminopropylamino-2-methylpyrimidine	80	—
		40	—
5242	4-*p*-Chlorophenylguanidino-6-γ-diethylaminopropylamino-2-methylpyrimidine	120	++
		40	++
		20	±
5165	2-*N*^{1}-*p*-Chlorophenyl-*N*^{2}-methylguanidino-*N*^{3}-4-*β*-diethylaminoethylamino-6-methylpyrimidine	40	++
		20	+
5324	2-*N*^{1}-*p*-Chlorophenyl-*N*^{2}-ethylguanidino-*N*^{3}-4-*β*-diethylaminoethylamino-6-methylpyrimidine	40	++
		20	++
		10	—
5369	2-*N*^{1}-*p*-Chlorophenyl-*N*^{2}-*n*-butylguanidino-*N*^{3}-4-*β*-diethylaminoethylamino-6-methylpyrimidine	80	+
		40	±
5334	2-*N*^{1}-*p*-Chlorophenyl-*N*^{2}-methylguanidino-*N*^{3}-4-γ-diethylaminopropylamino-6-methylpyrimidine	40	+
		20	±

The following compounds were also tested for prophylactic activity against *P. gallinaceum* but were found to be inactive: 5236, 5242, and 5165 at 80 mg./kg.; 5334 at 160 mg./kg.

Experimental.

Benzoylcyanamide.—Diels and Wagner (*Ber.*, 1912, **45**, 876) found that this compound was conveniently made from commercial sodium cyanamide and benzoyl chloride. The following describes its preparation from commercial calcium cyanamide. Finely powdered commercial calcium cyanamide (800 g.) was stirred with water (4 l.) and cooled to 10—15°. Benzoyl chloride (200 c.c.) was added dropwise with stirring at this temperature during 5 hours, and stirring then continued for 16 hours. The mixture was filtered and the residue stirred with water (1½ l.), filtered off, and washed with water (500 c.c.). Calcium chloride (800 g.) was added gradually with cooling to the combined filtrates and washings. The calcium salt of benzoylcyanamide thereby precipitated was collected, drained thoroughly, and dissolved in water (2 l.), and the solution filtered from a little insoluble matter. Hydrochloric acid was added to the filtrate to render it just acid to Congo-red, and the precipitated benzoyl cyanamide collected, washed with water, and dried (yield, 66% on the benzoyl chloride used). Crystallised once from acetone it had m. p. 142—143°. Diels and Wagner (*loc. cit.*) give m. p. 141—142°; Hantzsch and Dollfus (*Ber.*, 1902, **35**, 255) give m. p. 143°.

p-*Chlorophenylguanidine.*—The following method is based on the work of Arndt and Rosenau (*Ber.*, 1917, **50**, 1261) who condensed benzoylcyanamide with aniline in presence of a little hydrochloric acid to give benzoylphenylguanidine, and of Pierron (*Compt. rend.*, 1910, **151**, 1364) who hydrolysed this to

phenylguanidine. The method was found to be more convenient than that described in G.P. 172,979 (*Chem. Zent.*, 1906, II, 984) which describes the preparation of the nitrate (m. p. 166°) from cyanamide itself.

Benzoylcyanamide (120 g.), *p*-chloroaniline hydrochloride (270 g.), and alcohol (250 c.c.) were mixed, and the clear solution thus obtained was evaporated to dryness on the steam-bath in an open dish. The solid residue was finely ground, stirred for several hours with water (1·5 l.) at room temperature, and the undissolved *N*-benzoyl-*N'*-*p*-chlorophenylguanidine hydrochloride collected and washed with water until free from diazotisable amine. The filter cake was then added to a mixture of sodium hydroxide (410 c.c. of 32%) and water (2 l.) and refluxed with stirring for 20 minutes. The resulting solution was treated with decolorising carbon and filtered hot. After cooling, sodium hydroxide (1300 c.c. of 32%) was added to the filtrate. The oil which was precipitated crystallised on standing. The solid was collected, washed with a little water, and dried (yield, 81%). Crystallisation from benzene gave p-*chlorophenylguanidine* as colourless prisms, m. p. 121° (Found : C, 49·6; H, 4·6; N, 24·0. $C_7H_8N_3Cl$ requires C, 49·5; H, 4·8; N, 24·8%).

Condensation of p-*Chlorophenylguanidine and* 2-*Chloro*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine*.—2-Chloro-4-*β*-diethylaminoethylamino-6-methylpyrimidine (4·05 g.) (Part XV, *loc. cit.*) and *p*-chlorophenylguanidine (2·83 g.) were mixed and heated at 110—120° for 18 hours. The mixture was cooled, dissolved in dilute acetic acid, and filtered from a little insoluble matter. Addition of sodium hydroxide precipitated an oil which was extracted with benzene, and the benzene solution was dried (NaOH) and evaporated. Treatment of a portion of the oil with methanolic picric acid gave the dipicrate of 2-*p*-chloroanilino-4-*β*-diethylaminoethylamino-6-methylpyrimidine, identical with an authentic specimen (Curd and Rose, *J.*, 1946, 343) after crystallisation from 2-ethoxyethanol, m. p. and mixed m. p. 218—219°. The rest of the oil was dissolved in alcohol, made just acid to Congo-red with alcoholic hydrochloric acid, and ethyl acetate added. The resulting white precipitate was collected and recrystallised from alcohol–ethyl acetate, giving 2-*p*-chloroanilino-4-*β*-diethylaminoethylamino-6-methylpyrimidine dihydrochloride, m. p. 266° undepressed on admixture with an authentic sample.

Condensation of 4-*Chloro*-2-*β*-*diethylaminoethylamino*-6-*methylpyrimidine with* p-*Chlorophenylguanidine*.—4-Chloro-2-*β*-diethylaminoethylamino-6-methylpyrimidine (4·85 g.) (Part VI, *loc. cit.*) and *p*-chlorophenylguanidine (3·73 g.) were heated at 110—120° with stirring for 22 hours. The cooled melt was dissolved in dilute acetic acid, filtered from a little insoluble matter, and added to excess of dilute sodium hydroxide solution. The precipitated viscous oil was separated by decantation and washed twice with boiling water (30 c.c.). It was then dissolved in dilute hydrochloric acid and the solution evaporated to dryness. Crystallisation of the residue from alcohol gave 4-*p*-chloroanilino-2-*β*-diethylaminoethylamino-6-methylpyrimidine dihydrochloride, m. p. and mixed m. p. 268—269° (Found : N, 16·4; Cl, 24·7; Cl′, 16·2. Calc. for $C_{17}H_{24}N_5Cl,2HCl,1·5\ H_2O$: N, 16·2; Cl, 24·6; Cl′, 16·4%). The corresponding dipicrate crystallised from 2-ethoxyethanol, m. p. 228—229° undepressed on admixture with an authentic specimen (see Part VI) (Found : C, 44·0; H, 4·0; N, 19·5. Calc. for $C_{17}H_{24}N_5Cl,2C_6H_3O_7N_3$: C, 44·0; H, 3·8; N, 19·5%).

The same result was obtained when the two reactants were heated at 150—160° for 17 hours, but there was no reaction at 80° for 22 hours, in acetic acid at 100°, in water at 80° in presence of calcium carbonate as acid-binding agent, at the boil in the presence of chlorobenzene and dilute sodium hydroxide, or at the boil with the addition of 1·1 mols. of hydrochloric acid. With 2·1 mols. of hydrochloric acid and refluxing for 21 hours, the only product which could be isolated was 4-*p*-chloroanilino-2-*β*-diethylaminoethylamino-6-methylpyrimidine. In phenol at 100—110° for 22 hours, 2-*β*-diethylaminoethylamino-4-phenoxy-6-methylpyrimidine appeared to be formed and was isolated as its *dipicrate* which formed yellow crystals from 2-ethoxyethanol, m. p. 194—195° (Found : N, 18·1. $C_{17}H_{24}ON_4,2C_6H_3O_7N_3$ requires N, 18·5%). In boiling xylene (although not in chlorobenzene) in presence of potassium carbonate and copper bronze 4-*p*-chloroanilino-2-*β*-diethylaminoethylamino-6-methylpyrimidine was the only product.

N-p-*Chlorophenyl*-S-*methyl*isothiourea.—*p*-Chlorophenylthiourea (74·6 g.) (Stollé, *J. pr. Chem.*, 1932, **134**, 298) and water (28 c.c.) were mixed into a paste and methyl sulphate (55·2 g., 0·5 mol.) added. On gentle warming a vigorous reaction ensued. When this had subsided the clear solution was refluxed for 1 hour, cooled, and sodium carbonate added to give a faintly alkaline reaction. An oil separated which crystallised almost immediately. It was collected, washed with water, drained well, and recrystallised from methanol (yield, 72%), giving colourless needles, m. p. 83° (Found : C, 47·9; H, 4·2; S, 15·8. $C_8H_9N_2ClS$ requires C, 47·9; H, 4·5; S, 15·95%).

Condensation of N-p-*Chlorophenyl*-S-*methyl*isothiourea *with* 4-*Chloro*-2-*β*-*diethylaminoethylamino*-6-*methylpyrimidine*.—*N*-*p*-Chlorophenyl-*S*-methylisothiourea (4·0 g.) and 4-chloro-2-*β*-diethylaminoethylamino-6-methylpyrimidine (4·85 g.) were stirred and heated at 100—110° for 24 hours. The viscous mixture was dissolved in dilute acetic acid, and the solution filtered, made alkaline with sodium hydroxide, and extracted with benzene. Evaporation of the dried (NaOH) benzene extract left an oil which was dissolved in methanol and sufficient alcoholic hydrochloric acid added to render the solution acid to litmus. Ethyl acetate was then added, and the precipitated hydrochloride collected and crystallised from butanol. It proved to be 4-*p*-chloroanilino-2-*β*-diethylaminoethylamino-6-methylpyrimidine dihydrochloride (Part VI, *loc. cit.*), m. p. and mixed m. p. 264—266°.

2-*Hydroxy*-4-p-*chlorophenylguanidino*-6-*methylpyrimidine* [VII ; X = NH·C(:NH)·NH, R = OH].—2-Hydroxy-4-methylthio-6-methylpyrimidine (15·6 g.) (Wheeler and McFarland, *loc. cit.*) and *p*-chlorophenylguanidine (18·65 g.) were boiled in *o*-dichlorobenzene (100 c.c.) for 48 hours. Complete solution was initially obtained and methylthiol evolved, followed at a later stage by the separation of crystalline material. After cooling, the product was collected, washed with *o*-dichlorobenzene, then with alcohol, and dried. Extraction with hot 2N-hydrochloric acid and treatment with carbon gave, on standing, 2-*hydroxy*-4-p-*chlorophenylguanidino*-6-*methylpyrimidine hydrochloride* as colourless crystals, m. p. 198° (decomp.) (Found : C, 43·8; H, 4·6; N, 21·1; Cl′, 10·3. $C_{12}H_{12}ON_5Cl,HCl,H_2O$ requires C, 43·5; H, 4·5; N, 21·1; Cl′, 10·7%).

For the subsequent synthetic work, described below, the crude base, m. p. > 300°, obtained by precipitation of the above 2N-hydrochloric acid extract with ammonia was used.

4-p-*Chlorophenylguanidino*-2-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* {II; X = NH·C(:NH)·NH, R = $[CH_2]_2$·NEt_2}.—(*a*) The above crude hydroxy-compound, finely ground, (10·9 g.) was added, during 15 minutes, to a mixture of chlorobenzene (30 c.c.) and phosphoryl chloride (4·5 c.c.) at 95—100° with stirring. When the addition was complete the mixture was stirred at the same temperature for a further 15 minutes and then poured on to a mixture of ice (200 g.) and sodium hydroxide (30 c.c. of 35%). The crude 2-chloro-4-*p*-chlorophenylguanidino-6-methylpyrimidine, deposited as a gum, was separated and washed with water by decantation. It was then added to a mixture of *β*-diethylaminoethylamine (6·7 g.), chlorobenzene (30 c.c.), water (30 c.c.), and aqueous sodium hydroxide (17 c.c. of 35%), and the mixture refluxed with stirring for 2 hours. The chlorobenzene and excess of *β*-diethylaminoethylamine were then removed by steam distillation. The residual undissolved product was separated and extracted with dilute acetic acid, leaving an undissolved residue (see later). The acetic acid extract was treated with decolorising carbon, filtered, and the filtrate run into a mixture of sodium hydroxide (170 c.c. of 15%) and alcohol (150 c.c.) at 75° with stirring. The crystalline precipitate thus obtained was collected, washed with water, and crystallised from alcohol, giving 4-p-*chlorophenylguanidino*-2-*β*-*diethylamino*-*ethylamino*-6-*methylpyrimidine* (yield, 1·65 g.) as small colourless plates, m. p. 184° (Found: C, 57·1; H, 7·0; N, 25·7; Cl, 9·2. $C_{18}H_{26}N_7Cl$ requires C, 57·5; H, 7·0; N, 26·1; Cl, 9·4%) (4924).

(*b*) 4-*p*-Chlorophenylthioureido-2-*β*-diethylaminoethylamino-6-methylpyrimidine (1·0 g.) (see below), copper sulphate (pentahydrate, 1·0 g.), and methanolic ammonia (20 c.c. of 18%) were stirred at 40—45° for 4 hours. The mixture was then cooled, acidified with dilute hydrochloric acid, and the excess of copper precipitated with sodium sulphide. After filtration, the solution was poured into ice-cold dilute sodium hydroxide solution, and the precipitated solid collected, washed with water, and dried. Crystallisation from benzene then gave 4-*p*-chlorophenylguanidino-2-*β*-diethylaminoethylamino-6-methylpyrimidine (yield, 94%), m. p. 183—184°, either alone or admixed with material made by method (*a*).

4-p-*Chlorophenylguanidino*-2-*γ*-*diethylaminopropylamino*-6-*methylpyrimidine*{II; X=NH·C(:NH)·NH, R = $[CH_2]_3$·NEt_2}.—Crude 2-hydroxy-4-*p*-chlorophenylguanidino-6-methylpyrimidine (5·55 g.) was stirred with phosphoryl chloride (3·7 c.c.) at 100° for 30 minutes and then refluxed gently for 15 minutes. The mixture was poured into a mixture of ice and sodium hydroxide solution. The solid chloro-compound formed was broken up, filtered, washed with water, and drained. Without being dried it was heated with *γ*-diethylaminopropylamine (5·2 g.) at 100° for 1 hour. The mixture was treated with dilute acetic acid, the insoluble material (see below) filtered off, and the filtrate treated with decolorising carbon and again filtered. The filtrate was then added gradually with stirring to a mixture of excess of aqueous sodium hydroxide and alcohol. The resulting precipitate was collected, washed with water, and crystallised from aqueous alcohol, giving 4-p-*chlorophenylguanidino*-2-*γ*-*diethylamino*-*propylamino*-6-*methylpyrimidine* as minute colourless prisms (yield, 1·25 g.), m. p. 170—171° (Found: C, 58·1; H, 6·8; Cl, 9·7. $C_{19}H_{28}N_7Cl$ requires C, 58·5; H, 7·2; Cl, 9·1%) (4985).

4-p-*Chlorophenylguanidino*-2-*γ*-*di*-n-*butylaminopropylamino*-6-*methylpyrimidine* {II; X = NH·C(:NH)·NH, R = $[CH_2]_3$·NBu^n_2}.—Crude 2-hydroxy-4-*p*-chlorophenylguanidino-6-methylpyrimidine (7·0 g.) was added during 15 minutes to phosphoryl chloride (20 c.c.) at 70°. The temperature was then raised to 100° and the mixture stirred at this temperature for 15 minutes. Most of the excess of phosphoryl chloride was then removed under diminished pressure and the residue added to ice and ammonia. The precipitated solid was filtered off, washed with water, and added to a mixture of *γ*-di-*n*-butylaminopropylamine (7·0 g.), chlorobenzene (30 c.c.), water (30 c.c.), and sodium hydroxide (15 c.c. of 35%), and the whole boiled under reflux for 2 hours with stirring. The chlorobenzene and excess of amine were then removed by steam distillation, and the residue collected, washed with water, and extracted with dilute acetic acid. After removal of the insoluble matter by filtration, the acid extract was treated with decolorising carbon and then added to a mixture of dilute sodium hydroxide and alcohol. The solid product on crystallisation from aqueous alcohol gave 4-p-*chlorophenylguanidino*-2-*γ*-*di*-n-*butylaminopropylamino*-6-*methylpyrimidine* (yield, 1·6 g.) as minute colourless prisms, m. p. 168° (Found: N, 22·0; Cl, 8·2. $C_{23}H_{36}N_7Cl$ requires N, 22·0; Cl, 8·0%) (4986).

The material insoluble in dilute acetic acid, from this and the two preceding similar experiments (9·0 g.), was added to phosphoryl chloride (30 c.c.) at 80° during 10 minutes. After being stirred at 100° for 1 hour the mixture was drowned into crushed ice and excess of ammonia. The resulting solid was collected, washed with water, and dried. It was then added to *γ*-dimethylaminopropylamine (7·4 g.) and the mixture heated at 100—110° with stirring for 1·5 hours. The mass was then dissolved in 5% acetic acid, filtered from insoluble matter, and the filtrate decolorised with charcoal and made alkaline with sodium hydroxide. The oily base was separated, washed with water, and dried. It was then dissolved in alcohol, the solution made acid to Congo-red with alcoholic hydrogen chloride, and ethyl acetate added. The precipitated hydrochloride was filtered off and crystallised from alcohol, m. p. 268—270°, either alone or admixed with authentic 4-*p*-chloroanilino-2-*γ*-dimethylaminopropylamino-6-methylpyrimidine (Part VI, *loc. cit.*) (Found: N, 17·2; Cl, 26·8. Calc. for $C_{16}H_{22}N_5Cl,2HCl$: N, 17·8; Cl, 27·1%).

4-*Amino*-2-*β*-*diethylaminoethylamino*-6-*methylpyrimidine*.—2-Chloro-4-amino-6-methylpyrimidine (4 g.) (Gabriel and Colman, *Ber.*, 1899, **32**, 2923) and *β*-diethylaminoethylamine (20 g.) were boiled under reflux for 6 hours. The mixture was then diluted with water (400 c.c.), sodium hydroxide solution (50 c.c. of 35%) added, and the excess of *β*-diethylaminoethylamine distilled off in steam. The residual mixture was acidified with hydrochloric acid, stirred with decolorising carbon, and filtered. Addition of sodium hydroxide to the filtrate liberated an oil which was extracted with benzene, and the extract dried (KOH) and evaporated. Crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave 4-amino-2-*β*-diethylaminoethylamino-6-methylpyrimidine, m. p. 100—101° identical with material made by the method described in Part XI (*loc. cit.*) (Found: C, 59·1; H, 9·3; N, 31·7. Calc. for $C_{11}H_{21}N_5$: C, 59·2; H, 9·4; N, 31·4%).

4-p-*Chlorophenylthioureido*-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (II; X = NH·CS·NH, R = $[CH_2]_2$·NEt_2).—4-Amino-2-β-diethylaminoethylamino-6-methylpyrimidine (3·0 g.) and *p*-chlorophenyl *iso*thiocyanate (2·54 g., 1·1 mols.) were heated in boiling xylene (6 c.c.) for 1 hour. The product which separated on cooling was collected, washed with a little xylene, then with benzene, and crystallised from benzene, giving 4-p-*chlorophenylthioureido*-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (yield, 46%) as practically colourless prisms, m. p. 165—166° (Found: C, 54·5; H, 6·3; N, 21·4; Cl, 9·9; S, 8·5. $C_{18}H_{25}N_6ClS$ requires C, 55·0; H, 6·4; N, 21·4; Cl, 9·1; S, 8·2%).

4-*Amino*-2-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine*.—(*a*) 4-Chloro-2-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (11·0 g.) (Part VI, *loc. cit.*) and alcoholic ammonia (10 c.c. of 13%) were heated in a sealed tube at 200° for 4 hours. The evaporated reaction mixture was dissolved in 2N-hydrochloric acid, the solution made alkaline with sodium hydroxide, and the liberated oil extracted with benzene. Evaporation of the dried (NaOH) extract and distillation of the residue gave the 4-*amino*-compound as a colourless oil (yield, 63%), b. p. 152—156°/0·17 mm. (Found: C, 63·9; H, 10·1. $C_{14}H_{27}N_5$ requires C, 63·5; H, 10·2%).

(*b*) 2-Chloro-4-amino-6-methylpyrimidine (10 g.) and δ-diethylamino-α-methylbutylamine (50 c.c.) were refluxed for 6 hours. Water (1 l.) and sodium hydroxide (200 c.c. of 35%) were added and the mixture steam distilled to remove excess of diamine. The residual oil was separated and purified by dissolution in acid, filtration, and precipitation with sodium hydroxide. The product, isolated with benzene, had b. p. 152—156°/0·17 mm. The *dipicrate* crystallised from alcohol–2-ethoxyethanol as minute yellow prisms, m. p. 138—139° undepressed on admixture with the picrate of material made by method (*a*) (Found: C, 43·2; H, 4·5; N, 21·4. $C_{14}H_{27}N_5,2C_6H_3O_7N_3$ requires C, 43·1; H, 4·6; N, 21·3%).

The product of interaction of this compound with *p*-chlorophenyl *iso*thiocyanate could not be characterised.

Condensation of p-*Chlorophenylguanidine with* 4-*Hydroxy*-2-*methylthio*-6-*methylpyrimidine*.—(*a*) *p*-Chlorophenylguanidine (3·39 g.) and 4-hydroxy-2-methylthio-6-methylpyrimidine (3·12 g.) (Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 478) were stirred and heated at 160—170° for 24 hours. After cooling, the hard mass was broken up and boiled with 2-ethoxyethanol. The undissolved solid was filtered off, washed with alcohol, and dried, giving crude 4-hydroxy-2-*p*-chlorophenylguanidino-6-methylpyrimidine [VIII; X = NH·C(:NH)·NH, R = Cl, R′ = OH], m. p. 276° (yield, 28%). After crystallisation from nitrobenzene the material was identical with that described in Part IV (*loc. cit.*), m. p. and mixed m. p. 288—289°.

(*b*) *p*-Chlorophenylguanidine (8·5 g.), 4-hydroxy-2-methylthio-6-methylpyrimidine (7·8 g.), and *o*-dichlorobenzene (30 c.c.) were boiled under reflux for 21 hours. Methylthiol was evolved, and the solution, initially clear, deposited solid. After cooling, this was collected, washed with methanol, and dried, m. p. 252—258° (yield, 5·65 g.). Without further purification the finely powdered solid was added during 10 minutes, with stirring, to phosphoryl chloride (15 c.c.) preheated to 90—95°. The mixture was then refluxed for 15 minutes and the excess of phosphoryl chloride removed under diminished pressure. The residue was added to ice and water (100 g.). The resulting gummy solid, separated by decantation, was dissolved in acetic acid (25 c.c.) and the solution added to water (100 c.c.). The resulting precipitate was filtered off, washed with water, and dried. Crystallisation from alcohol gave 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine (VIII; X = NH, R = R′ = Cl), m. p. 127—128° alone or mixed with authentic material (Part I, *J.*, 1946, 343). The above acetic acid filtrate was made alkaline with ammonia and the precipitated product collected, washed with water, and dried. Crystallisation from acetone gave a product, m. p. 180—182°, which proved to be 4-chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine [VIII; X = NH·C(:NH)·NH, R = R′ = Cl] (mixed m. p. 180—182°).

Condensation of p-*Anisylguanidine with* 4-*Hydroxy*-2-*methylthio*-6-*methylpyrimidine*.—p-Anisylguanidine (4·12 g.) (prepared by condensing *p*-anisidine with *S*-methyl*iso*thiourea sulphate; recipe kindly supplied by Sir Robert Robinson) and 4-hydroxy-2-methylthio-6-methylpyrimidine (3·9 g.) were finely ground together and heated at 160—170° for 6 hours. The cooled melt was lixiviated with warm alcohol (15 c.c.) and the resulting white solid collected, washed with alcohol, and dried, m. p. 247—248°. Crystallisation from 2-ethoxyethanol gave 4-hydroxy-2-*p*-anisylguanidino-6-methylpyrimidine [VIII; X = NH·C(:NH)·NH, R = OMe, R′ = OH], m. p. 253° alone or admixed with material made by condensation of *p*-anisyldiguanide and ethyl acetoacetate (Part IV, *loc. cit.*).

4-*Hydroxy*-2-*guanidino*-6-*methylpyrimidine* [X; R = C(:NH)·NH_2].—2-Cyanoamino-4-hydroxy-6-methylpyrimidine (45 g.) (X; R = CN) (Pohl, *loc. cit.*), ammonia (21 c.c., *d* 0·88), ammonium chloride (16 g.), and 2-ethoxyethanol (180 c.c.) were stirred at 140—150° in an autoclave for 21 hours. After cooling, the solid product was collected and washed with 2-ethoxyethanol. The greyish crystals were stirred with water (1 l.) and ammonia (15 c.c., *d* 0·88) for ¼ hour, filtered off, and washed with water and then with water containing a few drops of acetic acid. The resulting yellowish product (yield, 61%) had m. p. 303° (decomp.). The m. p. was not raised by dissolving in boiling 30% acetic acid, filtering, and neutralising the hot solution with sodium hydroxide (Found: C, 42·9; H, 5·5. $C_6H_9ON_5$ requires C, 43·1; H, 5·4%. Nitrogen determinations were unsatisfactory).

Condensation of 4-*Hydroxy*-2-*guanidino*-6-*methylpyrimidine with* p-*Chloroaniline*.—The preceding compound (6·7 g.) and *p*-chloroaniline hydrochloride (6·6 g.) in water (50 c.c.) were stirred and boiled under reflux for 60 hours. After cooling, the insoluble material was filtered off and stirred with 2N-sodium hydroxide to remove unchanged material. The insoluble portion was dissolved in boiling 3N-hydrochloric acid, the solution filtered hot, and the filtrate made alkaline with sodium hydroxide. The precipitated product was collected, washed with water, dried, and crystallised from nitrobenzene giving 4-hydroxy-2-*p*-chlorophenylguanidino-6-methylpyrimidine, m. p. and mixed m. p. 285—287° (Found: N, 25·0. Calc. for $C_{12}H_{12}ON_5Cl$: N, 25·2%).

4-p-*Chlorophenylthioureido*-6-β-*diethylaminoethylamino*-2-*methylpyrimidine* (III; X = NH·CS·NH, R = $[CH_2]_2$·NEt_2).—4-Amino-6-β-diethylaminoethylamino-2-methylpyrimidine (11·3 g.) (Hull, Lovell,

Openshaw, Payman, and Todd, *J.*, 1946, 357), *p*-chlorophenyl *iso*thiocyanate (9·45 g.), and toluene (20 c.c.) were boiled under reflux for 20 minutes. After cooling, the precipitated product was collected, washed with benzene, dried, and crystallised from light petroleum (b. p. 120—140°), giving the *thiourea* as pale fawn needles, m. p. 169° (Found: N, 21·4; Cl, 9·1; S, 7·6. $C_{18}H_{25}N_6ClS$ requires N, 21·4; Cl, 9·1; S, 8·1%) (5227).

4-p-*Chlorophenylguanidino*-6-*β*-*diethylaminoethylamino*-2-*methylpyrimidine* {III; X = NH·C(:NH)·NH, R = $[CH_2]_2$·NEt_2}.—The above thioureido-compound (5·0 g.), mercuric oxide (5·0 g.), and methanolic ammonia (90 c.c. of 18%) were stirred at 30—40° for 4·5 hours and the mixture then treated with dilute hydrochloric acid and sodium sulphide. The mercuric sulphide was filtered off and the filtrate added dropwise to ice-cold 2N-sodium hydroxide with stirring. The solid thus precipitated was filtered off, washed with water, and dried (yield, 94%). Crystallised from light petroleum (b. p. 120—140°), 4-p-*chlorophenylguanidino*-6-*β*-*diethylaminoethylamino*-2-*methylpyrimidine* was obtained as colourless needles, m. p. 154—155° (Found: C, 57·0; H, 6·2; N, 25·7. $C_{18}H_{26}N_7Cl$ requires C, 57·5; H, 6·9; N, 26·1%) (5236).

4-p-*Chlorophenylthioureido*-6-*γ*-*diethylaminopropylamino*-2-*methylpyrimidine* (III; X = NH·CS·NH, R = $[CH_2]_3$·NEt_2).—4-Amino-6-*γ*-diethylaminopropylamino-2-methylpyrimidine (10 g.) (Hull *et al.*, *loc. cit.*) and *p*-chlorophenyl *iso*thiocyanate (7·85 g.) in toluene (20 c.c.) were refluxed for 20 minutes. The crystalline material which separated on cooling was collected, washed first with toluene then with benzene, and dried (yield, 59%). Crystallisation from benzene–xylene gave 4-p-*chlorophenylthioureido*-6-*γ*-*diethylaminopropylamino*-2-*methylpyrimidine* as light fawn plates, m. p. 187° (Found: C, 56·2; H, 6·7; N, 20·7; Cl, 8·9; S, 8·2. $C_{19}H_{27}N_6ClS$ requires C, 56·2; H, 6·7; N, 20·7; Cl, 8·7; S, 7·9%) (5218).

4-p-*Chlorophenylguanidino*-6-*γ*-*diethylaminopropylamino*-2-*methylpyrimidine* {III; X = NH·C(:NH)·NH, R = $[CH_2]_3$·NEt_2}.—The preceding compound (5·0 g.) was stirred with mercuric oxide (5·0 g.) and methanolic ammonia (70 c.c. of 18%) at room temperature for 12 hours and then at 36—40° for 3 hours. The mixture was worked up as described above for the corresponding *β*-diethylaminoethylamino-compound (yield, 93%). 4-p-*Chlorophenylguanidino*-6-*γ*-*diethylaminopropylamino*-2-*methylpyrimidine* crystallised from light petroleum as minute colourless prisms, m. p. 112—113° (Found: C, 58·2; H, 7·0; Cl, 9·1. $C_{19}H_{28}N_7Cl$ requires C, 58·5; H, 7·2; Cl, 9·1%) (5243).

4-Amino-6-*δ*-diethylamino-*α*-methylbutylamino-2-methylpyrimidine, prepared by the method of Hull *et al.* (*loc. cit.*), was obtained as a colourless oil, b. p. 180—182°/0·13 mm. It gave a *dipicrate* which crystallised from methanol–2-ethoxyethanol, m. p. 139—141° (Found: C, 42·8; H, 4·4; N, 20·8. $C_{14}H_{27}N_5,2C_6H_3O_7N_3$ requires C, 43·2; H, 4·6; N, 21·3%). Attempts to condense this aminopyrimidine with *p*-chlorophenyl *iso*thiocyanate led to a product which could not be characterised.

2-N^1-p-*Chlorophenyl*-N^2-*methylguanidino*-N^3-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* {I; X = NH·C(:NMe)·NH, R = $[CH_2]_2$·NEt_2}.—2-*p*-Chlorophenylthioureido-4-*β*-diethylaminoethylamino-6-methylpyrimidine (4·0 g.) (preceding paper), aqueous methylamine (25 c.c. of 22%), and mercuric oxide (4·0 g.) were added consecutively to alcohol (40 c.c.) with stirring. The mixture darkened rapidly and was stirred at 50—55° for 2 hours. After cooling, the mixture was acidified with hydrochloric acid, excess of sodium sulphide added, and the mercuric sulphide filtered off and washed with water. The filtrate and washings were added to excess of cold 2N-sodium hydroxide, and the precipitated solid collected, washed with water, and dried in a vacuum. It was then dissolved in a slight excess of alcoholic hydrogen chloride and ethyl acetate added. The precipitated *trihydrochloride* was filtered off, dried, and recrystallised from alcohol–ethyl acetate, giving a colourless microcrystalline powder, m. p. 181—182° (Found: C, 44·1; H, 6·2; N, 18·7; Cl, 27·0. $C_{19}H_{28}N_7Cl,3HCl,H_2O$ requires C, 44·1; H, 6·4; N, 18·95; Cl, 27·5%) (5165). The *base*, liberated from the hydrochloride with sodium hydroxide, crystallised from light petroleum (b. p. 120—140°) as minute colourless prisms, m. p. 95·5° (Found: C, 58·1; H, 7·2; N, 25·4; Cl, 9·5. $C_{19}H_{28}N_7Cl$ requires C, 58·5; H, 7·2; N, 25·2; Cl, 9·1%).

2-N^1-p-*Chlorophenyl*-N^2-*ethylguanidino*-N^3-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* {I; X = NH·C(:NEt)·NH, R = $[CH_2]_2$·NEt_2}, prepared by using ethylamine in place of methylamine, crystallised from light petroleum (b. p. 100—120°) as minute colourless prisms, m. p. 92° (Found: C, 60·1; H, 7·1; N, 23·7; Cl, 8·8. $C_{20}H_{30}N_7Cl$ requires C, 59·5; H, 7·5; N, 24·3; Cl, 8·8%) (5324).

2-N^1-p-*Chlorophenyl*-N^2-n-*butylguanidino*-N^3-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* {I; X = NH·C(:NBu^n)·NH, R = $[CH_2]_2$·NEt_2}, prepared by using *n*-butylamine, crystallised from aqueous methanol in colourless needles, m. p. 85—87° (Found: C, 58·4; H, 8·1. $C_{23}H_{34}N_7Cl,H_2O$ requires C, 58·8; H, 8·0%). The *dihydrochloride* crystallised from alcohol–ethyl acetate as a colourless microcrystalline powder, m. p. 168—169° (Found: C, 50·9; H, 7·3; N, 19·0; Cl, 20·3. $C_{23}H_{34}N_7Cl,2HCl,H_2O$ requires C, 50·6; H, 7·3; N, 18·8; Cl, 20·4%) (5369).

2-N^1-p-*Chlorophenyl*-N^2-*methylguanidino*-N^3-4-*γ*-*diethylaminopropylamino*-6-*methylpyrimidine* {I; X = NH·C(:NMe)·NH, R = $[CH_2]_3$·NEt_2}.—2-*p*-Chlorophenylthioureido-4-*γ*-diethylaminopropylamino-6-methylpyrimidine (4·0 g.) (preceding paper), mercuric oxide (4·0 g.), alcohol (45 c.c.), 2-ethoxyethanol (20 c.c.), and methylamine (25 c.c. of 21%) were stirred at 50—55° for 4 hours. The mixture was acidified with hydrochloric acid, excess of sodium sulphide added, and the mixture filtered. The filtrate was drowned into excess of ice-cold sodium hydroxide and the sticky base, washed by decantation, dried in a vacuum. It was then dissolved in alcoholic hydrochloric acid and ethyl acetate added. The solid *trihydrochloride* was filtered off and crystallised from alcohol–ethyl acetate, giving a colourless microcrystalline powder, m. p. 175—176° (Found: C, 44·5; H, 6·2; N, 18·1; Cl, 25·5. $C_{20}H_{30}N_7Cl$, 3HCl,1·5H_2O requires C, 44·5; H, 6·7; N, 18·3; Cl, 26·3%) (5334).

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