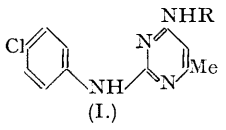
333. *Synthetic Antimalarials. Part XXIX. The Preparation of Some* N^1-*Aryl*-N^2-*alkyl*-N^5-*alkyl- and -dialkyl-diguanides.*

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

In order to extend the investigation of the relationship between chemical structure and antimalarial activity among N^1-aryl-N^5-alkyl- and -dialkyl-diguanides (Part X, Curd and Rose, *J.*, 1946, 729), a number of homologous N^2-alkyl derivatives have been prepared. Synthesis has been by two routes : (*a*) from mono- and di-alkylamines and N^1-aryl-N^2-alkyldicyandiamides, the latter prepared by condensation of an aryl *iso*thiocyanate with sodium cyanamide and treatment of the *S*-alkylated product with an alkylamine, and (*b*) by desulphurisation with mercuric oxide in the presence of an alkylamine of the *N*-aryl-*N'*-alkyl- (or dialkyl-)guanylthioureas resulting from the reaction of an aryl *iso*thiocyanate with a mono- or di-alkylguanidine. The use of ammonia in method (*b*) afforded the parent N^1-aryl-N^5-alkyl- and -dialkyl-diguanides, which were also formed by the action of ammonia alone on *N*-aryl-*N'*-alkyl- (or dialkyl-)guanyl-*S*-alkyl*iso*thioureas.

The novel character of the diguanide type of antimalarial first described in Part X (Curd and Rose, *J.*, 1946, 729) called for a thorough investigation of the relationship between chemical structure and biological activity. The early preparations were mainly N^1-aryl-N^5-alkyl- and -dialkyl-diguanides of types (IV) and (V), although one or two derivatives carrying a methyl group on N^1 were also described. The influence of alkylation on N^2 was made the subject of early study, in particular because of the structural significance of this type in relation to the genesis of the diguanide drug type. Briefly, this arose from consideration of the activity of the *p*-chloroanilinodialkylaminoalkylaminopyrimidine types (I) and (II) in contrast to the inactivity of the isomeric 4-*p*-chloroanilino-6-dialkylaminoalkylamino-2-methylpyrimidines, first described in Part VIII (*J.*, 1946, 713), and the ultimate association of positive therapeutic activity with the presence in the first two molecular types of two linked amidine systems, each capable of independent tautomerism. It followed that this feature did not require the presence of a heterocyclic system *per se* but only of the functional skeleton (III), and although the analogous diguanide (IV; R = Cl, R' = $[CH_2]_2{\cdot}NEt_2$) modelled on this structure was without antimalarial activity, omission of part of the basic side chain led to active substances (V; R' and R'' = alkyl) and in due course to " Paludrine " (IV; R = Cl, R' = Pr^{β}). Closer inspection of the diguanide types (IV) and (V) and their pyrimidine prototype (I) shows the former to be derived by elimination of the carbon atoms in positions 5 and 6 of the pyrimidine ring and the introduction of an additional nitrogen atom. If, on the other hand, one or both of the carbon atoms in positions 5 and 6 of type (I) are retained, the corresponding diguanide is seen to be a N^1-aryl-N^2 : N^5-dialkyldiguanide [cf. (VI) and (VII; R'' = alkyl)].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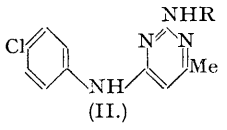
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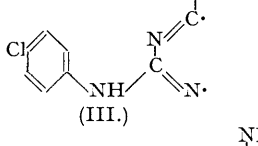
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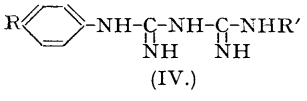
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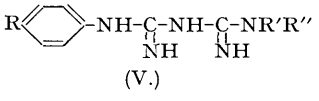
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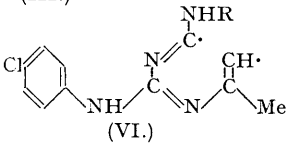
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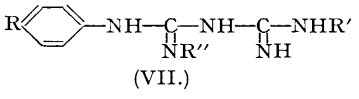
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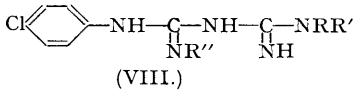
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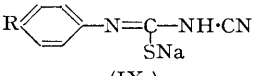
The most remarkable property of the diguanide types (IV) and (V) was the prophylactic action they were found to exert against the different avian malarias (see Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, **39**, 208). This prophylactic property moreover extends to human malaria (Fairley *et al.*, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1946—47, **40**, 105, 621). Since the compounds of type (I) were inactive as prophylactics against avian malaria, it was clearly desirable to determine whether closer approximation of the diguanides of types (VII) and (VIII) to the skeleton (VI) of type (I) led to a loss of prophylactic activity, or whether the activity of the N^2-alkyl compounds on both the blood forms and early exo-erythrocytic forms of the avian malarias, relative to the parent types (III) and (IV), varied in the same way.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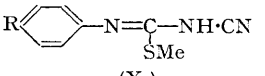
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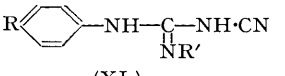
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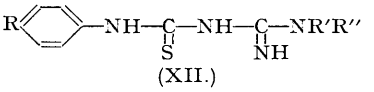
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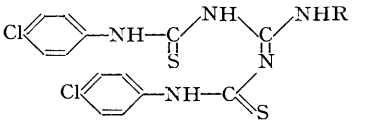
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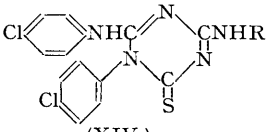
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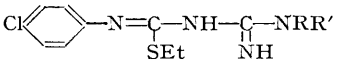
(XV.)

The diguanides of types (VII) and (VIII) have been synthesised by two main methods. The more obvious approach seemed to be an adaptation of the original method described in Part X for the preparation of types (IV) and (V), namely, condensation of a N^1-aryl-N^2-alkyldicyandiamide (XI) with a mono- or di-alkylamine. For the preparation of the necessary intermediates (XI) a modification of the method used by Wheeler and Jamieson (*J. Amer. Chem. Soc.*, 1903, **25**, 119) for the initial preparation of N^1-phenyldicyandiamide was employed. Thus *p*-chlorophenyl *iso*thiocyanate reacted with sodium cyanamide to give the *sodium* salt of N-*cyano*-N′-p-*chlorophenylthiourea* (IX; R = Cl) which with methyl iodide then gave N-*cyano*-N′-p-*chlorophenyl*-S-*methyl*isothiourea (X; R = Cl); treatment of this with aqueous or alcoholic methylamine at 50—60° yielded N^1-p-*chlorophenyl*-N^2-*methyldicyandiamide* (XI; R = Cl, R′ = Me), and with ethylamine in a similar manner afforded N^1-p-*chlorophenyl*-N^2-*ethyldicyandiamide* (XI; R = Cl, R′ = Et). Analogous reaction series, involving the steps (IX) ⟶ (X) ⟶ (XI), were used to prepare N^1-p-*bromophenyl*-N^2-*methyldicyandiamide*, N^1-p-*iodophenyl*-N^2-*methyldicyandiamide* and the corresponding N^2-*ethyl* derivative. These various dicyandiamides of type (XI) were converted into diguanides either by direct fusion with a mono- or di-alkylamine hydrochloride or by heating the two reactants together in nitrobenzene at 130—135° (cf. Part XXVIII, preceding paper). In this way (XI; R = Cl, R′ = Me) and *iso*propylamine hydrochloride gave N^1-*p*-chlorophenyl-N^2-methyl-N^5-*iso*propyldiguanide (VII; R = Cl, R′ = Pr$^\beta$, R″ = Me) isolated as its *picrate*, while (XI; R = Cl, R′ = Et) afforded N^1-p-*chlorophenyl*-N^2-*ethyl*-N^5-iso*propyldiguanide hydrochloride*, both of which were identical with the products made by an alternative method described below. Numerous other examples of this type of synthesis are given in the experimental section. The dicyandiamides (XI; R = Cl, R′ = Me and Et) were also condensed with *p*-chloroaniline to give N^1 : N^5-*di*-p-*chlorophenyl*-N^2-*methyldiguanide* (VII; R = Cl, R′ = *p*-Cl·C$_6$H$_4$, R″ = Me) and the corresponding N^2-*ethyldiguanide* (VII; R = Cl, R′ = *p*-Cl·C$_6$H$_4$, R″ = Et), but these compounds were devoid of antimalarial activity, and the type was not further investigated.

A method having advantages over that described above, since it has allowed facile variation of the N^2-alkyl group, involved conversion of the corresponding *N*-aryl-*N*′-alkyl- (and dialkyl-) guanylthioureas (XII) into diguanides of types (VII) and (VIII) by their reaction with alkylamines in presence of a desulphurising agent. The approach was specifically suggested by the method utilised in Part XXV (*J.*, 1948, 586) for the preparation of a number of 2-N^1-*p*-chlorophenyl-N^2-alkylguanidino-N^3-4-β-diethylaminoethylamino-6-methylpyrimidines, namely, the reaction of 2-*p*-chlorophenylthioureido-4-β-diethylaminoethylamino-6-methylpyrimidine with

an alkylamine in the presence of a desulphurising agent. There was also some indication in the literature that the desired analogous conversion might be effected in the diguanide series, Bamberger (*Ber.*, 1880, **13**, 1580) having shown that *N*-phenyl-*N'*-guanylthiourea (XII; R = R' = R'' = H) was convertible into phenyldiguanide by reaction with ammonia in the presence of a salt or oxide of silver or mercury. The same author and also Cramer (*Ber.*, 1901, **34**, 2602) found that the ammonia could be replaced by an arylamine with formation of a $N^1 : N^2$-diaryldiguanide. Further, Rathke and Oppenheim (*ibid.*, 1890, **23**, 1668) had demonstrated the conversion of *N*-phenyl-*N'*-(*NN'*-diphenylguanyl)thiourea into $N^1 : N^2 : N^5$-triphenyldiguanide by treatment with ammonia and silver nitrate.

For our investigations the synthesis of certain *N*-aryl-*N'*-alkyl- (and dialkyl-) guanylthioureas (XII) was required. Bamberger (*loc. cit.*; *Ber.*, 1881, **14**, 2638), Michael (*J. pr. Chem.*, 1894, **49**, 42), and Cramer (*loc. cit.*) have all described the preparation of *N*-phenyl-*N'*-guanylthiourea from guanidine and phenyl *iso*thiocyanate. Slotta, Tschesche, and Dressler (*Ber.*, 1930, **63**, 208; see also D.R.-P. 504,996) treated guanidine thiocyanate with acetone in which sodium had previously been dissolved, and brought the solution thus obtained into reaction with each one of a series of aryl *iso*thiocyanates. They were unable, however, to condense *iso*thiocyanates with mono- and tri-substituted guanidines. Methods of preparation of guanylthioureas other than by the condensation of a guanidine with an *iso*thiocyanate have been described by Slotta *et al.* (*loc. cit.*) who condensed the sodium salt of *N*-cyano-*N'*-phenylthiourea (IX; R = H) with aniline hydrochloride to give, in poor yield, *N*-phenyl-*N'*-phenylguanylthiourea, and by Fromm *et al.* (*Annalen*, 1908, **361**, 306, 319; 1912, **394**, 258) who caused 1-arylthioureas to react with arylamines to give, usually, mixtures of guanylthioureas.

Contrary to the statement of Slotta, Tschesche, and Dressler (*loc. cit.*), we have been able to effect the reaction of aryl *iso*thiocyanates not only with *NN*-dialkyl- but also with monoalkyl-guanidines to give guanylthioureas of the type (XII; R' = alkyl, R'' = H or alkyl). The conditions employed were essentially the same as those employed by Slotta and co-workers for many of their successful condensations, *i.e.*, by using the reaction mixture of sodium and acetone to liberate the guanidine from its salt and then effecting the condensation with the aryl *iso*thiocyanate in this mixture at about 30°. In this way *p*-chlorophenyl *iso*thiocyanate and *iso*propylguanidine gave N-p-*chlorophenyl*-N'-iso*propylguanylthiourea* (XII; R = Cl, R' = H, R'' = Pr$^\beta$), but condensations with some other monoalkylguanidines were more complex. Thus, in the preparation of N-p-*chlorophenyl*-N'-n-*butylguanylthiourea* (XII; R = Cl, R' = H, R'' = Bu$^\alpha$) a by-product was isolated and analytical evidence suggested that it was 6-p-*chloroanilino*-4-n-*butylamino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-1 : 3 : 5-*triazine*-2-*thione* (XIV; R = Bu$^\alpha$). It was presumably formed by the condensation of 2 mols. of *p*-chlorophenyl *iso*thiocyanate with 1 mol. of *n*-butylguanidine followed by cyclisation of the resulting (XIII; R = Bu$^\alpha$) to give (XIV; R = Bu$^\alpha$) with elimination of hydrogen sulphide, and in this connection it may be noted that Slotta and co-workers (*loc. cit.*) observed that both allyl and *iso*amyl *iso*thiocyanate condensed with guanidine to give, in addition to the guanylthioureas, some of the corresponding dicondensation products or *NN'*-bis(alkylthiocarbamyl)guanidines. A product of similar type was formed in the reaction between *p*-chlorophenyl *iso*thiocyanate and methylguanidine and was presumed to be (XIV; R = Me), but none of the required *N*-*p*-chlorophenyl-*N'*-methylguanylthiourea could be isolated. However, *p*-chlorophenyl *iso*thiocyanate and ethylguanidine condensed normally to give N-p-*chlorophenyl*-N'-*ethylguanylthiourea* (XII; R = Cl, R' = H, R'' = Et) and other examples are described below.

The formation of *N*-aryl-*N'*-dialkylguanylthioureas was demonstrated by the reaction of phenyl *iso*thiocyanate with *NN*-dimethylguanidine to give N-*phenyl*-N'-(NN-*dimethylguanyl*)-*thiourea* (XII; R = H, R' = R'' = Me), by the preparation of the corresponding p-*chlorophenyl* derivative (XII; R = Cl, R' = R'' = Me), using *p*-chlorophenyl *iso*thiocyanate in place of phenyl *iso*thiocyanate, and by the condensation of *p*-chlorophenyl *iso*thiocyanate with *NN-cyclo*pentamethyleneguanidine to give (XII; R = Cl, R'R'' = $[CH_2]_5$).

As a model for the conversion of guanylthioureas of type (XII) into N^1-aryl-N^2-alkyl-N^5-mono- and di-alkyldiguanides, their conversion into diguanides of types (IV) and (V) was first investigated. This was achieved by stirring the guanylthiourea in alcoholic ammonia solution with mercuric oxide. In this way *N*-*p*-chlorophenyl-*N'*-*iso*propylguanylthiourea (XII; R = Cl, R' = H, R'' = Pr$^\beta$) was converted into N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide (IV; R = Cl, R' = Pr$^\beta$) ("Paludrine") and *N*-*p*-chlorophenyl-*N'*-(*NN*-dimethylguanyl)thiourea (XII; R = Cl, R' = R'' = Me) into N^1-*p*-chlorophenyl-$N^5 : N^5$-dimethyldiguanide (V; R = Cl, R' = R'' = Me). Several other similar conversions are described in the experimental section.

In the same way, using an alkylamine in place of ammonia, it was found possible to prepare

N^1-aryl-N^2-alkyl-N^5-mono- or di-alkyldiguanides. Thus *N-p*-chlorophenyl-*N'-iso*propylguanylthiourea with methylamine gave N^1-*p*-chlorophenyl-N^2-methyl-N^5-*iso*propyldiguanide (VII; R = Cl, R' = Pr$^\beta$, R'' = Me), and with ethylamine afforded N^1-*p*-chlorophenyl-N^2-ethyl-N^5-*iso*propyldiguanide (VII; R = Cl, R' = Pr$^\beta$, R'' = Et), while N-p-*chlorophenyl*-N'-(NN-cyclo*pentamethyleneguanyl*)*thiourea* (XII; R = Cl, R'R'' = $[CH_2]_5$) was converted by the action of methylamine, under similar conditions, into N^1-p-*chlorophenyl*-N^5 : N^5-cyclo*pentamethylene*-N^2-*methyldiguanide* (VIII; RR' = $[CH_2]_5$, R'' = Me) identical with the product of interaction of N^1-*p*-chlorophenyl-N^2-methyldicyandiamide with piperidine.

An alternative method for the conversion of guanylthioureas of type (XII) into diguanides of types (IV) and (V) is by *S*-alkylation to give the corresponding guanyl-*S*-alkyl*iso*thioureas followed by reaction of these with ammonia; a desulphurising agent is unnecessary. This was demonstrated by the conversion of (XII; R = Cl, R' = H, R'' = Pr$^\beta$) and (XII; R = Cl, R' = R'' = Me) into N-p-*chlorophenyl*-N'-iso*propylguanyl*-S-*ethyl*iso*thiourea hydrobromide* (as XV; R = H, R' = Pr$^\beta$) and N-p-*chlorophenyl*-N'-(NN-*dimethylguanyl*)-S-*ethyl*iso*thiourea hydrobromide* (as XV; R = R' = Me) respectively by the action of ethyl bromide, followed by heating of each of these latter compounds in turn with alcoholic ammonia at 100° in a closed vessel to give N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide (IV; R = Cl, R' = Pr$^\beta$) and N^1-*p*-chlorophenyl-N^5 : N^5-dimethyldiguanide (V; R = Cl, R' = R'' = Me) as the respective products. The investigation of this method was prompted by the work of Slotta and Tschesche (*Ber.*, 1929, **62**, 1390, 1398) who prepared a number of N^1-substituted alkyldiguanides and alkylenebisdiguanides by interaction of guanyl-*S*-ethyl*iso*thiourea with substituted alkylamines and alkylenediamines, and described the preparation of N^1 : N^2-dimethyldiguanide and N^1 : N^1 : N^2-trimethyldiguanide by interaction of *N*-methyl-*N'*-guanyl-*S*-ethyl-*iso*thiourea and methylamine and dimethylamine respectively. U.S.P. 2,213,474 describes the preparation of N^1-dodecyldiguanide by an analogous method.

Many of the *N*-aryl-*N'*-alkyl- (and dialkyl-) guanylthioureas were tested by Dr. D. G. Davey for antimalarial activity against *P. gallinaceum* in chicks, but none was found to be active. The results of antimalarial tests on the N^2-alkyldiguanides of types (VII) and (VIII) will be discussed elsewhere.

Experimental.

N^1-*Aryl*-N^2-*alkyldicyandiamides and their Conversion into Diguanides.*

N-*Cyano*-N'-p-*chlorophenyl*-S-*methyl*iso*thiourea* (X; R = Cl).*—*p*-Chlorophenyl *iso*thiocyanate (50·75 g.) was added to a suspension of sodium cyanamide (19·2 g.) in alcohol (30 c.c.) with stirring. The sodium cyanamide gradually dissolved but before solution was complete the *sodium* salt of N-*cyano*-N'-p-*chlorophenylthiourea* began to separate. After 2 hours this was filtered off, washed with alcohol, and dried (Found: C, 41·1; H, 2·4. $C_8H_5N_3ClSNa$ requires C, 41·1; H, 2·1%) (yield, 36·2 g.). This compound (31·2 g.) was suspended in alcohol (200 c.c.) and methyl iodide (37·6 g.) added with rapid stirring. Heat was evolved and the product soon separated. When cold this was filtered off, washed with water and dried (yield, 26·2 g.). It crystallised from chlorobenzene and then had m. p 190—192° (Found: C, 47·9; H, 3·8; N, 18·5; Cl, 15·9; S, 14·9. $C_9H_8N_3ClS$ requires C, 47·9; H, 3·5; N, 18·6; Cl, 15·7; S, 14·2%).

N^1-p-*Chlorophenyl*-N^2-*methyldicyandiamide* (XI; R = Cl, R' = Me).*—*N*-Cyano-*N'*-*p*-chlorophenyl-*S*-methyl*iso*thiourea (15 g.) was added to an alcoholic solution of methylamine (79·5 c.c. containing 4·14 g. of methylamine) and the mixture heated at 50° in a pressure bottle for 4 hours. The resulting clear solution was gradually diluted with water (75 c.c.); the *product* then crystallised out. It was filtered off (yield, 85%) and purified for analysis by crystallisation from water; colourless prisms, m. p. 169—171° (Found: C, 52·1; H, 4·6; N, 26·6; Cl, 16·8. $C_9H_9N_4Cl$ requires C, 51·8; H, 4·3; N, 26·8; Cl, 17·0%).

N^1-*p*-Chlorophenyl-N^2-methyldicyandiamide was also satisfactorily prepared by using aqueous methylamine in place of alcoholic methylamine.

N^1-p-*Chlorophenyl*-N^2-*ethyldicyandiamide* (XI; R = Cl, R' = Et).*—Prepared similarly using alcoholic ethylamine in place of methylamine, this *compound* crystallised from water and then from benzene as colourless elongated prisms, m. p. 141—143° (Found: C, 54·2; H, 5·0; N, 25·6; Cl, 15·2. $C_{10}H_{11}N_4Cl$ requires C, 53·9; H, 4·9; N, 25·2; Cl, 15·95%).

N-*Cyano*-N'-p-*bromophenyl*-S-*methyl*iso*thiourea* (X; R = Br).—Sodium cyanamide (6·4 g.) was suspended in alcohol (100 c.c.) and *p*-bromophenyl *iso*thiocyanate (21·4 g.) (Dyson and George, *J.*, 1924, **125**, 1702) added. After 2 hours' stirring, methyl iodide (28·4 g.) was added and the stirring continued for a further 2 hours. The product was then filtered off, washed with water, dried, and crystallised from chlorobenzene, giving N-*cyano*-N'-p-*bromophenyl*-S-*methyl*iso*thiourea* as colourless thin prisms, m. p. 192—193° (decomp.) (Found: C, 40·3; H, 2·9; N, 15·8. $C_9H_8N_3Br$ requires C, 40·0; H, 3·0; N, 15·6%) (yield, 11·2 g.).

N-*Cyano*-N'-p-*iodophenyl*-S-*methyl*iso*thiourea* (X; R = I), prepared similarly from sodium cyanamide and *p*-iodophenyl *iso*thiocyanate [made from *p*-iodoaniline and thiocarbonyl chloride, m. p. 76—77° (Found: C, 32·3; H, 1·9; N, 5·7. Calc. for C_7H_4NIS: C, 32·6; H, 1·5; N, 5·4%); Losanitsch, *Ber.*, 1872, **5**, 156, gives m. p. 65°; Dyson and George, *loc. cit.*, give m. p. 63°], crystallised from chlorobenzene

* We are indebted to Dr. E. C. Owen for help with these preparations.

(a) N¹-*Phenyl*-N²-*alkyl*-N⁵-*alkyldiguanides* (Type VII).

Ref. No.	Substituent. R.	R′.	R″.	M. p.	Appearance.	Formula.	Analysis. Found, %. C.	H.	N.	Cl′.	Required, %. C.	H.	N.	Cl′.
5451	Cl	Et	Me	175—177°	Colourless prisms	$C_{11}H_{16}N_5Cl,HCl$	45·8	5·9	23·8	12·6	45·5	5·9	24·1	12·2
5495	Cl	Pr$^{\alpha}$	Me	177—179	Colourless flat prisms	$C_{12}H_{18}N_5Cl,HCl$	47·2	6·2	22·9	—	47·4	6·3	23·0	—
5471	Cl	Me	Et	174	Colourless prisms	$C_{11}H_{16}N_5Cl,HCl$	45·3	5·7	24·2	12·3	45·5	5·9	24·1	12·2
5453	Cl	Et	Et	175—177	Colourless rectangular prisms	$C_{12}H_{18}N_5Cl,HCl$	47·7	6·3	22·7	11·8	47·4	6·3	23·0	11·7
5496	Cl	Pr$^{\alpha}$	Et	175—177	Colourless prisms	$C_{13}H_{20}N_5Cl,HCl$	49·0	6·2	21·9	—	49·1	6·6	22·0	—
5511	Cl	CH_2Ph	Et	180—181	Colourless flat prisms	$C_{17}H_{20}N_5Cl,HCl$	55·6	5·7	19·6	—	55·7	5·7	19·1	—
5692	Br	Pr$^{\beta}$	Me	182—184	Colourless needles	$C_{12}H_{18}N_5Br,HCl$	41·3	5·8	20·3	—	41·3	5·5	20·1	—
6278	I	Pr$^{\beta}$	Me	212—214	Colourless elongated prisms	$C_{12}H_{18}N_5I,HCl$	36·5	4·8	17·0	9·3	36·4	4·8	17·7	9·0
6279	I	Pr$^{\beta}$	Et	219—220	Colourless elongated prisms	$C_{13}H_{20}N_5I,HCl$	37·9	5·0	17·1	—	38·1	5·1	17·1	—

(b) N¹-p-*Chlorophenyl*-N²-*alkyl*-N⁵-*disubstituted diguanides* (Type VIII).

Ref. No.	Substituent. R.	R′.	R″.	M. p.	Appearance.	Formula.	Analysis. Found, %. C.	H.	N.	Cl.	Required, %. C.	H.	N.	Cl.
5518	Et	Et	Me	165—167°	Colourless blunt-ended needles	$C_{13}H_{20}N_5Cl,C_2H_4O_2$	52·5	7·1	20·1	—	52·7	7·0	20·5	—
5472	$[CH_2]_5$		Me	204	Colourless prisms	$C_{14}H_{20}N_5Cl,HCl$	50·3	6·2	21·1	10·8 [Cl′]	50·9	6·4	21·2	10·75 [Cl′]
5520	Me	Pr$^{\beta}$	Et	184	Colourless blunt-ended needles	$C_{14}H_{22}N_5Cl,C_2H_4O_2$	54·0	7·6	19·1	—	54·0	7·3	19·7	—
5515	Et	Et	Et	173—174	Colourless blunt-ended needles	$C_{14}H_{22}N_5Cl,C_2H_4O_2$	54·0	6·9	19·4	—	54·0	7·3	19·7	—
5516	Me	Ph	Me	159—161	Colourless clumps of prisms	$C_{16}H_{18}N_5Cl,C_2H_4O_2$	57·2	5·6	18·6	8·9	57·5	5·8	18·6	9·0

as colourless prisms, m. p. 200—202° (decomp.) (Found : C, 34·2; H, 2·8; N, 13·3; S, 10·6. $C_9H_8N_3IS$ requires C, 34·1; H, 2·5; N, 13·2; S, 10·1%).

N^1-p-*Bromophenyl*-N^2-*methyldicyandiamide* (XI; R = Br, R′ = Me).—*N*-Cyano-*N*′-*p*-bromophenyl-*S*-methyl*iso*thiourea (10·8 g.), methylamine (12·4 g. of 21% aqueous solution), and alcohol (100 c.c.) were heated in a pressure bottle at 55—60° for 4 hours. After cooling, the contents were filtered and diluted with water to precipitate the *product* which crystallised from chlorobenzene as colourless flat prisms, m. p. 164—166° (Found : C, 42·9; H, 3·4; N, 21·5. $C_9H_9N_4Br$ requires C, 42·7; H, 3·6; N, 22·1%).

N^1-p-*Iodophenyl*-N^2-*methyldicyandiamide* (XI; R = I, R′ = Me), prepared similarly from *N*-cyano-*N*′-*p*-iodophenyl-*S*-methyl*iso*thiourea, crystallised from chlorobenzene as colourless flat prisms, m. p. 177—179° (Found : C, 36·3; H, 3·0; N, 18·3. $C_9H_9N_4I$ requires C, 36·0; H, 3·0; N, 18·7%).

N^1-p-*Iodophenyl*-N^2-*ethyldicyandiamide* (XI; R = I, R′ = Et), obtained in a similar manner from *N*-cyano-*N*′-*p*-iodophenyl-*S*-methyl*iso*thiourea and ethylamine, crystallised from benzene as colourless plates, m. p. 156—158° (Found : C, 38·3; H, 3·6; N, 17·6. $C_{10}H_{11}N_4I$ requires C, 38·2; H, 3·5; N, 17·8%).

N^1-p-*Chlorophenyl*-N^2-*methyl*-N^5-iso*propyldiguanide* (VII; R = Cl, R′ = Pr$^\beta$, R″ = Me).—*N*^{1}-*p*-Chlorophenyl-*N*^{2}-methyldicyandiamide (6·95 g.), *iso*propylamine hydrochloride (4·7 g.), and nitrobenzene (50 c.c.) were heated and stirred at 130—135° for 16 hours. The nitrobenzene solution was extracted with 2N-hydrochloric acid and the acid extract evaporated to dryness under reduced pressure. The residue was dissolved in water and the solution made alkaline with sodium hydroxide. The liberated base was extracted with ether and the ether extract dried (K_2CO_3). Evaporation left an oil which afforded, with picric acid in acetic acid solution, a *picrate*; yellow blunt ended needles from chlorobenzene, m. p. 163—164° (Found : C, 43·7; H, 4·4; N, 22·9. $C_{12}H_{18}N_5Cl,C_6H_3O_7N_3$ requires C, 43·5; H, 4·2; N, 22·6%).

N^1-p-*Chlorophenyl*-N^2-*ethyl*-N^5-iso*propyldiguanide* (VII; R = Cl, R′ = Pr$^\beta$, R″ = Et).—*N*^{1}-*p*-Chlorophenyl-*N*^{2}-ethyldicyandiamide (7·41 g.) and *iso*propylamine hydrochloride (4·7 g.) were heated in nitrobenzene (50 c.c.) at 130—135° for 16 hours. The solution was extracted with 2N-hydrochloric acid, and the acid solution evaporated to dryness. A solution of the residue in water was treated with decolourising carbon, filtered, and made slightly alkaline by addition of ammonia. The addition of salt; precipitated the *hydrochloride* which was collected, dried, and crystallised from alcohol–ethyl acetatet colourless plates, m. p. 174—176° (Found : C, 49·1; H, 6·7; N, 22·1; Cl′, 11·3. $C_{13}H_{20}N_5Cl,HCl$ requires C, 49·1; H, 6·6; N, 22·0; Cl′, 11·2%) (5335).

N^1-p-*Chlorophenyl*-N^2 : N^5-*dimethyl*-N^5-iso*propyldiguanide* (VIII; R = R″ = Me, R′ = Pr$^\beta$).—A mixture of *N*^{1}-*p*-chlorophenyl-*N*^{2}-methyldicyandiamide (6·95 g.), methyl*iso*propylamine hydrochloride (5·5 g.), and nitrobenzene (50 c.c.) was heated at 130—135° for 16 hours with stirring. The cooled mixture was extracted with 2N-hydrochloric acid, and the extract clarified with charcoal and made alkaline with sodium hydroxide. The precipitated base was extracted with ether, and the ethereal extract dried (Na_2SO_4) and evaporated. The residue was dissolved in acetone, and the solution made acid to litmus by addition of acetic acid. This precipitated the *acetate* which was collected and washed with acetone; it crystallised from acetone as colourless prisms, m. p. 192—194° (decomp.) (Found : C, 52·8; H, 6·9; N, 20·3. $C_{13}H_{20}N_5Cl,C_2H_4O_2$ requires C, 52·7; H, 7·0; N, 20·5%) (5523).

N^1-p-*Chlorophenyl*-N^2 : N^5-*dimethyldiguanide* (VII; R = Cl, R′ = R″ = Me).—*N*^{1}-*p*-Chlorophenyl-*N*^{2}-methyldicyandiamide (6·95 g.) and methylamine hydrochloride (3·37 g.) were stirred and heated at 130—135° for 16 hours. The resulting melt was dissolved in the minimum quantity of hot water, and the solution filtered and made alkaline with sodium hydroxide. The precipitated base was isolated by extraction with ether and evaporation of the dried (K_2CO_3) extract. The residual solid crystallised from light petroleum (b. p. 100—120°) to give N^1-p-*chlorophenyl*-N^2 : N^5-*dimethyldiguanide* as colourless prisms, m. p. 138° (Found : C, 50·4; H, 5·5; N, 28·6. $C_{10}H_{14}N_5Cl$ requires C, 50·1; H, 5·8; N, 29·2%). The *hydrochloride* separated from alcohol–ethyl acetate as colourless blunt-ended needles, m. p. 177—179° (Found : C, 42·9; H, 5·8; N, 25·0; Cl′, 13·3. $C_{10}H_{14}N_5Cl,HCl$ requires C, 43·5; H, 5·4; N, 25·4; Cl′, 12·9%) (5470).

By one or other of the above procedures, the *N*^{1}-aryl-*N*^{2}-alkyl-*N*^{5}-alkyl- and -*N*^{5} : *N*^{5}-dialkyl-diguanides described in the table were made.

N^1 : N^5-*Di*-p-*chlorophenyl*-N^2-*methyldiguanide* (VII; R = Cl, R′ = *p*-Cl·C_6H_4, R″ = Me).—*N*^{1}-*p*-Chlorophenyl-*N*^{2}-methyldicyandiamide (5·21 g.), *p*-chloroaniline hydrochloride (6·97 g.), dioxan (20 c.c.), and water (4 c.c.) were refluxed for 3½ hours. The mixture was cooled, diluted with water (175 c.c.), and allowed to stand overnight. The product was then collected, washed with water, dried, and crystallised from alcohol–ethyl acetate, giving the *hydrochloride* (5352) as clumps of colourless prisms, m. p. 239—241° (Found : C, 48·3; H, 4·3; N, 19·3; Cl, 28·1. $C_{15}H_{15}N_5Cl_2,HCl$ requires C, 48·3; H, 4·3; N, 18·8; Cl, 28·6%). This hydrochloride was converted into the *base* by dissolving it in alcohol, making the solution alkaline with sodium hydroxide, and diluting it with water. Isolated by extraction with chloroform and purified by crystallisation from light petroleum (b. p. 100—120°), it had m. p. 101—103° (Found : C, 54·3; H, 4·4; N, 20·1. $C_{15}H_{15}N_5Cl_2$ requires C, 53·6; H, 4·5; N, 20·8%).

N^1 : N^5-*Di*-p-*chlorophenyl*-N^2-*ethyldiguanide* (VII; R = Cl, R′ = *p*-Cl·C_6H_4, R″ = Et), prepared similarly, crystallised from light petroleum (b. p. 100—120°); m. p. 126—128° (Found : C, 55·1; H, 5·0; N, 19·7; Cl, 19·5. $C_{16}H_{17}N_5Cl_2$ requires C, 54·9; H, 4·9; N, 20·0; Cl, 20·3%). The *hydrochloride* crystallised from chlorobenzene as colourless prisms, m. p. 174—176° (Found : C, 49·5; H, 4·7; N, 18·1; Cl, 27·2. $C_{16}H_{17}N_5Cl_2,HCl$ requires C, 49·7; H, 4·7; N, 18·1; Cl, 27·6%) (5353).

N-*Aryl*-N′-*substituted-guanylthioureas.*

iso*Propylguanidine*.—*iso*Propylamine (118 g.) was added gradually, with stirring and cooling in an ice–salt bath, to a mixture of *S*-methyl*iso*thiourea sulphate (278 g.) and water (200 c.c.). The mixture was allowed to regain room temperature and left for 16 hours. It was then stirred at 30° for 3 hours and finally refluxed for 4·5 hours. The solution thus obtained was evaporated to dryness on the steam-bath and the residue crystallised from 95% alcohol, giving iso*propylguanidine sulphate* as colourless needles, m. p. 270—271° (Found : C, 31·7; H, 8·0. $C_4H_{11}N_3,0{\cdot}5H_2SO_4$ requires C, 32·0; H, 8·0%).

N-p-*Chlorophenyl*-N′-iso*propylguanylthiourea* (XII; R = Cl, R′ = H, R″ = Pr$^{\beta}$).—Sodium (0·75 g.) was gradually added with stirring and cooling to acetone (25 c.c.) which had previously been dried over anhydrous potassium carbonate and distilled over phosphoric oxide. *iso*Propylguanidine sulphate (4·85 g.) was then added and the mixture stirred for 1 hour at 30°. *p*-Chlorophenyl *iso*thiocyanate (4·2 g.) was added, and the stirring at 30° continued for 1 hour. Dilution of the mixture with water precipitated the *product* which was collected, washed with water, and crystallised, first from aqueous alcohol, and then from benzene; colourless flat prisms, m. p. 143° (Found: C, 49·2; H, 5·3; N, 20·8; Cl, 13·0. $C_{11}H_{15}N_4ClS$ requires C, 48·8; H, 5·5; N, 20·7; Cl, 13·1%) (5166).

N-p-*Chlorophenyl*-N′-iso*propylguanyl*-S-*ethyl*iso*thiourea* (XV; R = H, R′ = Pr$^{\beta}$).—The above compound (2·7 g.) was dissolved in methanol (10 c.c.), and ethyl bromide (1·2 g.) added. The solution was refluxed for 2 hours and then evaporated to dryness on the steam-bath. The residual oil crystallised readily on cooling but could not be satisfactorily recrystallised. Analysis showed it to be substantially pure N-p-*chlorophenyl*-N′-iso*propylguanyl*-S-*ethyl*iso*thiourea hydrobromide*, m. p. 146—148° (Found: C, 41·4; H, 5·4. $C_{13}H_{19}N_4ClS,HBr$ requires C, 41·1; H, 5·3%).

N-p-*Chlorophenyl*-N′-n-*butylguanylthiourea* (XII; R = Cl, R′ = H, R″ = Bu$^{\alpha}$).—*n*-Butylguanidine sulphate (35 g.) (m. p. 214—215°, prepared by interaction of *S*-methyl*iso*thiourea sulphate and *n*-butylamine; Davis and Elderfeld, *J. Amer. Chem. Soc.*, 1932, **54**, 1502, record m. p. 206°) was treated with sodium (3·74 g.) in dry acetone (125 c.c.), and then with *p*-chlorophenyl *iso*thiocyanate (21·2 g.) as described above in the case of the corresponding *iso*propyl compound. The crude product obtained on dilution of the reaction mixture with water was crystallised from a small amount of methanol. The product thus obtained was then crystallised from alcohol. A small crop of colourless needles separated. These were removed (see below) and the mother liquors diluted with water. The colourless plates thereby precipitated were collected, dried, and crystallised from benzene giving N-p-*chlorophenyl*-N′-n-*butylguanylthiourea* (5404), m. p. 114—116° (Found: C, 51·0; H, 5·4; N, 19·7; Cl, 12·0. $C_{12}H_{17}N_4ClS$ requires C, 50·6; H, 6·0; N, 19·7; Cl, 12·5%). The first substance obtained from the alcohol crystallisation was recrystallised from alcohol–2-ethoxyethanol and then had m. p. 182—183° (Found: C, 54·4; H, 4·4; N, 17·3; Cl, 16·8. $C_{19}H_{19}N_5Cl_2S$ requires C, 54·3; H, 4·5; N, 16·7; Cl, 16·9%). It was considered to be 6-p-*chloroanilino*-4-n-*butylamino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-1 : 3 : 5-*triazine*-2-*thione* (XIV; R = Bu$^{\alpha}$).

Condensation of p-*Chlorophenyl* iso*Thiocyanate with Methylguanidine*.—Methylguanidine sulphate (9·16 g.) was added to dry acetone (50 c.c.) containing dissolved sodium (1·5 g.) and the mixture stirred at 30° for 30 minutes. *p*-Chlorophenyl *iso*thiocyanate (8·48 g.) was then added at 10°, and the mixture stirred at 30—35° for 45 minutes and poured into water (300 c.c.). The reddish-brown oil which was precipitated was separated by decantation and stirred with aqueous alcohol. The crystalline material thus obtained was collected, washed with aqueous alcohol, dried, and crystallised from alcohol. The product formed hexagonal prisms, m. p. 233° (decomp.) (Found: C, 50·9; H, 3·6; N, 18·6; Cl, 19·2 $C_{16}H_{13}N_5Cl_2S$ requires C, 50·8; H, 3·4; N, 18·5; Cl, 18·8%), and appeared to be 6-p-*chloroanilino*-4-*methylamino*-1 : 2-*dihydro*-1 : 3 : 5-*triazine*-2-*thione* (XIV; R = Me). It was not desulphurised by alcoholic ammonia and mercuric oxide. The same substance was formed when methylguanidine was liberated from its sulphate by aqueous alcoholic potassium hydroxide and brought into reaction with *p*-chlorophenyl *iso*thiocyanate.

Ethylguanidine.—Ethylamine (68 g., 33% aqueous solution) was stirred with *S*-methyl*iso*thiourea sulphate (69·5 g.) at 30° for 6 hours and then at 90—100° for 16 hours. The mixture was evaporated to dryness on the steam bath, and the crystalline residue broken up, and washed with alcohol. Crystallisation from aqueous alcohol gave *ethylguanidine sulphate* (yield, 62·5 g.) as colourless plates, m. p. 244—245° (Found: C, 26·7; H, 7·1. $C_3H_9N_3,0{\cdot}5H_2SO_4$ requires C, 26·5; H, 7·4%) (cf. Schenck and Kirchoff, *Z. physiol. Chem.*, 1926, **154**, 292, who prepared the hydriodide in a similar manner).

N-p-*Chlorophenyl*-N′-*ethylguanylthiourea* (XII; R = Cl, R′ = H, R″ = Et).—Ethylguanidine sulphate (39·4 g.) was treated with sodium (4·9 g.) dissolved in dry acetone (170 c.c.) and then with *p*-chlorophenyl *iso*thiocyanate (32·8 g.). The crude product, precipitated from the reaction mixture with water, was an oil but crystallised on trituration with benzene. It was then collected, washed with benzene, dried, and crystallised from alcohol, giving N-p-*chlorophenyl*-N′-*ethylguanylthiourea* as colourless needles, m. p. 134—135° (Found: C, 47·2; H, 5·4; N, 21·2; Cl, 14·1. $C_{10}H_{13}N_4ClS$ requires C, 46·8; H, 5·1; N, 21·8; Cl, 13·8%) (5465).

N-*Phenyl*-N′-(NN-*dimethylguanyl*)*thiourea* (XII; R = H, R′ = R″ = Me).—Sodium (3·0 g.) was dissolved in dry acetone (100 c.c.), *NN*-dimethylguanidine sulphate (20·4 g.) (Phillips and Clarke, *J. Amer. Chem. Soc.*, 1923, **45**, 1755; Davis and Elderfeld, *loc. cit.*) added, and the mixture stirred for 1 hour at 30°. Phenyl *iso*thiocyanate (13·4 g.) was then slowly added and stirring continued for 1 hour at 30°. The resulting mixture was poured into water (1 l.), and the precipitated product filtered off, washed with water, and crystallised from alcohol. Recrystallisation from alcohol gave N-*phenyl*-N′-(NN-*dimethylguanyl*)*thiourea*; colourless needles, m. p. 164° (Found: C, 53·6; H, 6·2. $C_{10}H_{14}N_4S$ requires C, 54·0; H, 6·3%).

N-p-*Chlorophenyl*-N′-(NN-*dimethylguanyl*)*thiourea* (XII; R = Cl, R′ = R″ = Me), prepared similarly from *NN*-dimethylguanidine sulphate and *p*-chlorophenyl *iso*thiocyanate, crystallised from methanol as colourless prisms, m. p. 160—161° (Found: C, 46·5; H, 5·1; N, 21·8. $C_{10}H_{13}N_4ClS$ requires C, 46·8; H, 5·1; N, 21·8%) (5385).

N-p-*Chlorophenyl*-N′-(NN-*dimethylguanyl*)-S-*ethyl*iso*thiourea* (XV; R = R′ = Me).—The preceding compound (2·56 g.), ethyl bromide (1·19 g.), and methanol (10 c.c.) were gradually heated to boiling during 30 minutes. A further amount of ethyl bromide (0·76 g.) was added and the solution refluxed for 2 hours. Evaporation to dryness on the steam-bath gave a solid residue which on crystallisation from water afforded N-p-*chlorophenyl*-N′-(NN-*dimethylguanyl*)-S-*ethyl*iso*thiourea hydrobromide* as colourless crystals, m. p. 204° (Found: C, 39·4; H, 5·2. $C_{12}H_{17}N_4ClS,HBr$ requires C, 39·4; H, 4·9%) (5403).

NN-cyclo*Pentamethyleneguanidine*.—Piperidine (61 g.), *S*-methyl*iso*thiourea sulphate (100 g.), and water (80 c.c.) were stirred and the temperature gradually raised to 40° and kept there for 16 hours.

The mixture was then boiled for 8 hours under reflux. Subsequent evaporation to dryness on the steam-bath and lixiviation of the residue with alcohol (100 c.c.) gave the *sulphate* which crystallised from aqueous alcohol as colourless bipyramids, charring at 290° (Found: C, 41·1; H, 7·3; N, 23·8. $C_6H_{13}N_3,0{\cdot}5H_2SO_4$ requires C, 40·8; H, 7·9; N, 23·8%).

N-p-*Chlorophenyl*-N′-(NN-cyclo*pentamethyleneguanyl*)*thiourea* (XII; R = Cl, R′R″ = $[CH_2]_5$), prepared, in the manner described above, from NN-*cyclo*pentamethyleneguanidine sulphate and *p*-chlorophenyl *iso*thiocyanate, crystallised from xylene as almost colourless plates, m. p. 170° (Found: C, 52·8; H, 5·1; N, 18·8. $C_{13}H_{17}N_4ClS$ requires C, 52·6; H, 5·7; N, 18·9%) (5419).

N-p-*Bromophenyl*-N′-iso*propylguanylthiourea* (XII; R = Br, R′ = H, R″ = Pr$^\beta$).—Sodium (0·75 g.) was dissolved in dry acetone (25 c.c.), and finely divided *iso*propylguanidine sulphate (5·63 g.) added. After 1 hour's stirring *p*-bromophenyl *iso*thiocyanate (5·35 g.) was added with cooling, and the mixture then stirred for 1 hour at 30°. Dilution of the mixture with water (200 c.c.) gave a dark oil which hardened on being stirred. This product, isolated by decantation, was dissolved in alcohol (50 c.c.), and water gradually added with stirring to give a pale yellow solid. Crystallisation of this from benzene then gave N-p-*bromophenyl*-N′-iso*propylguanylthiourea* as small colourless plates, m. p. 146° (Found: C, 42·2; H, 4·6; N, 18·1. $C_{11}H_{15}N_4BrS$ requires C, 41·9; H, 4·8; N, 17·8%).

N-p-*Nitrophenyl*-N′-iso*propylguanylthiourea* (XII; R = NO_2, R′ = H, R″ = Pr$^\beta$), from *iso*propylguanidine sulphate and *p*-nitrophenyl *iso*thiocyanate [m. p. 110—111°, prepared by the method described by Dyson (*J.*, 1934, 176) for *o*-nitrophenyl *iso*thiocyanate; Jacobsen and Klein (*Ber.*, 1893, **26**, 2369) give m. p. 112—113°], formed lemon-yellow prisms from alcohol, m. p. 135° (Found: C, 46·8; H, 5·1; N, 25·1. $C_{11}H_{15}O_2N_5S$ requires C, 47·0; H, 5·3; N, 24·9%) (5772).

N-p-*Chlorophenyl*-N′-p-*chlorophenylguanylthiourea* (XII; R = Cl, R′ = H, R″ = *p*-Cl·C_6H_4).—(*a*) *p*-Chlorophenylguanidine (12 g.) (cf. Part XXV, this vol., p. 586) and *p*-chlorophenyl *iso*thiocyanate (12 g.) were heated in toluene (30 c.c.) at steam-bath temperature for 4 hours. The resulting mixture was filtered hot and the crystalline material which separated on cooling was collected, washed with benzene, and dried. Crystallisation from xylene gave the *compound* as colourless elongated prisms, m. p. 146—148° (Found: Cl, 20·3; S, 9·0. $C_{14}H_{12}N_4Cl_2S$ requires Cl, 20·9; S, 9·4%).

(*b*) *p*-Chlorophenyl *iso*thiocyanate (3 g.) and *p*-chlorophenylguanidine (3 g.) were heated on the steam-bath for 1 hour. The mixture gradually became homogeneous, and on cooling set to a yellowish transparent glass. Boiled with 2N-hydrochloric acid, this gave N-p-*chlorophenyl*-N′-p-*chlorophenylguanylthiourea hydrochloride* which crystallised from alcohol as clusters of colourless needles, m. p. 170—171° (Found: C, 44·9; H, 3·8; N, 14·9; Cl, 27·6. $C_{14}H_{12}N_4Cl_2S,HCl$ requires C, 44·7; H, 3·5; N, 14·9; Cl, 28·4%) (5373).

N^1-*Aryl*-N^5-*substituted-diguanides from* N-*aryl*-N′-*substituted-guanylthioureas.*

N^1-p-*Chlorophenyl*-N^5-iso*propyldiguanide* (IV; R = Cl, R′ = Pr$^\beta$).—(*a*) *N-p*-Chlorophenyl-*N′-iso*propylguanylthiourea (5 g.), mercuric oxide (5 g.), and methanolic ammonia (100 c.c. of 14%) were stirred for 3 hours at 35°. The mixture was then filtered and the residue washed with methanol. The filtrate and washings were evaporated on the steam-bath, leaving an oil which was dissolved in ethyl acetate (75 c.c.), and the solution filtered. Addition of acetic acid (2·5 c.c.) gave a copious white precipitate on standing, which was collected, dried, and identified as *N*^{1}-*p*-chlorophenyl-*N*^{5}-*iso*propyldiguanide acetate (cf. Part X, *J.*, 1946, 729), m. p. and mixed m. p. 185°. Conversion of a portion of the acetate into the base by dissolving it in water and making the solution alkaline with ammonia, gave a product which crystallised from toluene and then had m. p. and mixed m. p. 130—131°.

(*b*) *N-p*-Chlorophenyl-*N′-iso*propylguanyl-*S*-ethyl*iso*thiourea hydrobromide (1 g.) was heated with saturated alcoholic ammonia (7 c.c.) in a sealed tube at 100° for 1 hour. On opening the tube there was a strong odour of ethylthiol. The contents of the tube were evaporated to dryness, the residue extracted with 2N-hydrochloric acid, and the extract, after treatment with decolourising carbon, made alkaline with sodium hydroxide and extracted with benzene. After evaporation of the dried benzene extract, the residue was dissolved in ethyl acetate and treated with acetic acid to give *N*^{1}-*p*-chlorophenyl-*N*^{5}-*iso*propyldiguanide acetate, m. p. and mixed m. p. 185°.

N^1-p-*Chlorophenyl*-N^5-*ethyldiguanide* (IV; R = Cl, R′ = Et).—*N-p*-Chlorophenyl-*N′*-ethylguanylthiourea (1 g.), mercuric oxide (2 g.), and alcoholic ammonia (20 c.c.) were kept at 30—35° for 22 hours, and the mixture then worked up as described under (*a*) above to give *N*^{1}-*p*-chlorophenyl-*N*^{5}-ethyldiguanide acetate, m. p. 161—162° undepressed on admixture with an authentic sample (Part X, *loc. cit.*).

N^1-p-*Chlorophenyl*-N^5-n-*butyldiguanide* (IV; R = Cl, R′ = Bu^n).—*N-p*-Chlorophenyl-*N′-n*-butylguanylthiourea (1·14 g.) was treated in a similar manner with mercuric oxide (2·28 g.) and alcoholic ammonia (20 c.c.), and the mixture was then filtered and evaporated to dryness. The residue was dissolved in alcoholic hydrogen chloride and excess of ethyl acetate added. The precipitated hydrochloride crystallised from water to give *N*^{1}-*p*-chlorophenyl-*N*^{5}-*n*-butyldiguanide hydrochloride, m. p. 208° undepressed by admixture with an authentic specimen (Part X, *loc. cit.*).

N^1-p-*Bromophenyl*-N^5-iso*propyldiguanide* (IV; R = Br, R′ = Pr$^\beta$).—*N-p*-Bromophenyl-*N′-iso*propylguanylthiourea (1·5 g.), mercuric oxide (3·0 g.), and alcoholic ammonia (25 c.c.) were stirred at 30—40° for 17 hours. The mixture was then made acid with 2N-hydrochloric acid, treated with sodium sulphide, and filtered. The filtrate was basified with sodium hydroxide and extracted with benzene. Evaporation of the dried benzene extract, dissolution of the residue in 2N-hydrochloric acid, and filtration, gave a solution from which the hydrochloride was precipitated by neutralisation with ammonia and addition of salt. Crystallisation of the dried crude hydrochloride from alcohol–ethyl acetate gave colourless rosettes of needles, m. p. and mixed m. p. 245—246° (Curd *et al.*, preceding paper, give m. p. 246°).

N^1-*Phenyl*-N^5: N^5-*dimethyldiguanide* (V; R = H, R′ = R″ = Me).—*N*-Phenyl-*N′*-(*NN*-dimethylguanyl)thiourea (10 g.), mercuric oxide (15 g.), and alcoholic ammonia (70 c.c. of 6%) were stirred at 30—40° for 17 hours. The mixture was then filtered, and the black residue washed with alcohol. The filtrate and washings were combined and evaporated to dryness, the residue dissolved in 2N-hydrochloric

acid, and the solution filtered and neutralised (to litmus) with ammonia. Addition of salt precipitated a solid which was collected, washed with brine, dried, and crystallised from alcohol–ethyl acetate to give N^1-*phenyl*-N^5 : N^5-*dimethyldiguanide hydrochloride* as colourless feathery needles, m. p. 240° (Found : C, 49·6; H, 6·4; N, 28·5. $C_{10}H_{15}N_5$,HCl requires C, 49·7; H, 6·6; N, 29·0%).

N^1-p-*Chlorophenyl*-N^5 : N^5-*dimethyldiguanide* (V; R = Cl, R′ = R″ = Me).—(*a*) A mixture of *N*-*p*-chlorophenyl-*N*′-(*NN*-dimethylguanyl)thiourea (1·28 g.), mercuric oxide (2·16 g.), and alcoholic ammonia (20 c.c.) were treated as described above for *N*^{1}-*p*-chlorophenyl-*N*^{5}-*iso*propyldiguanide, to give the base which crystallised from toluene as colourless needles, m. p. 168—169°, identical with an authentic specimen made from *p*-chlorophenyldicyandiamide and dimethylamine (Part X).

(*b*) *N*-*p*-Chlorophenyl-*N*′-(*NN*-dimethylguanyl)-*S*-ethyl*iso*thiourea hydrobromide (1 g.) was heated with alcoholic ammonia (5 c.c.) in a sealed tube at 100° for 1 hour. After cooling, the contents of the tube were evaporated to dryness and the residue extracted with 2N-hydrochloric acid. The acid extract was filtered and then poured into dilute sodium hydroxide solution. The precipitated solid was filtered off, washed with water, dried, and crystallised from toluene, giving *N*^{1}-*p*-chlorophenyl-*N*^{5} : *N*^{5}-dimethyldiguanide, m. p. and mixed m. p. 169°.

N^1-*p*-Chlorophenyl-*N*^{5} : *N*^{5}-*cyclo*pentamethylenediguanide (V; R = Cl, R′R″ = $[CH_2]_5$), prepared by the action of alcoholic ammonia (20 c.c.) and mercuric oxide (2 g.) on *N*-*p*-chlorophenyl-*N*′-(*NN*-*cyclo*pentamethyleneguanyl)thiourea (1 g.), crystallised from xylene as colourless rods, m. p. 190—191°, undepressed on admixture with material made by the method described in Part X.

N^1 : N^5-*Di*-p-*chlorophenyldiguanide* (IV; R = Cl, R′ = *p*-Cl·C_6H_4).—A mixture of *N*-*p*-chlorophenyl-*N*′-(*p*-chlorophenylguanyl)thiourea (4 g.), mercuric oxide (4 g.), and alcoholic ammonia (25 c.c.) was stirred at 30—35° for 22 hours. Evaporation of the filtered reaction mixture gave the base which was dissolved in alcoholic hydrogen chloride and the solution evaporated to dryness. The residual *hydrochloride* crystallised from alcohol as colourless needles (yield, 1·2 g.), m. p. 250° (Found : C, 46·9; H, 3·7; N, 19·8; Cl, 29·8. $C_{14}H_{13}N_5Cl_2$,HCl requires C, 46·9; H, 3·9; N, 19·5; Cl, 29·7%) (5367).

N^1-*Aryl*-N^2-*alkyl*-N^5-*alkyl- and -dialkyl-diguanides from* N-*Aryl*-N′-*alkyl- and -dialkyl-guanylthioureas.*

N^1-p-*Chlorophenyl*-N^2-*methyl*-N^5-iso*propyldiguanide* (VII; R = Cl, R′ = Pr$^\beta$, R″ = Me).—*N*-*p*-Chlorophenyl-*N*′-*iso*propylguanylthiourea (4 g.), mercuric oxide (4 g.), aqueous methylamine (25 c.c. of 21%), alcohol (35 c.c.), and 2-ethoxyethanol (10 c.c.) were stirred at 50° for 20 hours. The mixture was then filtered and the filtrate evaporated to dryness. The residue was extracted with 2N-hydrochloric acid, the extract added to sodium hydroxide, and the precipitated base filtered off, washed with water, and dried. The base could not be crystallised satisfactorily, but its identity with the product made by condensation of *N*^{1}-*p*-chlorophenyl-*N*^{2}-methyldicyandiamide with *iso*propylamine (see above) was demonstrated by conversion into the picrate, m. p. and mixed m. p. 163—164°. The *dihydrochloride* (5333), prepared by dissolving the base in alcohol and making the solution faintly acid to Congo-red with alcoholic hydrogen chloride, followed by precipitation with ethyl acetate, separated from alcohol–ethyl acetate as a colourless microcrystalline powder, m. p. 166—168° (Found : C, 40·1; H, 5·9; N, 20·4; Cl, 29·4. $C_{12}H_{18}N_5Cl,2HCl,H_2O$ requires C, 40·2; H, 6·1; N, 19·5; Cl, 29·7%).

N^1-p-*Chlorophenyl*-N^2-*ethyl*-N^5-iso*propyldiguanide* (VII; R = Cl, R′ = Pr$^\beta$, R″ = Et).—*N*-*p*-Chlorophenyl-N′-*iso*propylguanylthiourea (4 g.), mercuric oxide (4 g.), aqueous ethylamine (20 c.c. of 33%), and alcohol (35 c.c.) were stirred at 50—55° for 4 hours. 2N-Hydrochloric acid was added followed by sodium sulphide, and the mixture filtered. The filtrate was added to sodium hydroxide, and the crude base thereby precipitated was collected, dried, and dissolved in alcoholic hydrogen chloride. Addition of ethyl acetate precipitated the hydrochloride which was filtered off, dried, and crystallised from alcohol–ethyl acetate to give the same hydrochloride as described above, m. p. and mixed m. p. 174—176°.

N^1-p-*Chlorophenyl*-N^2 : N^5-*di*iso*propyldiguanide* (VII; R = Cl, R′ = R″ = Pr$^\beta$).—*N*-*p*-Chlorophenyl-*N*′-*iso*propylguanylthiourea (5 g.), mercuric oxide (5 g.), and *iso*propylamine (5 c.c.) were kept in alcohol (25 c.c.) at 30—35° for 6 hours and worked up as described above to give the *hydrochloride* which crystallised from alcohol–ethyl acetate as colourless feathery needles, m. p. 200—202° (Found : C, 50·2; H, 7·0; N, 20·9; Cl, 21·9. $C_{14}H_{22}N_5Cl$,HCl requires C, 50·6; H, 6·9; N, 21·1; Cl, 21·4%) (5351).

N^1-p-*Chlorophenyl*-N^5-iso*propyl*-N^2-n-*butyldiguanide* (VII; R = Cl, R′ = Pr$^\beta$, R″ = Bu$^\alpha$).—Prepared similarly using *n*-butylamine in place of *iso*propylamine, this formed a *hydrochloride* which crystallised from alcohol–ethyl acetate as colourless prisms, m. p. 182—183° (Found : C, 51·8; H, 7·2; N, 20·8; Cl, 20·9. $C_{15}H_{24}N_5Cl$,HCl requires C, 52·0; H, 7·2; N, 20·2; Cl, 20·5%) (5350).

N^1-p-*Chlorophenyl*-N^5-*ethyl*-N^2-n-*propyldiguanide* (VII; R = Cl, R′ = Et, R″ = Pr$^\alpha$).—*N*-*p*-Chlorophenyl-*N*′-ethylguanylthiourea (6 g.), mercuric oxide (12 g.), *n*-propylamine (6 c.c.), and alcohol (30 c.c.) were heated at 30—40° for 18 hours with stirring. 2N-Hydrochloric acid and sodium sulphide were added to precipitate all the mercury in the form of sulphide. The mixture was filtered, and the filtrate made alkaline with sodium hydroxide and extracted with benzene. Removal of the solvent from the extract left the base which was dissolved in 2N-hydrochloric acid, and the solution neutralised with ammonia. Addition of salt precipitated a solid which was collected, washed with water, and dried. Crystallisation of this from alcohol–ethyl acetate afforded the *hydrochloride* as colourless needles, m. p. 136° (Found : C, 48·8; H, 6·1; N, 22·5; Cl, 22·1. $C_{13}H_{20}N_5Cl$,HCl requires C, 49·1; H, 6·6; N, 22·0; Cl, 22·3%) (5541).

The following were made in an analogous manner : N^1-p-*chlorophenyl*-N^5-*ethyl*-N^2-iso*propyldiguanide hydrochloride* (as VII; R = Cl, R′ = Et, R″ = Pr$^\beta$), minute colourless prisms, m. p. 178—179°, from alcohol–ethyl acetate (Found : C, 48·9; H, 6·8; N, 21·9; Cl, 21·9. $C_{13}H_{20}N_5Cl$,HCl requires C, 49·1; H, 6·6; N, 22·0; Cl, 22·3%) (5576); N^1-p-*chlorophenyl*-N^5-*ethyl*-N^2-n-*butyldiguanide hydrochloride* (as VII; R = Cl, R′ = Et, R″ = Bu$^\alpha$), small colourless needles, m. p. 152°, from alcohol–ethyl acetate (Found : C, 50·4; H, 6·6; N, 20·6; Cl, 21·4. $C_{14}H_{22}N_5Cl$,HCl requires C, 50·6; H, 6·9; N, 21·1; Cl, 21·4%) (5577); N^1-p-*chlorophenyl*-N^5-*ethyl*-N^2-iso*butyldiguanide hydrochloride* (as VII; R = Cl, R′ = Et, R″ = Bu$^\beta$), hexagonal prisms, m. p. 175°, from alcohol–ethyl acetate (Found : C, 50·9; H, 7·2; N, 20·9; Cl, 21·2. $C_{14}H_{22}N_5Cl$,HCl requires C, 50·6; H, 6·9; N, 21·1; Cl, 21·4%) (5601).

N¹-p-*Chlorophenyl*-N²-*methyl*-N⁵-n-*butyldiguanide* (VII; R = Cl, R′ = Bu$^{\alpha}$, R″ = Me).—*N*-*p*-Chlorophenyl-*N*′-*n*-butylguanylthiourea (6 g.) in alcohol (120 c.c.) was treated with aqueous methylamine (30 c.c. of 21%) and mercuric oxide (12 g.), and the reaction mixture worked up as described above for 5541. The *hydrochloride* crystallised from alcohol–ethyl acetate as colourless prisms, m. p. 160° (Found: C, 48·6; H, 6·3; N, 21·5; Cl, 22·3. $C_{13}H_{20}N_5Cl$,HCl requires C, 49·1; H, 6·6; N, 22·0; Cl, 22·3%) (5600).

The following were made in an analogous manner: N¹-p-*chlorophenyl*-N²-*ethyl*-N⁵-n-*butyldiguanide hydrochloride* (as VII; R = Cl, R′ = Bu$^{\alpha}$, R″ = Et), colourless prisms, m. p. 177°, from water (Found: C, 50·6; H, 6·8; N, 21·2; Cl, 21·2. $C_{14}H_{22}N_5Cl$,2HCl requires C, 50·5; H, 6·9; N, 21·1; Cl, 21·4%) (5542); *N*¹-*p*-bromophenyl-*N*²-methyl-*N*⁵-*iso*propyldiguanide hydrochloride (as VII; R = Br, R′ = Pr$^{\beta}$, R″ = Me), from *N*-*p*-bromophenyl-*N*′-*iso*propylguanylthiourea and methylamine, m. p. 182—184° undepressed in admixture with material prepared from *N*¹-*p*-bromophenyl-*N*²-methyldicyandiamide and *iso*propylamine (see above); N¹-p-*bromophenyl*-N²-*ethyl*-N⁵-iso*propyldiguanide hydrochloride* (as VII; R = Br, R′ = Pr$^{\beta}$, R″ = Et), small colourless needles, m. p. 180°, from alcohol–ethyl acetate (Found: C, 42·5; H, 5·6. $C_{13}H_{20}N_5Br$,HCl requires C, 43·0; H, 5·8%) (5693).

N¹-p-*Chlorophenyl*-N⁵ : N⁵-cyclo*pentamethylene*-N²-*methyldiguanide* (VIII; R and R′ = $[CH_2]_5$, R″ = Me).—*N*-*p*-Chlorophenyl-*N*′-(*NN*-*cyclo*pentamethyleneguanyl)thiourea (5 g.), mercuric oxide (10 g.), aqueous methylamine (25 c.c. of 21%), and alcohol (75 c.c.) were stirred at 30—35° for 22 hours. The filtered reaction mixture was evaporated to dryness on the steam-bath, and the residue crystallised from aqueous alcohol, giving the *base* as colourless prisms, m. p. 142—143° (Found: C, 57·2; H, 6·8; Cl, 12·0. $C_{14}H_{20}N_5Cl$ requires C, 57·2; H, 6·8; Cl, 12·1%). The hydrochloride crystallised from alcohol–ethyl acetate as colourless rods, m. p. 204° either alone or admixed with material made from *N*¹-*p*-chlorophenyl-*N*²-methyldicyandiamide and piperidine (see Table).

N¹-p-*Chlorophenyl*-N⁵ : N⁵-cyclo*pentamethylene*-N²-*ethyldiguanide* (VIII; R and R′ = $[CH_2]_5$, R″ = Et), prepared similarly using ethylamine in place of methylamine, crystallised from aqueous alcohol as long colourless needles, m. p. 121—123° (Found: C, 58·0; H, 6·9. $C_{15}H_{22}N_5Cl$ requires C, 58·5; H, 7·2%) (5473).

N¹-p-*Chlorophenyl*-N² : N⁵ : N⁵-*trimethyldiguanide* (VIII; R = R′ = R″ = Me).—*N*-*p*-Chlorophenyl-*N*′-(*NN*-dimethylguanyl)thiourea (5 g.) in alcohol (75 c.c.) was treated with mercuric oxide (10 g.) and aqueous methylamine (25 c.c. of 21%) at 30—35° for 22 hours. The filtered mixture was evaporated on the steam-bath, the residual crude base dissolved in ethyl acetate, and the solution neutralised with acetic acid to give the acetate. This was reconverted into the base by dissolution in water and treatment with sodium hydroxide. The base was then extracted with benzene, and the solution dried (K_2CO_3) and evaporated. The residue was then again dissolved in ethyl acetate and treated with acetic acid to give the *acetate* which crystallised from alcohol–acetone as colourless needles, m. p. 172° (Found: C, 49·2; H, 6·4; N, 22·3; Cl, 11·2. $C_{11}H_{16}N_5Cl$,$C_2H_4O_2$ requires C, 49·8; H, 6·4; N, 22·3; Cl, 11·3%) (5462).

N¹-p-*Chlorophenyl*-N⁵ : N⁵-*dimethyl*-N²-*ethyldiguanide* (VIII; R = R′ = Me, R″ = Et).—Similarly prepared using ethylamine in place of methylamine, this formed an *acetate* which crystallised from acetone–alcohol as colourless needles, m. p. 185° (Found: C, 51·6; H, 6·6; N, 10·5. $C_{12}H_{18}N_5Cl$,$C_2H_4O_2$ requires C, 51·3; H, 6·7; Cl, 10·8%) (5454).

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