107. *Synthetic Antimalarials. Part XXXVII. Some* N^1-p-*Chlorophenyl*-N^2 : N^4 : N^5-*trialkyldiguanides and Other Related Miscellaneous Diguanide Types.*

By R. de B. Ashworth, A. F. Crowther, (the late) F. H. S. Curd, J. A. Hendry, (Miss) D. N. Richardson, and F. L. Rose.

The reaction between guanidines and thioureas in presence of a desulphurising agent to give diguanides, first investigated by Cramer (*Ber.*, 1901, **34**, 2594), has been further explored, and it has been demonstrated that *N*^{1}-aryl-*N*^{5}-alkyldiguanides can be made, although in small yield, by condensing an arylguanidine with an alkylthiourea or by interaction of an arylthiourea with an alkylguanidine. Variants of these methods which have also been investigated comprise the reaction of *N*-aryl-*S*-alkyl*iso*thioureas with alkylguanidines and of *NS*-dialkyl*iso*thioureas with arylguanidines.

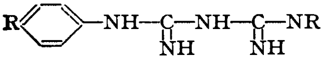
A number of *N*^{1}-*p*-chlorophenyl-*N*^{2} : *N*^{4}-dialkyl-*N*^{5}-*iso*propyldiguanides have been made by the action of alkylamines, in presence of mercuric oxide, on *N*-(*N*-*p*-chlorophenyl-*N'*-alkylguanyl)-*N'*-*iso*propylthioureas which were obtained by the interaction of *iso*propyl *iso*thiocyanate and *N*-*p*-chlorophenyl-*N'*-alkylguanidines. An alternative route to the same type of compound was provided by the corresponding reaction of a *N*-*p*-chlorophenyl-*N'*-(*NN'*-dialkylguanyl)thiourea with an alkylamine.

Analogous reactions have been employed for the preparation of a number of *N*^{1} : *N*^{2}-diaryl-*N*^{5}-alkyldiguanides.

A number of *N*^{2}-alkylated derivatives of *N*^{1}-*p*-chlorophenyldiguanide have been made for biological comparison with the corresponding *N*^{5}-alkyl compounds (Part X, *J.*, 1946, 729), which possess high antimalarial activity, by the reaction of *N*-*p*-chlorophenyl-*N'*-guanylthiourea with alkylamines and mercuric oxide.

In previous papers of this series we have described the preparation of diguanides of type (II; R and R'' = alkyl, R' = H; and R and R' = alkyl, R'' = H) (Parts XXIX and XXX, *J.*, 1948, 1636, 1645) in which additional alkyl groups were attached to either *N*^{2} or *N*^{4} of the original highly active *N*^{1}-*p*-chlorophenyl-*N*^{5}-alkyldiguanide type (I; R = Cl, R' = H, R'' = alkyl) (see Part X, *loc. cit.*). Despite the fact that both these modifications produced a dystherapeutic effect on antimalarial activity (unpublished experiments by Dr. D. G. Davey) it was thought advisable to examine a few compounds in which alkyl groups were attached to both *N*^{2} and *N*^{4} (type II; R, R', R'' = alkyl).

The work of Cramer (*loc. cit.*), who condensed a number of *NN'*-diarylthioureas with guanidine in presence of mercuric oxide to give *N*^{1} : *N*^{2}-diaryldiguanides and obtained *N*^{1}-phenyl-*N*^{2}-ethyldiguanide from *N*-phenyl-*N'*-ethylthiourea and guanidine by a similar reaction, suggested that an analogous synthetic method might be applied to the preparation of the desired compounds using a *N*-*p*-chlorophenyl-*N'*-alkylthiourea and a *NN'*-dialkylguanidine. It was decided, however, first to explore the applicability of the method to the preparation of the parent type (I), and when *p*-methoxyphenylguanidine (III; R = OMe, R' = H) was condensed with *iso*propylthiourea (IV; R = Pr^i, R' = H), in alcoholic solution in presence of mercuric oxide, a small but useful yield of *N*^{1}-*p*-methoxyphenyl-*N*^{5}-*iso*propyldiguanide (I; R = OMe, R' = H, R'' = Pr^i) was isolated as its *hydrochloride*. The identity of the product with that prepared by condensation of *p*-methoxyphenyl *iso*thiocyanate with *iso*propylguanidine (V; R = Pr^i, R' = R'' = H), followed by reaction of the resulting N-p-*methoxyphenyl*-N'-iso*propyl guanylthiourea* (VI; R = OMe, R' = R''' = H, R'' = Pr^i) with alcoholic ammonia in presence of mercuric oxide (cf. Part XXIX, *loc. cit.*), proved that the desired reaction had taken place. Similarly, a reverse type of synthesis, namely the condensation of *p*-chlorophenylthiourea (IV; R = *p*-C_6H_4Cl, R' = H) with *NN*-dimethylguanidine (V; R = R' = Me, R'' = H) proceeded to give *N*^{1}-*p*-chlorophenyl-*N*^{5} : *N*^{5}-dimethyldiguanide (I; R = Cl, R' = R'' = Me) in about 6% yield, identical with the material described previously (Part X). However, only minute yields of *N*^{1}-*p*-chlorophenyl-*N*^{5}-*iso*propyldiguanide (I; R = Cl, R' = H, R'' = Pr^i) resulted from the condensation of *p*-chlorophenylguanidine (III; R = Cl, R' = H) with *iso*propylthiourea (IV; R = Pr^i, R' = H) and from the reaction of *p*-chlorophenylthiourea (IV; R = *p*-C_6H_4Cl, R' = H) with *iso*propylguanidine. Further, in an attempt to approach more closely the ultimate type of reaction projected, the condensation of *N*-*p*-chlorophenyl-*N'*-methylthiourea (IV; R = *p*-C_6H_4Cl, R' = Me) with *iso*propylguanidine led to no greater success, since only a very small yield of *N*^{1}-*p*-chlorophenyl-*N*^{2}-methyl-*N*^{5}-*iso*propyldiguanide (II; R = Pr^i, R' = H, R'' = Me) was isolated as its picrate. Condensation of *p*-chlorophenylguanidine with *p*-chlorophenylthiourea in presence of mercuric oxide was also disappointing in respect of the yield of N^1 : N^5-di-*p*-chlorophenyldiguanide (I; R = Cl, R′ = H, R″ = *p*-C_6H_4Cl) isolated.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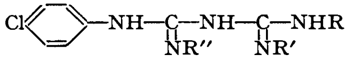
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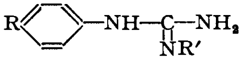
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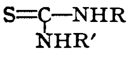
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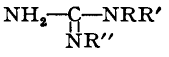
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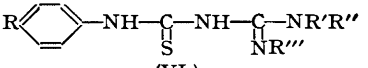
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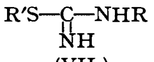
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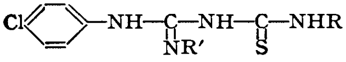
(VII.)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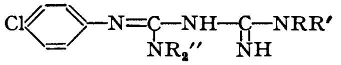
(IX.)

Attempts to utilise the *S*-alkyl*iso*thioureas in place of the thioureas themselves were likewise unpromising. Thus, interaction of *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea (VII; R = *p*-C_6H_4Cl, R′ = Me) with *iso*propylguanidine in boiling alcoholic solution gave only a small yield of (I; R = Cl, R′ = H, R″ = Pr^i) and the condensation of *NS*-dialkyl*iso*thioureas with arylguanidines gave no better results. Reactions of the latter type investigated, included the condensation of *S*-ethyl-*N*-*iso*propyl*iso*thiourea (VII; R = Pr^i, R′ = Et) hydriodide and of other *S*-alkyl derivatives of (IV; R = Pr^i, R′ = H) with *p*-chlorophenylguanidine to give N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide, the reaction of phenylguanidine (III; R = R′ = H) carbonate with NS-*di*iso*propyl*iso*thiourea* (VII; R = R′ = Pr^i) *hydrobromide* to give N^1-phenyl-N^5-*iso*propyldiguanide (I; R = R′ = H, R″ = Pr^i) and of *p*-chlorophenylguanidine with NS-*diethyl*iso*thiourea hydrobromide* (as VII; R = R′ = Et) to give (I; R = Cl, R′ = H, R″ = Et).

Since the above work indicated that a satisfactory method for the synthesis of the required compounds of type (II; R, R′, R″ = alkyl) would not be provided by an elaboration of the Cramer method, attention was directed to a modification of methods described in Parts XXIX and XXX (*locc. cit.*) for type (II; R and R″ = alkyl, R′ = H; and R and R′ = alkyl, R″ = H). *N*-*p*-Chlorophenyl-*N*′-methylguanidine (III; R = Cl, R′ = Me) was prepared by the action of methylamine on *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea (VII; R = *p*-C_6H_4Cl, R′ = Me), and reacted with *iso*propyl *iso*thiocyanate to give N-(N-p-*chlorophenyl*-N′-*methylguanyl*)-N′-iso-*propylthiourea* (VIII; R = Pr^i, R′ = Me) *hydrochloride*. The constitution of this compound was settled by its conversion with alcoholic ammonia and mercuric oxide into the known N^1-*p*-chlorophenyl-N^2-methyl-N^5-*iso*propyldiguanide (II; R = Pr^i, R′ = H, R″ = Me), and, when methylamine was used in place of ammonia, N^1-p-*chlorophenyl*-N^2 : N^4-*dimethyl*-N^5-iso*propyldiguanide hydrochloride* (as II; R = Pr^i, R′ = R″ = Me) was obtained. The preparation of the same compound was then approached in another way, *p*-chlorophenyl *iso*thiocyanate being condensed with *N*-methyl-*N*′-*iso*propylguanidine (V; R = Pr^i, R′ = H, R″ = Me) to give N-p-*chlorophenyl*-N′-(N-*methyl*-N′-iso*propylguanyl*)*thiourea* (VI; R = Cl, R′ = Pr^i, R″ = H, R‴ = Me) which was converted into (II; R = Pr^i, R′ = R″ = Me) by the action of methylamine and mercuric oxide. Further analogous syntheses were then carried out. *iso*Propyl *iso*thiocyanate reacted with *N*-*p*-chlorophenyl-*N*′-ethylguanidine (III; R = Cl, R′ = Et) (prepared from *p*-chlorophenyl-*S*-methyl*iso*thiourea and ethylamine and characterised as its *picrate*) to give N-(N-p-*chlorophenyl*-N′-*ethylguanyl*)-N′-iso*propylthiourea* (VIII; R = Pr^i, R′ = Et); this by the action of ammonia, methylamine, and ethylamine in presence of a desulphurising agent gave respectively N^1-*p*-chlorophenyl-N^2-ethyl-N^5-*iso*propyldiguanide (II; R = Pr^i, R′ = H, R″ = Et), N^1-p-*chlorophenyl*-N^4-*methyl*-N^2-*ethyl*-N^5-iso*propyldiguanide* (II; R = Pr^i, R′ = Me, R″ = Et) *hydrochloride*, and N^1-p-*chlorophenyl*-N^2 : N^4-*diethyl*-N^5-iso*propyldiguanide* (II; R = Pr^i, R′ = R″ = Et) *hydrochloride*. The identification of the product from the ammonia reaction with that obtained from the interaction of N^1-*p*-chlorophenyl-N^2-ethyldicyandiamide with *iso*propylamine hydrochloride (see Part XXIX) served to prove not only its constitution but also the constitutions of the other two products.

The course of the above reactions between *p*-chlorophenyl *iso*thiocyanate and *N*-methyl-*N'*-*iso*propylguanidine on the one hand, and between *iso*propyl *iso*thiocyanate and *N*-*p*-chlorophenyl-*N'*-alkylguanidines on the other, was analogous to that of the corresponding condensations described in Part XXXIII (this vol., p. 98) in which a cyanamide was used in place of the *iso*thiocyanate. In all cases it was the unsubstituted NH-group of the guanidine which entered into the reaction, and this was in accord with the structure assigned to the product of interaction of phenyl *iso*thiocyanate and *NN'*-diphenylguanidine (Rathke, *Ber.*, 1887, **20**, 1072; Rathke and Oppenheim, *Ber.*, 1890, **23**, 1669). A similar method was then used to prepare a number of $N^1 : N^2$-diaryl-N^5-alkyldiguanides and their constitutions followed by analogy. *iso*Propyl *iso*thiocyanate was condensed with N-*phenyl*-N'-p-*chlorophenylguanidine* to give N-(N-*phenyl*-N'-p-*chlorophenylguanyl*)-N'-iso*propylthiourea* (VIII; $R = \mathrm{Pr^i}$, $R' = \mathrm{Ph}$) [cf. the reaction of methyl *iso*thiocyanate with *NN*-diphenylguanidine to give *N*-(*NN*-diphenylguanyl)-*N'*-methylthiourea, D.R.-P. 464,319] which was desulphurised with mercuric oxide in presence of ammonia to give N^1-phenyl-N^2-*p*-chlorophenyl-N^5-*iso*propyldiguanide (II; $R = \mathrm{Pr^i}$, $R' = \mathrm{H}$, $R'' = \mathrm{Ph}$) isolated as its *acetate*. N^1-*p*-Chlorophenyl-N^2-*p*-tolyl-N^5-*iso*propyldiguanide (II; $R = \mathrm{Pr^i}$, $R' = \mathrm{H}$, $R'' = p\text{-}C_6H_4Me$) and $N^1 : N^2$-di-*p*-chlorophenyl-N^5-*iso*propyldiguanide (II; $R = \mathrm{Pr^i}$, $R' = \mathrm{H}$, $R'' = p\text{-}C_6H_4Cl$) were prepared similarly starting from N-p-*chlorophenyl*-N'-p-*tolylguanidine* and *NN'*-di-*p*-chlorophenylguanidine, while the reaction of N-(NN'-*di*-p-*chlorophenylguanyl*)-N'-iso*propylthiourea* (VIII; $R = \mathrm{Pr^i}$, $R' = p\text{-}C_6H_4Cl$) with ethylamine in presence of mercuric oxide gave $N^1 : N^2$-*di*-p-*chlorophenyl*-N^4-*ethyl*-N^5-iso*propyldiguanide* (II; $R = \mathrm{Pr^i}$, $R' = \mathrm{Et}$, $R'' = p\text{-}C_6H_4Cl$).

The investigation of higher *N*-alkylated derivatives of the original N^1-*p*-chlorophenyl-N^5-alkyldiguanides included also the preparation of N^1-p-*chlorophenyl*-$N^2 : N^2$-*dimethyl*-N^5-iso*propyldiguanide* (IX; $R = \mathrm{H}$, $R' = \mathrm{Pr^i}$, $R'' = \mathrm{Me}$) *hydrochloride* and of N^1-p-*chlorophenyl*-$N^2 : N^2 : N^5 : N^5$-*tetramethyldiguanide hydrochloride* (as IX; $R = R' = R'' = \mathrm{Me}$) which resulted from the action of dimethylamine and mercuric oxide on *N*-*p*-chlorophenyl-*N'*-(*N*-*iso*propylguanyl)thiourea (VI; $R = \mathrm{Cl}$, $R' = \mathrm{Pr^i}$, $R'' = R''' = \mathrm{H}$) and *N*-*p*-chlorophenyl-*N'*-(*NN*-dimethylguanyl)thiourea (VI; $R = \mathrm{Cl}$, $R' = R'' = \mathrm{Me}$, $R''' = \mathrm{H}$) respectively.

Finally, for biological comparison with the corresponding N^1-*p*-chlorophenyl-N^5-alkyldiguanides, a number of N^1-*p*-chlorophenyl-N^2-alkyldiguanides were made by interaction of N-p-*chlorophenyl*-N'-*guanylthiourea* (VI; $R = \mathrm{Cl}$, $R' = R'' = R''' = \mathrm{H}$) with alkylamines; the N^2-iso*propyl* compound (II; $R = R' = \mathrm{H}$, $R'' = \mathrm{Pr^i}$) from *iso*propylamine, the n-*propyl* compound (II; $R = R' = \mathrm{H}$, $R'' = \mathrm{Pr^n}$) from *n*-propylamine, and N^1-p-*chlorophenyl*-$N^2 : N^2$-*diethyldiguanide* (IX; $R = R' = \mathrm{H}$, $R'' = \mathrm{Et}$) from diethylamine.

EXPERIMENTAL.

Condensation of p-*Methoxyphenylguanidine with* iso*Propylthiourea*.—*p*-Methoxyphenylguanidine (6·6 g.), *iso*propylthiourea (4·72 g.), mercuric oxide (13 g.), and alcohol (50 c.c.) were stirred at 30—40° for 23 hours. 2N-Hydrochloric acid (100 c.c.) was added to the mixture followed by excess of sodium sulphide. The filtered mixture was then made alkaline with sodium hydroxide and extracted with benzene. Evaporation of the benzene left an oil which was dissolved in 2N-hydrochloric acid, and the solution filtered and neutralised with ammonia. Addition of salt precipitated the product which was collected, washed, and dried. It was dissolved in alcohol, and the solution filtered and precipitated with ethyl acetate to give N^1-p-*methoxyphenyl*-N^5-iso*propyldiguanide hydrochloride* which thereafter crystallised from alcohol–ethyl acetate as a colourless microcrystalline powder (yield, 4·4%), m. p. 231° (Found: C, 50·4; H, 7·1; N, 23·9; Cl, 12·5. $C_{12}H_{19}ON_5,HCl$ requires C, 50·4; H, 7·0; N, 24·5; Cl, 12·4%).

N-p-*Methoxyphenyl*-N'-iso*propylguanylthiourea* (VI; $R = \mathrm{OMe}$, $R' = R''' = \mathrm{H}$, $R'' = \mathrm{Pr^i}$).—*iso*Propylguanidine sulphate (23·8 g.) was added to acetone (100 c.c.) containing dissolved sodium (3·17 g.), and the mixture was stirred for 1 hour. *p*-Methoxyphenyl *iso*thiocyanate (17·5 g.) (Dyson and George, *J.*, 1924, **125**, 708) was then added, and the stirring continued for a further hour at 30°. The mixture was then drowned into water (1500 c.c.) and the resulting solid collected, washed with water, and dried. Crystallisation from benzene gave the *product* as colourless elongated prisms, m. p. 98° (Found: C, 54·5; H, 6·9; N, 21·0; S, 12·2. $C_{12}H_{18}ON_4S$ requires C, 54·1; H, 6·8; N, 21·05; S, 12·0%).

Conversion of N-p-*Methoxyphenyl*-N'-iso*propylguanylthiourea into* N^1-p-*Methoxyphenyl*-N^5-iso*propyldiguanide*.—The preceding compound (6 g.), mercuric oxide (12 g.), saturated alcoholic ammonia (30 c.c.), and alcohol (20 c.c.) were stirred at 30—35° for 16 hours, and the mixture was then acidified with hydrochloric acid and treated with sodium sulphide. After filtration and basification with sodium hydroxide, the liberated oil was isolated by extraction with benzene and evaporation of the benzene extract. It was then dissolved in 2N-hydrochloric acid, and the solution neutralised with ammonia and treated with salt. The resulting solid was collected, washed, dried, and crystallised from alcohol–ethyl acetate to give N^1-*p*-methoxyphenyl-N^5-*iso*propyldiguanide hydrochloride, m. p. and mixed m. p. 231°.

Condensation of p-*Chlorophenylthiourea with* NN-*Dimethylguanidine*.—Sodium (1·15 g., 0·05 g.-atom) was dissolved in alcohol (50 c.c.), *NN*-dimethylguanidine sulphate (6·7 g., 0·05 g.-mol.) added to the cold solution, and the mixture stirred at room temperature for 4 hours. *p*-Chlorophenylthiourea (3·2 g., 0·017 g.-mol.) and mercuric oxide (7·22 g., 0·034 g.-mol.) were then added, and stirring continued for

17 hours. The mixture was filtered and the residue washed with alcohol. The combined filtrate and washings were evaporated to dryness, and the residual gum extracted with 2N-hydrochloric acid (60 c.c.). The filtered extract was neutralised with ammonia, and the solid thereby precipitated filtered off, washed with water, and redissolved in dilute hydrochloric acid. The resulting solution was carbon-treated, filtered, and made alkaline with 10N-sodium hydroxide, whereupon small colourless needles of N^1-*p*-chlorophenyl-N^5 : N^5-dimethyldiguanide were precipitated (yield, 5·7%), m. p. 165—166° either alone or in admixture with an authentic specimen (Part X).

When sodium hydroxide was used in place of sodium in the above condensation and equimolecular quantities of *NN*-dimethylguanidine sulphate and *p*-chlorophenylthiourea employed, the main reaction product was not N^1-*p*-chlorophenyl-N^5 : N^5-dimethyldiguanide but *NN'*-di-*p*-chlorophenylguanidine (see below), m. p. and mixed m. p. 146—147° (Found : C, 55·7; H, 4·1; N, 15·2; Cl, 25·5. Calc. for $C_{13}H_{11}N_3Cl_2$: C, 55·7; H, 3·9; N, 15·0; Cl, 25·4%).

Condensation of p-*Chlorophenylguanidine with* iso*Propylthiourea.*—*p*-Chlorophenylguanidine (3·39 g.), *iso*propylthiourea (2·36 g.), and lead monoxide (8·9 g.) were boiled in alcohol (50 c.c.) for 18 hours with stirring. The mixture was then cooled and filtered, and the residue washed with alcohol. The combined filtrate and washings were evaporated to dryness, and the residue extracted with 2N-hydrochloric acid. The filtered extract was then added to excess of ice-cold 5N-sodium hydroxide, and the precipitated base isolated by extraction with benzene and evaporation of the dried (K_2CO_3) extract. The base was dissolved in ethyl acetate, and acetic acid added to render the solution faintly acid to litmus. On standing, N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate separated (yield, 1·6%), m. p. 187°, undepressed in admixture with an authentic specimen (Part X).

Condensation of p-*Chlorophenylthiourea with* iso*Propylguanidine.*—Sodium (0·92 g.) was dissolved in dry acetone (35 c.c.) at 30°, *iso*propylguanidine sulphate (6 g.) added, and the mixture stirred for 2 hours at 20—30°. *p*-Chlorophenylthiourea (7·46 g.) and mercuric oxide (17 g.) were then added, and the mixture stirred at room temperature for 19 hours and filtered, the residue being washed with acetone. Evaporation of the combined filtrate and washing left a gum which was extracted with benzene. The benzene extract was shaken with 2N-hydrochloric acid, and the acid solution was separated and treated with ammonium chloride, copper sulphate solution, and sodium hydroxide to render it strongly alkaline. The copper complex of the diguanide was extracted with benzene, and the benzene solution in turn extracted with 2N-hydrochloric acid. Sodium sulphide was added to the acid extract which was filtered and then made strongly alkaline with sodium hydroxide and extracted with benzene. After evaporation of the dried benzene extract, the residue was dissolved in dry ethyl acetate (7 c.c.), and acetic acid added to give an acid reaction to litmus; a small amount of crystalline material then separated, and was collected and identified as N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate (yield, 0·8%), m. p. and mixed m. p. 187°.

Condensation of N-p-*Chlorophenyl*-N'-*methylthiourea with* iso*Propylguanidine.*—*iso*Propylguanidine sulphate (5·7 g.) was added to a solution of sodium hydroxide (1·4 g.) in alcohol (40 c.c.), and the mixture stirred at room temperature for 1 hour. *N*-*p*-Chlorophenyl-*N'*-methylthiourea (7 g.) (Hunter and Jones, *J.*, 1930, 2203) and mercuric oxide (14 g.) were then added, and the mixture stirred at 30—40° for 18 hours. 2N-Hydrochloric acid and excess of sodium sulphide were added, the mixture filtered, and the filtrate made strongly alkaline with sodium hydroxide. The liberated oil was extracted with benzene, and the benzene solution dried (K_2CO_3) and evaporated. The residue was dissolved in acetic acid, treated with methanolic picric acid, and diluted with water. The precipitated oily picrate was separated by decantation and triturated with methanol, whereupon it solidified. Crystallisation from aqueous methanol afforded N^1-*p*-chlorophenyl-N^2-methyl-N^5-*iso*propyldiguanide picrate (cf. Part XXIX), m. p. and mixed m. p. 163—164° (Found : N, 22·8. Calc. for $C_{12}H_{18}N_5Cl,C_6H_3O_7N_3$: N, 22·6%).

Condensation of p-*Chlorophenylthiourea with* p-*Chlorophenylguanidine.*—*p*-Chlorophenylthiourea (3·73 g.), *p*-chlorophenylguanidine (3·39 g.), and lead monoxide (8·9 g.) were boiled in alcohol (50 c.c.) for 18 hours. The mixture was then filtered and the filtrate evaporated to dryness. The residue was dissolved in alcoholic hydrogen chloride and the solution evaporated to dryness. Crystallisation of the residue from alcohol–ethyl acetate gave N^1 : N^5-di-*p*-chlorophenyldiguanide hydrochloride (yield, 3·1%), m. p. 250°, either alone or in admixture with an authentic specimen (see Part XXIX, *loc. cit.*).

Condensation of N-p-*Chlorophenyl*-S-*methyl*iso*thiourea with* iso*Propylguanidine.*—Sodium hydroxide (0·8 g.) was dissolved in alcohol (20 c.c.), and *iso*propylguanidine sulphate (3 g.) added. After 1 hour's stirring at room temperature, *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea (4 g.) (Part XXV, Crowther, Curd, and Rose, *J.*, 1948, 586) was added, and the mixture refluxed for 30 hours with stirring. It was then poured into water (100 c.c.) and made acid to Congo-red with hydrochloric acid, and the solution was carbon-treated and filtered. The filtrate was made strongly alkaline with sodium hydroxide, and shaken with benzene and ammoniacal copper sulphate solution. The benzene layer was separated, washed with water, and extracted with 2N-hydrochloric acid. The acid extract was freed from copper salts by the addition of sodium sulphide and filtration. The filtrate was then made alkaline with sodium hydroxide and extracted with benzene, and the benzene extract dried and evaporated. The residue, dissolved in ethyl acetate and treated with acetic acid, afforded N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate (yield, 3·1%), m. p. 187°, either alone or in admixture with an authentic sample.

S-*Ethyl*-N-iso*propyl*iso*thiourea* (VII; $R = Pr^i$, $R' = Et$).—*iso*Propylthiourea (2·36 g.) (May, *J. Org. Chem.*, 1947, **12**, 437), ethyl iodide (3·5 g.), and alcohol (10 c.c.) were refluxed for ½ hour, and the mixture evaporated to dryness to leave *S*-ethyl-*N*-*iso*propyl*iso*thiourea hydriodide as an oil which could not be crystallised.

*iso*Propylthiourea (11·8 g.), treated with ethyl bromide (12 g.) in alcohol (50 c.c.) under reflux for 18 hours, gave the corresponding *hydrobromide* which was isolated by evaporation to dryness and stirring the residual solid with ethyl acetate (yield, 21·7 g.); m. p. 126—128° (Found : C, 31·9; H, 6·5; N, 12·3. $C_6H_{14}N_2S,HBr$ requires C, 31·7; H, 6·6; N, 12·3%).

Condensation of S-*Ethyl*-N-iso*propyl*iso*thiourea Hydriodide with* p-*Chlorophenylguanidine.*—The above oily *S*-ethyl-*N*-*iso*propyl*iso*thiourea hydriodide (5·5 g.), *p*-chlorophenylguanidine (3·7 g.), and alcohol (20 c.c.) were refluxed for 18 hours. Ethylthiol was evolved. The solution was then evaporated to dryness, and the residue treated with sodium hydroxide and extracted with ether. The ether extract was shaken with 5% acetic acid, the acid extract separated, and made alkaline with sodium hydroxide, and the product again extracted with ether. The ether extract was dried and evaporated, the residue dissolved in acetone, and the alkalinity destroyed by the addition of acetic acid. On scratching, a small crop of crystalline material was obtained which proved to be N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate, m. p. and mixed m. p. 185° (Found : C, 49·4; H, 6·2; N, 22·3. Calc. for $C_{11}H_{16}N_5Cl,C_2H_4O_2$: C, 49·7; H, 6·4; N, 22·3%).

NS-*Di*iso*propyl*iso*thiourea* (VII; $R = R' = Pr^i$).—Prepared in the same way as the *S*-ethyl compound described above, the *hydrobromide* had m. p. 134—136° (Found: C, 34·6; H, 6·8; N, 11·6. $C_7H_{16}N_2S,HBr$ requires C, 34·9; H, 7·1; N, 11·6%).

Condensation of NS-*Di*iso*propyl*iso*thiourea Hydrobromide with* p-*Chlorophenylguanidine*.—*NS*-Di*iso*propyl*iso*thiourea hydrobromide (2·5 g.), *p*-chlorophenylguanidine (1·7 g.), and alcohol (10 c.c.) were refluxed for 24 hours, and the product worked up as in the similar reaction described above, to give a very small yield of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate, m. p. and mixed m. p. 185°.

S-*Benzyl*-N-iso*propyl*iso*thiourea* (VII; $R = Pr^i$, $R' = CH_2Ph$).—*iso*Propylthiourea (11·8 g.) and benzyl chloride (14 g.) were boiled in alcohol (50 c.c.) for 15 hours. The mixture was evaporated to small bulk, and ethyl acetate added to precipitate the *hydrochloride* (yield, 23·5 g.), which crystallised from water, m. p. 147—148° (Found : C, 54·0; H, 7·1; N, 11·6. $C_{11}H_{16}N_2S,HCl$ requires C, 54·0; H, 6·95; N, 11·5%). A solution of the hydrochloride in water added to 2N-sodium hydroxide gave the *base* which, after drying, crystallised from light petroleum (b. p. 80—100°) as colourless glistening needles, m. p. 67—68° (Found : C, 63·2; H, 7·4; N, 13·1. $C_{11}H_{16}N_2S$ requires C, 63·5; H, 7·7; N, 13·5%).

Condensation of S-*Benzyl*-N-iso*propyl*iso*thiourea Hydrochloride with* p-*Chlorophenylguanidine*.—*p*-Chlorophenylguanidine (1·7 g.) and *S*-benzyl-*N*-*iso*propyl*iso*thiourea hydrochloride (2·5 g.) were heated in boiling alcohol for 24 hours. The mixture was evaporated to dryness, and the residue treated with water (10 c.c.) and hydrochloric acid (5 c.c.) and extracted with ether. The acid solution was made alkaline to brilliant-yellow with ammonia; a small amount of oil then separated. This gradually solidified, and was then collected, dried, and triturated with ethyl acetate. Crystallisation from water gave N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide hydrochloride (0·5 g.), m. p. and mixed m. p. 244—245°.

Condensation of Phenylguanidine Carbonate with NS-*Di*iso*propyl*iso*thiourea Hydrobromide*.—Phenylguanidine carbonate (1·7 g.), *NS*-di*iso*propyl*iso*thiourea hydrobromide (2·5 g.), and alcohol (10 c.c.) were boiled under reflux for 24 hours, and the solution then evaporated to dryness under reduced pressure. The residue was treated with 2N-sodium hydroxide and extracted with ether. The ether extract was washed with water and then extracted with 5% acetic acid. The acid extract was made alkaline with sodium hydroxide and extracted with ether, and the ether extract washed, dried (Na_2SO_4), and evaporated. The residual oil was dissolved in 2-ethoxyethanol, and 2-ethoxyethanolic hydrogen chloride added until alkalinity to brilliant-yellow had been destroyed. After addition of ethyl acetate, crystallisation of the product was induced by scratching. When separation was complete the product was collected, washed with ethyl acetate, and dried. Crystallisation from water gave material (yield, 0·2 g.), m. p. 235—236° undepressed in admixture with N^1-phenyl-N^5-*iso*propyldiguanide hydrochloride (Part XXVIII, *loc. cit.*).

NS-*Diethyl*iso*thiourea* (VII; $R = R' = Et$).—Prepared from ethylthiourea and ethyl bromide as in the case of similar compounds, the *hydrobromide* had m. p. 77—79° (Found : C, 28·0; H, 5·9; N, 13·2. $C_5H_{12}N_2S,HBr$ requires C, 28·2; H, 6·1; N, 13·15%).

Condensation of p-*Chlorophenylguanidine with* NS-*Diethyl*iso*thiourea Hydrobromide*.—*p*-Chlorophenylguanidine (1·7 g.), *NS*-diethyl*iso*thiourea hydrobromide (2·2 g.), and alcohol (10 c.c.) were refluxed for 24 hours. The mixture was then evaporated to dryness, and the residue treated with sodium hydroxide and extracted with ether. The ether extract was shaken with 5% acetic acid, and the acid extract made alkaline and re-extracted with ether. Evaporation of the washed and dried ether extract left a base which was converted into its acetate by treatment with acetic acid in acetone. The very small amount of material (<0·2 g.) obtained, was identified as N^1-*p*-chlorophenyl-N^5-ethyldiguanide acetate (Part X), m. p. and mixed m. p. 160—161°.

N-p-*Chlorophenyl*-N′-*methylguanidine* (III; $R = Cl$, $R' = Me$).—*N*-*p*-Chlorophenyl-*S*-methyl*iso*thiourea (10 g.), methylamine (25 c.c. of 21% solution), and alcohol (20 c.c.) were heated in a closed vessel at 80—90° for 4 hours. The mixture was then evaporated to dryness and the residue crystallised from toluene and then from benzene. Material of constant m. p. could not be obtained, but it was shown to be substantially *N*-*p*-chlorophenyl-*N*′-methylguanidine since it afforded the *picrate* which crystallised from alcohol as yellow needles, m. p. 90°, then solidifying and remelting at 151—152° (Found : C, 40·8; H, 3·1; N, 20·8. $C_8H_{10}N_3Cl,C_6H_3O_7N_3$ requires C, 40·7; H, 3·2; N, 20·4%).

N-(N-p-*Chlorophenyl*-N′-*methylguanyl*)-N′-iso*propylthiourea* (VIII; $R = Pr^i$, $R' = Me$).—A mixture of N-*p*-chlorophenyl-N′-methylguanidine (9·9 g.) and *iso*propyl *iso*thiocyanate (4·4 g.) was heated on the steam-bath for 4 hours. The mixture was then steam-distilled to remove unchanged *iso*thiocyanate, and the residue separated by decantation and dissolved in alcohol (20 c.c.). Addition of 10N-hydrochloric acid to this solution to render it faintly acid to Congo-red precipitated the *hydrochloride* as an oil which soon crystallised. Recrystallised from alcohol–ethyl acetate it formed colourless prisms, m. p. 171° (Found: C, 44·8; H, 5·8; N, 17·3; Cl, 22·2. $C_{12}H_{17}N_4ClS,HCl$ requires C, 44·9; H, 5·6; N, 17·4; Cl, 22·1%).

Reaction of N-(N-p-*Chlorophenyl*-N′-*methylguanyl*)-N′-iso*propylthiourea with Ammonia*.—The above hydrochloride (2 g.), mercuric oxide (4 g.), and alcoholic ammonia (35 c.c. of 13%) were stirred at 30—40° for 20 hours. The mixture was acidified with dilute hydrochloric acid, treated with excess of sodium sulphide, and filtered. The filtrate was made alkaline with sodium hydroxide, and the precipitated base extracted with benzene. The base left on evaporation of the dried benzene extract was dissolved in alcoholic hydrogen chloride, ethyl acetate added, and the precipitated material crystallised from alcohol–ethyl acetate to give N^1-*p*-chlorophenyl-N^2-methyl-N^5-*iso*propyldiguanide hydrochloride, m. p. 166—168°, undepressed in admixture with an authentic sample (Part XXIX, *loc. cit.*).

N-*Methyl*-N′-iso*propylguanidine* (V; $R = H$, $R' = Pr^i$, $R'' = Me$).—*iso*Propylthiourea (4·3 g.), methyl iodide (2·5 c.c.), and alcohol (5 c.c.) were warmed gently. When the ensuing vigorous reaction had subsided the mixture was refluxed for 1 hour and then evaporated to dryness. The residual syrup of *S*-methyl-*N*-*iso*propylthiourea hydriodide could not be induced to crystallise (cf. the corresponding *S*-ethyl derivative above), and was therefore heated with 21% aqueous methylamine (6·2 g.) for 16 hours at 100° in a closed vessel. Evaporation of the mixture gave *N*-methyl-*N'*-*iso*propylguanidine hydriodide as a colourless syrup which could not be induced to crystallise. An aqueous solution of a small portion treated with methanolic picric acid gave the *picrate* which separated from water as yellow needles, m. p. 148° (Found : C, 38·8; H, 4·6; N, 24·4. $C_5H_{13}N_3,C_6H_3O_7N_3$ requires C, 38·4; H, 4·65; N, 24·4%).

N-p-*Chlorophenyl*-N'-(N-*methyl*-N'-iso*propylguanyl*)*thiourea* (VI; R = Cl, R' = Pr^i, R'' = H, R''' = Me).—Sodium (0·57 g.) was dissolved in dry acetone (30 c.c.), *N*-methyl-*N'*-*iso*propylguanidine hydriodide (9 g.) added, and the mixture stirred at 20—30° until homogeneous. *p*-Chlorophenyl *iso*thiocyanate (4·2 g.) was then added, and the mixture stirred at 30° for 1·5 hours. The clear mixture was poured into water, and after several hours' stirring, the *product* was separated by decantation, dried in a vacuum, and crystallised from benzene–light petroleum (b. p. 40—60°) (yield, 39%); colourless needles, m. p. 128° (Found : C, 50·7; H, 5·8; N, 20·1; Cl, 12·4. $C_{12}H_{17}N_4ClS$ requires C, 50·6; H, 6·0; N, 19·7; Cl, 12·5%).

N^1-p-*Chlorophenyl*-N^2 : N^4-*dimethyl*-N^5-iso*propyldiguanide* (II; R = Pr^i, R' = R'' = Me).—(*a*) *N*-(*N*-*p*-Chlorophenyl-*N'*-methylguanyl)-*N'*-*iso*propylthiourea hydrochloride (7 g.), mercuric oxide (10 g.), 21% aqueous methylamine (21 c.c.), and alcohol (50 c.c.) were stirred at 30—35° for 20 hours. The mixture was treated with dilute hydrochloric acid and sodium sulphide, filtered, and made alkaline with sodium hydroxide. The precipitated product was extracted with benzene, and the solution dried and evaporated. The residue remaining after evaporation of the benzene was dissolved in 2N-hydrochloric acid, and the solution filtered and neutralised with ammonia. Addition of salt precipitated the *hydrochloride* which was collected, washed with sodium chloride solution, then with water, and dried. Crystallised from alcohol–ethyl acetate it formed small colourless needles (3·1 g.), m. p. 177—178° (Found : C, 49·2; H, 6·4; N, 22·4; Cl, 22·6. $C_{13}H_{20}N_5Cl,HCl$ requires C, 49·1; H, 6·6; N, 22·0; Cl, 22·3%) (5731). With ammoniacal copper sulphate it gave a green copper complex soluble in benzene.

(*b*) *N*-*p*-Chlorophenyl-*N'*-(*N*-methyl-*N'*-*iso*propylguanyl)thiourea (1 g.), mercuric oxide (2 g.), 21% aqueous methylamine (5 c.c.), and alcohol (20 c.c.) were stirred at 30—35° for 23 hours, and the mixture worked up as in (*a*) to give the same product (0·55 g.), m. p. 176—177°, either alone or in admixture.

N-p-*Chlorophenyl*-N'-*ethylguanidine* (III; R = Cl, R' = Et).—*N*-*p*-Chlorophenyl-*S*-methyl*iso*thiourea (20 g.), 33% aqueous ethylamine (15 g.), and alcohol (20 c.c.) were heated at 80° for 4 hours in a closed vessel. The mixture was evaporated to dryness, and the residual gum dried by evaporation with benzene. The product could not be induced to crystallise, but it afforded a *picrate* which crystallised from alcohol as yellow prisms, m. p. 165° (Found : C, 42·8; H, 4·2; N, 20·5. $C_9H_{12}N_3Cl,C_6H_3O_7N_3$ requires C, 42·2; H, 3·5; N, 19·7%).

N-(N-p-*Chlorophenyl*-N'-*ethylguanyl*)-N'-iso*propylthiourea* (VIII; R = Pr^i, R' = Et).—The above crude guanidine (18 g.) and *iso*propyl *iso*thiocyanate (8·3 g.) were heated at steam-bath temperature for 6 hours, and then steam-distilled to remove unchanged *iso*thiocyanate. After cooling, the residual product was separated by decantation and crystallised from alcohol to give (VIII; R = Pr^i, R' = Et) as colourless prisms, m. p. 132—133° (Found : C, 52·3; H, 6·3; N, 19·0; Cl, 12·3. $C_{13}H_{19}N_4ClS$ requires C, 52·3; H, 6·4; N, 18·8; Cl, 11·9%).

Reaction of N-(N-p-*Chlorophenyl*-N'-*ethylguanyl*)-N'-iso*propylthiourea with Ammonia*.—The preceding compound (2 g.), mercuric oxide (4 g.), and alcoholic ammonia (25 c.c. of 13%) were stirred at room temperature for 20 hours and worked up to give the base as a non-crystallisable gum. This was dissolved in 2N-hydrochloric acid, and the solution neutralised with ammonia and treated with sodium chloride. The aqueous layer was decanted from the gummy precipitate which was dried by repeated evaporation of the solution in alcohol, followed by crystallisation from ethyl acetate to give N^1-*p*-chlorophenyl-N^2-ethyl-N^5-*iso*propyldiguanide hydrochloride, m. p. 174—176°, identical with the material described in Part XXIX.

N^1-p-*Chlorophenyl*-N^4-*methyl*-N^2-*ethyl*-N^5-iso*propyldiguanide* (II; R = Pr^i, R' = Me, R'' = Et).—*N*-(*N*-*p*-Chlorophenyl-*N'*-ethylguanyl)-*N'*-*iso*propylthiourea (5 g.), mercuric oxide (10 g.), and methylamine (15 c.c. of 21% aqueous solution) were kept at 30—35° in alcohol (50 c.c.) for 20 hours, and the mixture worked up to give a base which was dissolved in 2N-hydrochloric acid. The solution was neutralised with ammonia and saturated with sodium chloride; the precipitated *hydrochloride* crystallised on standing, and was collected, washed, dried, and crystallised from alcohol–ethyl acetate (yield, 2·2 g.). It formed tiny colourless rods, m. p. 152° (Found : C, 50·6; H, 6·8; N, 20·8; Cl, 21·0. $C_{14}H_{22}N_5Cl,HCl$ requires C, 50·6; H, 6·9; N, 21·1; Cl, 21·4%) (5757).

N^1-p-*Chlorophenyl*-N^2 : N^4-*diethyl*-N^5-iso*propyldiguanide* (II; R = Pr^i, R' = R'' = Et).—Prepared similarly using ethylamine in place of methylamine, the *hydrochloride* could only be crystallised after dissolving it in alcohol and evaporating the solution to dryness several times. It then separated from ethyl acetate as tiny colourless rods, m. p. 145—146° (Found : C, 51·9; H, 6·9; N, 20·7; Cl, 20·7. $C_{15}H_{24}N_5Cl,HCl$ requires C, 52·0; H, 7·2; N, 20·2; Cl, 20·5%) (5758).

N-*Phenyl*-N'-p-*chlorophenylthiourea*.—A mixture of phenyl *iso*thiocyanate (16·1 g.) and *p*-chloroaniline (15·2 g.) was gradually heated to 100° and kept there for ½ hour. The cooled melt was ground and crystallised from alcohol to give the product (20·5 g.) as colourless plates, m. p. 156—158° (Found : C, 58·9; H, 4·2; N, 11·0. Calc. for $C_{13}H_{11}N_2ClS$: C, 59·4; H, 4·2; N, 10·7%). The same compound (m. p. and mixed m. p. 156—157°) was obtained from *p*-chlorophenyl *iso*thiocyanate and aniline (cf. Losanitsch, *Ber.*, 1872, **5**, 157, and Kjellin, *ibid.*, 1903, **36**, 197).

N-p-*Chlorophenyl*-N'-p-*tolylthiourea*.—Prepared similarly from *p*-chlorophenyl *iso*thiocyanate and *p*-toluidine, the *compound* crystallised from xylene as colourless plates, m. p. 174—175° (Found : C, 61·3; H, 4·7; N, 10·5. $C_{14}H_{13}N_2ClS$ requires C, 60·8; H, 4·7; N, 10·1%).

N-*Phenyl*-N'-p-*chlorophenylguanidine* (III; R = Cl, R' = Ph).—*N*-Phenyl-*N'*-*p*-chlorophenylthiourea (26·25 g.) and mercuric oxide (43·4 g.) were added to ice-cold saturated alcoholic ammonia (400 c.c.), and, with stirring, the temperature was gradually raised to 30°. After stirring at 30—35° overnight, the mixture was raised to the boil to drive off excess of ammonia, then cooled and filtered. The filtrate was evaporated to dryness, and the residue crystallised from benzene to give the *product* (12·7 g.) as colourless prisms, m. p. 149—151° (Found : C, 64·1; H, 4·8; N, 17·1. $\mathrm{C_{13}H_{12}N_3Cl}$ requires C, 63·5; H, 4·9; N, 17·1%).

N-p-*Chlorophenyl*-N′-p-*tolylguanidine* (III; R = Cl, R′ = *p*-$\mathrm{C_6H_4Me}$).—Prepared from *N*-*p*-chlorophenyl-*N′*-*p*-tolylthiourea, this *compound* formed colourless long flat prisms from benzene, m. p. 148—150° (Found : N, 16·6. $\mathrm{C_{14}H_{14}N_3Cl}$ requires N, 16·2%).

NN′-*Di*-p-*chlorophenylguanidine* (III; R = Cl, R′ = *p*-$\mathrm{C_6H_4Cl}$).—Prepared analogously from *NN′*-di-*p*-chlorophenylthiourea, the compound was obtained as colourless fine needles by crystallisation from toluene, m. p. 146—147° (Losanitsch, *Bull. Soc. chim.*, 1879, **32**, 170, gives m. p. 140—141°).

N-(N-*Phenyl*-N′-p-*chlorophenylguanyl*)-N′-iso*propylthiourea* (VIII; R = $\mathrm{Pr^i}$, R′ = Ph).—*N*-Phenyl-*N′*-*p*-chlorophenylguanidine (4·09 g.) and *iso*propyl *iso*thiocyanate (1·7 g.) were boiled in benzene (25 c.c.) for 5 hours. The benzene was evaporated and the residue extracted with boiling light petroleum (b. p. 100—120°). On cooling, the extract deposited a sticky solid which was further purified by crystallisation from alcohol to give (VIII; R = $\mathrm{Pr^i}$, R′ = Ph), m. p. 133—135° (Found : C, 58·5; H, 5·5; N, 16·4; Cl, 10·4. $\mathrm{C_{17}H_{19}N_4ClS}$ requires C, 58·9; H, 5·5; N, 16·2; Cl, 10·2%).

N-(N-p-*Chlorophenyl*-N′-p-*tolylguanyl*)-N′-iso*propylthiourea* (VIII; R = $\mathrm{Pr^i}$, R′ = *p*-$\mathrm{C_6H_4Me}$).—Similarly prepared from *iso*propyl *iso*thiocyanate and N-*p*-chlorophenyl-N′-*p*-tolylguanidine, this *compound* crystallised from light petroleum, m. p. 138—140° (Found : C, 60·2; H, 5·6; N, 15·2. $\mathrm{C_{18}H_{21}N_4ClS}$ requires C, 59·9; H, 5·8; N, 15·5%).

N-(NN′-*Di*-p-*chlorophenylguanyl*)-N′-iso*propylthiourea* (VIII; R = $\mathrm{Pr^i}$, R′ = *p*-$\mathrm{C_6H_4Cl}$).—Prepared in a corresponding manner from *NN′*-di-*p*-chlorophenylguanidine and *iso*propyl *iso*thiocyanate and crystallised from benzene, this *compound* formed colourless long flat prisms, m. p. 154—156° (Found : C, 53·9; H, 4·8; N, 14·9; Cl, 18·7. $\mathrm{C_{17}H_{18}N_4Cl_2S}$ requires C, 53·5; H, 4·7; N, 14·7; Cl, 18·6%).

N^1-*Phenyl*-N^2-p-*chlorophenyl*-N^5-iso*propyldiguanide* (II; R = $\mathrm{Pr^i}$, R′ = H, R″ = Ph).—*N*-(*N*-Phenyl-*N′*-*p*-chlorophenylguanyl)-*N′*-*iso*propylthiourea (3·25 g.), mercuric oxide (4·34 g.), and saturated alcoholic ammonia (50 c.c.) were stirred at 40—45° overnight. The mixture was then filtered and the filtrate evaporated to dryness. The residue was dissolved in a warm mixture of acetic acid (30 c.c.) and water (70 c.c.), and the solution carbon-treated and filtered. Addition of sodium hydroxide to the filtrate precipitated the *acetate* which was collected, washed with water, and dried. Crystallised from chlorobenzene it formed colourless needles (1·5 g.), m. p. 170—172° (Found : C, 58·0; H, 6·2; N, 18·3. $\mathrm{C_{17}H_{20}N_5Cl,C_2H_4O_2}$ requires C, 58·5; H, 6·2; N, 18·0%) (5604).

N^1-p-*Chlorophenyl*-N^2-p-*tolyl*-N^5-iso*propyldiguanide* (III; R = $\mathrm{Pr^i}$, R′ = H, R″ = *p*-$\mathrm{C_6H_4Me}$).—Similarly prepared from *N*-(*N*-*p*-chlorophenyl-*N′*-*p*-tolylguanyl)-*N′*-*iso*propylthiourea, the *acetate* crystallised from chlorobenzene as colourless blunt-ended needles, m. p. 174—176° (Found : C, 60·0; H, 6·6; N, 17·0. $\mathrm{C_{18}H_{22}N_5Cl,C_2H_4O_2}$ requires C, 59·5; H, 6·4; N, 17·4%) (5605).

N^1 : N^2-*Di*-p-*chlorophenyl*-N^5-iso*propyldiguanide* (III; R = $\mathrm{Pr^i}$, R′ = H, R″ = *p*-$\mathrm{C_6H_4Cl}$).—Likewise prepared from N-(*NN′*-di-*p*-chlorophenylguanyl)-*N′*-*iso*propylthiourea, the *acetate* crystallised from chlorobenzene as colourless prisms, m. p. 176° (Found : C, 53·5; H, 5·6; Cl, 16·1. $\mathrm{C_{17}H_{19}N_5Cl_2,C_2H_4O_2}$ requires C, 53·8; H, 5·4; Cl, 16·7%) (5603).

N^1 : N^2-*Di*-p-*chlorophenyl*-N^4-*ethyl*-N^5-iso*propyldiguanide* (III; R = $\mathrm{Pr^i}$, R′ = Et, R″ = *p*-$\mathrm{C_6H_4Cl}$).—*N*-(*NN′*-Di-*p*-chlorophenylguanyl)-*N′*-*iso*propylthiourea (6·35 g.), mercuric oxide (8 g.), ethylamine (12·1 g. of 31%), and alcohol (100 c.c.) were stirred at 30—35° for 16 hours, and the mixture then filtered. The filtrate was evaporated to dryness under reduced pressure and the residue dissolved in hot water (80 c.c.) and acetic acid (40 c.c.). The solution was carbon-treated, filtered, and added to sodium hydroxide to precipitate the product which was filtered off, washed with water, and dried. Crystallised from chlorobenzene, the *base* formed colourless long flat prisms, m. p. 167—169° (Found : C, 55·4; H, 6·2; N, 16·6; Cl, 16·9. $\mathrm{C_{19}H_{23}N_5Cl_2,H_2O}$ requires C, 55·6; H, 6·1; N, 17·1; Cl, 17·3%) (5785).

N^1-p-*Chlorophenyl*-N^2 : N^2-*dimethyl*-N^5-iso*propyldiguanide* (IX; R = H, R′ = $\mathrm{Pr^i}$, R″ = Me).—*N*-*p*-Chlorophenyl-*N′*-*iso*propylguanylthiourea (5 g.) (Part XXIX), mercuric oxide (5 g.), 2-ethoxyethanol (40 c.c.), and 25% aqueous dimethylamine (25 c.c.) were stirred for 6 hours at 55°. The mixture was diluted with acetone (100 c.c.) and filtered, and the filtrate evaporated. The residual base was converted into its *dihydrochloride* by dissolving it in alcoholic hydrogen chloride and adding ethyl acetate. This salt separated from alcohol–ethyl acetate as a colourless microcrystalline powder (4·15 g.), m. p. 191—193° (Found : C, 43·8; H, 6·1; N, 19·3; Cl, 30·0. $\mathrm{C_{13}H_{20}N_5Cl,2HCl}$ requires C, 44·0; H, 6·2; N, 19·7; Cl, 30·0%) (5368).

N^1-p-*Chlorophenyl*-N^2 : N^2 : N^5 : N^5-*tetramethyldiguanide* (IX; R = R′ = R″ = Me).—*N*-*p*-Chlorophenyl-*N′*-(*NN*-dimethylguanyl)thiourea (6 g.) (Part XXIX), mercuric oxide (10 g.), alcohol (100 c.c.), and aqueous dimethylamine (30 c.c. of 25%) were stirred for 16 hours at 30—40°. Dilute hydrochloric acid was then added to render the mixture acid to Congo-red, followed by excess of sodium sulphide, and the whole was then filtered and made alkaline with sodium hydroxide. The base, isolated by extraction with benzene and evaporation of the dried benzene solution, was dissolved in 2N-hydrochloric acid, and the solution neutralised with ammonia and treated with a litttle sodium chloride. The precipitated *hydrochloride* crystallised on long standing and was collected, dried, and recrystallised from alcohol–ethyl acetate (yield, 1·85 g.); colourless rods, m. p. 212° (Found : C, 46·4; H, 6·9; Cl, 22·4. $\mathrm{C_{12}H_{18}N_5Cl,HCl,0{\cdot}5H_2O}$ requires C, 46·0; H, 6·4; Cl, 22·7%) (5710).

N-p-*Chlorophenyl*-N′-*guanylthiourea* (VI; R = Cl, R′ = R″ = R‴ = H).—Sodium (1·5 g.) was dissolved in acetone (50 c.c.), and to the resulting sludge guanidine nitrate (8·8 g.) was added. After stirring for a short time, during which the mixture became more fluid, *p*-chlorophenyl *iso*thiocyanate (8·4 g.) was added with cooling. The mixture was then stirred for ½ hour at 30° and poured on ice (500 g.). The precipitated product was collected, washed with water, dried, and crystallised from methanol. Recrystallisation from xylene–butanol gave N-p-*chlorophenyl*-N′-*guanylthiourea* as colourless long thin prisms (yield, 43·5%), m. p. 195° (Found : C, 41·9; H, 4·0; N, 24·8; S, 13·9. $\mathrm{C_8H_9N_4ClS}$ requires C, 42·0; H, 3·9; N, 24·5; S, 14·0%) (4588).

N^1-p-*Chlorophenyl*-N^2-iso*propyldiguanide* (II; R = R′ = H, R″ = Pr^i).—The preceding compound (9·2 g.), mercuric oxide (8·8 g.), and *iso*propylamine (6 c.c.) were shaken in a closed vessel overnight. The mixture was diluted with ether (50 c.c.) and filtered, and the ether evaporated. The residue was crystallised first from dilute alcohol and then from benzene–light petroleum (b. p. 60—80°) to give the *product* as colourless boat-shaped crystals, m. p. 166—168° (Found: C, 52·1; H, 6·2; N, 27·4. $C_{11}H_{16}N_5Cl$ requires C, 52·1; H, 6·3; N, 27·6%) (4765).

N^1-p-*Chlorophenyl*-N^2-n-*propyldiguanide* (II; R = R′ = H, R″ = Pr^n).—Prepared similarly using *n*-propylamine in place of *iso*propylamine, the *compound* was crystallised from benzene–light petroleum (b. p. 80—100°) and recrystallised from methyl*cyclo*hexane (yield, 45%); it was a colourless microcrystalline powder, m. p. 152·5—153·5° (Found: C, 51·7; H, 6·1; N, 14·2. $C_{11}H_{16}N_5Cl$ requires C, 52·1; H, 6·3; Cl, 14·0%) (4769).

N^1-p-*Chlorophenyl*-N^2 : N^2-*diethyldiguanide* (IX; R = R′ = H, R″ = Et).—Prepared analogously using diethylamine, the *product* crystallised from alcohol–light petroleum (b. p. 100—120°) as clusters of colourless needles, m. p. 174—175° (Found: C, 53·5; H, 7·0; Cl, 12·7. $C_{12}H_{18}N_5Cl$ requires C, 53·8; H, 6·7; Cl, 13·3%) (4766).

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