388. *Synthetic Antimalarials. Part XLVIII. The Action of Halogens on* N^1*-Aryldiguanides.*

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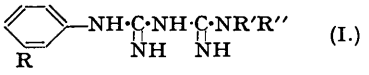
Direct halogenation by chlorine, bromine, or iodine chloride (iodine failed to react) of N^1-aryl-, N^1-aryl-N^5-alkyl-, N^1-aryl-N^5N^5-dialkyl-, N^1-aryl-N^2N^5-dialkyl-, and N^1-aryl-N^4N^5-dialkyl-diguanides without a substituent in the *para*-position has provided a further method for the preparation of members of this class with high antimalarial activity (see preceding paper). Substitution took place preferentially in the *para*-position, even when a halogen atom was already present in the *meta*-position, but in this case there was a tendency for mixtures to be formed.

There was no evidence that the diguanide group was attacked under the conditions employed.

The preparation of a large number of diguanide derivatives has been reported in previous papers in this series (Parts X, *J.*, 1946, 729; XXVIII, *J.*, 1948, 1630: XXIX, *J.*, 1948, 1636; XXX, *J.*, 1948, 1645; XXXIII, *J.*, 1949, 98; XXXVII, *J.*, 1949, 475; XLVII, preceding paper). In most cases, the compounds of biological interest have carried a *p*-halogenophenyl

group at N^1 of the diguanide chain. The purpose of this paper is to report the direct halogenation of N^1-phenyldiguanide derivatives (I; R = H, halogen, OMe, Me; R′ = H or alkyl; R″ = H or alkyl), in which the *para*-position is unsubstituted.



(I.)

The diguanide base, or hydrochloride, was dissolved in either acetic acid or concentrated sulphuric acid and treated with a calculated quantity of chlorine, bromine, or iodine chloride. The diguanide molecule was found to be extremely stable under these conditions.

N^1-Phenyldiguanide (I; R = R′ = R″ = H), N^1-phenyl-N^5-*iso*propyldiguanide (I; R = R′ = H, R″ = Pr^i) and N^1-methyl-N^5-phenyl-N^1-*iso*propyldiguanide (I; R = H, R′ = Me, R″ = Pr^i) were first examined. The corresponding *p*-halogenophenyl derivatives were formed in good yield in each case from each of the three halogenating agents. With two molecular equivalents of chlorine, (I; R = R′ = H, R″ = Pr^i) gave the 2 : 4-dichlorophenyl compound (preceding paper). We were unable to effect any reaction between elementary iodine and (I; R = R′ = R″ = H).

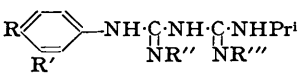
Some evidence was obtained of substitution at more than a single position with N^1-phenyldiguanide derivatives bearing *meta*-substituents. Chlorination of N^1-*m*-chlorophenyl-N^5-*iso*propyldiguanide (I; R = Cl, R′ = Pr^i, R″ = H) gave a product which only after repeated crystallisation of the hydrochloride yielded pure N^1-3 : 4-dichlorophenyl-N^5-*iso*propyldiguanide (preceding paper). Bromination gave a mixture from which no pure constituent could be isolated. On the other hand, by the use of iodine chloride, N^1-3-chloro-4-iodophenyl-N^5-*iso*propyldiguanide hydrochloride (preceding paper) was readily obtainable. Impure products were obtained by the chlorination and bromination of N^1-*m*-bromophenyl-N^5-*iso*propyldiguanide (I; R = Br, R′ = Pr^i, R″ = H) although in both cases the hydrochlorides isolated undoubtedly contained a high proportion of the corresponding 3 : 4-disubstituted phenyl compounds. In neither case was there a depression of melting point when admixed with the corresponding 3-bromo-4-chloro- and 3 : 4-dibromo-derivatives. Iodine chloride reacted only partially with (I; R = Br, R′ = Pr^i, R″ = H) even after prolonged heating.

It seems likely that additional *ortho*-substitution was taking place in those cases where mixtures of products were obtained, with the formation of 2 : 5-disubstituted derivatives. It may be, also, that some trihalogeno-derivatives were formed.

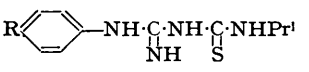
Bromination of N^1-3 : 5-dichlorophenyl-N^5-*iso*propyldiguanide proceeded almost entirely at the 4-position. An identical product was obtained from 4-bromo-3 : 5-dichloroaniline hydrochloride (Hurtley, *J.*, 1901, **79**, 1303) and *iso*propyldicyandiamide.

Other *ortho–para*-directing groups used as substituents in the 3-position gave rise to simple chlorination in the 4-position. Thus the product of chlorination of N^1-*m*-methoxyphenyl-N^5-*iso*propyldiguanide hydrochloride (I; R = OMe, R′ = Pr^i, R″ = H) was the 4-chloro-3-methoxy-compound, identical with the product of the reaction of the hydrochloride of 5-amino-2-chloroanisole (Reverdin and Eckhard, *Ber.*, 1899, **32**, 2626) and *iso*propyldicyandiamide. Similarly, N^1-*iso*propyl-N^5-*m*-tolyldiguanide hydrochloride (I; R = Me, R′ = Pr^i, R″ = H) yielded N^1-4-chloro-3-methylphenyl-N^5-*iso*propyldiguanide.

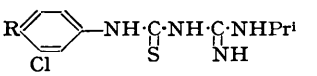
Introduction of alkyl groups at positions N^2 and N^4 of the diguanide molecule had little effect on the course of halogenation. N^4-Methyl-N^1-phenyl-N^5-*iso*propyldiguanide hydrochloride (II; R = R′ = R″ = H, R‴ = Me) [prepared from *N*-phenylguanyl-*N*′-*iso*propylthiourea (III; R = H) by a method similar to those described in Part XXX, *loc. cit.*] reacted with chlorine in acetic acid to give the *p*-chlorophenyl analogue. N^1-3 : 4-Dichlorophenyl-N^2-methyl-N^5-*iso*propyldiguanide hydrochloride (II; R = R′ = Cl, R″ = Me, R‴ = H) was formed by the chlorination of N^1-*m*-chlorophenyl-N^2-methyl-N^5-*iso*propyldiguanide hydro-



(II.)



(III.)



(IV.)

chloride (II; R = R‴ = H, R′ = Cl, R″ = Me) which was obtained from *N*-*m*-chlorophenyl-*N*′-*iso*propylguanylthiourea (IV; R = H), methylamine, and mercuric oxide as described in Part XXIX (*loc. cit.*). The identity of this chlorination product was established by its unambiguous synthesis from *N*-3 : 4-dichlorophenyl-*N*′-*iso*propylguanylthiourea (IV; R = Cl).

Experimental.

Chlorination of N^1-*Phenyldiguanide* (I; R = R′ = R″ = H).—Into a solution of *N*^{1}-phenyldiguanide (8·85 g.; Cohn, *J. pr. Chem.*, 1911, **84**, 394) in glacial acetic acid (30 c.c.) a stream of gaseous chlorine (3·55 g.) was passed, with cooling. The mixture was kept at room temperature for 30 minutes and then filtered. Acetone (100 c.c.) was added to the filtrate and the crystals which separated were collected, washed with acetone, and dried (5·6 g.). Crystallisation from water afforded colourless needles of *N*^{1}-*p*-chlorophenyldiguanide hydrochloride, m. p. 253—254°, undepressed on admixture with authentic material (Part IV, *J.*, 1946, 362).

Chlorination of N^1-*Phenyl*-N^5-iso*propyldiguanide* (I; R = R′ = H, R″ = Pr^i).—(*a*) A solution of *N*^{1}-phenyl-*N*^{5}-*iso*propyldiguanide hydrochloride (I; R = R′ = H, R″ = Pr^i, 2·56 g.; Part XXVIII, *loc. cit.*) in water (50 c.c.) was made alkaline with 10N-sodium hydroxide, and the liberated base was extracted with benzene, dried (K_2CO_3), filtered, and evaporated. The residue was dissolved in acetic acid (10 c.c.), and chlorine was passed into the solution at 0—10° until 0·71 g. had been absorbed. The mixture was allowed to warm to room temperature, then diluted with water (40 c.c.), stirred with carbon, filtered, and poured into an excess of 5N-sodium hydroxide. The precipitate was separated, washed with water, dissolved in 2N-hydrochloric acid, and made faintly alkaline to brilliant-yellow with dilute aqueous ammonia. The solid was filtered off, washed with water, and dried (2·4 g., 83%). Crystallisation from water gave colourless needles of *N*^{1}-*p*-chlorophenyl-*N*^{5}-*iso*propyldiguanide hydrochloride, m. p. 243—244°, alone and mixed with an authentic sample (Part X, *loc. cit.*). The hydrochloride, converted into the base, dissolved in ethyl acetate and neutralised with acetic acid, gave the acetate, m. p. 184—185° undepressed by admixture with an authentic specimen.

(*b*) *N*^{1}-Phenyl-*N*^{5}-*iso*propyldiguanide hydrochloride (1·27 g.), dissolved in acetic acid (10 c.c.) and treated with chlorine gas (0·37 g.), gave, after working up as in (*a*), *N*^{1}-*p*-chlorophenyl-*N*^{5}-*iso*propyldiguanide hydrochloride (1·3 g.), m. p. 243—244° alone and mixed with an authentic specimen.

(*c*) *N*^{1}-Phenyl-N^5-*iso*propyldiguanide hydrochloride (1·9 g., 1 mol.) was converted into the base, dissolved in acetic acid (10 c.c.), and treated with gaseous chlorine (1·55 g., 2 mols.). The solution was kept for 16 hours at room temperature, then diluted with water, and the small amount of oil present was removed by extraction with benzene. The aqueous part was made strongly alkaline with sodium hydroxide and extracted with benzene, and the benzene solution shaken with 2N-hydrochloric acid (10 c.c.). The separated acid layer was treated with carbon and filtered, and the filtrate made faintly alkaline with aqueous ammonia. The colourless solid was filtered off, washed with water, and dried (1·0 g.). Colourless plates of *N*^{1}-2 : 4-dichlorophenyl-*N*^{5}-*iso*propyldiguanide hydrochloride were obtained by crystallisation from water, and had m. p. 240—241°, alone or mixed with an authentic specimen (preceding paper).

Chlorination of N^1-*Methyl*-N^5-*phenyl*-N^1-iso*propyldiguanide*.—N^1-*Methyl*-N^5-*phenyl*-N^1-iso*propyldiguanide hydrochloride* (I; R = H, R′ = Me, R″ = Pr^i) was obtained (cf. Part X, *loc. cit.*) from phenyldicyandiamide (Part X, *loc. cit.*) and methyl*iso*propylamine hydrochloride in nitrobenzene at 140°, and had m. p. 212° (Found: N, 25·7, 25·85. $C_{12}H_{19}N_5$,HCl requires N, 25·9%). The derived base (2·5 g.) was treated with chlorine (0·65 g.) in acetic acid. By working as before *N*^{1}-*p*-chlorophenyl-*N*^{5}-methyl-*N*^{5}-*iso*propyldiguanide (1·61 g.) was obtained and converted into the acetate which crystallised as colourless rods (from methanol–ethyl acetate), m. p. 212°, alone or mixed with an authentic specimen (Part X, *loc. cit.*).

Bromination of N^1-*Phenyldiguanide*.—(*a*) *N*^{1}-Phenyldiguanide (3·54 g.) was dissolved in acetic acid (10 c.c.) and to the chilled solution was added a solution of bromine (3·2 g.) in acetic acid (5 c.c.). The mixture was kept at room temperature for 1 hour, then water (70 c.c.) was added, and the mixture warmed to give a clear solution, filtered, and made strongly alkaline with 10N-sodium hydroxide. The solid formed was filtered off, washed with water, and dried (3·6 g.). It crystallised from aqueous ethanol in feathery needles which when heated rapidly had m. p. 95—98° but when heated slowly had m. p. 136°, softening at 95°. The base was converted into the *dipicrate*, prisms (from ethanol), m. p. 190°, alone or mixed with *N*^{1}-*p*-bromophenyldiguanide dipicrate [prepared from the base (Part IV, *loc. cit.*), yellow prisms (from ethanol), m. p. 190° (Found: N, 20·5, 20·6; loss at 100°, 2·7. $C_8H_{10}N_5Br,2C_6H_3O_7N_3,\frac{1}{2}C_2H_6O$ requires N, 20·9; C_2H_6O, 3·1%)].

(*b*) *N*^{1}-Phenyldiguanide (10·62 g.), dissolved in sulphuric acid 45 c.c.; *d* 1·84), was stirred with bromine (9·6 g.) at room temperature for 30 hours. Most of the bromine had reacted by this time. The mixture was poured into water (300 c.c.), stirred with carbon, filtered, and made alkaline with 10N-sodium hydroxide. The solid was filtered off, washed with water, extracted with ethanol, and evaporated to small bulk. To the hot solution, water was added and, on cooling, colourless needles of the base separated (11·2 g.). It gave *N*^{1}-*p*-bromophenyldiguanide hydrochloride, m. p. 242—244°, and dipicrate, m. p. 189—190°, both m. p.s undepressed by admixture with authentic materials.

(*c*) Equimolecular proportions of bromine and *N*^{1}-phenyldiguanide in nitrobenzene at 20° gave *N*^{1}-*p*-bromophenyldiguanide, isolated as the hydrochloride, in small yield.

Bromination of N^1-*Phenyl*-N^5-*isopropyldiguanide*.—The diguanide hydrochloride (2·56 g.) was allowed to react with bromine (1·6 g.) in sulphuric acid as in (*b*) above. *N*^{1}-*p*-Bromophenyl-*N*^{5}-*iso*propyldiguanide hydrochloride (2·5 g.) was isolated as minute rods (from ethanol–ethyl acetate), m. p. 246° alone or mixed with an authentic specimen (Part XXVIII, *loc. cit.*).

Bromination of N^1-*Methyl*-N^5-*phenyl*-N^1-iso*propyldiguanide*.—The base prepared from the diguanide hydrochloride (1·35 g.) was treated in acetic acid (9 c.c.) with bromine (0·8 g.). *N*^{1}-*p*-Bromophenyl-*N*^{5}-methyl-*N*^{5}-*iso*propyldiguanide hydrochloride was isolated as needles (from water), m. p. 251° alone or mixed with an authentic specimen (Part XXXIII, *loc. cit.*).

Iodination of N^1-*Phenyldiguanide*.—*N*^{1}-Phenyldiguanide (1·77 g.), iodine chloride (1·62 g.), and acetic acid (20 c.c.) were heated on the steam-bath for 6 hours. The mixture was cooled, and the solid filtered off, washed with acetic acid and then acetone, and dried (1·25 g.). Crystallisation from water gave colourless rods of *N*^{1}-*p*-iodophenyldiguanide hydrochloride, m. p. 234°, undepressed on admixture with an authentic specimen (Part IV, *loc. cit.*).

All attempts to bring the diguanide into reaction with elementary iodine failed.

Iodination of N^1-*Phenyl*-N^5-iso*propyldiguanide*.—The base from *N*^{1}-phenyl-*N*^{5}-*iso*propyldiguanide hydrochloride (1·28 g.), iodine chloride (0·89 g.), and acetic acid (11·5 c.c.) were heated together at 95—100° for 8 hours. The mixture was diluted with water (50 c.c.) and shaken with benzene to remove a little oil. The aqueous part was basified with 10N-sodium hydroxide, and the base extracted with benzene and re-extracted with 2N-hydrochloric acid. The acid solution was stirred with carbon, filtered, and made faintly alkaline with aqueous ammonia, and the solid formed filtered off, washed with water, and dried (1·3 g.). Crystallisation from water afforded *N*^{1}-*p*-iodophenyl-*N*^{5}-*iso*propyldiguanide hydrochloride as small colourless needles, m. p. 239° alone or mixed with an authentic specimen (Part XXVIII, *loc. cit.*).

N^1-p-*Iodophenyl*-N^5-*methyl*-N^5-iso*propyldiguanide*.—(*a*) *N*^{1}-Methyl-*N*^{5}-phenyl-*N*^{1}-*iso*propyldiguanide was iodinated as in the preceding experiment. N^1-p-*Iodophenyl*-N^5-*methyl*-N^5-iso*propyldiguanide hydrochloride* was obtained as fine colourless needles (from water), m. p. 236—237° (Found: C, 36·9; H, 4·95; N, 17·9. $C_{12}H_{18}N_5I$,HCl requires C, 36·4; H, 4·8; N, 17·7%).

(*b*) *N*-Methyl-*N*-*iso*propyldicyandiamide (1·15 g.; Part XXVIII, *loc. cit.*) was added to a mixture of *p*-iodoaniline (1·57 g.), 10N-hydrochloric acid (0·64 c.c.), and water (3 c.c.) and heated at 100° for 90 minutes. The mixture was cooled, and the solid filtered off, washed with water and dried (2·4 g.). The product crystallised from water in fine needles, m. p. 236—237° alone or mixed with material from (*a*) above.

Chlorination of N^1-m-*Chlorophenyl*-N^5-*isopropyldiguanide* (I; R = Cl, R′ = H, R″ = Pr^i).—The diguanide hydrochloride (Part XXVIII, *loc. cit.*) was converted into the base and allowed to react with chlorine in acetic acid. The crude hydrochloride isolated was crystallised several times from water, giving *N*^{1}-3 : 4-dichlorophenyl-*N*^{5}-*iso*propyldiguanide hydrochloride (II; R = R′ = Cl, R″ = R‴ = H) as small colourless rods, m. p. 244°, undepressed on admixture with an authentic specimen (preceding paper).

Bromination of N^1-m-*Chlorophenyl*-N^5-iso*propyldiguanide*.—The diguanide base in acetic acid gave with bromine a product, the hydrochloride of which had m. p. 220—222°, unaffected by further crystallisation. [*N*^{1}-4-Bromo-3-chlorophenyl-*N*^{5}-*iso*propyldiguanide hydrochloride (II; R = Br, R′ = Cl, R″ = R‴ = H) has m. p. 237° (preceding paper).]

Iodination of N^1-m-*Chlorophenyl*-N^5-iso*propyldiguanide*.—The base from the diguanide hydrochloride (5·88 g.) was dissolved in acetic acid (44 c.c.) and heated with iodine chloride (3·6 g.) at 95—100° for 17 hours. Isolated in the usual manner N^1-3-*chloro*-4-*iodophenyl*-N^5-iso*propyldiguanide hydrochloride* (II; R = I, R′ = Cl, R″ = R‴ = H) formed a colourless microcrystalline powder (from water), m. p. 221—222° alone or on admixture with a sample prepared from 3-chloro-4-iodoaniline and *iso*propyldicyandiamide (preceding paper) (Found: C, 31·9; H, 4·1; N, 17·45. $C_{11}H_{15}N_5ClI$,HCl requires C, 31·7; H, 3·9; N, 16·8%).

Chlorination of N^1-m-*Bromophenyl*-N^5-*isopropyldiguanide* (I; R = Br, R′ = H, R″ = Pr^i).—Reaction between chlorine and this diguanide or its hydrochloride (Part XXVIII, *loc. cit.*) gave a mixture of hydrochlorides which, crystallised from water, had m. p. 230°. Three further crystallisations raised the m. p. to 231°. A mixture with *N*^{1}-3-bromo-4-chlorophenyl-*N*^{5}-*iso*propyldiguanide hydrochloride (II; R = Cl, R′ = Br, R″ = R‴ = H) (preceding paper, m. p. 239°) had m. p. 231—232°.

Bromination of N^1-m-*Bromophenyl*-N^5-iso*propyldiguanide*.—The crude bromination product gave colourless prisms of a hydrochloride (from water), m. p. 228—229°. Further crystallisation raised the m. p. to 230—231°. A mixture with *N*^{1}-3 : 4-dibromophenyl-*N*^{5}-*iso*propyldiguanide hydrochloride (II; R = R′ = Br, R″ = R‴ = H; preceding paper, m. p. 240°) had m. p. 232—233°.

Iodination of N^1-m-*Bromophenyl*-N^5-iso*propyldiguanide*.—The diguanide did not react completely with iodine chloride in acetic acid at 95—100° during 46 hours. The hydrochloride of the reaction product contained a much higher proportion of carbon and nitrogen than was required for the corresponding bromo-iodo-compound.

N^1-4-*Bromo*-3 : 5-*dichlorophenyl*-N^5-*isopropyldiguanide*.—(*a*) *N*^{1}-3 : 5-Dichlorophenyl-*N*^{5}-*iso*propyldiguanide hydrochloride (preceding paper; 6·49 g.) in acetic acid (40 c.c.) was heated at 60° for 5 hours with bromine (3·36 g.) in acetic acid (15 c.c.). The mixture was set aside for 16 hours at room temperature, then diluted with water (150 c.c.), and poured into an excess of 10N-sodium hydroxide. The precipitate was filtered off, drained, and dissolved in 3N-hydrochloric acid (75 c.c.). Suspended material was filtered off and ammonia was added slowly to the filtrate. When the solution was only faintly acid to Congo-red, carbon was added and the mixture was stirred and then filtered. The filtrate was then made faintly alkaline to brilliant-yellow by the further addition of ammonia. The crystalline solid which separated was collected, washed with water, and crystallised from aqueous ethanol. Repeated crystallisation from water gave small, colourless plates of N^1-4-*bromo*-3 : 5-*dichlorophenyl*-N^5-iso*propyldiguanide hydrochloride*, m. p. 244—245° (Found: C, 32·25; H, 3·75; N, 17·2. $C_{11}H_{14}N_5Cl_2Br$,HCl requires C, 32·7; H, 3·7; N, 17·35%).

(*b*) 4-Bromo-3 : 5-dichloroaniline (1·2 g.) (prepared by bromination of 3 : 5-dichloroacetanilide and hydrolysis of the product by 5N-hydrochloric acid; cf. Hurtley, *loc. cit.*) was converted into the hydrochloride and treated with *iso*propyldicyandiamide (0·66 g.) in water (7 c.c.) in the usual manner. The *N*^{1}-4-bromo-3 : 5-dichlorophenyl-*N*^{5}-*iso*propyldiguanide hydrochloride crystallised from water in minute colourless plates, m. p. 244—245° alone and mixed with material from (*a*).

5-Amino-2-chloroanisole.—The crude base was prepared by the method described by Reverdin and Eckhard (*loc. cit.*) and was converted into the *hydrochloride* by dissolution in ethanol followed by the addition of ethanolic hydrogen chloride. Precipitation was completed by the addition of ethyl acetate. The product was filtered off and washed with a mixture of ethanol and ethyl acetate. Crystallisation from a similar mixture gave the product as colourless plates, m. p. 265—266° (Found: C, 43·6; H, 4·5; N, 7·5. C_7H_8ONCl,HCl requires C, 43·3; H, 4·6; N, 7·2%).

N¹-4-*Chloro*-3-*methoxyphenyl*-N⁵-iso*propyldiguanide* (II; R = Cl, R′ = OMe, R″ = R‴ = H).—(*a*) The above amine hydrochloride reacted in the usual manner with *iso*propyldicyandiamide in 2-ethoxyethanol and gave N¹-4-*chloro*-3-*methoxyphenyl*-N⁵-iso*propyldiguanide hydrochloride* as colourless, feathery needles (from water), m. p. 234—235° (Found: C, 45·45; H, 5·75; N, 22·15. $C_{12}H_{18}ON_5Cl,HCl$ requires C, 45·0; H, 5·9; N, 21·9%).

(*b*) Concentrated sulphuric acid (100 g.) was added dropwise at 15—20° to a stirred suspension of 2-amino-5-nitroanisole (84 g.) in ethanol (570 c.c.). The mixture thickened and ethanol (100 c.c.) was added. Sodium nitrite (38 g.) was added gradually during 1½ hours at 20° with stirring. The temperature was raised to 45—50° and stirring at that temperature was continued for 2 hours. The mixture was steam-distilled, the first runnings of ethanol being discarded. *m*-Nitroanisole distilled over as a yellow oil which solidified on cooling and, filtered off, washed with water, and dried (47·6 g.), had m. p. 34°. G.P. 98637 ("Friedländer," V, 67) records the preparation of *m*-nitroanisole from 2-amino-5-nitroanisole but gives no details. Baultin (*Ber.*, 1878, **11**, 2100) gives m. p. 38°. The *m*-nitroanisole was reduced by stannous chloride and hydrochloric acid in the presence of ethanol to *m*-anisidine, b. p. 122°/13 mm. (yield, 75%). The *hydrochloride* crystallised from ethanol–ethyl acetate in colourless needles, m. p. 167—168° (Found: N, 9·05. C_7H_9ON,HCl requires N, 8·8%). Condensation of *m*-anisidine hydrochloride with *iso*propyldicyandiamide in 2-ethoxyethanol gave N¹-m-*methoxyphenyl*-N⁵-iso*propyldiguanide hydrochloride* (I; R = OMe, R′ = Pr^i, R″ = H) as colourless needles, m. p. 212—213°, from ethanol–ethyl acetate (Found: C, 50·3; H, 7·0; N, 24·15. $C_{12}H_{19}ON_5,HCl$ requires C, 50·45; H, 7·0; N, 24·5%). *N*¹-*m*-Methoxyphenyl-*N*⁵-*iso*propyldiguanide hydrochloride (2·85 g.) was dissolved in glacial acetic acid (50 c.c.) and gaseous chlorine (0·71 g.) was passed into the solution during 15 minutes at 10—15°. The mixture was set aside at room temperature for 4 hours and was then poured into a cooled mixture of 10N-sodium hydroxide (80 c.c.) and water (100 c.c.). A gum was precipitated which solidified when kept and was filtered off, washed with water, and drained. The filter cake was dissolved in 2N-hydrochloric acid (20 c.c.), the whole was filtered, and the filtrate was made faintly alkaline to brilliant-yellow with ammonia. The precipitated solid was filtered off, washed with water, and dried (2·8 g.). Two recrystallisations from water gave *N*¹-4-chloro-3-methoxyphenyl-*N*⁵-*iso*propyldiguanide hydrochloride, m. p. 232—233° undepressed by material from (*a*) above.

N¹-4-*Chloro*-3-*methylphenyl*-N⁵-iso*propyldiguanide* (II; R = Cl, R′ = Me, R″ = R‴ = H).—(*a*) *N*¹-4-Chloro-3-methylphenyl-*N*⁵-*iso*propyldiguanide hydrochloride, obtained from 4-chloro-3-methylaniline hydrochloride and *iso*propyldicyandiamide (we are indebted to Mr. S. Birtwell for this preparation) was converted into the *base* which crystallised from a mixture of benzene and light petroleum (b. p. 80—100°) in very fine, colourless rods, m. p. 137° (Found: C, 53·6; H, 6·7; N, 26·2. $C_{12}H_{18}N_5Cl$ requires C, 53·6; H, 6·7; N, 26·3%).

(*b*) *N*¹-*iso*Propyl-*N*⁵-*m*-tolyldiguanide hydrochloride (Part XXVIII, *loc. cit.*; 10 g.) was dissolved in acetic acid, and chlorine (2·79 g.) was passed in at 10° during 15 minutes. The solution was kept at room temperature for 2 hours and then was poured into 10N-sodium hydroxide (150 c.c.) in water (1 l.). The gummy precipitate formed solidified on storage, was filtered off, washed with water, and dried. Crystallisation from benzene–light petroleum (b. p. 80—100°) gave material of m. p. 118—126°, raised by two further recrystallisations from light petroleum (b. p. 80—100°) to 133—134°, undepressed on admixture wth material from (*a*) above.

N-*Phenylguanyl*-N′-iso*propylthiourea* (III; R = H).—Phenylguanidine (27·7 g.) (Smith, *J. Amer. Chem. Soc.*, 1929, **51**, 476) and *iso*propyl *iso*thiocyanate (20·7 g.) were warmed together gently on the steam-bath. After a few minutes a vigorous reaction started and was controlled by external cooling. When the reaction had subsided the mixture was heated on the steam-bath for 4 hours. Excess of *iso*propyl *iso*thiocyanate was removed by steam-distillation. The residual oil hardened to a glass on cooling, was separated by decantation, and allowed to dry in air at 20°. The glass was dissolved in ethyl acetate (200 c.c.), filtered from a little suspended matter, and made acid to Congo-red with ethanolic hydrogen chloride. Light petroleum (b. p. 80—100°) was added to precipitate an oil which crystallised on storage. The product was filtered off, washed with ethyl acetate, and dried at 60° (17·0 g.). Recrystallisation from a mixture of ethanol and ethyl acetate did not affect the m. p. and gave colourless prisms of N-*phenylguanyl*-N′-iso*propylthiourea hydrochloride*, m. p. 176—177° (Found: C, 48·6; H, 6·4; N, 20·75. $C_{11}H_{16}N_4S,HCl$ requires C, 48·4; H, 6·2; N, 20·55%)

N⁴-*Methyl*-N¹-*phenyl*-N⁵-iso*propyldiguanide* (II; R = R′ = R″ = H, R‴ = Me).—*N*-Phenylguanyl-*N*′-*iso*propylthiourea (7·0 g.), methylamine (21% aqueous solution; 80 c.c.), mercuric oxide (20 g.), and ethanol (200 c.c.) were stirred together at 40—50° for 16 hours. The mixture was filtered and the filtrates were distilled to a small bulk. The residue was dissolved in 2N-hydrochloric acid and then made faintly alkaline to brilliant-yellow with ammonia. Addition of brine precipitated the hydrochloride as a gum which rapidly solidified. The product was filtered off, washed with brine, and dried. Crystallisation from ethanol–ethyl acetate gave N⁴-*methyl*-N¹-*phenyl*-N⁵-iso*propyldiguanide hydrochloride* as small, elongated prisms, m. p. 198° (Found: C, 53·9; H, 7·5; N, 25·9, 26·0. $C_{12}H_{19}N_5,HCl$ requires C, 53·4; H, 7·4; N, 26·0%).

Chlorination of N⁴-*Methyl*-N¹-*phenyl*-N⁵-iso*propyldiguanide.*—*N*⁴-Methyl-*N*¹-phenyl-*N*⁵-*iso*propyldiguanide hydrochloride (2·1 g.) was dissolved in glacial acetic acid (15 c.c.), and gaseous chlorine (0·557 g.) was passed in during 15 minutes at 10°. The solution was kept at 10—20° for 2 hours and was then poured into a mixture of 10N-sodium hydroxide (40 c.c.) and water (80 c.c.) with cooling. The base was

precipitated as a gum which refused to crystallise. It was separated by decantation, washed with water, dissolved in 2N-hydrochloric acid, and made faintly alkaline to brilliant-yellow with ammonia. Addition of brine caused the precipitation of the crude hydrochloride as a gum which was separated from the liquors, dissolved in ethanol, filtered from sodium chloride, and evaporated to dryness. The semisolid residue crystallised on treatment with ethyl acetate. Crystallisation first from a mixture of ethanol and ethyl acetate and then from water gave colourless rods of N^1-*p*-chlorophenyl-N^4-methyl-N^5-*iso*propyldiguanide hydrochloride, m. p. 207° alone or on admixture with an authentic specimen (Found: C, 47·45; H, 6·1; N, 22·6. Calc. for $C_{12}H_{18}N_5Cl$,HCl: C, 47·4; H, 6·25; N, 23·0%). See Part XXX (*loc. cit.*).

N-m-*Chlorophenyl*-N′-iso*propylguanylthiourea* (IV; R = H).—Sodium (5·9 g.) was dissolved in dry acetone (200 c.c.) at 20°, finely ground *iso*propylguanidine sulphate (44·5 g.) was added and the mixture was stirred at 20° for 2 hours. A solution of *m*-chlorophenyl *iso*thiocyanate (33·5 g.) (Dyson, George, and Hunter, *J.*, 1926, 3041) in dry acetone (100 c.c.) was added, with stirring at 10° during 40 minutes. The mixture was stirred at 10° for a further 30 minutes, then at 30° for 30 minutes, and poured into water (1 l.). The oil formed was extracted with benzene (3 × 150 c.c.), washed with water, dried (Na_2SO_4), and filtered and light petroleum (b. p. 60—80°) was added until a faint opalescence appeared. Seeding with a small test portion, which had crystallised, induced the product to crystallise. The solid, when filtered off, washed with benzene–light petroleum (b. p. 60—80°), and dried at 50° (12·8 g.), had m. p. 120—122°. A further crystallisation from benzene gave N-m-*chlorophenyl*-N′-iso*propylguanylthiourea*, m. p. 121—122° (Found: C, 48·8; H, 5·45; N, 20·8. $C_{11}H_{15}N_4ClS$ requires C, 48·8; H, 5·55; N, 20·7%).

N^1-m-*Chlorophenyl*-N^2-*methyl*-N^5-iso*propyldiguanide* (II; R = R″ = R‴ = H, R′ = Cl).—N-*m*-Chlorophenyl-N′-*iso*propylguanylthiourea (11·0 g.), mercuric oxide (20 g.), methylamine (20% aqueous solution; 120 c.c.), and ethanol (250 c.c.) were stirred together at 20° for 16 hours. Reaction was not then complete and more mercuric oxide (10 g.) was therefore added and stirring at 40—45° was continued for 5 hours. The mixture was filtered and washed with methanol, and the filtrates and washings were distilled together to a bulk of 100 c.c. A colourless oil separated. The mixture was cooled, made acid to Congo-red with 10N-hydrochloric acid, filtered from a little suspended matter, and neutralised (brilliant-yellow) with ammonia. The solution was distilled under reduced pressure to a small bulk and cooled. Addition of brine completed the precipitation of a gum which slowly crystallised. The solid was filtered off, washed with a little water, and dried. The product was dissolved in ethanol, evaporated to dryness, and triturated with ethyl acetate. The crystals thus obtained gave N^1-m-*chlorophenyl*-N^2-*methyl*-N^5-iso*propyldiguanide hydrochloride* after crystallisation from ethanol–ethyl acetate as needles, m. p. 137—138° (Found: C, 47·7; H, 6·3; N, 23·05. $C_{12}H_{18}N_5Cl$,HCl requires C, 47·4; H, 6·25; N, 23·0%).

N-3 : 4-*Dichlorophenyl*-N′-iso*propylguanylthiourea* (IV; R = Cl).—3 : 4-Dichlorophenyl *iso*thiocyanate (51·55 g.) (Dyson, George, and Hunter, *loc. cit.*) was allowed to react with *iso*propylguanidine [from sulphate (57·0 g.)], as for the corresponding *m*-chlorophenyl derivative. The crude product, crystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 120—122° (10·7 g.). Further crystallisation from benzene gave N-3 : 4-*dichlorophenyl*-N′-iso*propylguanylthiourea* as almost colourless rods, m. p. 124—125° (Found: C, 43·55; H, 4·75; N, 18·4. $C_{11}H_{14}N_4Cl_2S$ requires C, 43·3; H, 4·6; N, 18·4%).

N^1-3 : 4-*Dichlorophenyl*-N^2-*methyl*-N^5-iso*propyldiguanide* (II; R = R′ = Cl, R″ = Me, R‴ = H).—(*a*) *N*-3 : 4-Dichlorophenyl-*N*′-*iso*propylguanylthiourea (4 g.), mercuric oxide (8·5 g.), methylamine (22% aqueous solution; 40 c.c.), and ethanol (80 c.c.) were stirred together at 40—45° for 18 hours. The mixture was cooled and filtered, and the filtrates were evaporated to dryness under reduced pressure. The residue crystallised rapidly, but resisted attempts at recrystallisation. It was therefore dissolved in 2N-hydrochloric acid, and ammonia was added until the mixture was almost neutral to Congo-red. The gum which formed was removed by filtration and the filtrate on being made faintly alkaline to brilliant-yellow with ammonia deposited a gum which rapidly crystallised and was filtered off, washed with water, and dried. Crystallisation from ethanol–ethyl acetate afforded colourless rods of N^1-3 : 4-*dichlorophenyl*-N^2-*methyl*-N^5-iso*propyldiguanide hydrochloride*, m. p. 165—166° (Found: C, 42·2; H, 5·0; N, 20·45. $C_{12}H_{17}N_5Cl_2$,HCl requires C, 42·5; H, 5·3; N, 20·7%).

(*b*) N^1-*m*-Chlorophenyl-N^2-methyl-N^5-*iso*propyldiguanide hydrochloride (1·52 g.) in acetic acid (30 c.c.) was treated with chlorine (0·355 g.). The solution was kept at 20° for 48 hours and poured into 10N-sodium hydroxide (50 c.c.) in water (100 c.c.) at 0—5°. The precipitated gum slowly solidified and was filtered off, washed with water, and dissolved in N-hydrochloric acid. The solution was filtered from suspended matter and made alkaline to brilliant-yellow with ammonia. The gum thus formed was separated by decantation, dissolved in methanol, and evaporated to dryness on the steam-bath. Repetition of this drying process gave a glass which crystallised on treatment with ethyl acetate. Recrystallisation from ethanol–ethyl acetate gave rods of N^1-3 : 4-dichlorophenyl-N^2-methyl-N^5-*iso*propyldiguanide hydrochloride, m. p. 165—166° alone or on admixture with material from (*a*) above.

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