22. *Synthetic Antimalarials. Part XXXIII. An Alternative Route to* N^1-*Aryl*-N^5-*Alkyldiguanides and Related Compounds: the Condensation of Guanidines and Cyanamides.*

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Alternative methods for the preparation of the highly active antimalarial diguanide types (N^1-*p*-chlorophenyl-N^5-alkyl- and -N^5 : N^5-dialkyl-diguanides) described in Part X (*J.*, 1946, 729) have been discovered in the condensation of *p*-chlorophenylcyanamide with mono- and *NN*-di-alkylguanidines and in the reaction of mono- and di-alkylcyanamides with *p*-chlorophenylguanidine. The most suitable conditions were found to be the interaction of the two substances

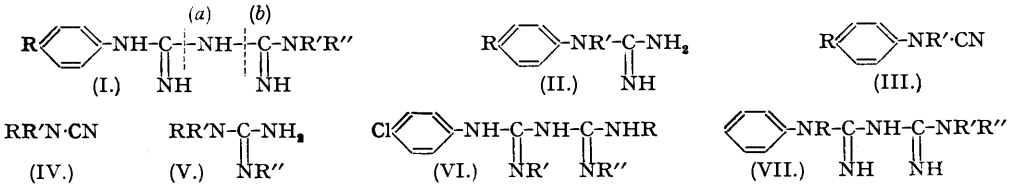
in boiling butanol (or pentanol or toluene) solution. The scope of these reactions for the preparation of other types of diguanides has also been explored.

The condensation of *iso*propylcyanamide with *N*-*p*-chlorophenyl-*N'*-methylguanidine has been shown to give rise to N^1-*p*-chlorophenyl-N^2-methyl-N^5-*iso*propyldiguanide and not the corresponding N^1-*p*-chlorophenyl-N^3-methyl compound. Similarly, *p*-chlorophenylcyanamide and *N*-methyl-*N'*-*iso*propylguanidine afforded N^1-*p*-chlorophenyl-N^4-methyl-N^5-*iso*propyldiguanide.

The new methods have been used, in conjunction with the methods described in earlier papers (Part X, *loc. cit.*; Part XXVIII, *J.*, 1948, 1630), to prepare an extensive series of N^1-*p*-bromophenyl-N^5-substituted diguanides for biological comparison with the corresponding N^1-*p*-chlorophenyl compounds.

In previous papers of this series we have described the synthesis of N^1-aryl-N^5-alkyl- and -N^5 : N^5-dialkyl-diguanides (I; R' = alkyl, R'' = H or alkyl) not only by condensation of an aryldicyandiamide with a mono- or di-alkylamine (Part X, *J.*, 1946, 729) but also from an N^3-alkyl- or N^3 : N^3-dialkyl-dicyandiamide and an arylamine (Part XXVIII, *J.*, 1948, 1630). Theoretically it seemed possible that the diguanides (I) should also be capable of synthesis from different fragments indicated by the lines (*a*) and (*b*), and this was supported by the work of Rathke (*Ber.*, 1879, **12**, 776) who condensed cyanamide with guanidine and with salts of guanidine to give diguanide, although only in minute yields, and of Schotte, Priewe, and Roescheisen (*Z. physiol. Chem.*, 1928, **174**, 119) who showed that diethylcyanamide will condense with guanidine and guanidine hydrobromide on long standing in alcoholic solution in the cold to give N^1 : N^1-diethyldiguanide. The latter workers also isolated N^1 : N^1 : N^5 : N^5-tetraethyldiguanide (as its picrate), likewise in small yield, from condensation of diethylcyanamide with *NN*-diethylguanidine and its hydrobromide under similar conditions. We accordingly decided to investigate the condensation of mono- and di-alkylcyanamides with arylguanidines and of arylcyanamides with mono- and di-alkylguanidines.

When this work had been in progress for some time, and the results made the subject of B.P.Appln. 35238/45, Das Gupta, Gupta, and Basu (*Science and Culture*, 1946, **11**, 704) reported the preparation of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide nitrate by heating *p*-chlorophenylguanidine nitrate with *iso*propylcyanamide, although they gave no experimental data. More recently Bami, Iyer, and Guha (*J. Ind. Inst. Sci.*, 1947, **29***A*, 1) have given details of the same process.



In view of the known ease with which the lower monoalkylcyanamides polymerise (McKee, *Amer. Chem. J.*, 1906, **36**, 208), our initial experiments were carried out with the more stable dialkylcyanamides. Dimethylcyanamide (IV; R = R' = Me) was found to condense with *p*-chlorophenylguanidine (II; R = Cl, R' = H) hydrochloride in boiling butanol solution (cf. the condensation of cyanamides with amine hydrochlorides in boiling butanol, King and Tonkin, *J.*, 1946, 1063) to give N^1-*p*-chlorophenyl-N^5 : N^5-dimethyldiguanide (I; R = Cl, R' = R'' = Me), but diethylcyanamide (IV; R = R' = Et) failed to react under similar conditions. However, dimethylcyanamide did not react with *N*-phenyl-*N*-methylguanidine (II; R = H, R' = Me) hydrochloride, nor was the analogous condensation of phenylmethylcyanamide (III; R = H, R' = Me) with dimethylguanidine (V; R = R' = Me, R'' = H) sulphate achieved. Further, an attempt to condense methyl*iso*propylcyanamide (IV; R = Me, R' = Pr^i) with *p*-chlorophenylguanidine hydrochloride by fusion at 120—140° led to a trace only of diguanide formation, but *p*-chlorophenylguanidine nitrate similarly fused with *iso*propylcyanamide (IV; R = H, R' = Pr^i) gave easily isolatable amounts of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide (" Paludrine ") nitrate (cf. Das Gupta *et al.*, *loc. cit.*; Bami *et al.*, *loc. cit.*).

In B.P. 279,884 it is claimed that improved yields of guanidines are obtained from the reaction of cyanamide with amines when a mixture of the amine and amine salt is used. This led us to try the condensation of diethylcyanamide with *p*-chlorophenylguanidine together with its hydrochloride in boiling butanol solution; this gave a small yield of N^1-*p*-chlorophenyl-N^5 : N^5-diethyldiguanide. Other solvents such as toluene could also be used. The method was then found to be equally applicable to the preparation of (I; R = Cl, R' = H, R'' = Pr^i), either

from *iso*propylcyanamide, *p*-chlorophenylguanidine and its hydrochloride, or from *iso*propylguanidine (V; R = R″ = H, R′ = Pr^i) and its sulphate with *p*-chlorophenylcyanamide (III; R = Cl, R′ = H). The last substance reacted similarly with dimethylguanidine and the sulphate of (V; R = R′ = Me, R″ = H) to give N^1-*p*-chlorophenyl-N^5 : N^5-dimethyldiguanide, while with methylguanidine and the corresponding sulphate (I; R = Cl, R′ = H, R″ = Me) resulted.

Subsequent work showed that when the fusion or solvent methods were employed it was unnecessary to have the guanidine present in part as its salt, and the use of the base alone is exemplified in the following reactions. *iso*Propylcyanamide condensed with *NN*-diphenylguanidine (II; R = H, R′ = Ph) and diphenylcyanamide (III; R = H, R′ = Ph) with *iso*propylguanidine to give N^1 : N^1-*diphenyl*-N^5-iso*propyldiguanide* (VII; R = Ph, R′ = H, R″ = Pr^i), while *p*-chlorophenylcyanamide reacted with phenylguanidine to give N^1-*phenyl*-N^5-p-*chlorophenyldiguanide* (VII; R = R′ = H, R″ = *p*-C_6H_4Cl) and with *p*-tolylguanidine to give (I; R = Cl, R′ = H, R″ = *p*-C_6H_4Me). *cyclo*Pentamethylenecyanamide and *NN*-diphenylguanidine gave N^1 : N^1-*diphenyl*-N^5 : N^5-cyclo*pentamethylenediguanide* (VII; R = Ph, R′R″ = $[CH_2]_5$); phenylmethylcyanamide reacted with methylguanidine to give N^1-*phenyl*-N^1 : N^5-*dimethyldiguanide* (VII; R′ = H, R = R″ = Me), with *NN*-dimethylguanidine to give N^1-*phenyl*-N^1 : N^5 : N^5-*trimethyldiguanide* (VII; R = R′ = R″ = Me), with *N*-phenyl-*N*-methylguanidine to give N^1 : N^5-*diphenyl*-N^1 : N^5-*dimethyldiguanide* (VII; R = R′ = Me, R″ = Ph), and with *p*-chlorophenylguanidine to give N^1-*phenyl*-N^5-p-*chlorophenyl*-N^1-*methyldiguanide* (I; R = Cl, R′ = Me, R″ = Ph). N^1 : N^1-*Diphenyl*-N^5 : N^5-*dimethyldiguanide* (VII; R = Ph, R′ = R″ = Me) resulted from the reaction of diphenylcyanamide with *NN*-dimethylguanidine.

The successful use of the lower monoalkylcyanamides was surprising on account of the ease with which they polymerise at elevated temperatures. This polymerisation was found to be of only minor importance, however, since the yields of diguanide obtained from reactions in which they were employed were of the same order as those from the corresponding reactions using the more stable dialkylcyanamides. Another contributory factor would appear to be the much greater rate of reaction of the monoalkylcyanamides compared with that of the dialkylcyanamides, maximum diguanide formation being obtained in 15—30 minutes with the mono- and only after 2—3 hours with the di-alkyl compounds. Diguanide formation was conveniently followed by withdrawing aliquot samples during the course of the reaction, shaking with standard amounts of ammoniacal copper sulphate and benzene, and comparing the colour intensities of the benzene layers (cf. Gage and Rose, *Ann. Trop. Med. Parasit.*, 1946, **40**, 333).

Our investigation was then extended to the condensation of substituted cyanamides with *NN*′-disubstituted guanidines in order to determine whether a N^1 : N^2 : N^5- or a N^1 : N^3 : N^5-trisubstituted diguanide, or a mixture of both, would be formed. There was no reference in the literature to such a condensation having been tried, although Slotta and Tschesche (*Ber.*, 1929, **62**, 1390) had shown that *NN*′*N*″-triphenylguanidine condensed with cyanamide to give N^1 : N^2 : N^3-triphenyldiguanide whereas they failed to effect the reaction of cyanamide with *NN*′*N*″-tri-*p*-ethoxyphenyl- and *NN*′*N*″-trimethyl-guanidine.

*iso*Propylcyanamide was found to condense with *N*-*p*-chlorophenyl-*N*′-methylguanidine (V; R = H, R′ = *p*-C_6H_4Cl, R″ = Me) to give N^1-*p*-chlorophenyl-N^2-methyl-N^5-*iso*propyldiguanide (VI; R = Pr^i, R′ = Me, R″ = H) and not N^1-*p*-chlorophenyl-N^3-methyl-N^5-*iso*propyldiguanide, and *p*-chlorophenylcyanamide reacted with *N*-methyl-*N*′-*iso*propylguanidine (V; R = H, R′ = Pr^i, R″ = Me) to give N^1-*p*-chlorophenyl-N^4-methyl-N^5-*iso*propyldiguanide (VI; R = Pr^i, R′ = H, R″ = Me), both products being identical with those described previously (Parts XXIX and XXX, *J.*, 1948, 1636, 1645). The reactions were carried out in boiling butanol solution and appeared to proceed as readily as in the case of *NN*-disubstituted guanidines. No evidence of the formation of a second isomer was obtained.

In addition to the above exploration of the scope of the reaction between cyanamides and guanidines, the method has been used for the preparation of a number of N^1-*p*-bromophenyl-N^5-mono- and -N^5 : N^5-di-alkyldiguanides. These were required for comparison with the corresponding chloro-compounds for both therapeutic and prophylactic activity, since the assay of N^1-*p*-bromophenyl-N^5-*iso*propyldiguanide (Part XXVIII, *loc. cit.*) had disclosed that it possessed somewhat higher antimalarial activity than N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide (unpublished results by Dr. D. G. Davey).

Condensation of *p*-bromophenylcyanamide with methylguanidine gave N^1-*p*-bromophenyl-N^5-methyldiguanide (I; R = Br; R′ = H, R″ = Me), isolated as its *hydrochloride*, and with *cyclo*hexylguanidine (V; R = C_6H_{11}, R′ = R″ = H) afforded N^1-p-*bromophenyl*-N^5-cyclo-

hexyldiguanide (I; R = Br, R′ = H, R″ = C_6H_{11}). *iso*Propylcyanamide was successfully condensed with *p*-bromophenylguanidine to give N^1-*p*-bromophenyl-N^5-*iso*propyldiguanide identical with the compound described previously, and the same guanidine was then condensed with other monoalkylcyanamides to give the following N¹-p-*bromophenyl*-N⁵-*alkyldiguanide hydrochlorides* (as I; R = Br, R′ = H, R″ = alkyl): N⁵-*ethyl*, N⁵-n-*propyl*, N⁵-n-*butyl*, and N⁵-iso*butyl*. Similarly, by using the appropriate dialkylcyanamide a number of N^1-*p*-bromophenyl-N^5 : N^5-dialkyldiguanides were made. These included the N⁵ : N⁵-*dimethyl*- (I; R = Br, R′ = R″ = Me), N⁵ : N⁵-*diethyl* (I; R = Br, R′ = R″ = Et), N^5-methyl-N^5-*iso*propyl (I; R = Br, R′ = Me, R″ = Pr^i) (*hydrochloride*), N⁵-*methyl*-N⁵-n-*butyl*- (I; R = Br, R′ = Me, R″ = Bu^n), and N⁵ : N⁵-cyclo*pentamethylene* (I; R = Br, R′R″ = $[CH_2]_5$) compounds. Reaction of phenylmethylcyanamide with *p*-bromophenylguanidine gave N⁵-*phenyl*-N¹-p-*bromophenyl*-N⁵-*methyldiguanide* (I; R = Br, R′ = Ph, R″ = Me).

The authenticity of some of the above compounds was proved by their identity with the products obtained by condensing p-*bromophenyldicyandiamide*, readily prepared from *p*-bromoaniline hydrochloride and sodium dicyanamide by the method described in Part XXVIII (*loc. cit.*), with the hydrochlorides of *iso*propyl-, *n*-propyl-, *iso*butyl-, and methyl*iso*propylamines.

The condensation of *p*-bromophenyldicyandiamide with amine salts was also used to prepare N^1-*p*-bromophenyl-N^5-*sec.*-butyldiguanide and N^1-*p*-bromophenyl-N^5-*tert.*-butyldiguanide (I; R = Br, R′ = H, R″ = Bu^s and Bu^t) *hydrochlorides*.

Finally *p*-bromoaniline hydrochloride was condensed with ethyldicyandiamide (Part XXVIII) to give N^1-*p*-bromophenyl-N^5-ethyldiguanide, identical with the substance obtained from *p*-bromophenylguanidine and (IV; R = H, R′ = Et), and with methyl-*n*-propyldicyandiamide (forthcoming publication) to give N¹-p-*bromophenyl*-N⁵-*methyl*-N⁵-n-*propyldiguanide* (I; R = Br, R′ = Me, R″ = Pr^n).

The antimalarial activities of the new diguanides described in this communication will be published elsewhere.

Experimental.

Intermediates.

Monoalkylcyanamides.—The alkylamine (0·1 g.-mol.) was dissolved in dry ether (50 c.c.), and cyanogen bromide (0·05 g.-mol.) added slowly to the stirred solution cooled to −5° to −10°. The addition of cyanogen bromide was regulated so that the temperature never rose above −5°. When the addition was complete, the mixture was stirred for ½ hour, and the alkylamine hydrobromide filtered off and washed with ether. The filtrate and washings were combined and evaporated either to small bulk or to dryness under reduced pressure. Owing to the ease with which the lower monoalkylcyanamides polymerise, no attempt was made to purify the products, and they were used either as crude oils or as concentrated ethereal solutions. The above method was used for the preparation of ethyl-, *iso*propyl-, *n*-propyl-, *n*-butyl-, *iso*butyl-, and *cyclo*hexyl-cyanamides.

Dialkylcyanamides.—These were prepared either by the method given above for the monoalkylcyanamides or by the modification described in U.S.P. 2,331,670 for the preparation of monoalkylcyanamides in which the alkyl group contains more than 5 carbon atoms. The dialkylamine (1 g.-mol.) dissolved in benzene (400 c.c.) was treated with cyanogen bromide (1 g.-mol.) and sodium hydroxide (1 g.-mol.) (as 35% aqueous solution), the last two reactants being added stepwise and alternately so that the dialkylamine was regenerated from its hydrobromide before the next addition of cyanogen bromide. When the additions were complete the benzene layer was separated, dried, and evaporated under diminished pressure to leave the dialkylcyanamide as an oil which was purified by vacuum distillation. The following dialkylcyanamides were made in this way: dimethyl- and diethyl- (McKee, *loc. cit.*), *cyclo*pentamethylene- (McKee, *loc. cit.*; Wallach, *Ber.*, 1899, **32**, 1873), *methyliso*propyl-, colourless oil, b. p. 78—80°/18 mm. (Found: N, 28·2. $C_5H_{10}N_2$ requires N, 28·6%), and *methyl*-n-*butyl*-, b. p. 87—88°/12 mm. (Found: N, 24·6. $C_6H_{12}N_2$ requires N, 25·0%).

Arylcyanamides.—*p*-Chlorophenylcyanamide was prepared from *p*-chlorophenylthiourea by treatment with lead hydroxide (cf. the preparation of *p*-tolylcyanamide from *p*-tolylthiourea by King and Tonkin, *loc. cit.*); colourless needles from water, m. p. 106—107° (Mann, Naylor, and Porter, *J.*, 1947, 916, give m. p. 103°). *p*-Bromophenylcyanamide was prepared similarly from *p*-bromophenylthiourea, and formed long thin colourless prisms from alcohol, m. p. 123—124° (Pierron, *Bull. Soc. chim.*, 1906, **35**, 1203, records m. p. 112°). Phenylmethylcyanamide prepared by the method of Wallach (*loc. cit.*) was obtained as a pale yellow oil, b. p. 137—139°/15 mm., which slowly crystallised, m. p. 29°. Diphenylcyanamide was prepared by the following variation of the method of von Braun (*Ber.*, 1900, **33**, 1450). Diphenylamine (150 g.) was dissolved in benzene (100 c.c.) at 50°, cyanogen bromide (50 g.) added in small portions, and the whole then heated for 17 hours at 70—80°. After cooling, the diphenylamine hydrobromide was filtered off, the benzene evaporated, and the residual oil dissolved in dry ether (300 c.c.). Saturation of the ethereal solution with dry hydrogen chloride precipitated some diphenylamine hydrochloride which was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure to leave an oil which partly crystallised on cooling. The crystalline material was freed from oil as far as possible by filtration, and finally crystallised from a small volume of alcohol to give diphenylcyanamide as colourless prisms, m. p. 69°.

Guanidines.—Methylguanidine and *NN*-dimethylguanidine sulphates were prepared from the

respective amines and *S*-methyl*iso*thiourea sulphate (Phillips and Clarke, *J. Amer. Chem. Soc.*, 1923, **45**, 1755). *iso*Propylguanidine sulphate was prepared by a similar process, as described in Part XXIX (*loc. cit.*). *cyclo*Hexylguanidine hydrochloride was prepared as follows. *cyclo*Hexylamine (99 g.) was dissolved in water (100 c.c.), and a solution of *S*-methyl*iso*thiourea sulphate (139 g.) in water (250 c.c.) added. After being left at 35° ± 2° for 17 hours, the mixture was boiled under reflux for 4 hours, treated with carbon, and filtered, and the filtrate evaporated to dryness under reduced pressure. The residual crude *cyclo*hexylguanidine sulphate was treated with excess of sodium hydroxide solution, the liberated base extracted with ether, and the dried ethereal solution saturated with dry hydrogen chloride to precipitate the hydrochloride. This was collected, dried, and crystallised from alcohol; colourless prisms, m. p. 226° (King and Tonkin, *loc. cit.*, give m. p. 227°). *p*-Chlorophenylguanidine (Part XXV, *J.*, 1948, 590) afforded a *hydrochloride* which crystallised from alcohol as colourless prisms, m. p. 166—167° (Found: C, 41·2; H, 4·4; N, 20·5; Cl′, 17·1. $C_7H_8N_3Cl,HCl$ requires C, 40·8; H, 4·4; N, 20·4; Cl′, 17·2%), and a *nitrate* which formed colourless plates from water, m. p. 162—163° (Found: C, 36·5; H, 3·9; N, 24·2. $C_7H_8N_3Cl,HNO_3$ requires C, 36·1; H, 3·9; N, 24·1%). For the nitrate, G.P. 172,979 (Höchster Farbwerke) records m. p. 166° but gives no analysis. Das Gupta *et al.* (*loc. cit.*) give m. p. 140—141°, and Bami *et al.* (*loc. cit.*) give m. p. 142—143°. *p*-Bromophenylguanidine hydrochloride, m. p. 175—176°, was prepared from *p*-bromoaniline hydrochloride and cyanamide in alcohol according to the method of Braun, Erit, and Crooks (*J. Org. Chem.*, 1938, **3**, 146). Condensation of cyanamide with the appropriate amine hydrochloride was also used to prepare *p*-tolylguanidine (cf. U.S.P. 1,575,865), *NN*-diphenylguanidine (Arndt and Rosenau, *Ber.*, 1917, **50**, 1262), and *N*-phenyl-*N*-methylguanidine hydrochloride (U.S.P. 1,575,865; Braun, *J. Amer. Chem. Soc.*, 1933, **55**, 1282). *p*-Methoxyphenylguanidine sulphate was prepared by the following method which was based on a recipe kindly supplied by Sir Robert Robinson (cf. Part I, *J.*, 1946, 343). *p*-Anisidine (48 g.), *S*-methyl*iso*thiourea sulphate (37·5 g.), and water (300 c.c.) were boiled under reflux for 27 hours. Some dark impurities were removed by filtration, and the filtrate, on cooling, deposited *p*-methoxyphenylguanidine sulphate (yield, 39·4 g.) which crystallised from alcohol–water as colourless prisms, m. p. 244—245°.

p-*Bromophenyldicyandiamide.*—A solution of *p*-bromoaniline hydrochloride (49·2 g.) in water (150 c.c.) was added to a solution of sodium dicyanamide (24 g.) in water (300 c.c.). The precipitate, formed on mixing, readily redissolved on warming to 30—35°, and the mixture was stirred at 55—60° for 8 hours. After cooling, the product which had separated was collected, washed with water, and stirred with a solution of sodium hydroxide (36 g.) in water (400 c.c.) at 70—75° for 15 minutes. The mixture was then cooled to 40° by the addition of ice and filtered, and the filtrate made just acid with hydrochloric acid. The precipitated p-*bromophenyldicyandiamide* (yield, 44 g.) crystallised from alcohol as colourless prismatic needles, m. p. 203—204° (Found: C, 40·0; H, 3·1; N, 23·6. $C_8H_7N_4Br$ requires C, 40·2; H, 2·9; N, 23·4%).

Preparation of Diguanides from Guanidines and Cyanamides.

Condensation of Dimethylcyanamide with p-*Chlorophenylguanidine Hydrochloride.*—*p*-Chlorophenylguanidine hydrochloride (10·3 g.) and dimethylcyanamide (3·5 g.) in butanol (10 c.c.) were refluxed for 16 hours. On cooling, the mixture deposited crystalline material which was collected, washed with light petroleum (b. p. 60—80°), and dried. This was dissolved in dilute hydrochloric acid, the solution filtered from a little insoluble matter, and the filtrate made just alkaline to brilliant-yellow with ammonia. The hydrochloride thereby precipitated was filtered off, washed with water, and converted into the base by redissolving it in dilute hydrochloric acid and pouring the solution into excess of sodium hydroxide solution. The precipitated crystalline material was collected, dried, and identified as N^1-*p*-chlorophenyl-N^5 : N^5-dimethyldiguanide (I; R = Cl, R′ = R″ = Me) (see Part X, *loc. cit.*), m. p. and mixed m. p. 168—169° (yield, 2·03 g.).

The reaction of dimethylcyanamide with *N*-phenyl-*N*-methylguanidine hydrochloride and of phenylmethylcyanamide with *NN*-dimethylguanidine sulphate failed under these conditions.

Condensation of iso*Propylcyanamide with* p-*Chlorophenylguanidine Nitrate.*—*p*-Chlorophenylguanidine nitrate (5·8 g.) was heated to 100° by means of an oil-bath, and excess of *iso*propylcyanamide (from *iso*propylamine, 11·8 g.) added. The mixture fell in temperature to 60°, and on being raised to 140°, became homogeneous at 80—85°. The reaction was slightly exothermic, the internal temperature reaching 148° with the bath maintained at 140°. At this temperature diguanide formation appeared to reach a maximum after 15 minutes [as shown by the colour produced in the benzene layer on shaking a sample of the mixture (0·1 c.c.) with ammoniacal copper sulphate (1 c.c.) and benzene (1 c.c.)]. The mixture was thereupon cooled and extracted with boiling water (2 × 50 c.c.), and the extract filtered and cooled. The crystalline material which separated was shown to be N¹-p-*chlorophenyl*-N⁵-iso*propyldiguanide nitrate*; long thin colourless needles from aqueous alcohol, m. p. 163—164° (Found: C, 39·8; H, 5·7; N, 24·7. $C_{11}H_{16}N_5Cl,HNO_3,H_2O$ requires C, 39·4; H, 5·7; N, 25·0%). It showed no depression of m. p. on admixture with an authentic specimen, m. p. 163—164° (Found: C, 39·8; H, 5·3; N, 24·7%), prepared by dissolving N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide (Part X) in a slight excess of 2N-nitric acid followed by neutralisation with ammonia. In admixture with *p*-chlorophenylguanidine nitrate, m. p. 162—163°, the m. p. was depressed to 138—140°.

A similar attempt to condense methyl*iso*propylcyanamide with *p*-chlorophenylguanidine hydrochloride gave only a faint indication of diguanide formation even after prolonged heating (22 hours).

Condensation of Diethylcyanamide with p-*Chlorophenylguanidine and* p-*Chlorophenylguanidine Hydrochloride.*—*p*-Chlorophenylguanidine (8·5 g.), *p*-chlorophenylguanidine hydrochloride (10·3 g.), diethylcyanamide (4·9 g.), and butanol (20 c.c.) were refluxed for 1·5 hours. The mixture was then cooled, diluted with ether (120 c.c.), and left overnight. The small amount of material which separated was removed by filtration, and the filtrate extracted with 2N-hydrochloric acid. Addition of ammonia to the acid extract precipitated a sticky solid which was redissolved in dilute hydrochloric acid; copper sulphate and benzene were added, followed by ammonia to render the mixture alkaline. The benzene layer was then separated and the aqueous layer re-extracted with benzene. The combined benzene extracts containing the copper complex of the diguanide were shaken with dilute hydrochloric acid, the

acid extract separated, and the copper removed by precipitation with sodium sulphide. After filtration from the copper sulphide, the filtrate was neutralised with ammonia, and the precipitated solid collected and redissolved in dilute hydrochloric acid. Addition of this solution to excess of dilute sodium hydroxide precipitated N^1-*p*-chlorophenyl-N^5 : N^5-diethyldiguanide which was collected, dried (yield, 0·83 g.), and crystallised from light petroleum (b. p. 100—120°); colourless needles, m. p. 134—135° either alone or in admixture with authentic material (Found : C, 53·5; H, 6·5. Calc. for $C_{12}H_{18}N_5Cl$: C, 53·8; H, 6·7%).

Diethylcyanamide was also condensed with *p*-chlorophenylguanidine and its hydrochloride in boiling toluene solution to give (I; R = Cl, R′ = R″ = Et). No diguanide formation could be detected in an experiment similar to that described above, with butanol as solvent, in which the *p*-chlorophenylguanidine base was omitted.

Condensation of iso*Propylcyanamide with* p-*Chlorophenylguanidine and* p-*Chlorophenylguanidine Hydrochloride.*—*p*-Chlorophenylguanidine (8·5 g.), *p*-chlorophenylguanidine hydrochloride (10·0 g.), and butanol (20 c.c.) were heated on the steam-bath to 70—80°, and an ether–light petroleum solution of *iso*propylcyanamide (from *iso*propylamine, 8 g.) gradually added. The ether and light petroleum were evaporated, and the mixture then boiled for 2·5 hours and worked up as in the preceding experiment. The resulting base was dissolved in acetone and treated with acetic acid until just acid to litmus. This precipitated the acetate which was crystallised from acetone and shown to be identical with the acetate of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide, m. p. and mixed m. p. 189—190° (Found : C, 49·7; H, 6·4. Calc. for $C_{11}H_{16}N_5Cl,C_2H_4O_2$: C, 49·8; H, 6·4%).

Condensation of p-*Chlorophenylcyanamide with* iso*Propylguanidine and* iso*Propylguanidine Sulphate.*—Sodium (0·55 g.) was dissolved in butanol (20 c.c.), *iso*propylguanidine sulphate (7·5 g.) added, and the mixture stirred and shaken (warm) for 15 minutes. *p*-Chlorophenylcyanamide (3·8 g.) was then added to the suspension at 30°, and the mixture refluxed for 3 hours. After cooling, the mixture was diluted with 3 volumes of ether and filtered. The filtrate was extracted with 2N-hydrochloric acid, and the extract neutralised with ammonia. The precipitated solid was redissolved in 2N-hydrochloric acid, the solution added to dilute sodium hydroxide, and the precipitated solid collected, washed, and dried. This base was converted into the acetate as described above, and the product shown to be identical with N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate, m. p. and mixed m. p. 189—190°.

Condensation of p-*Chlorophenylcyanamide with* NN-*Dimethylguanidine and* NN-*Dimethylguanidine Sulphate.*—Sodium (1·15 g.) was dissolved in butanol (20 c.c.), dimethylguanidine sulphate (13·6 g.) added, and the mixture kept at 35° for 15 minutes with occasional shaking. *p*-Chlorophenylcyanamide (7·6 g.) was then added and the mixture refluxed for 3 hours. The mixture was worked up as in the last experiment to give N^1-*p*-chlorophenyl-N^5 : N^5-dimethyldiguanide, m. p. and mixed m. p. 168—169°.

Condensation of p-*Chlorophenylcyanamide with Methylguanidine and Methylguanidine Sulphate.*—Sodium (1·15 g.) was dissolved in butanol (35 c.c.), the solution cooled, and methylguanidine sulphate (12·2 g.) added. After addition of *p*-chlorophenylcyanamide (7·6 g.) the mixture was boiled for 2·25 hours and then worked up as in the preceding two experiments to give a base which was converted into its hydrochloride by dissolving it in excess of 2N-hydrochloric acid and neutralising the solution with ammonia. This salt was found to be identical with N^1-*p*-chlorophenyl-N^5-methyldiguanide hydrochloride (Part X), m. p. and mixed m. p. 227—228° (Found : N, 26·5. Calc. for $C_9H_{12}N_5Cl,HCl$: N, 26·7%).

Condensation of Dimethylcyanamide with p-*Chlorophenylguanidine.*—Dimethylcyanamide (1·75 g.) and *p*-chlorophenylguanidine (4·25 g.) were mixed and heated on the steam-bath for 2·5 hours. No exothermic reaction was detected. The melt became homogeneous at *ca.* 80°, and then slowly crystallised during the reaction. The mass was dissolved in dilute hydrochloric acid, the solution filtered, and the filtrate made just alkaline to brilliant-yellow with ammonia. The resulting precipitate was collected, washed with water, and redissolved in dilute hydrochloric acid. When this solution was poured into excess of dilute sodium hydroxide solution, a white precipitate of N^1-*p*-chlorophenyl-N^5 : N^5-dimethyldiguanide resulted (yield, 1·89 g.). It had m. p. and mixed m. p. 168—169° (Found : C, 50·2; H, 5·8. Calc. for $C_{10}H_{14}N_5Cl$: C, 50·0; H, 5·8%).

Condensation of Diethylcyanamide with p-*Chlorophenylguanidine.*—*p*-Chlorophenylguanidine (4·25 g.) and diethylcyanamide (2·25 g.) were mixed and heated on the steam-bath for 19·5 hours, and the mixture worked up as in the preceding experiment to give N^1-*p*-chlorophenyl-N^5 : N^5-diethyldiguanide (yield, 1·35 g.), m. p. and mixed m. p. 134—135°.

Condensation of Methyl iso*Propylcyanamide with* p-*Chlorophenylguanidine.*—*p*-Chlorophenylguanidine (8·5 g.) and methyl*iso*propylcyanamide (7·4 g.) were heated by means of an oil-bath at 120° ± 5° for 3·5 hours. After being left overnight the melt had partly crystallised, and was then diluted with an equal volume of toluene and extracted with 2N-hydrochloric acid (30 c.c.). The acid extract was made faintly alkaline to brilliant-yellow with ammonia, and the precipitated mixture of solid and oil separated by filtration and washing with ether. The solid was redissolved in 2N-hydrochloric acid, and the filtered solution poured into excess of dilute sodium hydroxide solution. The precipitated base was collected, washed with water, dried, and crystallised from toluene to give N^1-*p*-chlorophenyl-N^5-methyl-N^5-*iso*propyldiguanide (see Part X) (yield, 23%), m. p. and mixed m. p. 175° (Found : C, 53·9; H, 6·7. Calc. for $C_{12}H_{18}N_5Cl$: C, 53·8; H, 6·7%).

Condensation of Dimethylcyanamide with p-*Methoxyphenylguanidine.*—*p*-Methoxyphenylguanidine (8·25 g.), dimethylcyanamide (3·5 g.), and butanol (20 c.c.) were boiled under reflux for 1·25 hours. The cooled mixture was diluted with benzene and then extracted thoroughly with 2N-hydrochloric acid. Addition of ammonia to the acid extract precipitated N^1-p-*methoxyphenyl*-N^5 : N^5-*dimethyldiguanide hydrochloride* (yield, 30%) which crystallised from alcohol as aggregates of colourless fine prisms, m. p. 225—226° (Found : Cl, 12·5. $C_{11}H_{17}ON_5,HCl,0·5H_2O$ requires Cl, 12·25%). This hydrochloride was converted into the base, which was identical with that described in Part X; colourless prisms from toluene, m. p. and mixed m. p. 141—142° (Found : C, 55·7, H, 7·0; N, 30·4. Calc. for $C_{11}H_{17}ON_5$: C, 56·2; H, 7·2; N, 29·8%).

The following diguanides were made in a similar way.

N^1-p-*Tolyl*-N^5 : N^5-*diethyldiguanide* (I; R = Me, R′ = R″ = Et). Prepared from *p*-tolylguanidine and diethylcyanamide (reaction time 3·5 hours), the *base* crystallised from light petroleum (b. p. 80—100°)

as long thin colourless prisms (yield, 16%), m. p. 98—99° (Found: C, 63·0; H, 8·5; N, 28·2. $C_{13}H_{21}N_5$ requires C, 63·2; H, 8·5; N, 28·3%) (5805).

N^1-p-*Chlorophenyl*-N^5-iso*propyldiguanide*. Prepared from *p*-chlorophenylguanidine and *iso*propylcyanamide (reaction time 0·75 hour) and isolated as the acetate (yield, 37·5%), m. p. and mixed m. p. 189—190°.

N^1-p-*Chlorophenyl*-N^5-cyclo*hexyldiguanide* (I; R = Cl, R′ = H, R″ = C_6H_{11}). Prepared from *p*-chlorophenylguanidine and *cyclo*hexylcyanamide (reaction time 0·75 hour); colourless prisms from alcohol (yield, 29%), m. p. 172—173° undepressed in admixture with authentic material (see Part X).

N^1-p-*Methoxyphenyl*-N^5-cyclo*hexyldiguanide* (I; R = OMe, R′ = H, R″ = C_6H_{11}). Prepared from *p*-methoxyphenylguanidine and *cyclo*hexylcyanamide (reaction time 0·75 hour), and isolated as the *hydrochloride*, colourless plates from alcohol, m. p. 245° (Found: C, 54·0; H, 7·6; N, 20·6; Cl′, 10·8. $C_{15}H_{23}ON_5$,HCl,0·5H_2O requires C, 53·8; H, 7·5; N, 20·9; Cl′, 10·6%) (5803).

N^1-p-*Tolyl*-N^5-cyclo*hexyldiguanide* (I; R = Me, R′ = H, R″ = C_6H_{11}). Prepared from *p*-tolylguanidine and the same cyanamide (reaction time 0·75 hour), and first isolated as the *hydrochloride* (5806) which crystallised from alcohol (yield, 30%), m. p. 252—253° (Found: Cl, 11·3. $C_{15}H_{23}N_5$,HCl requires Cl, 11·5%). The *base* separated from alcohol, as colourless plates, m. p. 176—177° (Found: C, 66·0; H, 8·3; N, 25·9. $C_{15}H_{23}N_5$ requires C, 65·9; H, 8·4; N, 25·6%).

N^1 : N^1-*Diphenyl*-N^5-iso*propyldiguanide* (VII; R = Ph, R′ = H, R″ = Pr^i). Prepared from *iso*propylcyanamide and *NN*-diphenylguanidine (reaction time 0·75 hour), the *base* crystallised from light petroleum (b. p. 100—120°) as long thin colourless prisms (yield, 48%), m. p. 143° (Found: C, 68·6; H, 6·9; N, 24·2. $C_{17}H_{21}N_5$ requires C, 69·15; H, 7·1; N, 23·7%) (5812). The *hydrochloride* crystallised from water as colourless prisms, m. p. 234—235° (Found: Cl′, 10·1. $C_{17}H_{21}N_5$,HCl,H_2O requires Cl′, 10·4%).

N^1 : N^1-*Diphenyl*-N^5 : N^5-cyclo*pentamethylenediguanide* (VII; R = Ph, R′R″ = $[CH_2]_5$). Prepared from *cyclo*pentamethylenecyanamide and *NN*-diphenylguanidine (reaction time 1 hour), the *base* (yield, 17%) formed colourless prisms from butanol, m. p. 127° (Found: C, 71·0; H, 7·2; N, 22·3. $C_{19}H_{23}N_5$ requires C, 71·0; H, 7·2; N, 21·8%) (5813).

N^1-*Phenyl*-N^5-p-*chlorophenyl*-N^1-*methyldiguanide* (I; R = Cl, R′ = Me, R″ = Ph). Prepared from *p*-chlorophenylguanidine and *N*-phenyl-*N*-methylcyanamide (reaction time 2 hours), the *base* (yield, 39%) crystallised from toluene as colourless plates, m. p. 179—180° (Found: C, 59·6; H, 5·2; N, 23·8; Cl, 11·5. $C_{15}H_{16}N_5Cl$ requires C, 59·6; H, 5·3; N, 23·2; Cl, 11·8%) (5801).

N^1-*Phenyl*-N^5-p-*chlorophenyldiguanide*. Prepared from *p*-chlorophenylcyanamide and phenylguanidine carbonate (Smith, *J. Amer. Chem. Soc.*, 1929, **51**, 476) (reaction time 3 hours), the *base* (mentioned in Part X) crystallised from methanol as colourless plates, m. p. 148—149° (Found: C, 58·4; H, 4·9. $C_{14}H_{14}N_5Cl$ requires C, 58·3; H, 4·9%).

N^1-p-*Chlorophenyl*-N^5-p-*tolyldiguanide* (I; R = Cl, R′ = H, R″ = *p*-C_6H_4Me). Prepared from *p*-chlorophenylcyanamide and *p*-tolylguanidine (reaction time 2·5 hours), the *base* (yield, 18%) formed colourless rectangular plates from alcohol, m. p. 175—176° (Found: C, 60·0; H, 5·6; N, 23·0. $C_{15}H_{16}N_5Cl$ requires C, 59·6; H, 5·3; N, 23·2%) (5802).

As an alternative to the process used above for the preparation of the preceding 11 diguanides it was sometimes found to be more convenient, particularly when using alkyl- or *NN*-dialkyl-guanidines, to employ a salt of the guanidine and to generate the base *in situ* by treatment of the guanidine salt with an equimolecular proportion of sodium butoxide. The inorganic salt was often removed by filtration before adding the cyanamide.

Condensation of Phenylmethylcyanamide with Methylguanidine.—Sodium (1·15 g.) was dissolved in butanol (20 c.c.), methylguanidine sulphate (6·1 g.) added, and the mixture refluxed for ½ hour and then filtered from sodium sulphate. This was washed with butanol (10 c.c.), the butanol filtrate and washings combined, and phenylmethylcyanamide (6·6 g.) added. The mixture was then boiled for 0·75 hour, cooled, and diluted with benzene. The diguanide was extracted by shaking the solution several times with 2N-hydrochloric acid, and the acid extracts were combined and poured into sodium hydroxide solution. The oil thereby precipitated was extracted with benzene, and the extract dried and evaporated to leave an oil which partly solidified. The oil was removed by stirring with ether, and the undissolved solid crystallised from benzene to give N^1-*phenyl*-N^1 : N^5-*dimethyldiguanide* (VII; R′ = H, R = R″ = Me) as colourless, long thin prisms (yield, 34%), m. p. 110—111° (Found: C, 56·4; H, 7·2; N, 33·0. $C_{10}H_{15}N_5$,0·5H_2O requires C, 56·1; H, 7·5; N, 32·7%) (5810).

The following diguanides were prepared by the same type of process.

N^1-*Phenyl*-N^1-*methyl*-N^5-iso*propyldiguanide* (VII; R = Me, R′ = H, R″ = Pr^i). Prepared from phenylmethylcyanamide and *iso*propylguanidine (reaction time 0·5 hour), the *base* crystallised from light petroleum (b. p. 100—120°) as colourless prisms (yield, 39%), m. p. 70—71° (Found: C, 60·0; H, 8·7; N, 28·9. $C_{12}H_{19}N_5$,0·5H_2O requires C, 59·5; H, 8·3; N, 28·9%) (5809). The hydrochloride (not analysed) had m. p. 209—210°.

N^1-*Phenyl*-N^1 : N^5 : N^5-*trimethyldiguanide* (VII; R = R′ = R″ = Me). Prepared from phenylmethylcyanamide and dimethylguanidine (reaction time 0·5 hour), the *base* separated from light petroleum (b. p. 60—80°) as colourless prisms (yield, 59%), m. p. 103—104° (Found in material dried in a vacuum at 80°: C, 60·3; H, 7·6; N, 32·2. $C_{11}H_{17}N_5$ requires C, 60·3; H, 7·8; N, 32·0%) (5808).

N^1 : N^5-*Diphenyl*-N^1 : N^5-*dimethyldiguanide* (VII; R = R′ = Me, R″ = Ph). Prepared from phenylmethylcyanamide and *N*-phenyl-*N*-methylguanidine (reaction time 1 hour), the *base* crystallised from butanol as colourless plates, m. p. 103° (Found: C, 68·5; H, 6·4; N, 24·7. $C_{16}H_{19}N_5$ requires C, 68·3; H, 6·8; N, 24·9%) (5807).

N^1 : N^1-*Diphenyl*-N^5 : N^5-*dimethyldiguanide* (VII; R = Ph, R′ = R″ = Me). Prepared from diphenylcyanamide and dimethylguanidine (reaction time 1·5 hours), the *base* (yield, 29%) formed colourless prisms from alcohol, m. p. 139—140° (Found: C, 68·4; H, 6·5; N, 25·3. $C_{16}H_{19}N_5$ requires C, 68·3; H, 6·8; N, 24·9%). The *hydrochloride* formed colourless prisms from water, m. p. 215—216° (Found: Cl′, 10·8. $C_{16}H_{19}N_5Cl$,HCl requires Cl′, 11·2%) (5811).

N^1 : N^1-*Diphenyl*-N^5-iso*propyldiguanide*. Prepared from *NN*-diphenylcyanamide and *iso*propyl-

guanidine (reaction time 1·25 hours), the base (yield, 7%) crystallised from light petroleum (b. p. 100—120°), m. p. 143° either alone or in admixture with (VII; R = Ph, R′ = H, R″ = Pr^{i}) prepared from *iso*propylcyanamide and *NN*-diphenylguanidine (see above).

N^{1}-p-*Chlorophenyl*-N^{5}-*methyldiguanide*. Prepared from *p*-chlorophenylcyanamide and methylguanidine (reaction time 0·75 hour), and isolated as its hydrochloride. It was identified with authentic hydrochloride (Part X), m. p. and mixed m. p. 227—228°.

N^{1}-p-*Chlorophenyl*-N^{5}-*cyclohexyldiguanide*. Sodium (3·45 g.) was dissolved in methanol (35 c.c.), and a solution of *p*-chlorophenylcyanamide (15·25 g.) in ether (50 c.c.) added. Addition of ether (500 c.c.) precipitated sodium *p*-chlorophenylcyanamide (8·3 g.) which was collected and added to *cyclo*hexylguanidine hydrochloride (8·5 g.) and butanol (20 c.c.), and the mixture refluxed for 2 hours. The mixture was worked up by dilution with benzene, extraction with 2N-hydrochloric acid, and isolation of the monohydrochloride which was subsequently converted into the base. This crystallised from alcohol, and had m. p. 173—174° undepressed in admixture with the material made from *p*-chlorophenylguanidine and *cyclo*hexylcyanamide (see above) (Found: C, 57·2; H, 6·7. Calc. for $C_{14}H_{20}N_5Cl$: C, 57·2; H, 6·8%).

Condensation of iso*Propylcyanamide with* N-p-*Chlorophenyl*-N′-*methylguanidine*.—A solution of *N*-*p*-chlorophenyl-*N*′-methylguanidine (9·2 g.) (forthcoming publication) in butanol (20 c.c.) was heated to boiling, and an ethereal solution of *iso*propylcyanamide (from *iso*propylamine, 11·8 g.) gradually added. The ether was boiled off, and the mixture then refluxed for 0·75 hour. It was then cooled and worked up *via* the benzene-soluble copper complex as described above, to give *N*^{1}-*p*-chlorophenyl-*N*^{2}-methyl-*N*^{5}-*iso*propyldiguanide as an oil which afforded a picrate, m. p. 163—164°, identical with the picrate described in Part XXIX (*loc. cit.*) (Found: C, 43·8; H, 4·3; N, 23·1. Calc. for $C_{12}H_{18}N_5Cl,C_6H_3O_7N_3$: C, 43·5; H, 4·2; H, 22·6%).

Condensation of p-*Chlorophenylcyanamide with* N-*Methyl*-N′-iso*propylguanidine*.—Sodium (1·15 g.) was dissolved in butanol (20 c.c.), and a solution of *N*-methyl-*N*′-*iso*propylguanidine hydrobromide (10 g.) (forthcoming communication) in butanol (10 c.c.) added. The mixture was refluxed for 15 minutes and filtered, and the residue washed with butanol (5 c.c.). *p*-Chlorophenylcyanamide (7·6 g.) was added to the combined butanol filtrate and washings, and the whole refluxed for 3 hours. The cooled mixture was diluted with benzene (100 c.c.) and thoroughly extracted with 2N-hydrochloric acid (80 c.c. in portions). The acid extract was made faintly alkaline with ammonia, and the resulting precipitate collected and purified by crystallisation from water to give *N*^{1}-*p*-chlorophenyl-*N*^{4}-methyl-*N*^{5}-*iso*propyldiguanide hydrochloride, m. p. 205—206° undepressed in admixture with material made as described in Part XXX (*loc. cit.*) (Found: C, 46·9; H, 5·8. Calc. for $C_{12}H_{18}N_5Cl,HCl$: C, 47·4; H, 6·25%).

N^{1}-p-*Bromophenyl*-N^{5}-*substituted Diguanides*.

N^{1}-p-*Bromophenyl*-N^{5}-*methyldiguanide* (I; R = Br, R′ = H, R″ = Me).—Sodium (1·15 g.) was dissolved in butanol (20 c.c.), methylguanidine sulphate (6·1 g.) added, and the mixture refluxed for ½ hour, cooled, and filtered. The residue was washed with butanol (10 c.c.), and the butanol filtrate and washings were combined and refluxed for 3 hours with *p*-bromophenylcyanamide. The mixture was then cooled, diluted with benzene (50 c.c.), and extracted several times with 2N-hydrochloric acid. The combined acid extracts were neutralised with ammonia, and the precipitated product collected and crystallised from water to give the *hydrochloride* (yield, 33%) as clusters of colourless needles, m. p. 241—242° (Found: C, 35·2; H, 4·4; N, 22·7. $C_9H_{12}N_5Br,HCl$ requires C, 35·2; H, 4·2; N, 22·8%) (5884).

N^{1}-p-*Bromophenyl*-N^{5}-*ethyldiguanide*.—(*a*) *p*-Bromophenylguanidine (9·4 g.) was dissolved in butanol (10 c.c.), and an ethereal solution of ethylcyanamide (from ethylamine, 13 g.) added. After the ether had been boiled off, the mixture was refluxed for ½ hour, cooled, and diluted with benzene. It was then extracted with 2N-hydrochloric acid, and the acid extract neutralised with ammonia to precipitate the *hydrochloride* which separated from water as colourless, long thin prisms, m. p. 233—234° (Found: C, 35·8; H, 4·7. $C_{10}H_{14}N_5Br,HCl,H_2O$ requires C, 35·6; H, 4·7%) (5883).

(*b*) Ethyldicyandiamide (4·1 g.), *p*-bromoaniline hydrochloride (8·0 g.), and 2-ethoxyethanol (20 c.c.) were boiled under reflux for 1·75 hours. On cooling, the solution deposited a mass of crystals. The whole was dissolved in 2N-hydrochloric acid, the solution filtered and neutralised with ammonia, and the product salted out. Crystallised from water it had m. p. 233—234° undepressed in admixture with material made by method (*a*).

N^{1}-p-*Bromophenyl*-N^{5}-iso*propyldiguanide*.—(*a*) Prepared from *p*-bromophenylguanidine and *iso*propylcyanamide as described above for the corresponding *N*^{5}-ethyl compound (reaction time 0·5 hour), the *base* (yield, 28%) crystallised from light petroleum (b. p. 100—120°) in colourless plates, m. p. 137° (Found: C, 44·3; H, 5·4; Br, 27·5. $C_{11}H_{16}N_5Br$ requires C, 44·3; H, 5·4; Br, 26·9%).

(*b*) *p*-Bromophenyldicyandiamide (6·0 g.), *iso*propylamine hydrochloride (4·8 g.), and nitrobenzene (20 c.c.) were heated at 130—135° by means of an oil-bath for 16 hours. After cooling, the mixture was extracted with 2N-hydrochloric acid (5 × 25 c.c.), and the acid extracts were combined and neutralised with ammonia to give *N*^{1}-*p*-bromophenyl-*N*^{5}-*iso*propyldiguanide hydrochloride (5382), m. p. 246—247°, identical with the substance described in Part XXVIII (*loc. cit.*). A portion of the hydrochloride, dissolved in 2N-hydrochloric acid and added to sodium hydroxide, gave the base which was crystallised from light petroleum (b. p. 100—120°) and shown to be identical with that made by method (*a*), m. p. and mixed m. p. 137°.

N^{1}-p-*Bromophenyl*-N^{5}-n-*propyldiguanide*.—(*a*) Prepared as in the preceding experiment from *p*-bromophenyldicyandiamide and *n*-propylamine hydrochloride, the *hydrochloride* crystallised from water as small colourless plates, m. p. 221—222° (Found: C, 39·2; H, 5·0; N, 21·2. $C_{11}H_{16}N_5Br,HCl$ requires C, 39·5; H, 5·1; N, 20·9%) (5990).

(*b*) By reaction of *p*-bromophenylguanidine and *n*-propylcyanamide (reaction time 0·5 hour), the same hydrochloride was obtained in very small yield (2%), m. p. and mixed m. p. 221—222°.

N^{1}-p-*Bromophenyl*-N^{5}-n-*butyldiguanide*.—Prepared from *p*-bromophenylguanidine and *n*-butylcyanamide in boiling pentanol (reaction time 0·5 hour), and worked up *via* the benzene-soluble copper complex as described above for the condensation of diethylcyanamide with *p*-chlorophenylguanidine

and its hydrochloride, the *hydrochloride* crystallised from water as colourless needles, m. p. 210° (Found : C, 41·4; H, 5·4; N, 19·9. $C_{12}H_{18}N_5Br$,HCl requires C, 41·3; H, 5·5; N, 20·1%) (5945). The substance was found to be identical with that described in Part XXX (*loc. cit.*) which was made later.

N¹-p-*Bromophenyl*-N⁵-iso*butyldiguanide*.—(*a*) Prepared as described above for the corresponding *N*⁵-ethyl compound, from *p*-bromophenylguanidine and *iso*butylcyanamide, the *hydrochloride* (yield, 25%) crystallised from water as colourless plates, m. p. 243° (Found : C, 41·4; H, 5·4; Cl′, 9·7. $C_{12}H_{18}N_5Br$,HCl requires C, 41·3; H, 5·5; N, 20·1; Cl′, 10·2%) (5867).

(*b*) *p*-Bromophenyldicyandiamide and *iso*butylamine hydrochloride were brought into reaction in nitrobenzene, and the mixture worked up as described for (I; R = Br, R′ = H, R″ = Pr^i) to give the same hydrochloride as in (*a*), m. p. and mixed m. p. 242—243° (Found: C, 41·6; H, 5·6; N, 20·1; Cl′, 10·7%).

N¹-p-*Bromophenyl*-N⁵-sec.-*butyldiguanide*.—*p*-Bromophenyldicyandiamide and *sec.*-butylamine hydrochloride were condensed together to give the *hydrochloride* which separated from 50% aqueous alcohol as colourless long thin rectangular plates, m. p. 255—256° (Found : C, 41·6; H, 5·6; N, 20·5. $C_{12}H_{18}N_5Br$,HCl requires C, 41·3; H, 5·5; N, 20·1%) (6009).

N¹-p-*Bromophenyl*-N⁵-tert.-*butyldiguanide*.—Prepared from *p*-bromophenyldicyandiamide and *tert.*-butylamine hydrochloride in nitrobenzene, the *hydrochloride* formed colourless plates from aqueous alcohol, m. p. 260—261° (Found : C, 41·9; H, 5·6; N, 19·6; Cl′, 10·6. $C_{12}H_{18}N_5Br$,HCl requires C, 41·3; H, 5·5; N, 20·1; Cl′, 10·2%) (5991).

N¹-p-*Bromophenyl*-N⁵-cyclo*hexyldiguanide*.—Prepared from *p*-bromophenylcyanamide and *cyclo*hexylguanidine (hydrochloride) (reaction time 2·5 hours) by method (*a*) described above for the corresponding *N*⁵-methyl derivative, the *base* (yield, 28%) crystallised from benzene as colourless plates, m. p. 181—182° (Found : C, 49·8; H, 5·7; N, 20·7. $C_{14}H_{20}N_5Br$ requires C, 49·7; H, 5·9; N, 20·7%) (5938). The hydrochloride crystallised from water as aggregates of colourless needles, m. p. 252—253°.

N¹-p-*Bromophenyl*-N⁵ : N⁵-*dimethyldiguanide* (I; R = Br, R′ = R″ = Me).—Prepared from dimethylcyanamide and *p*-bromophenylguanidine in boiling butanol solution (reaction time 1·25 hours), the *base* (yield, 25%) crystallised from alcohol as long thin colourless needles, m. p. 175—176° (Found : C, 41·1; H, 4·9; N, 23·8. $C_{10}H_{14}N_5Br,0{\cdot}5H_2O$ requires C, 41·0; H, 5·1; N, 23·9%) (5834).

N¹-p-*Bromophenyl*-N⁵ : N⁵-*diethyldiguanide*.—Prepared as described above for (I; R = OMe, R′ = R″ = Me) from *p*-bromophenylguanidine and diethylcyanamide in boiling pentanol solution, the *hydrochloride* crystallised from water in long thin colourless needles, m. p. 224° (Found : Cl′, 10·4. $C_{12}H_{18}N_5Br$,HCl requires Cl′, 10·2%). The *base* separated from light petroleum (b. p. 100—120°) as colourless plates, m. p. 140—141° (Found : C, 46·5; H, 5·9; N, 22·0. $C_{12}H_{18}N_5Br$ requires C, 46·2; H, 5·8; N, 22·4%) (5851).

N¹-p-*Bromophenyl*-N⁵-*methyl*-N⁵-iso*propyldiguanide*.—(*a*) Similarly prepared from *p*-bromophenylguanidine and methyl*iso*propylcyanamide in boiling butanol solution (reaction time 3 hours), the *hydrochloride* (yield, 9%) was obtained as colourless needles from water, m. p. 251° (Found : C, 40·7; H, 5·6; N, 19·8. $C_{12}H_{18}N_5Br$,HCl requires C, 41·3; H, 5·5; N, 20·1%) (5879).

(*b*) *p*-Bromophenyldicyandiamide and methyl *iso*propylamine hydrochloride reacted together in nitrobenzene to give the same hydrochloride as in (*a*), m. p. and mixed m. p. 250—251°.

N¹-p-*Bromophenyl*-N⁵-*methyl*-N⁵-n-*propyldiguanide*.—Methyl-*n*-propyldicyandiamide (3·5 g.) (forthcoming communication), *p*-bromoaniline hydrochloride (5·2 g.), and 2-ethoxyethanol (15 c.c.) were boiled under reflux for 1·5 hours. The cooled mixture was stirred with warm 2N-hydrochloric acid and filtered, and the filtrate made faintly alkaline with ammonia. The precipitated product was collected, washed with water and, after drying, washed well with ether to remove unchanged *p*-bromoaniline. Crystallisation from water then gave the *hydrochloride* (yield, 2·4 g.) as long thin glistening prisms, m. p. 237° (Found : C, 41·7; H, 5·6. $C_{12}H_{18}N_5Br$,HCl requires C, 41·3; H, 5·2%) (6676). The *base* crystallised from light petroleum (b. p. 100—120°) as colourless plates, m. p. 124·5—125·5° (Found : C, 46·5; H, 5·8; N, 22·8. $C_{12}H_{18}N_5Br$ requires C, 46·2; H, 5·8; N, 22·4%).

N¹-p-*Bromophenyl*-N⁵-*methyl*-N⁵-n-*butyldiguanide*.—Prepared from *p*-bromophenylguanidine and methyl-*n*-butylcyanamide in boiling butanol (reaction time 2·5 hours), the *base* crystallised from light petroleum (b. p. 100—120°) as long colourless plates (yield, 17%), m. p. 123—124° (Found : C, 48·0; H, 6·2; N, 20·9. $C_{13}H_{20}N_5Br$ requires C, 47·8; H, 6·1; N, 21·4%) (5933).

N¹-p-*Bromophenyl*-N⁵ : N⁵-cyclo*pentamethylenediguanide* (I; R = Br, R′R″ = $[CH_2]_5$).—Prepared from *p*-bromophenylguanidine and *cyclo*pentamethylenecyanamide in boiling butanol (reaction time 1 hour), the *base* crystallised from butanol as long colourless plates (yield, 27%), m. p. 205—206° (Found : C, 48·2; H, 5·4; N, 21·0. $C_{13}H_{18}N_5Br$ requires C, 48·2; H, 5·6; N, 21·6%) (5871). The *hydrochloride* separated from water as colourless needles, m. p. 257° (Found : Cl′, 10·2. $C_{13}H_{18}N_5Br$,HCl required Cl′, 9·8%).

N¹-p-*Bromophenyl*-N⁵-*phenyl*-N⁵-*methyldiguanide* (I; R = Br, R′ = Ph, R″ = Me).—Prepared from phenylmethylcyanamide and *p*-bromophenylguanidine in boiling butanol (reaction time 0·75 hour), the *base*, isolated direct from the reaction mixture by filtration, crystallised from alcohol as long thin colourless prisms (yield, 27%), m. p. 179—180° (Found : C, 51·9; H, 4·6; N, 20·5; Br, 23·7. $C_{15}H_{16}N_5Br$ requires C, 52·0; H, 4·6; N, 20·2; Br, 23·1%) (5835).

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