539. *Synthetic Antimalarials. Part XLIV. The Preparation of Diguanides by the Reaction of Substituted Amino- (including Guanidino-)magnesium Halides with the* >N·C≡N *Group.*

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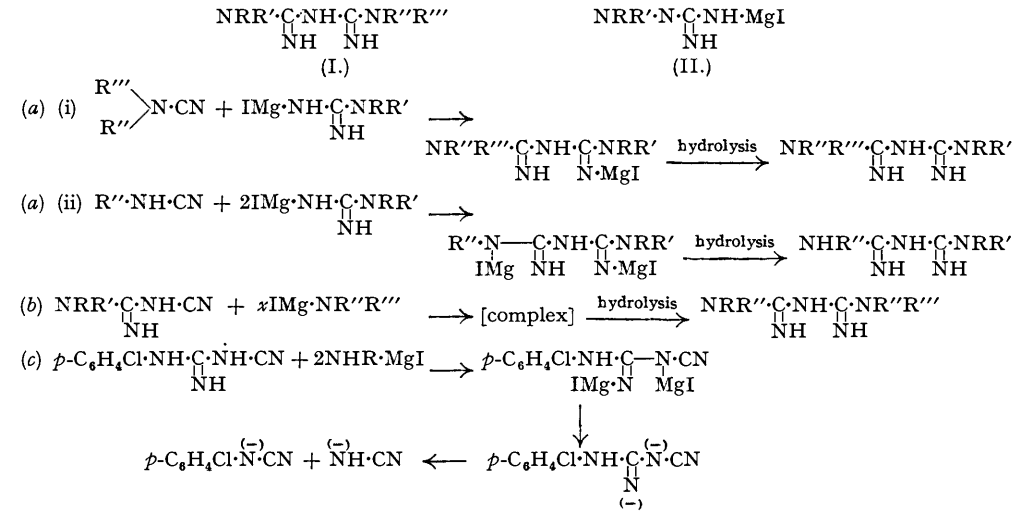
The addition of substituted aminomagnesium halides to compounds containing the >N·C≡N group has been investigated. Diguanides are formed from cyanamides and substituted guanidinomagnesium halides, and from cyanoguanidines and substituted aminomagnesium halides. With *N'*-cyano-*N*-*p*-chlorophenylguanidine however, the main product of the reaction is *N*-cyano-*N'*-*p*-chlorophenylcyanamide. The mechanism of its formation is considered to be the same as that outlined in the following paper (Part XLV) for the production of cyanamides from alkyl- and aryl-magnesium halides and cyanoguanidines.

Amino- and substituted amino-magnesium halides are known to react with esters (Bodroux, *Bull. Soc. chim.*, 1906, **35**, 519), aldehydes (Tschelinzeff *et al.*, *ibid.*, pp. 181, 184, 190), and carbon dioxide (Houben, *Ber.*, 1904, **37**, 3978; *ibid*, 1905, **38**, 3017) in substantially the same manner as ordinary Grignard reagents. Their reaction with nitriles has recently been utilised for the preparation of amidines by Hullin, Miller, and Short (*J.*, 1947, 394) who found that in some instances yields were poorer than those obtained by more orthodox methods and varied con-

siderably for different combinations of nitrile and substituted aminomagnesium halide. The route however has been found by Lorz and Baltzly (*J. Amer. Chem. Soc.*, 1948, **70**, 1904) to be of value when aromatic nitriles and dialkylaminomagnesium halides are employed and is recommended for the preparation of *NN*-dialkylated arylamidines containing a substituent *ortho* to the amidino-group since the addition is not subject to steric hindrance.



A result of particular interest to us was the observation by Hullin, Miller, and Short (*loc. cit.*) that *s*-tetraethylguanidine was formed in 58% yield by the reaction of diethylcyanamide and diethylaminomagnesium bromide, showing that the >N·C≡N group behaved in the same manner as simple nitriles (C·C≡N). Addition to this group was a potential preparative method for diguanides of the "Paludrine" type (I; R = *p*-C_6H_4Cl, R' = R'' = H, R''' = Pr^i) (*J.*, 1946, 730), and in the investigation to be described we have extended the reaction to cyanamides and guanidino-magnesium halides (*a*; i and ii) and to cyanoguanidines and amino-magnesium halides (*b*).

Preparatory to the study of reactions of type (*a*) it was established that the reaction of substituted guanidines—the particular case investigated was *p*-chlorophenylguanidine—with one molecule of ethylmagnesium iodide in ether at room temperature is principally one of metalation with evolution of ethane. The complex regenerates *p*-chlorophenylguanidine on hydrolysis, and a structure such as (II; R = *p*-C_6H_4Cl, R' = H) conveniently accounts for this and other reactions, although it is realised that the true structure will be essentially ionic and exhibit resonance effects.

Such guanidinomagnesium halides reacted with disubstituted cyanamides in boiling ether, to give complexes which yielded diguanides on hydrolysis (*a*; i). The diguanides were isolated mainly as their hydrochlorides, many of which are only slightly soluble in neutral solution (Part X, *J.*, 1946, 732). With phenylmethylcyanamide and *NN*-dimethylguanidinomagnesium iodide (II; R = R' = Me), ready addition occurred, giving, in anisole–ether as solvent, a 48% yield of pure N^1-*phenyl*-$N^1N^5N^5$-*trimethyldiguanide* (I; R = Ph, R', R'', R''' = Me). On the other hand, the same cyanamide with *p*-methoxyphenylguanidinomagnesium iodide in ether gave N^5-phenyl-N^1-*p*-methoxyphenyl-N^5-methyldiguanide (I; R = *p*-C_6H_4·OMe, R' = H, R'' = Ph, R''' = Me) (as *hydrochloride*) in only 7% yield. Diethylcyanamide and *p*-methoxyphenylguanidinomagnesium iodide gave 12% of diguanide. These large variations in yield are probably due to differences in solubility of the guanidinomagnesium halides and the resultant complex in ether, as well as to the electronic effect of substituent groups.

To effect the reaction (*a*, ii) with monosubstituted cyanamides, two molecules of guanidinomagnesium halide were employed to allow for replacement of the acidic cyanamide hydrogen by MgI and for liberation of guanidine. No diguanide formation was observed when *p*-chlorophenylcyanamide and *NN*-dimethylguanidinomagnesium iodide were heated together for 24 hours under reflux in ether, or from *cyclo*hexylcyanamide and *p*-chlorophenylguanidinomagnesium iodide under similar conditions, but in anisole at 95—100°, the latter components gave N^1-*p*-chlorophenyl-N^5-*cyclo*hexyldiguanide (I; R = C_6H_4Cl, R', R'' = H, R''' =

$CH<[CH_2]_5$), isolated as its hydrochloride, in 69% yield (calculated on cyanamide consumed). Similarly, *iso*propylcyanamide gave 55% of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide (I; R = *p*-C_6H_4Cl, R′ = H, R″ = Pr^i, R‴ = H). The use of anisole for the conversion of monoarylcyanamides into diguanides was not successful. Thus *p*-chlorophenylcyanamide could not be induced to react with methyl- or dimethyl-guanidinomagnesium iodide under any conditions, but when its sodium salt was employed approximately 1% of N^1-*p*-chlorophenyl-N^5-methyldiguanide (I; R = *p*-C_6H_4Cl, R′, R″ = H, R‴ = Me) was obtained. Only 2% of N^1-*p*-methoxyphenyl-N^5-*iso*propyldiguanide (I; R = *p*-C_6H_4·OMe, R′ = H, R″ = Pr^i, R‴ = H) resulted from the reaction between *p*-methoxyphenylcyanamide and *iso*propylguanidinomagnesium iodide in anisole at 95—100°.

A similar difficulty in the addition of alkylmagnesium halides to monosubstituted cyanamides was experienced by Busch and Hobein (*Ber.*, 1907, **40**, 4296), although Adams and Beebe (*J. Amer. Chem. Soc.*, 1900, **22**, 190) and Vuylsteke (*Bull. Acad. Sci. Belge*, 1926, **12**, 535) found that disubstituted cyanamides reacted with facility. The replacement of the acidic hydrogen of the monosubstituted cyanamides by MgI, giving a much less reactive compound, probably accounts for these differences.

No comprehensive study of the reaction between cyanoguanidines and aminomagnesium halides (*b*) has been made. A Zerewitinoff determination in amyl ether shows that two atoms of hydrogen in *N*-cyano-*N*′-*p*-chlorophenylguanidine are reactive and it is probable that the first reaction with aminomagnesium halides is metalation. We have made no attempt to ascertain either its extent or the particular hydrogen atoms replaced. Usually two molecules of Grignard reagent were employed to one of *N*-cyano-*N*′-*p*-chlorophenylguanidine, but solubility considerations make it probable that local reactions occur in which *more* than two molecular proportions of Grignard reagent are involved, with some of the cyanoguanidine remaining unattacked. The variable yields from this type of reaction are illustrated by the following examples.

Equimolecular proportions of *N*-cyano-*N*′-*p*-chlorophenylguanidine and *iso*propylaminomagnesium iodide, heated under reflux for 24 hours in ether, gave a trace of diguanide, detected by colour reaction with ammoniacal copper sulphate and benzene (cf. Gage and Rose, *Ann. Trop. Med. Parasit.*, 1946, **40**, 333), but 85% of the *N*-cyano-*N*′-*p*-chlorophenylguanidine was recovered unchanged. Doubling of the proportion of *iso*propylaminomagnesium iodide gave the diguanide hydrochloride in approximately 1% yield. On the other hand, *N*-cyano-*N*′-*iso*propylguanidine (1 mol.) and 3 : 4-dichloroanilinomagnesium bromide (1 mol.) under similar conditions gave an 8% yield of the diguanide. A 22% (crude) or 12% (pure) yield of N^1-*p*-chlorophenyl-N^5-methyl-N^5-*iso*propyldiguanide hydrochloride (I; R = *p*-C_6H_4Cl, R′ = H, R″ = Me, R‴ = Pr^i) was obtained from *N*-cyano-*N*′-*p*-chlorophenylguanidine and methyl-*iso*propylaminomagnesium iodide (2 mols.).

A feature of all the reactions investigated involving *N*-cyano-*N*′-*p*-chlorophenylguanidine and aminomagnesium halides was the production of considerable quantities of *p*-chlorophenylcyanamide : for example, 13% with one molecule of *iso*propylaminomagnesium iodide, 35% with two molecules thereof, and 24% with two molecules of methyl*iso*propylaminomagnesium iodide. Similar results were obtained with alkyl- or aryl-magnesium halides (see Part XLV). The mechanism (*c*) is proffered in explanation, involving initial replacement of two or more of the active hydrogen atoms of the cyanoguanidine, the particular hydrogen atoms replaced being unimportant, followed by ionisation and subsequent rearrangement of the intermediate complex ion to give the more stable cyanamide ions.

Experimental.

All m. p.s are uncorrected.

The Grignard reagents of approximately 2M. concentration which were used in this work were made in bulk and stored in amber-glass bottles under nitrogen for use as required (cf. Braude and Stern, *J.*, 1946, 404). They were standardised by the usual acidimetric titration method (Gilman *et al.*, *J. Amer. Chem. Soc.*, 1923, **45**, 150; Gilman, Zoellner, and Dickey, *ibid.*, 1929, **51**, 1576).

Reactions between Guanidinomagnesium Halides and Disubstituted Cyanamides.—The same procedure was adopted for all these reactions, but in individual cases special precautions were taken to obtain anhydrous guanidines, and different techniques were evolved for working up the products. The general method therefore is described and specific details are indicated under the headings of the individual diguanides.

General method. A solution of alkylmagnesium halide, approximately 2M., in ether (0·1 g.-mol.) was added gradually to the stirred suspension of the guanidine (0·1 g.-mol.) in dry ether or anisole (50 c.c.). The product of the reaction was usually a hard, tarry substance, and stirring was difficult. After the mixture had been heated under reflux for 15—30 minutes to ensure that reaction was complete, the flask and contents were cooled to room temperature. A solution of the disubstituted cyanamide (0·1

g.-mol.) in ether (50 c.c.) was added and the mixture heated under reflux, with stirring whenever possible, for 18—24 hours. It was then cooled in ice–water, and the complex decomposed by addition of hydrochloric acid (40 c.c.; *d* 1·18) in ice-water (100 c.c.), sufficient to dissolve all the solid. The two layers were then separated. The ethereal layer was decolourised by shaking it with dilute sodium hydrogen sulphite solution, separated, neutralised, dried ($NaHCO_3$–Na_2SO_4), and evaporated to dryness. The aqueous layer was made alkaline to brilliant-yellow test-paper with ammonia and worked up as described under the individual preparations.

N^1-*Phenyl*-N^5-p-*methoxyphenyldiguanide*. *p*-Methoxyphenylguanidine (16·5 g.), ethylmagnesium iodide in ether (55 c.c.), and phenylmethylcyanamide (13·2 g.) were treated as described above. The ethereal solution, on evaporation, yielded unchanged phenylmethylcyanamide (8·0 g.) as an oil which crystallised overnight to give a solid, m. p. 30—32°. The aqueous solution, on being made alkaline with aqueous ammonia, gave an oil which partly solidified when dissolved ether was removed on the steam-bath. The solution was decanted, and the residue stirred with benzene. The insoluble material was collected, washed with benzene, and dissolved in warm 2N-hydrochloric acid (50 c.c.). When this solution was poured into 2N-sodium hydroxide (100 c.c.), a solid was precipitated which was extracted with warm benzene. The benzene solution was filtered from crystals which were deposited on cooling and then extracted with 2N-hydrochloric acid. Rendering alkaline with aqueous ammonia precipitated an oil which solidified when kept and scratched. On recrystallisation from water the *diguanide hydrochloride* (2·3 g.), m. p. 216—218° (Found: C, 57·5; H, 5·8; Cl′, 10·8. $C_{15}H_{19}ON_5$,HCl requires C, 57·6; H, 6·0; Cl′, 10·7%), was obtained.

N^1-*Phenyl*-$N^1N^5N^5$-*trimethyldiguanide*. *NN*-Dimethylguanidine sulphate (13·6 g.) was heated under reflux for 45 minutes with a solution of sodium methoxide (sodium, 2·3 g.; methanol, 50 c.c.). Precipitated sodium sulphate was filtered off and washed with methanol (20 c.c.), and the filtrate evaporated to dryness under reduced pressure. Anisole (75 c.c.) was added and distilled off *in vacuo* to remove traces of methanol. The residue was suspended in anisole (50 c.c.) and treated with ethylmagnesium iodide (55 c.c.) and phenylmethylcyanamide (13·2 g.) as previously described. To facilitate separation of the anisole–ether layer a further quantity of ether was added. Only a trace of residue was obtained on evaporation of this extract *in vacuo*, and this was discarded.

The aqueous solution gave no deposit when made slightly alkaline with aqueous ammonia. Concentrated sodium hydroxide solution was therefore added until an alkaline reaction to Clayton-yellow was obtained. The precipitated magnesium hydroxide and diguanide were filtered off, and both solid and filtrate extracted with benzene. After being dried (Na_2SO_4), the benzene extract was evaporated to dryness under reduced pressure leaving the crude base (10·4 g.), m. p. 96—103°. After 2 recrystallisations from *cyclo*hexane (charcoal) the *diguanide* was obtained having m. p. 105—106° (Found: N, 32·1. $C_{11}H_{17}N_5$ requires N, 32·0%).

N^1-p-*Methoxyphenyl*-N^5N^5-*diethyldiguanide*. Diethylcyanamide (9·8 g.), *p*-methoxyphenylguanidine (16·5 g.), and ethylmagnesium iodide in ether (55 c.c.), after decomposition of the addition complex and treatment of the aqueous acid solution with aqueous ammonia, deposited the crude diguanide hydrochloride as an oil which solidified after removal of dissolved ether on the steam-bath. The hydrochloride was filtered off, washed with water, and dissolved in 2N-hydrochloric acid. Addition to excess of sodium hydroxide solution gave the base which was filtered off, washed with water, and dried at 65° (yield, 4 g.). After recrystallisation from *cyclo*hexane it had m. p. 97—98°, undepressed on admixture with an authentic specimen.

Reactions between Monosubstituted Cyanamides and Guanidinomagnesium Halides.—General method. The reactions were carried out at 95—100°. The guanidines (0·1 g.-mol.) were stirred in dry anisole (75 or 100 c.c.), and the ethereal solution of alkylmagnesium halide (0·1 g.-mol.) was added. The temperature was then gradually raised to 95—100°, distilling off the ether, this temperature was maintained for 15—30 minutes, and the cyanamide (0·05 g.-mol.) was added as a solution in anisole (25 c.c.) or in the pure state. The reaction temperature was maintained for 18—24 hours, and the product after cooling to 20° was decomposed with hydrochloric acid in the usual manner.

N^1-p-*Chlorophenyl*-N^5-*methyldiguanide*. Sodium (2·3 g.) was dissolved in methanol (25 c.c.), and *p*-chlorophenylcyanamide (15·2 g.) added. The solution was filtered and evaporated to small bulk under reduced pressure. The semisolid residue was stirred with dry ether, filtered off, and well washed. After being dried *in vacuo* over phosphoric oxide, the sodium salt of *p*-chlorophenylcyanamide was obtained as a fine white powder (10·9 g.).

Methylguanidine was obtained from methylguanidine sulphate (12·2 g.) by the technique described above for the preparation of dimethylguanidine from its sulphate (cf. N^1-phenyl-$N^1N^5N^5$-trimethyldiguanide). It was treated with ethylmagnesium iodide (48 c.c.) and sodium *p*-chlorophenylcyanamide (8·8 g.) in the manner outlined in the general method. *p*-Chlorophenylcyanamide (3·35 g.) was recovered by evaporation of the anisole–ether extract *in vacuo*. To the aqueous solution, concentrated sodium hydroxide solution was added until an alkaline reaction to Clayton-yellow test-paper was obtained. The magnesium hydroxide was filtered off, and the filtrate and filter-paste were extracted with benzene. The diguanide in the benzene was extracted with 2N-hydrochloric acid and precipitated as the hydrochloride by making it slightly alkaline with aqueous ammonia. The crude product was tarry, but the residue after stirring with ether and filtration was a white powder which after crystallisation from water had m. p. and mixed m. p. 239—240° (yield, 0·1 g.).

N^1-p-*Chlorophenyl*-N^5-cyclo*hexyldiguanide*. An ethereal solution containing approximately 0·05 g.-mol. of *cyclo*hexylcyanamide, prepared by the method described by Ainley, Curd, and Rose (this vol., p. 96), was evaporated under reduced pressure. The residue was dissolved in anisole (25 c.c.) and added to the product of reaction of *p*-chlorophenylguanidine (17·0 g.) and ethylmagnesium iodide in anisole (75 c.c.). The general method described above was subsequently followed. The diguanide hydrochloride was largely insoluble in the dilute hydrochloric acid–anisole mixture. It was filtered off, dissolved in 2N-hydrochloric acid (300 c.c.) at 60° and clarified and decolourised by filtration through keiselguhr and treatment of the filtrate with charcoal. The clear solution was made alkaline with aqueous ammonia and cooled, N^1-*p*-chlorophenyl-N^5-*cyclo*hexyldiguanide hydrochloride being deposited

(10·4 g.), having m. p. 256—258°. A further quantity of this material was obtained from the original anisole–hydrochloric acid filtrate. The anisole was separated and the aqueous solution made alkaline with aqueous ammonia. The precipitate was collected and washed, redissolved in boiling 2N-hydrochloric acid, and poured into excess of sodium hydroxide solution. The base was filtered off, washed well, redissolved in hot 2N-hydrochloric acid, and neutralised with aqueous ammonia. Yield, 1·0 g.; m. p. 256—258°. The free base was obtained from the hydrochloride by dissolving it in aqueous-alcoholic hydrochloric acid and pouring the mixture into excess of sodium hydroxide solution. The crystalline precipitate was collected, well washed with water, and recrystallised from ethanol (charcoal), whereafter it had m. p. and mixed m. p. 179—180° (yield, 6·0 g.).

N^1-p-*Chlorophenyl*-N^5-iso*propyldiguanide*. This was similarly prepared from an ethereal solution of *iso*propylcyanamide (0·05 g.-mol. approx.) (this vol., p. 96), *p*-chlorophenylguanidine (17·0 g.), and ethylmagnesium iodide. On decomposition with hydrochloric acid three layers formed. The aqueous solution was separated and the remainder extracted further with 0·1N-hydrochloric acid (2 × 50 c.c.) at 50—60°. The combined acid extracts were cooled, stirred with charcoal, and filtered. A precipitate was obtained by neutralisation with aqueous ammonia. It was collected, well washed with water, redissolved in 2N-hydrochloric acid (100 c.c.), and poured into excess of sodium hydroxide solution. The base was filtered off, washed, and redissolved in 2N-hydrochloric acid. The solution was clarified and the hydrochloride precipitated with aqueous ammonia (yield, 8·0 g.; m. p. 248—249°). After recrystallisation from water (carbon), it had m. p. and mixed m. p. 250—251° (yield, 6·2 g.).

N^1-p-*Methoxyphenyl*-N^5-iso*propyldiguanide*. (*a*) This was prepared as above from an ethereal solution of *iso*propylcyanamide (approx. 0·05 g.-mol.), *p*-methoxyphenylguanidine (16·5 g.), and ethylmagnesium bromide. The aqueous hydrochloric acid solution was separated from the anisole and neutralised with aqueous ammonia. When kept overnight the crude hydrochloride crystallised (1·3 g.) and had m. p. 208—210°. After two crystallisations from water it had m. p. and mixed m. p. 232—234°.

(*b*) Anhydrous *iso*propylguanidine was prepared from *iso*propylguanidine sulphate by the method previously described for *NN*-dimethylguanidine. It was treated in the usual manner with ethylmagnesium iodide and *p*-methoxyphenylcyanamide (7·4 g.). After decomposition of the complex with hydrochloric acid, the aqueous portion was separated and made alkaline to Clayton-yellow with concentrated sodium hydroxide solution. The precipitate of magnesium hydroxide and product was filtered off, and both filtrate and precipitate were extracted with benzene. The benzene solution was shaken with dilute hydrochloric acid, and the aqueous extract separated. On neutralisation with aqueous ammonia and salting out with ammonium chloride, a precipitate of the diguanide hydrochloride was obtained (0·6 g.), having m. p. 215—222°. Recrystallised from water (carbon) it had m. p. and mixed m. p. 230—231° (0·25 g.).

Reactions between Cyanoguanidines and Substituted Aminomagnesium Halides.—Cyano-p-*chlorophenylguanidine and* iso*propylaminomagnesium iodide*. (*a*) *iso*Propylamine (0·2 g.-mol., 11·8 g.), dissolved in ether (100 c.c.), was stirred while ethylmagnesium iodide solution (0·2 g.-mol., *ca.* 100 c.c.) was added gradually. The reaction was completed by heating the mixture under reflux for *ca.* 15 minutes. *N*-Cyano-*N'*-*p*-chlorophenylguanidine (0·1 g.-mol., 19·5 g.) was added, and the mixture stirred and heated under reflux for 18 hours. The flask was then cooled in ice, and the reaction product decomposed by the addition of hydrochloric acid solution (hydrochloric acid, *d* 1·18, 50 c.c.; ice-water, 250 c.c.). Unchanged guanidine (11·2 g.), m. p. 202—204°, was filtered off and the filtrates were separated into the two layers. The aqueous layer was made slightly alkaline with aqueous ammonia and dissolved ether removed *in vacuo*. The diguanide hydrochloride was salted out with ammonium chloride. It was redissolved in a small amount of 2N-hydrochloric acid, clarified, and poured into an excess of sodium hydroxide solution. The precipitate was dissolved in benzene and separated, and the diguanide extracted with 2N-hydrochloric acid. On neutralisation with aqueous ammonia a crystalline precipitate was obtained, identified as *N*^{1}-*p*-chlorophenyl-N^5-*iso*propyldiguanide hydrochloride (0·05 g.) by m. p. and mixed m. p. with an authentic specimen, 247—249°. The ethereal extract was washed with water and extracted with 2N-sodium hydroxide; p-*chlorophenylcyanamide* was precipitated by hydrochloric acid, with addition of ice. The precipitate was dissolved in ether and dried (Na_2SO_4), and the solution evaporated to dryness. Yield, 5·4 g. On recrystallisation from ether the substance was obtained as colourless prisms, m. p. 108—109° (Found: C, 55·2; H, 3·6; N, 18·2; Cl, 22·9. $C_7H_5N_2Cl$ requires C, 55·1; H, 3·3; N, 18·4; Cl, 23·3%). Its structure was confirmed by hydrolysis to *p*-chlorophenylurea, m. p. and mixed m. p. with an authentic specimen, 212—213°.

(*b*) The experiment described was repeated with use of only 0·1 g.-mol. of *iso*propylamine (5·9 g.). *N*-Cyano-*N'*-*p*-chlorophenylguanidine (16·6 g.) was recovered, and rather crude *p*-chlorophenylcyanamide (2·0 g.), m. p. 87—91°, was also obtained. The aqueous solution gave a positive colour reaction when tested with ammoniacal copper sulphate and benzene, but no diguanide was isolated.

N-*Cyano*-N'-p-*chlorophenylguanidine and methyl*iso*propylaminomagnesium iodide*. (*a*) *N*-Cyano-*N'*-*p*-chlorophenylguanidine (19·5 g.), treated in a similar manner with 0·2 g.-mol. of methyl*iso*propylaminomagnesium iodide (from 15 g. of methyl*iso*propylamine), gave largely unchanged material, m. p. 204—206°, but some crude diguanide hydrochloride (6·6 g.), m. p. 214—216°, was obtained on making the acid extract alkaline with aqueous ammonia. This, on purification by precipitation of the base, gave 3·6 g., having m. p. and mixed m. p. with an authentic specimen, 247—248°. The ethereal extract was washed and dried as previously described. It was then diluted with an equal volume of light petroleum (b. p. 40—60°), and a further amount of *N*-cyano-*N'*-*p*-chlorophenylguanidine (0·9 g.) which was precipitated was filtered off. The filtrate on evaporation to dryness gave *p*-chlorophenylcyanamide, m. p. 102—104° (3·6 g.).

(*b*) A similar result was obtained when the complex derived from the reaction between *N*-cyano-*N'*-*p*-chlorophenylguanidine and methyl*iso*propylmagnesium iodide was decomposed with ammonium chloride solution.

iso*Propyldicyandiamide and* p-*phenetidinomagnesium iodide*. The reaction was carried out in the usual way, but anisole (100 c.c.) was employed as the solvent, and the temperature was maintained at 20—25°. Molecular proportions of *p*-phenetidine (14·0 g.), ethylmagnesium iodide, and *N*-cyano-*N'*-

*iso*propylguanidine (12·6 g.) were also used. The aqueous extract resulting from the decomposition with dilute hydrochloric acid was clarified by stirring it with kieselguhr and filtration. The filtrate was made alkaline with aqueous ammonia and steam-distilled, and the residue filtered off after cooling. It was then dissolved in cold water (250 c.c.), some tarry substance filtered off, and the filtrate salted out with ammonium chloride (50 g.). The precipitate (5·8 g.), m. p. 244°, was recrystallised from water (75 c.c.) (charcoal), giving N^1-*p*-ethoxyphenyl-N^5-*iso*propyldiguanide hydrochloride (3·0 g.), m. p. 245—247°, undepressed on admixture with authentic material.

N-*Cyano*-N′-iso*propylguanidine and* 3 : 4-*dichloroanilinomagnesium bromide.* 3 : 4-Dichloroanilinomagnesium bromide was prepared from 3 : 4-dichloroaniline (10·9 g.) and a molecular proportion of ethylmagnesium bromide and treated in the usual way with *N*-cyano-*N′-iso*propylguanidine (8·5 g.) in ether under reflux. The neutralised hydrochloric acid extract yielded an oil which solidified on removal of ether on the steam-bath. It was filtered off and stirred with benzene, much material then dissolving. The residue was collected, well washed with benzene, dried, and recrystallised from water (carbon). N^1-3 : 4-Dichlorophenyl-N^5-*iso*propyldiguanide hydrochloride (1·8 g.) crystallised, having m. p. 245—246°, undepressed on admixture with an authentic specimen.

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