PATENT SPECIFICATION

638,695

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PROVISIONAL SPECIFICATION

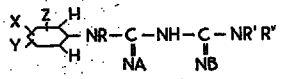
Manufacture of Biguanide Derivatives

I, STANLEY BIRTWELL, FRANCIS HENRY SWINDEN CURD and FRANCIS LESLIE ROSE, all of Hexagon House, Blackley, Manchester, all British Subjects, and IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a Company incorporated under the laws of Great Britain, do hereby declare the nature of this invention to be as follows:—

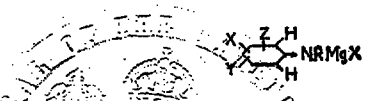
This invention relates to a process for the manufacture of biguanide derivatives and more particularly it relates to a process for the manufacture of biguanide derivatives which are useful as chemotherapeutic agents especially in the treatment of malaria.

It is known that biguanide derivatives may be made by interaction of a primary or a secondary amine with dicyandiamide or with a substituted dicyandiamide. See, for example, British Specification No. 577,843. We have now found that in place of the amine there may be used the Grignard compound derived therefrom, that is the aminomagnesium halide.

According to the invention we manufacture biguanide derivatives of the formula



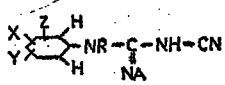
wherein R stands for hydrogen or for an alkyl radical of 1—3 carbon atoms, R^1 stands for hydrogen or for a lower alkyl radical and R^{11} stands for a lower alkyl radical such that R^1 and R^{11} together contain more than one and fewer than 8 carbon atoms, A and B stand for hydrogen or for alkyl radicals of 1—3 carbon atoms provided that both do not stand for alkyl radicals in one and the same substance, X stands for halogen, Y stands for hydrogen, halogen or for an alkyl radical or alkoxy radical of 1—3 carbon atoms, and Z stands for hydrogen or halogen, by a process which comprises first reacting a substituted aminomagnesium halide of the formula



or of the formula $R^1R^{11}NMgX$ with a substituted dicyandiamide, respectively of the formula



or of the formula



in all of which formulæ the symbols A, B, X, Y and Z, R, R^1 and R^{11} have the significance stated above, and then treating the reaction product with acid or an acid-reacting salt.

The substituted aminomagnesium halides which are used as starting materials in the process of the invention may be made by the interaction, for example, in ethereal solution or suspension, of the appropriate amine with an alkylmagnesium halide. Conveniently, the alkylmagnesium halide is chosen such that the by-product is gaseous. Thus an ethylmagnesium halide may be used which, in reaction with an amine, gives rise to the corresponding aminomagnesium halide and ethane.

Besides the substances whose manufacture by the process of this invention is described in the Examples below there may be made also, by processes differing only from those described in that the reactants and quantities thereof are appropriately changed, the following substances:—

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N^1-*p*-Chlorophenyl-N^5-*n*-propylbiguanide acetate, m.p. 164—165° C.
N^1-*p*-chlorophenyl-N^5-ethylbiguanide acetate, m.p. 160—161° C.
N^1-*p*-chlorophenyl-N^5-methyl-N^5-*n*-propylbiguanide, m.p. 125—126° C.
N^1-*p*-bromophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 246—247° C.
N^1-*p*-bromophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 221—222° C.
N^1-*p*-bromophenyl-N^5-ethylbiguanide hydrochloride, m.p. 233—234° C.
N^1-*p*-bromophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 251° C.
N^1-*p*-bromophenyl-N^5-methyl-N^5-*n*-propylbiguanide hydrochloride, m.p. ~~238°~~ 237°C.
N^1-*p*-iodophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 239° C.
N^1-*p*-iodophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 224° C.
N^1-*p*-iodophenyl-N^5-ethylbiguanide hydrochloride, m.p. 239—240° C.
N^1-*p*-iodophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 236—237° C.
N^1-*p*-iodophenyl-N^5-methyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 238° C.
N^1-*m*-chlorophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 232° C.
N^1-*m*-chlorophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 194—195° C.
N^1-*m*-bromophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 225° C.
N^1-*m*-bromophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 194—195° C.
N^1-*m*-iodophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 246° C.
N^1-*m*-iodophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 208—209° C.
N^1-3:4-dichlorophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 237—238° C.
N^1-3:4-dichlorophenyl-N^5-ethylbiguanide hydrochloride, m.p. 216° C.
N^1-3:4-dichlorophenyl-N^5-sec-butylbiguanide hydrochloride, m.p. 250° C.
N^1-3:4-dichlorophenyl-N^5-*n*-butylbiguanide hydrochloride, m.p. 197° C.
N^1-3:4-dichlorophenyl-N^5:N^5-diethylbiguanide hydrochloride, m.p. 231° C.
N^1-3:4-dichlorophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 251—252° C.
N^1-3:4-dichlorophenyl-N^5-methyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 236° C.
N^1-3:4:5-trichlorophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 254—255° C.
N^1-3:4:5-trichlorophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 228—229° C.
N^1-3:4:5-trichlorophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 234—235° C.
N^1-3:5-dichlorophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 239—240° C.
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N^1-3:4-dibromophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 240° C.
N^1-3:4-dibromophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 217.5—219° C.
N^1-3:4-dibromophenyl-N^5-ethylbiguanide hydrochloride, m.p. 213—214° C.
N^1-3:4-dibromophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 254—255° C.
N^1-3:4-dibromophenyl-N^5-methyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 234—235° C.

N^1-4-chloro-3-bromophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 239° C.
N^1-4-chloro-3-bromophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 197—198° C.
N^1-4-chloro-3-bromophenyl-N^5-ethylbiguanide hydrochloride, m.p. 215—216° C.
N^1-4-chloro-3-bromophenyl-N^5-methyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 232—235° C.
N^1-4-chloro-3-bromophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 240—241° C.
N^1-4-bromo-3-iodophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 239° C.
N^1-4-bromo-3-iodophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 232—233° C.
N^1-4-bromo-3-iodophenyl-N^5-ethylbiguanide hydrochloride, m.p. 200—201° C.
N^1-4-bromo-3-iodophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 241—242° C.
N^1-3-chloro-4-iodophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 219° C.
N^1-3-chloro-4-iodophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 225° C.
N^1-3-chloro-4-iodophenyl-N^5-ethylbiguanide hydrochloride, m.p. 226—227° C.
N^1-3-chloro-4-iodophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 231° C.
N^1-3-chloro-4-bromophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 237° C.
N^1-3-chloro-4-bromophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 217° C.
N^1-3-chloro-4-bromophenyl-N^5-ethylbiguanide hydrochloride, m.p. 217° C.
N^1-3-chloro-4-bromophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 244° C.
N^1-3-chloro-4-bromophenyl-N^5-methyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 234° C.
N^1-4-chloro-3-iodophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 238° C.
N^1-4-chloro-3-iodophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 198—199° C.
N^1-4-chloro-3-iodophenyl-N^5-ethylbiguanide hydrochloride, m.p. 197—198° C.
N^1-4-chloro-3-iodophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 239—240° C.
N^1-4-chloro-3-iodophenyl-N^5-methyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 205—206° C.
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N^1-3:4-diiodophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 235° C.
N^1-3:4-diiodophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 226—227° C.
N^1-3:4-diiodophenyl-N^5-ethylbiguanide hydrochloride, m.p. 212—213° C.
N^1-3:4-diiodophenyl-N^5-methyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 221° C.

The process of the invention is carried out by first mixing together the reagents, conveniently suspended or dissolved in a liquid medium. The ensuing reaction may proceed at atmospheric temperature or it may be assisted by the application of heat. Suitable liquid media for the reaction are for example anisole and diethyl ether.

The substituted aminomagnesium halide is preferably made immediately prior to its reaction with the dicyandiamide. For this reason it is frequently convenient to use as the liquid medium for the process of the invention the ethereal liquid medium used in the immediately prior preparation of the substituted aminomagnesium halide.

The initial reaction product of the substituted aminomagnesium halide and the dicyandiamide is a magnesium-containing complex compound. In order to obtain the biguanide derivative which is the final product of the process of the

invention this compound is, as said, treated with acid or an acid-reacting salt. Suitable acids and salts for this purpose are the mineral acids, for example hydrochloric acid, or their salts with weak bases, for example ammonium chloride.

The resulting biguanides of the stated formula are substances of great utility in the treatment of malaria.

The invention is illustrated but not limited by the following Examples in which the parts are by weight.

EXAMPLE 1.

A solution of 13.8 parts of isopropylamine in 44 parts of diethyl ether is added gradually, at room temperature, to a solution of ethylmagnesium iodide also in ether (made from 31.2 parts of ethyl iodide, 4.8 parts of magnesium and 44 parts of ether). The mixture is then heated under reflux for 15 minutes and then 19.5 parts of *p*-chlorophenyldicyandiamide and a further 44 parts of ether are added. Heating and stirring under reflux is continued for 16 hours and the mixture is then cooled to atmospheric temperature. A mixture of 59 parts of aqueous hydrochloric acid (density 1.18) and 250 parts of ice is then added and the mixture is stirred for 30 minutes. It is then filtered and the aqueous portion of the filtrate is separated from the ethereal portion and is made just alkaline to Brilliant Yellow by addition of aqueous ammonia. It is then cooled and solid ammonium chloride is added. The precipitate is filtered off and washed with water. It consists essentially of N^1-*p*-chlorophenyl-N^5 - isopropylbiguanide and may be purified as follows:—

The precipitate is dissolved in cold 7% aqueous hydrochloric acid, the solution is filtered and the filtrate is added to an excess of dilute aqueous caustic soda. The precipitate is extracted with benzene. The benzene solution is filtered and then shaken with 7% aqueous hydrochloric acid. The acid layer is separated and neutralised with ammonia. The precipitate is filtered off, washed with water and dried. There is thus obtained N^1-*p*-chlorophenyl - N^5 - isopropylbiguanide of m.p. 243—244° C.

EXAMPLE 2.

A solution of 15 parts of methylisopropylamine in 44 parts of ether is added during 15 minutes at atmospheric temperature to an ethereal solution of ethylmagnesium iodide (made from 31.2 parts of ethyliodide, 4.8 parts of magnesium and 66 parts of ether). The mixture is stirred and heated under reflux condenser during 30 minutes. There are then added during 5 minutes 19.5 parts of *p*-chlorophenyldicyandiamide followed by 14 parts of ether and the mixture is heated under reflux condenser for 16 hours. It is then stirred for one hour at about 5° C. with a solution of 25 parts of ammonium chloride in 100 parts of water. The precipitate is filtered off, washed with aqueous ammonium chloride solution and then with water. It is then stirred with 100 parts of 7% aqueous hydrochloric acid and the solution is heated to 50—60° C. for 5 minutes. It is then filtered and the filtrate is cooled and made slightly alkaline to Brilliant Yellow by addition of aqueous ammonia. The precipitate, which consists essentially of N^1 - *p* - chlorophenyl-N^5- methyl - N^5 - isopropylbiguanide hydrochloride, is filtered off and recrystallised from water. It has m.p. 247—8° C.

EXAMPLE 3.

10.9 Parts of 3:4 - dichloroaniline are dissolved in 72 parts of ether and an ethereal solution of ethylmagnesium bromide (from 7.75 parts of ethylbromide, 2.1 parts of magnesium, 23 parts of ether) is added to the solution gradually. The mixture is then heated under reflux for 15 minutes and then 8.5 parts of isopropyldicyandiamide are added and the mixture is stirred and boiled under reflux condenser for 18 hours. It is then cooled to atmospheric temperature and 47 parts of aqueous hydrochloric acid (density 1.18), 100 parts of ice, and 150 parts of water are added to it. The aqueous layer is separated and neutralised by addition of aqueous ammonia. It is then boiled for 15 minutes and filtered. The filter cake is stirred with benzene at 50—60° C., the solution is filtered, washed with benzene and dried at 60—65° C. It consists of N^1-3:4-dichlorophenyl - N^5 - isopropylbiguanide hydrochloride which is recrystallised from water. It has m.p. 245—6° C.

Dated the 28th day of January, 1948.

E. A. BINGEN,
Solicitor for the Applicants.

COMPLETE SPECIFICATION

Manufacture of Biguanide Derivatives

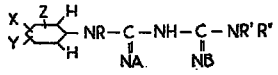
We, MURIEL RUTH CURD, a British Subject, of Tree Tops, Highfield Parkway, Bramhall, Cheshire, legal representative of FRANCIS HENRY SWINDEN CURD, deceased, a British Subject, late of Hexagon House, Blackley, Manchester, STANLEY BIRTWELL and FRANCIS LESLIE ROSE, both of Hexagon House, Blackley,

Manchester, both British Subjects, and IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a Company incorporated under the laws of Great Britain, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

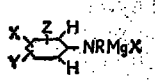
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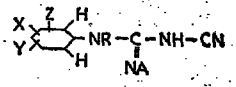
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or of the formula $R^1R^{11}NMgX$ with a substituted dicyandiamide, respectively of the formula

$$R^1R^{11}N-\underset{\underset{NB}{\|}}{C}-NH-CN$$

or of the formula



in all of which formulæ the symbols A, B, X, Y and Z, R, R^1 and R^{11} have the significance stated above, and then treat the reaction product with acid or an acid-reacting salt.

The substituted aminomagnesium halides which are used as starting materials in the process of the invention may be made by the interaction, for example, in ethereal solution or suspension, of the appropriate amine with a alkylmagnesium halide. Conveniently, the alkylmagnesium halide is chosen such that the by-product is gaseous. Thus an ethylmagnesium halide may be used which, in reaction with an amine, gives rise to the corresponding aminomagnesium halide and ethane.

Besides the substances whose manufacture by the process of this invention is described in the Examples below there may be made also, by processes differing only from those described in that the reactants and quantities thereof are appropriately changed, the following substances:—

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N^1-4-chloro-3-bromophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 240—241° C.
N^1-4-bromo-3-iodophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 239° C.
N^1-4-bromo-3-iodophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 232—233° C.

N^1-4-bromo-3-iodophenyl-N^5-ethylbiguanide hydrochloride, m.p. 200—201° C.
N^1-4-bromo-3-iodophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 241—242° C.
N^1-3-chloro-4-iodophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 219° C.
N^1-3-chloro-4-iodophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 225° C.
N^1-3-chloro-4-iodophenyl-N^5-ethylbiguanide hydrochloride, m.p. 226—227° C.
N^1-3-chloro-4-iodophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 231° C.
N^1-3-chloro-4-bromophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 237° C.
N^1-3-chloro-4-bromophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 217° C.
N^1-3-chloro-4-bromophenyl-N^5-ethylbiguanide hydrochloride, m.p. 217° C.
N^1-3-chloro-4-bromophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 244° C.
N^1-3-chloro-4-bromophenyl-N^5-methyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 234° C.
N^1-4-chloro-3-iodophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 238° C.
N^1-4-chloro-3-iodophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 198—199° C.
N^1-4-chloro-3-iodophenyl-N^5-ethylbiguanide hydrochloride, m.p. 197—198° C.
N^1-4-chloro-3-iodophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 239—240° C.
N^1-4-chloro-3-iodophenyl-N^5-methyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 205—206° C.
N^1-3:4-diiodophenyl-N^5-isopropylbiguanide hydrochloride, m.p. 237° C.
N^1-3:4-diiodophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, m.p. 235° C.
N^1-3:4-diiodophenyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 226—227° C.
N^1-3:4-diiodophenyl-N^5-ethylbiguanide hydrochloride, m.p. 212—213° C.
N^1-3:4-diiodophenyl-N^5-methyl-N^5-*n*-propylbiguanide hydrochloride, m.p. 221° C.

The process of the invention is carried out by first mixing together the reagents, conveniently suspended or dissolved in a liquid medium. The ensuing reaction may proceed at atmospheric temperature or it may be assisted by the application of heat. Suitable liquid media for the reaction are for example anisole and diethyl ether.

The substituted aminomagnesium halide is preferably made immediately prior to its reaction with the dicyandiamide. For this reason it is frequently convenient to use as the liquid medium for the process of the invention the ethereal liquid medium used in the immediately prior preparation of the substituted aminomagnesium halide.

The initial reaction product of the substituted aminomagnesium halide and the dicyandiamide is a magnesium-containing complex compound. In order to obtain the biguanide derivative which is the final product of the process of the invention this compound is, as said, treated with acid or an acid-reacting salt. Suitable acids and salts for this purpose are the mineral acids, for example hydrochloric acid, or their salts with weak bases, for example ammonium chloride.

The resulting biguanides of the stated formula are substances of great utility in the treatment of malaria.

The invention is illustrated but not limited by the following Examples in which the parts are by weight.

EXAMPLE 1.

A solution of 13.8 parts of isopropylamine in 44 parts of diethyl ether is added gradually, at room temperature, to a solution of ethylmagnesium iodide also in ether (made from 31.2 parts of ethyl iodide, 4.8 parts of magnesium and 44 parts of ether). The mixture is then heated under reflux for 15 minutes and then 19.5 parts of *p*-chlorophenyldicyandiamide and a further 44 parts of ether are added. Heating and stirring under reflux is continued for 16 hours and the mixture is then cooled to atmospheric temperature. A mixture of 59 parts of aqueous hydrochloric acid (density 1.18) and 250 parts of ice is then added and the mixture is stirred for 30 minutes. It is then filtered and the aqueous portion of the filtrate is separated from the ethereal

portion and is made just alkaline to Brilliant Yellow by addition of aqueous ammonia. It is then cooled and solid ammonium chloride is added. The precipitate is filtered off and washed with water. It consists essentially of N^1-*p*-chlorophenyl-N^5-isopropylbiguanide and may be purified as follows:—

The precipitate is dissolved in cold 7% aqueous hydrochloric acid, the solution is filtered and the filtrate is added to an excess of dilute aqueous caustic soda. The precipitate is extracted with benzene. The benzene solution is filtered and then shaken with 7% aqueous hydrochloric acid. The acid layer is separated and neutralised with ammonia. The precipitate is filtered off, washed with water and dried. There is thus obtained N^1-*p*-chlorophenyl-N^5-isopropylbiguanide hydrochloride of m.p. 243—244° C.

EXAMPLE 2.

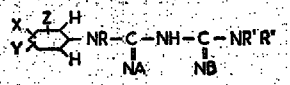
A solution of 15 parts of methylisopropylamine in 44 parts of ether is added during 15 minutes at atmospheric temperature to an ethereal solution of ethylmagnesium iodide (made from 31.2 parts of ethyliodide, 4.8 parts of magnesium and 66 parts of ether). The mixture is stirred and heated under reflux condenser during 30 minutes. There are then added during 5 minutes 19.5 parts of *p*-chlorophenyldicyandiamide followed by 14 parts of ether and the mixture is heated under reflux condenser for 16 hours. It is then cooled for one hour at about 5° C. with a solution of 25 parts of ammonium chloride in 100 parts of water. The precipitate is filtered off, washed with aqueous ammonium chloride solution and then with water. It is then stirred with 100 parts of 7% aqueous hydrochloric acid and the solution is heated to 50—60° C. for 5 minutes. It is then filtered and the filtrate is cooled and made slightly alkaline to Brilliant Yellow by addition of aqueous ammonia. The precipitate, which consists essentially of N^1-*p*-chlorophenyl-N^5-methyl-N^5-isopropylbiguanide hydrochloride, is filtered off and recrystallised from water. It has m.p. 247—8° C.

EXAMPLE 3.

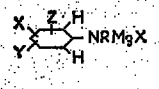
10.9 Parts of 3:4-dichloroaniline are dissolved in 72 parts of ether and an ethereal solution of ethylmagnesium bromide (from 7.75 parts of ethylbromide, 2.1 parts of magnesium, 23 parts of ether) is added to the solution gradually. The mixture is then heated under reflux for 15 minutes and then 8.5 parts of isopropyldicyandiamide are added and the mixture is stirred and boiled under reflux condenser for 18 hours. It is then cooled to atmospheric temperature and 47 parts of aqueous hydrochloric acid (density 1.18), 100 parts of ice, and 150 parts of water are added to it. The aqueous layer is separated and neutralised by addition of aqueous ammonia. It is then boiled for 15 minutes and filtered. The filter cake is stirred with benzene at 50—60° C., the solution is filtered, washed with benzene and dried at 60—65° C. It consists of N^1-3:4-dichlorophenyl-N^5-isopropylbiguanide hydrochloride which is recrystallised from water. It has m.p. 245—6° C.

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

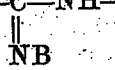
1. Process for the manufacture of biguanide derivatives of the formula



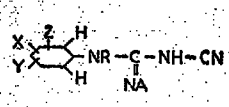
wherein R stands for hydrogen or for an alkyl radical of 1—3 carbon atoms, R^1 stands for hydrogen or for a lower alkyl radical and R^{11} stands for a lower alkyl or cycloalkyl radical such that R^1 and R^{11} together contain more than one and fewer than 8 carbon atoms, A and B stand for hydrogen or for alkyl radicals of 1—3 carbon atoms provided that both do not stand for alkyl radicals in one and the same substance, X stands for halogen, Y stands for hydrogen, halogen or for an alkyl radical or alkoxy radical of 1—3 carbon atoms, and Z stands for hydrogen or halogen, which comprises first reacting a substituted aminomagnesium halide of the formula



or of the formula $R^1R^{11}NMgX$ with a substituted dicyandiamide, respectively of the formula



or of the formula



in all of which formulæ the symbols A, B, X, Y and Z, R, R^1 and R^{11} have the significance stated above, and then treating the reaction product with acid or an acid-reacting salt.

portion and is made just alkaline to Brilliant Yellow by addition of aqueous ammonia. It is then cooled and solid ammonium chloride is added. The precipitate is filtered off and washed with water. It consists essentially of N^1-*p*-chlorophenyl-N^5 - isopropylbiguanide and may be purified as follows:—

The precipitate is dissolved in cold 7% aqueous hydrochloric acid, the solution is filtered and the filtrate is added to an excess of dilute aqueous caustic soda. The precipitate is extracted with benzene. The benzene solution is filtered and then shaken with 7% aqueous hydrochloric acid. The acid layer is separated and neutralised with ammonia. The precipitate is filtered off, washed with water and dried. There is thus obtained N^1-*p*-chlorophenyl - N^5 - isopropylbiguanide hydrochloride of m.p. 243—244° C.

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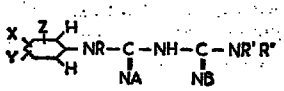
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EXAMPLE 3.

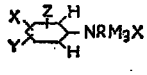
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Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. Process for the manufacture of biguanide derivatives of the formula



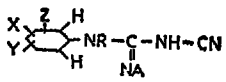
wherein R stands for hydrogen or for an alkyl radical of 1—3 carbon atoms, R^1 stands for hydrogen or for a lower alkyl radical and R^{11} stands for a lower alkyl or cycloalkyl radical such that R^1 and R^{11} together contain more than one and fewer than 8 carbon atoms, A and B stand for hydrogen or for alkyl radicals of 1—3 carbon atoms provided that both do not stand for alkyl radicals in one and the same substance, X stands for halogen, Y stands for hydrogen, halogen or for an alkyl radical or alkoxy radical of 1—3 carbon atoms, and Z stands for hydrogen or halogen, which comprises first reacting a substituted aminomagnesium halide of the formula



or of the formula $R^1R^{11}NMgX$ with a substituted dicyandiamide, respectively of the formula



or of the formula



in all of which formulæ the symbols A, B, X, Y and Z, R, R^1 and R^{11} have the significance stated above, and then treating the reaction product with acid or an acid-reacting salt.

2. Process for the manufacture of biguanide derivatives as hereinbefore particularly described and ascertained especially with reference to the foregoing Examples.

3. Biguanide derivatives whenever manufactured by the process of either of the preceding claims or by any process which is the obvious chemical equivalent thereof.

Dated the 5th day of January, 1949.
E. A. BINGEN,
Solicitor for the Applicants.

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