[Second Edition.]

PATENT SPECIFICATION

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PROVISIONAL SPECIFICATION.

Biguanide Derivatives.

We, FRANCIS HENRY SWINDEN CURD 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 to be as follows:—

This invention relates to the manufacture of new biguanide derivatives and more particularly to the manufacture of biguanides bearing either two, three or four substituents upon the terminal nitrogen atoms.

According to the invention we make new compounds of the formula—

$$A—NX—C(NH)—NH—C(NH)—NRR^1$$
$$\alpha \qquad\qquad\qquad\qquad \omega$$

wherein A represents an aryl group, X represents hydrogen or an alkyl group. R represents a hydrocarbon radical, R^1 represents hydrogen or a hydrocarbon radical and also R and R^1 may be joined together to form an alkylene chain, and further any or all of the groups A, R and R^1 may bear one or more simple neutral or basic substituents, by a process comprising bringing into reaction an aryldicyandiamide of the formula

$$A—NX—C(NH)—NH—CN$$

with an amine of the formula

$$NHRR^1,$$

A, X, R and R^1 in these formulæ having the same meanings as before.

The reaction is conveniently brought about by heating the reagents together, if desired in presence of a solvent or diluent which for convenience may be an excess of the amine when this is liquid under the reaction conditions employed.

The amine may be used either in the form of the free base, or in the form of a salt. Further the reaction may be carried out in the presence of a metal salt such as copper sulphate, which may be used as such or in the form of a pre-formed addition compound with the amine. We find that in many cases, the presence of the metal salt increases the speed of the reaction and improves the yield of the biguanide. Also the biguanide can frequently be conveniently isolated directly from the reaction mixture in the form of a sparingly soluble complex, with the metal salt.

The aryl dicyandiamides used as starting materials, wherein X in the above general formula represents hydrogen, are a known class of compounds. They have been described by Walther and Grieshammer, Journal für praktische Chemie (2), vol. 92, pp. 209—255. They are more conveniently obtained by the method described in our copending application No. 8888/44 (Serial No. 576,401).

The following Examples illustrate, but do not limit, the invention. The parts are by weight.

EXAMPLE 1.

19.5 Parts of *p*-chlorophenyl dicyandiamide, 20 parts of diethylamine, 140 parts of ethyl alcohol, and a solution of 12.5 parts of copper sulphate pentahydrate in 60 parts of water, are mixed and the mixture is stirred and heated under reflux for 2 hours. The resultant suspension is cooled, diluted with 300 parts of water and filtered. The light-brown solid residue which is mainly the copper complex of Nα-*p*-chlorophenyl-Nω-diethylbiguanide, is dissolved in a mixture of 100 parts of 36% aqueous hydrochloric acid and 600 parts of water. A solution of 40 parts of sodium sulphide nonahydrate in 100 parts of water is slowly added. Copper sulphide is precipitated and is filtered off. The clear filtrate is made strongly alkaline with caustic soda. The precipitate of the crude biguanide so formed is collected, dried and crystallised from petroleum ether. It forms colourless needles which melt at 133°—134° C. uncorr.

In a similar manner, there may be obtained the following biguanides having the melting points indicated.

Nα - *p* - chlorophenyl - Nω - dimethylbiguanide; colourless plates from toluene, m.p. 169° C. uncorr.

Nα-*p*-chlorophenyl - Nω - methyl - Nω

isopropylbiguanide; colourless needles from toluene, m.p. 174°—175° C. uncorr.

Nα - *p* - chlorophenyl - Nω - dibutylbiguanide; the sulphate crystallises from aqueous ethyl alcohol in colourless prisms, m.p. 180°—182° C. uncorr.

Nα-*p*-chlorophenyl-Nω-methyl - Nω - β-methoxyethylbiguanide; colourless needles from methyl alcohol, m.p. 91°—93° C.

Nα-*p*-chlorophenyl - Nω - ethyl - Nω - β-diethylaminoethyl biguanide; colourless needles from petroleum ether, m.p. 78.5° —79.5° C.

Nα - *p* - chlorophenyl - Nω : Nω - tetramethylene biguanide; colourless plates from toluene, m.p. 206° C. uncorr.

Nα - phenyl - Nω - diethylbiguanide: colourless prisms from petroleum ether, m.p. 100°—101° C.

Nα - *p* - tolyl - Nω - dimethylbiguanide; colourless plates from toluene, m.p. 149° —149.5° C. uncorr.

Nα-*p*-anisyl - Nω - dimethylbiguanide; colourless prisms from toluene, m.p. 142° —143° C. uncorr.

Nα - *p* - anisyl - Nω - diethylbiguanide; colourless prisms from petroleum ether, m.p. 90°—91° C.

Nα - *p* - nitrophenyl - Nω - dimethylbiguanide; yellow prisms from aqueous dioxan, m.p. 167° C. uncorr.

Nα-*p*-nitrophenyl - Nω - diethylbiguanide; yellow prisms from aqueous β-ethoxyethanol, m.p. 121°—122° C.

Nα-*p*-chlorophenyl - Nα - methyl - Nω diethylbiguanide; the hydrochloride crystalises from water in colourless prisms, m.p. 182°—184° C.

The Nα - *p* - chlorophenyl - Nα - methyldicyandiamide used as starting material in making this last-named biguanide is itself made by interaction of *p*-chlorophenyldicyandiamide with dimethyl sulphate in a methyl alcoholic solution of caustic soda. Recrystallised from toluene it forms colourless needles of m.p. 164° C. uncorr.

EXAMPLE 2.

19.5 Parts of N-*p*-chlorophenyldicyandiamide, 12.8 parts of piperidene, 66 parts of β-ethoxyethanol, and a solution of 12.5 parts of copper sulphate pentahydrate in 60 parts of water, are mixed and the mixture is stirred and heated under reflux for 4 hours. The reaction mixture is worked up in the manner described in Example 1. There is thus obtained Nα-*p*-chlorophenyl-Nω : Nω-pentamethylene biguanide which crystallises from xylene in colourless needles of m.p. 191°—192° C. uncorr.

In a similar manner, there may be obtained the following biguanides having the melting points indicated.

Nα - *p* - chlorophenyl - Nω - cyclohexyl biguanide, m.p. 172°—173° C. uncorr.

Nα-*p*-chlorophenyl-Nω-β - diethylaminoethylbiguanide, m.p. 126°—128° C.

Nα - *p* - chlorophenyl - Nω - γ - diethylaminopropylbiguanide, colourless needles from petroleum ether, m.p. 81°—83° C.

Nα-*p*-anisyl - Nω : Nω - pentamethylene biguanide, colourless crystals from toluene, m.p. 142°—143° C.

EXAMPLE 3.

A mixture of 16 parts of phenyldicyandiamide, 20.8 parts of aniline hydrochloride, 80 parts of dioxan and 16 parts of water is heated under reflux for 2 hours. The mixture is cooled and the crystals which separate are filtered off and recrystallised from hot water. There is thus obtained Nα : Nω-diphenylbiguanide hydrochloride, colourless needles of m.p. 232° C. uncorr. The free base, recrystallised from methanol, forms colourless needles of m.p. 145°—146° C.

In a similar manner there may be obtained the following biguanides having the melting points indicated.

Nα - *p* - chlorophenyl - Nω - phenylbiguanide; colourless plates from methyl alcohol, m.p. 149° C. uncorr.

Nα-*p*-chlorophenyl - Nω - β - naphthylbiguanide; colourless crystals from methanol, m.p. 142°—143° C. uncorr.

Nα - *p* - chlorophenyl - Nω - *p* - anisylbiguanide; colourless needles from ethanol, m.p. 155° C. uncorr.

Nα : Nω-di-*p*-tolylbiguanide; colourless plates from ethanol, m.p. 187° C. uncorr.

Nα : Nω - di - *p* - anisylbiguanide hydrochloride; colourless prisms from water, m.p. 222° C. uncorr.

Nα-*p*-anisyl - Nω : Nω - pentamethylene biguanide; colourless crystals from toluene, m.p. 142°—143° C. uncorr.

Dated the 10th day of May, 1944.

E. A. BINGEN,
Solicitor for the Applicants.

COMPLETE SPECIFICATION

Biguanide Derivatives.

We, FRANCIS HENRY SWINDEN CURD 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 :—

This invention relates to the manufacture of new biguanide derivatives and more particularly to the manufacture of biguanides bearing either two, three or four substituents upon the terminal nitrogen atoms. The said new compounds are useful as chemotherapeutic agents or as intermediates for chemotherapeutic agents; many of them are valuable antimalarial agents.

According to the invention we make new compounds of the formula—

$$A\text{—}NX\text{—}C(NH)\text{—}NH\text{—}C(NH)\text{—}NRR^1$$
$$\alpha \qquad\qquad \omega$$

wherein A represents an aryl group, X represents hydrogen or an alkyl group, R represents a hydrocarbon radical, R^1 represents hydrogen or a hydrocarbon radical and also R and R^1 may be joined together to form a divalent aliphatic hydrocarbon chain, and further any or all of the groups A, R and R^1 may bear one or more non-acidic substituents, by a process comprising bringing into reaction an aryl-dicyandiamide of the formula

$$A\text{—}NX\text{—}C(NH)\text{—}NH\text{—}CN$$

with an amine of the formula

$$NHRR^1,$$

the symbols A, X, R and R^1 in these formulæ having the same meanings as before.

The reaction is conveniently brought about by heating the reagents together, if desired in presence of a solvent or diluent which for convenience may be an excess of the amine when this is liquid under the reaction conditions employed.

The amine may be used either in the form of the free base, or in the form of a salt. Further where R and R^1 are aliphatic the reaction may be advantageously carried out in the presence of a metal such as zinc or copper which may be used as such or in the form of an oxide, hydroxide or salt or a pre-formed addition compound with the amine. There may be used, for instance, copper powder, hydrated copper oxide, copper sulphate or zinc chloride. We find that in such cases, the presence of the metal increases the speed of the reaction and improves the yield of the biguanide. Also the biguanide can frequently be conveniently isolated directly from the reaction mixture in the form of a sparingly soluble complex with the metal salt.

The aryl dicyandiamides used as starting materials, wherein X in the above general formula represents hydrogen, are a known class of compounds. They have been described by Walther and Grieshammer, Journal für praktische Chemie (2), vol. 92, pp. 209—255. They are more conveniently obtained by the method described in our copending application No. 8888/44 (Serial No. 576,401).

The di-, tri- or tetra-substituted biguanides made according to this invention are strong bases; they form stable salts with organic and inorganic acids, which in many cases are freely soluble in water. The salts can be made by dissolving the biguanides in aqueous solutions of the acid and then evaporating off the water, but they are more conveniently obtained in a dry form by mixing the components together in an organic solvent such as acetone, or an alcohol in which the salts are sparingly soluble. In this manner there may be readily formed, for example, the salts with acetic acid, lactic acid, methane sulphonic acid, methylene-disalicylic acid, methylene - bis - 2 : 3-hydroxynaphthoic acid, and hydrochloric acid.

The following Examples illustrate, but do not limit, the invention. The parts are by weight.

EXAMPLE 1.

19.5 Parts of *p*-chlorophenyl dicyandiamide, 20 parts of diethylamine, 140 parts of ethyl alcohol, and a solution of 12.5 parts of copper sulphate pentahydrate in 60 parts of water, are mixed and the mixture is stirred and heated under reflux for 2 hours. The resultant suspension is cooled, diluted with 300 parts of water and filtered. The light-brown solid residue which is mainly the copper complex of N*α*-*p*-chlorophenyl-N*ω*-diethylbiguanide, is dissolved in a mixture of 100 parts of 36% aqueous hydrochloric acid and 600 parts of water. A solution of 40 parts of sodium sulphide nonahydrate in 100 parts of water is slowly added. Copper sulphide is precipitated and is filtered off. The clear filtrate is made strongly alkaline with caustic soda. The precipitate of the crude biguanide so formed is collected, dried and crystallised from petroleum ether. It forms colourless needles which melt at 133°—134° C. uncorr.

In a similar manner, there may be obtained the following biguanides having the melting points indicated.

EXAMPLE 2.

N*α* - *p* - chlorophenyl - N*ω* - dimethyl-

biguanide; colourless plates from toluene, m.p. 169° C. uncorr.

EXAMPLE 3.

Nα-*p*-chlorophenyl - Nω - methyl - Nω isopropylbiguanide; colourless needles from toluene, m.p. 174°—175° C. uncorr.

EXAMPLE 4.

Nα - *p* - chlorophenyl - Nω - dibutylbiguanide; the sulphate crystallises from aqueous ethyl alcohol in colourless prisms, m.p. 180°—182° C. uncorr.

EXAMPLE 5.

Nα-*p*-chlorophenyl-Nω-methyl - Nω - β-methoxyethylbiguanide; colourless needles from methyl alcohol, m.p. 91°—93° C.

EXAMPLE 6.

Nα-*p*-chlorophenyl - Nω - ethyl - Nω - β-diethylaminoethyl biguanide; colourless needles from petroleum ether, m.p. 78.5° —79.5° C.

EXAMPLE 7.

Nα - *p* - chlorophenyl - Nω : Nω - tetramethylene biguanide; colourless plates from toluene, m.p. 206° C. uncorr.

EXAMPLE 8.

Nα - phenyl - Nω - diethylbiguanide; colourless prisms from petroleum ether, m.p. 100°—101° C.

EXAMPLE 9.

Nα - *p* - tolyl - Nω - dimethylbiguanide; colourless plates from toluene, m.p. 149° —149.5° C. uncorr.

EXAMPLE 10.

Nα-*p*-anisyl - Nω - dimethylbiguanide; colourless prisms from toluene, m.p. 142° —143° C. uncorr.

EXAMPLE 11.

Nα - *p* - anisyl - Nω - diethylbiguanide; colourless prisms from petroleum ether, m.p. 90°—91° C.

EXAMPLE 12.

Nα - *p* - nitrophenyl - Nω - dimethylbiguanide; yellow prisms from aqueous dioxan, m.p. 167° C. uncorr.

EXAMPLE 13.

Nα-*p*-nitrophenyl - Nω - diethylbiguanide; yellow prisms from aqueous β-ethoxyethanol, m.p. 121°—122° C.

EXAMPLE 14.

Nα-3 : 4 - dimethylphenyl - Nω - diethylbiguanide; colourless plates from petroleum ether, m.p. 70°—71° C.

EXAMPLE 15.

Nα-*p*-chlorophenyl-Nω - allylbiguanide; colourless prisms from toluene, m.p. 99° —101° C.

EXAMPLE 16.

Nα-*p*-chlorophenyl-Nω - ethylbiguanide: colourless prisms from toluene, m.p. 99° —101° C.

EXAMPLE 17.

Nα - *p* - chlorophenyl - Nω - *n* - amylbiguanide; colourless needles from water, m.p. 229° C.

EXAMPLE 18.

Nα - *p* - chlorophenyl - Nω - *n* - propylbiguanide; colourless crystals from ethanol, m.p. 58.5°—60° C.

EXAMPLE 19.

Nα - *p* - chlorophenyl - Nω - isopropylbiguanide; colourless crystals from aqueous ethanol, m.p. 130°—131° C.; the acetate forms colourless crystals from acetone, m.p. 188°—189° C.

EXAMPLE 20.

Nα - *p* - chlorophenyl - Nω - *n* - butylbiguanide acetate; colourless prisms from acetone, m.p. 158° C.

EXAMPLE 21.

Nα - *p* - chlorophenyl - Nω - isobutylbiguanide hydrochloride; colourless plates from acetone, m.p. 232° C.

EXAMPLE 22.

Nα - *p* - chlorophenyl - Nω - tert-butylbiguanide hydrochloride; colourless crystals from acetone, m.p. 232°—234° C.

EXAMPLE 23.

Nα-*p*-chlorophenyl-Nω - ethyl - Nω - β-diethylaminoethylbiguanide; colourless crystals from petroleum ether, m.p. 78.5° C.—79.5° C.

EXAMPLE 24.

Nα-*p*-chlorophenyl-Nω-methyl - Nω - *n*-propylbiguanide; colourless plates from toluene, m.p. 125—126° C.

EXAMPLE 25.

Nα-*p*-acetylaminophenyl - Nω - methyl-Nω-isopropylbiguanide acetate; colourless prisms, m.p. 206°—208° C.

EXAMPLE 26.

Nα - *p* - chlorophenyl - Nω - methylbiguanide; colourless needles from toluene, m.p. 85°—86° C.

EXAMPLE 27.

Nα-*p*-chlorophenyl-Nω - (1 - methyl - 4-diethylamino)-butylbiguanide carbonate; formed as colourless crystalline solid by passing carbon dioxide into a solution of the free biguanide base in wet acetone; m.p. 78°—80° C. (decomp.).

EXAMPLE 28.

Nα - *p* - chlorophenyl - Nα - methyl - Nω - diethylbiguanide; the hydrochloride crystallises from water in colourless prisms, m.p. 182°—184° C.

The Nα - *p* - chlorophenyl - Nα - methyldicyandiamide used as starting material in making this last-named biguanide is itself made by interaction of *p*-chlorophenyldicyandiamide with dimethyl sulphate in a methyl alcoholic solution of caustic soda. Recrystallised from toluene it forms colourless needles, of m.p. 164° C. uncorr.

EXAMPLE 29.

19.5 Parts of *p*-chlorophenyldicyandiamide, 12.8 parts of piperidene, 66 parts of β-ethoxyethanol, and a solution of 12.5 parts of copper sulphate pentahydrate in

60 parts of water, are mixed and the mixture is stirred and heated under reflux for 4 hours. The reaction mixture is worked up in the manner described in Example 1. There is thus obtained Nα-*p*-chlorophenyl-Nω : Nω-pentamethylene biguanide which crystallises from xylene in colourless needles of m.p. 191°—192° C. uncorr.

In a similar manner, there may be obtained the following biguanides having the melting points indicated.

EXAMPLE 30.

Nα - *p* - chlorophenyl - Nω - cyclohexyl biguanide, m.p. 172°—173° C. uncorr.

EXAMPLE 31.

Nα-*p*-chlorophenyl-Nω-β - diethylaminoethylbiguanide, m.p. 126°—128° C.

EXAMPLE 32.

Nα - *p* - chlorophenyl - Nω - γ - diethylaminopropylbiguanide; colourless needles from petroleum ether, m.p. 81°—83° C.

EXAMPLE 33.

Nα-*p*-anisyl - Nω : Nω - pentamethylene biguanide, colourless crystals from toluene, m.p. 142°—143° C.

EXAMPLE 34.

A mixture of 16 parts of phenyldicyandiamide, 20.8 parts of aniline hydrochloride, 80 parts of dioxan and 16 parts of water is heated under reflux for 2 hours. The mixture is cooled and the crystals which separate are filtered off and recrystallised from hot water. There is thus obtained Nα - Nω-diphenylbiguanide hydrochloride, colourless needles of m.p. 232° C. uncorr. The free base, recrystallised from methanol, forms colourless needles of m.p. 145°—146° C.

In a similar manner there may be obtained the following biguanides having the melting points indicated.

EXAMPLE 35.

Nα - *p* - chlorophenyl - Nω - phenylbiguanide; colourless plates from methyl alcohol, m.p. 149° C. uncorr.

EXAMPLE 36.

Nα-*p*-chlorophenyl - Nω - β - naphthylbiguanide; colourless crystals from methanol, m.p. 142°—143° C. uncorr.

EXAMPLE 37.

Nα - *p* - chlorophenyl - Nω - *p* - anisylbiguanide; colourless needles from ethanol, m.p. 155° C. uncorr.

EXAMPLE 38.

Nα : Nω-di-*p*-tolylbiguanide; colourless plates from ethanol, m.p. 187° C. uncorr.

EXAMPLE 39.

Nα : Nω - di - *p* - anisylbiguanide hydrochloride; colourless prisms from water, m.p. 222° C. uncorr.

EXAMPLE 40.

Nα-*p*-anisyl - Nω : Nω - pentamethylene biguanide; colourless crystals from toluene, m.p. 142°—143° C. uncorr.

EXAMPLE 41.

19.5 Parts of *p*-chlorophenyldicyandiamide, 15 parts of piperidene, 200 parts of ethyl alcohol and 19 parts of copper bronze powder are mixed and the mixture is stirred and heated under reflux for 16 hours. The resultant suspension is cooled, diluted with 1250 parts of a 1.6% aqueous solution of hydrochloric acid, and filtered to remove the copper bronze. A solution of 17.5 parts of sodium sulphide nonahydrate in water is slowly added. Copper sulphide is precipitated and is filtered off. The clear filtrate is then made strongly alkaline with sodium hydroxide. Crude Nα - *p* - chlorophenyl - Nω : Nω - pentamethylene biguanide is precipitated and is filtered off, dried and crystallised from xylene, whereby colourless needles are formed, of m.p. 191°—192° C.

The product is identical with that made as described in Example 29.

EXAMPLE 42.

12.5 Parts of copper sulphate pentahydrate are dissolved in water and an excess of dilute aqueous caustic soda solution is added. The precipitate of hydrated copper oxide so formed is filtered off, washed with water and mixed with 19.5 parts of *p*-chlorophenyl dicyandiamide, 14.4 parts of isopropylamine hydrochloride, 250 parts of ethyl alcohol and 25 parts of water, and the mixture is stirred and heated under reflux for 24 hours. The ethyl alcohol is then distilled off, and the residue is dissolved in a mixture of 500 parts of water and 65 parts of 36% aqueous hydrochloric acid. A solution of 17.5 parts of sodium sulphide nonahydrate in water is added. Copper sulphide is precipitated, and is filtered off. The clear filtrate is made strongly alkaline with caustic soda and the semi-solid precipitate so obtained is washed with water by decantation, and then dissolved in acetone. The acetone solution is dried over anhydrous potassium bicarbonate, and is made just acid by the addition of glacial acetic acid. The colourless, crystalline precipitate of Nα-*p*-chlorophenyl-Nω-isopropylbiguanide acetate is filtered off, washed with acetone and dried. It melts at 188° —189° C.

EXAMPLE 43.

19.5 Parts of *p*-chlorophenyldicyandiamide, 140 parts of ethyl alcohol, 8.9 parts of isopropylamine and a solution of 6.8 parts of zinc chloride in 25 parts of water are mixed and the mixture is stirred and heated under reflux for 20 hours. The ethyl alcohol is then distilled off and the residue is stirred with 250 parts of an 8% aqueous solution of caustic soda. The solid which remains undissolved is crude Nα - *p* - chlorophenyl - Nω - isopropyl

biguanide. It is dissolved in acetone and converted to the monoacetate in the manner described in the preceding Example. It then forms a colourless crystalline solid, m.p. 188°—189° C.

EXAMPLE 44.

19.5 Parts of *p*-chlorophenyldicyandiamide and 25 parts of piperidene are refluxed together for 16 hours. The resultant solution is diluted with 500 parts of water and the suspension so formed is made acid with hydrochloric acid and filtered to remove unchanged *p*-chlorophenyldicyandiamide. The clear filtrate is made strongly alkaline with caustic soda and the precipitate which is formed is filtered off and recrystallised from petroleum ether. N*α*-*p*-chlorophenyl-Nω: Nω-pentamethylene biguanide is thus obtained in the form of colourless needles, m.p. 192°—193° 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 new substituted biguanides of the formula—

A—NX—C(NH)—NH—C(NH)—NRR^1

wherein A represents an aryl group, X represents hydrogen or an alkyl group, R represents a hydrocarbon radical and R^1 represents hydrogen or a hydrocarbon radical and also R and R^1 may be joined together to form a divalent aliphatic hydrocarbon chain, and further any or all of the groups A, R and R^1 may bear one or more non-acidic substituents, which comprises the interaction of an aryldicyandiamide of the formula

A—NX—C(NH)—NH—CN

with an amine

NHRR^1,

the symbols A, X, R and R^1 in these formulæ having the same meanings as before.

2. Process for the manufacture of new substituted biguanides substantially as described with reference to each of the foregoing Examples.

3. Substituted biguanides whenever made by the process of either of the preceding claims or by any process which is the obvious chemical equivalent thereof.

Dated the 8th day of May, 1945.

E. A. BINGEN,
Solicitor for the Applicants.

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biguanide. It is dissolved in acetone and converted to the monoacetate in the manner described in the preceding Example. It then forms a colourless crystalline solid, m.p. 188°—189° C.

EXAMPLE 44.

19.5 Parts of *p*-chlorophenyldicyandiamide and 25 parts of piperidene are refluxed together for 16 hours. The resultant solution is diluted with 500 parts of water and the suspension so formed is made acid with hydrochloric acid and filtered to remove unchanged *p*-chlorophenyldicyandiamide. The clear filtrate is made strongly alkaline with caustic soda and the precipitate which is formed is filtered off and recrystallised from petroleum ether. Nα-*p*-chlorophenyl-Nω: Nω-pentamethylene biguanide is thus obtained in the form of colourless needles, m.p. 192°—193° 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 new substituted biguanides of the formula—

A—NX—C(NH)—NH—C(NH)—NRR^1

wherein A represents an aryl group, X represents hydrogen or an alkyl group, R represents a hydrocarbon radical and R^1 represents hydrogen or a hydrocarbon radical and also R and R^1 may be joined together to form a divalent aliphatic hydrocarbon chain, and further any or all of the groups A, R and R^1 may bear one or more non-acidic substituents, which comprises the interaction of an aryldicyandiamide of the formula

A—NX—C(NH)—NH—CN

with an amine

NHRR^1,

the symbols A, X, R and R^1 in these formulæ having the same meanings as before.

2. Process for the manufacture of new substituted biguanides substantially as described with reference to each of the foregoing Examples.

3. Substituted biguanides whenever made by the process of either of the preceding claims or by any process which is the obvious chemical equivalent thereof.

Dated the 8th day of May, 1945.

E. A. BINGEN,
Solicitor for the Applicants.

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[Wt. 8268A.—4/1947.]

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