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COMPLETE SPECIFICATION

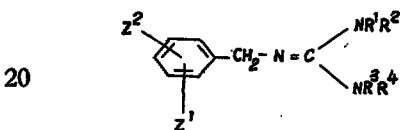
Benzyl-Guanidines, their preparation and Pharmaceutical Compositions containing them

We, THE WELLCOME FOUNDATION LIMITED, a company incorporated in England of 183—193 Euston Road, London, N.W.1, do hereby declare the invention for which we

5 pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

10 The present invention relates to chemical compounds, to the methods for preparing them and to pharmaceutical compositions containing them.

15 It has been found that benzylguanidines of formula (I) and the acid addition salts thereof selectively depress sympathetic nerve function and have little or no effect on the parasympathetic or central nerve functions. They are, therefore, useful in the treatment of hyper-



(I)

In formula (I):

25 Z¹ is a hydrogen atom or a substituent halogen atom or alkyl or nitro group in the 2 or 3 position, Z² is a hydrogen atom or a substituent halogen atom or alkyl group in the 4, 5 or 6 position, and R¹, R², R³ and R⁴ are the same or different and each is a hydrogen atom or a substituent alkyl group, provided that when Z¹ is a hydrogen atom at least two

30 of Z², R¹, R², R³ and R⁴ are not hydrogen but are substituents as defined. In the above definition each of the "alkyl" substituents contains from one to four carbon atoms.

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The activity of the benzylguanidines of formula (I) and the acid addition salts thereof resides in the base. For the salts, the acid used is of no consequence, though preferably it is pharmacologically and pharmaceutically acceptable; for example, it may be hydrochloric, hydrobromic, sulphuric, lactic, citric, tartaric, succinic, oxalic, *p*-toluenesulphonic or maleic acid.

The preferred benzylguanidines of formula (I) and the acid addition salts thereof are those in which R¹ is a hydrogen atom, R² and R³ are the same or different and each is a hydrogen atom or a methyl group, and R⁴ is a hydrogen atom or a methyl or ethyl group. The particularly preferred benzylguanidines of formula (I) and the acid addition salts thereof are *N*-benzyl-*N*¹, *N*¹¹-dimethylguanidine, *N*-2-bromo- and *N*-2,4-dichloro-benzylguanidine, *N*-2-chlorobenzyl-*N*¹-methylguanidine, *N*-2-bromo-, *N*-2-chloro-, *N*-2-methyl- and *N*-3-methyl-benzyl-*N*¹, *N*¹¹-dimethylguanidine, and *N*-2-methylbenzyl-*N*¹-methyl-*N*¹¹-ethylguanidine.

The present invention in one aspect, therefore, provides the benzylguanidines of formula (I) and the acid addition salts thereof.

The benzylguanidines of formula (I) and the acid addition salts thereof may be prepared by adaptation of any of the methods described in the literature for preparing derivatives of guanidine. For example, they are prepared by the reaction of a guanidine



or a salt thereof with a compound R¹⁰X, wherein R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are each as appropriate, and not as respective, a benzyl,

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R^1 , R^2 , R^3 and R^4 group and a hydrogen atom, and X is a reactive proton accepting atom or group such as a halogen atom or tosylate group. As a further example, they are also prepared by the reaction of ammonia or an ammonia derivative or a salt thereof with an S-substituted isothioureia or a salt thereof, or with a cyanamide; it will be understood by those skilled in the art that the last method with cyanamide is limited to the preparation of those benzylguanidines of formula (I) wherein at least R^1 and R^2 are hydrogen atoms. The ammonia derivative may be a primary or secondary amine, and the salt of ammonia may be ammonium sulphate, thiocyanate or benzenesulphonate.

The acid addition salts of the benzylguanidines of formula (I) produced by the above described reactions may be converted by double decomposition either during or after the reactions into other salts. For example, the hydrochlorides may be prepared from the hydriodides by reaction with silver chloride or by warming with methanolic hydrogen chloride.

The present invention in another aspect, therefore, provides the above described methods for the preparation of the benzylguanidines of formula (I) and the acid addition salts thereof.

The benzylguanidines of formula (I) and the acid addition salts thereof may be presented with an acceptable carrier therefor in pharmaceutical compositions, which are made by any method which comprises the admixture of the components. For oral administration, fine powders or granules of the guanidine or salt thereof may contain diluents and dispersing and surface active agents, and may be presented in a draft in water or in a syrup; in capsules or cachets in the dry state or in a non-aqueous suspension, when a suspending agent may be included; in tablets when binders and lubricants may be included; or in a suspension in water or a syrup or an oil, or in a water/oil emulsion, when flavouring, preserving, suspending, thickening and emulsifying agents may be included; the granules or the tablets may be coated. For parenteral administration, the guanidine or salt thereof may be presented in aqueous or non-aqueous injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the compound isotonic with the blood; or in aqueous suspensions when suspending agents and thickening agents may be included; extemporaneous injection solutions may be made from sterile pills, granules or tablets which may contain diluents, dispersing and surface active agents, binders and lubricants. The guanidine or salt thereof may also be presented in suppositories or pessaries by incorporation in a suppository base.

The dose range of the benzylguanidines of formula (I) and the acid addition salts thereof

suitable for administration depends on a number of variable factors such as the activity and toxicity of the particular guanidine or salt thereof, the mode and frequency of administration, and the method of making the composition. The dose range is, however, generally from 5 mg. to 500 mg. For continuous medication, dosing two or three times a day is usually desirable.

The present invention in yet further aspects, therefore, provides pharmaceutical compositions containing a benzylguanidine of formula (I) or an acid addition salt thereof and an acceptable carrier therefor, and the method of making such compositions by the admixture of the components.

The invention will now be described with reference to the following examples, in which all temperatures are given in degrees Centigrade.

EXAMPLE 1.

a) 2-Bromobenzylamine (12.5 g.), S-methylisothiuronium sulphate (10.0 g.) and water (20 ml.) were placed in a 100 ml. Erlenmeyer flask. The mixture was heated for $1\frac{1}{2}$ hours on a steam bath in a hood, during which methyl-mercaptan escaped (as evidenced by a foul odour). The reaction mixture was then cooled and diluted with alcohol (100 ml.). A colourless solid separated, was collected and washed with alcohol. This solid melted at $230-232^\circ$; it was recrystallised from water and then melted at $247-248^\circ$. It had the correct composition for 2-bromobenzylguanidine sulphate.

b) A mixture of 2-bromobenzylamine (14.0 g.), S-methylthiuronium sulphate (10.0 g.) and water (30 ml.) was heated on a steam-bath for about $\frac{1}{2}$ hour, during which time methylmercaptan was evolved. A white solid, consisting of 2-bromobenzylguanidine sulphate, separated; it was collected, washed with alcohol and ether, and recrystallised from water, with a melting point $244-246^\circ$.

EXAMPLE 2.

N-Ethyl-S-methylisothioureia hydriodide, melting point $83-85^\circ$ (5.29 g.), 2-chlorobenzylamine (3.2 g.) and water (3 ml.) were heated at 100° for 2 hours under reflux conditions, methylmercaptan being evolved. The mixture was evaporated to dryness *in vacuo*, and the residual oil basified with excess of strong hydroxide solution. The solid base, which separated, was extracted with ether and the extracts evaporated. The residue was dissolved in ethanol and a slight excess of succinic acid was added. Addition of ether gave N-2-chlorobenzyl-N-ethylguanidine hydrogen succinate, which was crystallised once from water and once from ethanol to give crystals, melting point $152-153^\circ$.

EXAMPLE 3.

A solution of 2,4-dichlorobenzylamine (4.2

- g) in ethanol (10 ml.) and a solution of *N,S*-dimethylisothiurea sulphate (5.5 g.) in water (10 ml) were mixed and heated at 100° for 3 hours. The product was evaporated to dryness, and the residual gum converted to base by addition of sodium hydroxide solution. It was extracted with ether, and the oily base, after removal of the ether, dissolved in a slight excess of hydrochloric acid. The hydrochloride solution was evaporated to dryness and the residue crystallised from ethanol-ether to give *N* - 2,4 - dichlorobenzyl - *N*¹ - methylguanidine hydrochloride, melting point 177—184°.

EXAMPLES 4 TO 15

Example	Z ¹	Z ²	R ¹	R ²	R ³	R ⁴	Salt	Solvent of Crystallisation	M.p.
4	H	H	CH ₃	H	CH ₃	H	Hydriodide	Ethanol/ether	191—196°
5	2-Cl	H	H	H	H	H	Sulphate	Hot water	237—240°
6	2-NO ₂	H	H	H	H	H	Sulphate	Ethanol/water	225—228°
7	2-Cl	4-Cl	H	H	H	H	Sulphate	Ethanol/water	219—220°
8	2-Br	H	CH ₃	H	H	H	Hydriodide	Methanol/water	138—141°
9	2-Cl	H	CH ₃	H	H	H	Hydriodide	Ether/propanol	112—115°
10	2-CH ₃	H	CH ₃	H	H	H	Hydriodide	Ethanol/ether	157—160°
11	2-Br	H	CH ₃	H	CH ₃	H	Hydriodide	Ethanol/ether	178—181°
12	3-Cl	H	CH ₃	H	CH ₃	H	Hydriodide	Methanol	216—218°
13	3-NO ₂	H	CH ₃	H	CH ₃	H	Hydriodide	Methanol/ether	227°
14	3-CH ₃	H	CH ₃	H	CH ₃	H	Hydriodide	Methanol/ethanol	233—234°
15	H	4-Cl	CH ₃	H	CH ₃	H	Hydriodide	Ethanol/ether	186—190°

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- EXAMPLE 16.**
To a solution of 2-chlorobenzylamine (23 g.) in ether (100 ml.) was added a solution of methylisothiocyanate (11.5 g.) in ether (50 ml.) with gentle shaking. Some heat developed, and after 5 minutes *N* - 2 - chlorobenzyl - *N*¹ - methylthiurea separated as a white crystalline solid, melting point 118—123°. The latter was collected, dissolved in methanol (60 ml.) and treated with methyl iodide (20 ml.). After being refluxed for ½ hour (it warmed spontaneously at first), this mixture was evaporated, and the residue crystallised from methanol-ether to give *N* - 2 - chlorobenzyl - *N*¹,*S* - dimethylisothiurea hydriodide, melting point 173—176°. A portion of this hydriodide (31 g.) was converted to base by shaking with excess sodium carbonate (30 g.) in water (75 ml.), and at the same time extracted into ether. The ethereal extract was dried and evaporated to give a colourless syrup, which was redissolved in dilute sulphuric acid to a solution of about pH 5.0. This solution was reduced to a volume of about 50 ml. by vacuum evaporation, treated with 35% aqueous methylamine (100 ml.) and sufficient

methanol to form a homogeneous solution, which was then gently refluxed for 6 hours. The solution was evaporated to dryness, and the white solid residue recrystallised from methanol-acetone to give *N* - 2 - chlorobenzyl - *N*¹,*N*¹¹ - dimethylguanidine sulphate, melting point 276—278°.

EXAMPLE 17.

2 - Bromobenzylisothiocyanate (9 g.) was added to a solution of 0.880 ammonia solution (100 ml) and ethanol (35 ml.) and the solution warmed on a steam-bath for ½ hour. The excess of ammonia was removed by evaporation to dryness *in vacuo*. The residue, crystallised from aqueous ethanol, gave 2-bromobenzylthiurea, melting point 127—128°. A portion of this (5.05 g.) was suspended in ethanol (5 ml.) and methyl iodide (4.26 g.) and the mixture refluxed for 20 minutes. The resulting solution was evaporated slightly to remove excess methyl iodide. Addition of ether caused *N* - 2 - bromobenzyl - *S* - methylisothiurea hydriodide to crystallise, melting point 126—127.5°. A portion of this (3.5 g.) with aqueous ethanol (50%, 5 ml.) and a

solution of dimethylamine (50% in methanol, 0.9 ml.) was refluxed for 2½ hours. After standing at room temperature overnight a further quantity of 50% methanolic dimethylamine (0.5 ml) was added, and the mixture refluxed for 2½ hours. The mixture was evaporated to dryness *in vacuo* and the residue, crystallised from n-propanol/ether, gave N-2-bromobenzyl - N¹,N¹ - dimethylguanidine hydriodide, melting point 162—163½°.

EXAMPLE 18.

N - 2 - Chlorobenzyl - N¹,S - dimethyl - isothiurea hydriodide (Example 15) (3.6 g.) dissolved in ethanol (10 ml.) was treated with 33% aqueous ethylamine (5 ml.) and the mixture refluxed for 6 hours. Evaporation *in vacuo* yielded a gum which crystallised from acetone/ether to give N - 2 - chlorobenzyl - N¹ - ethyl - N¹¹ - methylguanidine hydriodide, melting point 102—105°.

EXAMPLE 19.

To a solution of 2-methylbenzylamine (12 g.) in ether (100 ml.) was added a solution of methyl isothiocyanate (7.3 g.) in ether. After about 15 minutes, the resulting crystalline precipitate, consisting of N - methyl - N¹ - 2-methylbenzylthiurea, was collected. It melted at 130—135°.

This thiurea (12 g.) in methanol (100 ml.) was treated with methyl iodide (7.2 ml.), the mixture being refluxed for 1 hour and then cooled. Addition of ether gave a white crystalline precipitate, melting at 121—123° and consisting of N,S - dimethyl - N¹ - 2 - methylbenzylisothiurea hydriodide.

A solution of this hydriodide (7.9 g.) in warm water (30 ml.) was treated with 28% aqueous methylamine (6 ml.), and methanol (30 ml.) to give a clear solution. The mixture was gently refluxed for 12 hours, evaporated to dryness *in vacuo*, and the residue crystallised from methanol/ether to give N,N¹-dimethyl - N¹¹ - 2 - methylbenzylguanidine hydriodide, melting at 187—189°.

EXAMPLE 20.

N,S - Dimethyl - N¹ - 2 - methylbenzylisothiurea hydriodide (Example 18) (8 g.) dissolved in warm water (40 ml.) was treated with 33% aqueous ethylamine (8 ml.) and sufficient ethanol to give a clear solution (about 30 ml.). The mixture was refluxed for about 12 hours and then evaporated *in vacuo* to give a syrup, which crystallised from methanol/ether to give N - ethyl - N¹ - methyl - N¹¹ - 2 - methylbenzylguanidine hydriodide, melting at 142—146°.

EXAMPLE 21.

2-Bromobenzylisothiocyanate (9.2 g.) was added to a solution of ethylamine in water (6.8 ml. of 33% w/v) and the mixture warmed on a steam-bath for 5 minutes. Ethanol (10

ml.) was added to dissolve the oil. The mixture was refluxed for 30 minutes, and then evaporated *in vacuo* until an oil separated. The mixture was cooled and seeded to give N - 2 - bromobenzyl - N¹ - ethylthiurea, melting point 110½—111½°. A portion of this (10.95 g.) was suspended in ethanol (20 ml.) and methyl iodide (7.1 g.) added. Heat was evolved and the mixture was refluxed for 15 minutes. A further quantity of methyl iodide (2.3 g.) was added and the mixture warmed for 5 minutes. Excess methyl iodide was distilled off. Cooling and addition of ether gave N - 2 - bromobenzyl - N¹ - ethyl - S-methylisothiurea hydriodide, melting point 145—146°. A portion of this (2.0 g.) was refluxed with ethanol (10 ml.) and aqueous methylamine (7½ ml.; 40%) for 4½ hours. Methylmercaptan was evolved. The solution was evaporated to dryness *in vacuo* and the residue crystallised from n-propanol and ether to give N - 2 - bromobenzyl - N¹ - ethyl - N¹¹ - methylguanidine hydriodide, melting point 137½—138½°.

EXAMPLE 22.

2-Chlorobenzylisothiocyanate (6.62 g.) was added to a solution of aqueous methylamine (10 ml.; 35%) and ethanol (10 ml.). Heat was evolved and, after the reaction had slackened, the mixture was warmed for 5 minutes on a steam-bath. It was then concentrated *in vacuo* until crystallisation occurred, when the mixture was cooled and the solid filtered off and washed with aqueous ethanol to give N-2-chlorobenzyl - N¹ - methylthiurea, melting point 118—121°. A portion of this (7.55 g.) was converted to N - 2 - chlorobenzyl - N¹ - S - dimethylisothiurea hydriodide (as described in Example 20), some of which (3.56 g.) was refluxed with a solution of dimethylamine in methanol (10 ml.; 50%) for 8 hours. Methylmercaptan was evolved. The solution was evaporated to dryness *in vacuo*, the residue basified with sodium hydroxide solution, and the oil extracted with benzene and ether. Excess succinic acid in ethanol was added to this extract when the resultant oil slowly crystallised. Several crystallisations from n-propanol and ether gave pure N-2-chlorobenzyl - N¹,N¹¹ - trimethylguanidine hydrogen succinate, melting point 112—114°.

EXAMPLE 23.

N-Benzyl-N¹-ethylthiurea (21.6 g.) was suspended in ethanol (10 ml.) and methyl iodide (25 ml.) was added, the heat evolved causing a gentle reflux. After standing at room temperature for 25 minutes the solution was concentrated *in vacuo* and N - benzyl - N¹ - ethyl - S - methylisothiurea hydriodide crystallised, melting point 123—124°. A portion of this was basified and converted to the hydrogen oxalate, melting point 97—99°. Some of the salt (2.98 g.) was refluxed with



194—198°, after crystallisation from acetone-ether.

EXAMPLE 30.

A mixture of 2,4 - dichlorobenzyl chloride (2.2 g.) and guanidine base (2 g.) in ethanol (20 ml.) was refluxed on the steam-bath for 5 hours. The solvent was removed by evaporation and the residue treated with warm water plus dilute hydrochloric acid until just acid. Some undissolved solid was removed, and the filtrate washed with ether. The aqueous solution was made strongly alkaline with sodium hydroxide and extracted with ether, which on evaporation gave 2,4-dichlorobenzylguanidine, m.p. 120—125°, after two crystallisations from benzene.

EXAMPLE 31.

Tablets (0.555 g.) of *N* - 2 - chlorobenzyl-*N*¹,*N*¹¹ - dimethylguanidine sulphate were made by mixing the salt (0.25 g.) in a fine powder with lactose (0.25 g.) and starch (0.05 g.), granulating the mixture with alcohol or alcoholic polyvinyl pyrrolidone or a mixture of equal parts of alcohol and water, drying the granules at 40°, adding magnesium stearate (0.005 g.) as a lubricant and compressing the mixture.

EXAMPLE 32.

Tablets (0.505 g.) of *N*-2-chlorobenzyl-*N*¹,*N*¹¹ - dimethylguanidine sulphate were made by granulating the salt (0.5 g.) in a fine powder with equal parts of alcohol and water. Magnesium stearate (0.005 g.) as a lubricant was added, and the mixture compressed directly.

EXAMPLE 33.

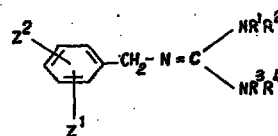
Injection solutions containing *N* - 2-chlorobenzyl - *N*¹,*N*¹¹ - dimethylguanidine sulphate in Water of Injection (0.2 g./per ml.) were made by autoclaving the solution at 15 lb. steam pressure for 30 minutes in unit dose ampoules or multidose containers. For the latter, the Water of Injection contained benzyl alcohol (1.0%), phenol (0.5%) or chlorocresol (0.1%).

EXAMPLE 34.

Tablets and injection solutions similar to those described in Examples 24, 25 and 26 and containing *N* - benzyl - *N*¹,*N*¹¹ - dimethylguanidine hydroiodide, *N* - 2 - bromobenzyl- or *N* - 2,4 - dichlorobenzyl - guanidine sulphate, *N* - 2,4 - dichlorobenzyl - *N*¹-methylguanidine hydrochloride or *N* - 3-methylbenzyl - *N*¹,*N*¹¹ - dimethylguanidine hydroiodide, instead of the *N* - 2 - chlorobenzyl - *N*¹,*N*¹¹ - dimethylguanidine sulphate, were made in analogous manners.

WHAT WE CLAIM IS:—

1. A method for the preparation of a benzylguanidine of the formula:



and acid addition salts thereof, wherein *Z*¹ is a hydrogen atom or a substituent halogen atom or alkyl or nitro group in the 2 or 3 position, *Z*² is a hydrogen atom or a substituent halogen atom or alkyl group in the 4, 5 or 6 position, and *R*¹, *R*², *R*³ and *R*⁴ are the same or different and each is a hydrogen atom or a substituent alkyl group, provided that when *Z*¹ is a hydrogen atom at least two of *Z*², *R*¹, *R*², *R*³ and *R*⁴ are not hydrogen but are substituents as defined, which method comprises the reaction of:

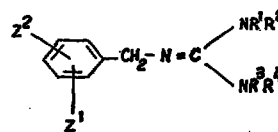
(i) a guanidine *R*⁵*N*=*C*(*N**R*⁶*R*⁷)(*N**R*⁸*R*⁹) or a salt thereof with a compound *R*¹⁰*X*, wherein *R*⁵, *R*⁶, *R*⁷, *R*⁸, *R*⁹ and *R*¹⁰ are each as appropriate, and not as respective, a benzyl, *R*¹, *R*², *R*³ and *R*⁴ group and a hydrogen atom, and *X* is a reactive proton accepting atom or group; or

(ii) ammonia or an ammonia derivative or a salt thereof with an *S*-substituted isothioureia or a salt thereof, or with a cyanamide.

2. A method of making a pharmaceutical composition containing a benzylguanidine of the formula defined in claim 1 or an acid addition salt thereof and an acceptable carrier therefor, which comprises the admixture of the components.

3. A pharmaceutical composition containing a benzylguanidine of the formula defined in claim 1 or an acid addition salt thereof and an acceptable carrier therefor.

4. A benzylguanidine of the formula:



wherein *Z*¹ is a hydrogen atom or a substituent halogen atom or alkyl or nitro group in the 2 or 3 position, *Z*² is a hydrogen atom or a substituent halogen atom or alkyl group in the 4, 5 or 6 position, and *R*¹, *R*², *R*³ and *R*⁴ are the same or different and each is a hydrogen atom or a substituent alkyl group, provided that when *Z*¹ is a hydrogen atom at least two of *Z*², *R*¹, *R*², *R*³ and *R*⁴ are not hydrogen but are substituents as defined; and acid addition salts thereof.

5. A benzylguanidine as claimed in claim 4 wherein *R*¹ is a hydrogen atom, *R*² and *R*³

a solution of methylamine in methanol (25 ml.; 40% w/v) and water (15 ml.) for 5 hours. The solution was evaporated to dryness *in vacuo* and the residue dissolved in dilute hydrochloric acid, washing with ether to remove some non-basic material. The acid solution was basified with sodium hydroxide solution and the oil extracted with ether. The ether extracts were evaporated to dryness and a solution of oxalic acid in n-propanol, followed by ether, was added. *N*-Benzyl-*N*¹-ethyl-*N*¹¹-methylguanidine hydrogen oxalate crystallised, melting point 162—163°.

EXAMPLE 24.

Benzylisothiocyanate (14.9 g.) was added slowly to a solution of n-propylamine (15 ml.) in n-propanol (20 ml.), cooling in water to moderate the exothermic reaction. The resultant solution after standing at room temperature for 20 minutes was evaporated to dryness *in vacuo* and the residue crystallised from benzene/light petroleum (boiling point 60—80°) to give *N*-benzyl-*N*¹-n-propylthiourea, melting point 93—94°. A portion of this (16.5 g.) was added to methyl iodide (20 ml.) when it dissolved with slight warming. After standing $\frac{1}{2}$ hour at room temperature the solution was evaporated to dryness *in vacuo* and the residue slowly crystallised on standing under ether. This was crude *N*-benzyl-*S*-methyl-*N*¹-n-propylisothiourea hydriodide, melting point 71—76° which was not purified further. A portion of the hydriodide (3.5 g.) was refluxed with a solution of methylamine in methanol (20 ml.; 40%) for 5 $\frac{1}{2}$ hours. The resultant solution was evaporated to dryness *in vacuo*; the residue was dissolved in dilute hydrochloric acid, the solution washed with ether and then basified with sodium hydroxide solution, and the oil extracted with ether. The extracts were evaporated to dryness *in vacuo* and a solution of oxalic acid in n-propanol, followed by ethyl acetate and ether, added. *N*-Benzyl-*N*¹-methyl-*N*¹¹-n-propylguanidine hydrogen oxalate crystallised, melting point 158 $\frac{1}{2}$ —159 $\frac{1}{2}$ °.

EXAMPLE 25.

A mixture of cyanamide (0.8 g.) and *o*-bromobenzylamine hydrochloride, m.p. 230—234° (2.5 g.) was heated in a silicone bath at 150° for about 20 minutes. The resulting gum was dissolved in methanol and treated slowly with dry ether. *o*-Bromobenzylguanidine hydrochloride separated as white crystals, which after recrystallisation from methanol-ether melted at 145—146°.

EXAMPLE 26.

A mixture of cyanamide (0.68 g.) and 2,4-dichlorobenzylamine hydrochloride was heated at 150° for 3 hours, and the resultant glass fractionally crystallised from ethanol-ether. The earlier crops contained some starting

material, i.e., 2,4-dichlorobenzylamine hydrochloride, but later crops consisted largely of the required guanidine hydrochloride, which was purified by dissolving in water and precipitating the solid base with sodium hydroxide. 2,4-Dichlorobenzylguanidine, after two crystallizations from benzene, had m.p. 120—125°.

EXAMPLE 27.

N-3,5-Dimethylbenzyl-*N*¹,*N*¹¹-dimethyl guanidine hydriodide was prepared by refluxing 3,5-dimethylbenzylamine (1.35 g.) and *N*,*N*¹,*S*-trimethylisothiourea hydriodide (2.46 g.) in alcohol (10 ml.) and cooling. The guanidine hydriodide was filtered off and washed with a 3:1 solution of ether/n-propanol, and crystallised from n-propanol/ether. It had melting point 212—213.5°.

EXAMPLE 28.

N-Benzyl-*S*-methylisothiourea hydriodide (3 g.) and 33% alcoholic methylamine (5 ml.) were heated on a steam bath for 3 hours under reflux. The product was evaporated (to dryness) to a syrup, which crystallised slowly on scratching to give crude *N*-benzyl-*N*¹-methylguanidine hydriodide, m.p. 85—92°. This hydriodide was stirred with excess of 10*N*-sodium hydroxide solution, and the resulting oil extracted with a comparatively large volume of ether (250—300 ml.), the ethereal extract being dried sodium hydroxide pellets. After removal of the ether, the residual base was treated with methyl iodide (about 0.5 ml.), when some heat developed. After $\frac{1}{2}$ hour, the product was suspended in water, carefully neutralised with decolourised hydriodic acid, and washed with ether. The aqueous layer, on evaporation to dryness, gave a gum, which was dissolved in acetone and fractionally crystallised by gradual addition of ether, to give a small crop of *N*-benzyl-*N*¹,*N*¹¹-dimethylguanidine hydriodide, m.p. 195—197°, after recrystallisation from methanol-ether.

EXAMPLE 29.

N,*N*¹-Dimethylguanidine sulphate (about 10 g.) was dissolved in a small volume of water and treated with the minimum amount of barium hydroxide solution to remove all the sulphate ion as barium sulphate. The filtrate, on evaporation *in vacuo* at 30°, gave *N*,*N*¹-dimethylguanidine as a strongly basic syrup. Some of this base (3 g.) and benzyl iodide (2.2 ml.) in ethanol (10 ml.) were warmed on the steam-bath for 1 hour. The solution was then evaporated, and the residual gum shaken with water and neutralised with decolourised hydriodic acid. The aqueous extract was washed with ether and evaporated to a colourless syrup, which was redissolved in a little water. Addition of potassium iodide and cooling to 0° led to the separation of *N*-benzyl-*N*¹,*N*¹¹-dimethylguanidine hydriodide, m.p.

194—198°, after crystallisation from acetone-ether.

EXAMPLE 30.

A mixture of 2,4 - dichlorobenzyl chloride (2.2 g.) and guanidine base (2 g.) in ethanol (20 ml.) was refluxed on the steam-bath for 5 hours. The solvent was removed by evaporation and the residue treated with warm water plus dilute hydrochloric acid until just acid. Some undissolved solid was removed, and the filtrate washed with ether. The aqueous solution was made strongly alkaline with sodium hydroxide and extracted with ether, which on evaporation gave 2,4-dichlorobenzylguanidine, m.p. 120—125°, after two crystallisations from benzene.

EXAMPLE 31.

Tablets (0.555 g.) of *N* - 2 - chlorobenzyl-*N*¹,*N*¹¹ - dimethylguanidine sulphate were made by mixing the salt (0.25 g.) in a fine powder with lactose (0.25 g.) and starch (0.05 g.), granulating the mixture with alcohol or alcoholic polyvinyl pyrrolidone or a mixture of equal parts of alcohol and water, drying the granules at 40°, adding magnesium stearate (0.005 g.) as a lubricant and compressing the mixture.

EXAMPLE 32.

Tablets (0.505 g.) of *N*-2-chlorobenzyl-*N*¹,*N*¹¹ - dimethylguanidine sulphate were made by granulating the salt (0.5 g.) in a fine powder with equal parts of alcohol and water. Magnesium stearate (0.005 g.) as a lubricant was added, and the mixture compressed directly.

EXAMPLE 33.

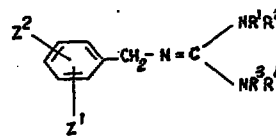
Injection solutions containing *N* - 2-chlorobenzyl - *N*¹,*N*¹¹ - dimethylguanidine sulphate in Water of Injection (0.2 g./per ml.) were made by autoclaving the solution at 15 lb. steam pressure for 30 minutes in unit dose ampoules or multidose containers. For the latter, the Water of Injection contained benzyl alcohol (1.0%), phenol (0.5%) or chlorocresol (0.1%).

EXAMPLE 34.

Tablets and injection solutions similar to those described in Examples 24, 25 and 26 and containing *N* - benzyl - *N*¹,*N*¹¹ - dimethylguanidine hydroiodide, *N* - 2 - bromobenzyl- or *N* - 2,4 - dichlorobenzyl - guanidine sulphate, *N* - 2,4 - dichlorobenzyl - *N*¹-methylguanidine hydrochloride or *N* - 3-methylbenzyl - *N*¹,*N*¹¹ - dimethylguanidine hydroiodide, instead of the *N* - 2 - chlorobenzyl - *N*¹,*N*¹¹ - dimethylguanidine sulphate, were made in analogous manners.

WHAT WE CLAIM IS:—

1. A method for the preparation of a benzylguanidine of the formula:



and acid addition salts thereof, wherein Z¹ is a hydrogen atom or a substituent halogen atom or alkyl or nitro group in the 2 or 3 position, Z² is a hydrogen atom or a substituent halogen atom or alkyl group in the 4, 5 or 6 position, and R¹, R², R³ and R⁴ are the same or different and each is a hydrogen atom or a substituent alkyl group, provided that when Z¹ is a hydrogen atom at least two of Z², R¹, R², R³ and R⁴ are not hydrogen but are substituents as defined, which method comprises the reaction of:

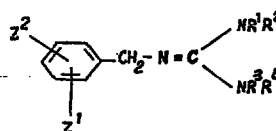
(i) a guanidine $R^5N=C(NR^6R^7)(NR^8R^9)$ or a salt thereof with a compound $R^{10}X$, wherein R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are each as appropriate, and not as respective, a benzyl, R¹, R², R³ and R⁴ group and a hydrogen atom, and X is a reactive proton accepting atom or group; or

(ii) ammonia or an ammonia derivative or a salt thereof with an *S*-substituted isothiourea or a salt thereof, or with a cyanamide.

2. A method of making a pharmaceutical composition containing a benzylguanidine of the formula defined in claim 1 or an acid addition salt thereof and an acceptable carrier therefor, which comprises the admixture of the components.

3. A pharmaceutical composition containing a benzylguanidine of the formula defined in claim 1 or an acid addition salt thereof and an acceptable carrier therefor.

4. A benzylguanidine of the formula:



wherein Z¹ is a hydrogen atom or a substituent halogen atom or alkyl or nitro group in the 2 or 3 position, Z² is a hydrogen atom or a substituent halogen atom or alkyl group in the 4, 5 or 6 position, and R¹, R², R³ and R⁴ are the same or different and each is a hydrogen atom or a substituent alkyl group, provided that when Z¹ is a hydrogen atom at least two of Z², R¹, R², R³ and R⁴ are not hydrogen but are substituents as defined; and acid addition salts thereof.

5. A benzylguanidine as claimed in claim 4 wherein R¹ is a hydrogen atom, R² and R³



are the same or different and each is a hydrogen atom or a methyl group, and R^4 is a hydrogen atom or a methyl or ethyl group, and acid addition salts thereof.

5 6. N - Benzyl - N^1, N^{11} - dimethylguanidine and acid addition salts thereof.

7. N - 2 - Bromobenzylguanidine and acid addition salts thereof.

10 8. N - 2,4 - Dichlorobenzylguanidine and acid addition salts thereof.

9. N - 2 - Chlorobenzyl - N^1 - methylguanidine and acid addition salts thereof.

15 10. N - 2 - Bromobenzyl - N^1, N^{11} - dimethylguanidine and acid addition salts thereof.

11. N - 2 - Chlorobenzyl - N^1, N^{11} - dimethylguanidine and acid addition salts thereof.

12. N - 2 - Methylbenzyl - N^1, N^{11} - dimethylguanidine and acid addition salts thereof. 20

13. N - 3 - Methylbenzyl - N^1, N^{11} - dimethylguanidine and acid addition salts thereof.

14. N - 2 - Methylbenzyl - N^1 - methyl- N^{11} -ethylguanidine and acid addition salts thereof. 25

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