

PATENT SPECIFICATION

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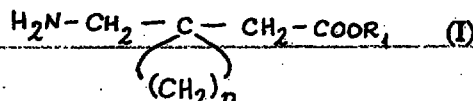


(54) CYCLIC AMINO ACIDS

(71) We, WARNER-LAMBERT COMPANY, of 201 Tabor Road, Morris Plains, New Jersey 07950, United States of America, a Corporation organised under the laws of the State of Delaware, United States of America, do hereby declare the invention, for which we 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:—

The present invention is concerned with new cyclic amino acids and with the preparation thereof.

The cyclic amino acids according to the present invention are compounds of the general formula:—



wherein R_1 is a hydrogen atom or a lower alkyl radical and n is 4, 5 or 6; and the pharmacologically compatible salts thereof. These compounds have been found to possess valuable pharmacodynamic properties.

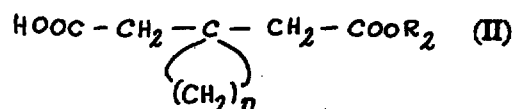
The lower alkyl radicals R_1 in the compounds according to the present invention are straight or branched chain alkyl radicals containing up to 8 and preferably up to 4 carbon atoms, especially methyl, ethyl, isopropyl and *tert*-butyl radicals.

The compounds of general formula (I) show hypothermal and, in some cases, narcosis-potentiating or sedating properties. They are also characterised by an extremely low toxicity. In animal experiments, there was, surprisingly, also found a remarkable protective effect against cramp induced by thiosemicarbazide. Some of the compounds according to the present invention also possess a considerable protective action against cardiac cramp. Thus these new compounds (I) can be used for the therapy of certain cerebral diseases, for example, they can be used for the treatment of certain forms of epilepsy, faintness attacks, hypokinesia and cranial traumas. They also bring about an improve-

ment of the cerebral functions. Consequently, they are also especially useful for the treatment of geriatric patients.

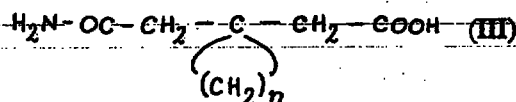
The compounds of general formula (I) according to the present invention can be prepared, for example, by one of the following methods:

a) converting a compound of the general formula:—



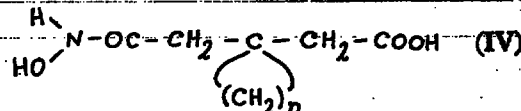
wherein R_2 is an alkyl radical containing up to 8 carbon atoms and n has the same meaning as above, via a reactive acid derivative thereof, into an azide which is then subjected to the Curtius rearrangement; or

b) subjecting a compound of the general formula:—



wherein n has the same meaning as above, to the Hofmann rearrangement; or

c) subjecting a compound of the general formula:—



wherein n has the same meaning as above, to the Lossen rearrangement.

When a free amino acid is obtained, it may be esterified to give a corresponding lower alkyl ester and/or the product obtained may be converted into a pharmacologically compatible salt by reaction with an acid or a base.

Since amino acids are amphoteric, pharmacologically compatible salts when R_1 is a

hydrogen atom can be salts of appropriate inorganic and organic acids, for example, hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, oxalic acid, lactic acid, citric acid, malic acid, salicylic acid, malonic acid, maleic acid, succinic acid or ascorbic acid, but also, starting from the corresponding hydroxides or carbonates, salts with alkali metals or alkaline earth metals, for example, sodium, potassium, magnesium or calcium. Salts with quaternary ammonium ions can also be prepared with, for example, the tetramethylammonium ion. Of course, when R_1 is a lower alkyl, it is only possible to form salts with acids.

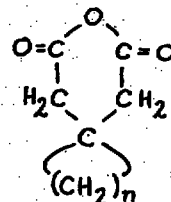
The reaction of the compounds of general formula (II) takes place according to the well-known Curtius rearrangement. The free carboxyl group is first activated by conversion into a reactive derivative, for example an acid halide or a mixed anhydride, and subsequently reacted with an appropriate azide, for example sodium azide. The acid azide thus obtained is then subjected to thermal decomposition in an organic solvent, for example, benzene or toluene, or in an alcohol, such as ethanol, during which nitrogen is split off and an intramolecular rearrangement to an isocyanate or, in the presence of an alcohol, to a urethane takes place. The isocyanates and the urethanes can easily be converted into the desired primary amine by basic or acid hydrolysis.

The well-known Hofmann rearrangement of compounds of general formula (III) also takes place via isocyanates. In this case, the acid amides are reacted with alkali metal hypohalites. Upon hydrolysis of the isocyanate formed by anionotropic rearrangement, the desired amine is formed, together with carbon dioxide.

The Lossen rearrangement of hydroxamic acids of general formula (IV) also takes a similar course. In this case, formally water is split off, the corresponding isocyanate first being formed, hydrolysis of which gives the desired amine. Usually the hydroxamic acids are reacted with bases *via* their O-acyl derivatives, for example, the O-acetyl-, O-benzoyl- and preferably O-sulphonyl-derivatives.

If R_1 is to be a lower alkyl radical, the carboxyl group of the amino acids obtained is esterified in known manner. Most simply, the reaction can be carried out by dissolving a free amino acid of general formula (I) or a salt thereof in an excess of the alcohol serving as the esterification component and the solution then saturated with hydrogen chloride. The corresponding amino acid ester hydrochloride is thus directly obtained. If it is desired to work without an excess of alcohol, then it is possible to employ the esterification methods known from amino acid chemistry, with masking of the amino group.

The compounds of general formula (II) used as starting materials can be prepared by reacting an acid anhydride of the general formula:—



(V) 70

wherein n has the same meaning as above, with one mole of an alcohol of the general formula:—



wherein R_2 has the same meaning as above.

The compounds of general formula (V) are known (cf. J. C. S., 115, 686/1919; Soc., 99, 446; J. C. S., 117, 639/1920).

Some of the compounds of general formula (III), as well as processes for the preparation thereof, are known (cf. Austral. J. C., 13, 127/1960) and can, for example, also be prepared by reacting a compound of general formula (V) with ammonia. In this case, it is advantageous to work at the lowest possible temperature. However, it is also possible first, as described above, to prepare a hemiester, then to react the free carboxylic acid group with, for example, ethyl chloroformate and subsequently to carry out a reaction with ammonia.

The hydroxamic acids of general formula (IV) can be prepared analogously by reacting the anhydride of general formula (V) with hydroxylamine.

Because of their low toxicity, the compounds of general formula (I) according to the present invention can be administered enterally or parenterally within wide dosage ranges in admixture with a liquid or solid pharmaceutical diluent or carrier. As injection solution, water is preferably employed which contains the usual additives for injection solutions, such as stabilising agents, solubilising agents and/or buffers.

Additives of this kind include, for example, tartrate and citrate buffers, ethanol, complex-forming agents (such as ethylenediaminetetraacetic acid and the non-toxic salts thereof), as well as high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation. Solid carrier materials include, for example, starch, lactose, mannitol, methyl cellulose, talc, highly-dispersed silicic acids, high molecular weight fatty acids, (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats and solid high molecular weight polymers (such as polyethylene glycol); compositions suitable

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for oral administration can, if desired, also contain flavouring and/or sweetening agents.

The individual dosage for the compounds according to the present invention can be 5—50 mg, parenterally and 20—200 mg. enterally.

Thus, the present invention also provides pharmaceutical compositions containing at least one compound of general formula (I) and/or at least one pharmacologically compatible salt thereof, in admixture with a solid or liquid pharmaceutical diluent or carrier.

The following Examples are given for the purpose of illustrating the present invention:—

Example 1

1 - Aminomethyl - 1 - cyclohexane - acetic acid.

5.6 ml Triethylamine in 16 ml. anhydrous acetone are added dropwise, with stirring and cooling to 0°C., to a solution of 7.28 g. monomethyl 1,1 - cyclohexane - diacetate, whereafter a solution of 3.6 ml. ethyl chloroformate in 16 ml. anhydrous acetone is added thereto. The reaction mixture is further stirred for 30 minutes at 0°C. and then a solution of 3.4 g. sodium azide in 12 ml. water added dropwise thereto. The reaction mixture is stirred for 1 hour at 0°C., then poured into ice water and extracted three times with 50 ml. amounts of ice-cold toluene. The combined extracts are dried over anhydrous sodium sulphate at 0°C. and subsequently introduced dropwise into a flask pre-heated to 100°C. The mixture is then heated for a further hour under reflux and thereafter evaporated in a vacuum. The crude methyl 1 - isocyanatomethyl - 1 - cyclohexaneacetate which remained behind is heated under reflux for 3 hours with 50 ml. 20% hydrochloric acid. After cooling the solution, it is extracted three times with 100 ml. amounts of chloroform to remove the 1 - aminomethyl - 1 - cyclohexane - acetic acid lactam formed as a by-product and the aqueous hydrochloric acid solution evaporated in a vacuum, whereby 1 - aminomethyl - 1 - cyclohexane - acetic acid crystallises as the hydrochloride; m.p. 117—118°C., after recrystallisation from acetone/methanol/diethyl ether. After recrystallisation from methanol/diethyl ether, the melting point of the product is 129—133°C.

Analysis:

55 $C_8H_{15}ClNO_2 \cdot 0.25 H_2O$
calc.: C 50.94%; H 8.79%;
Cl 16.70%; N 6.60%;
found: C 51.03%; H 8.56%;
Cl 16.34%; N 6.84%

60 By treatment with a basic ion-exchanger and crystallisation from ethanol/diethyl ether, there is obtained pure 1 - amino-

methyl - 1 - cyclohexane - acetic acid; m.p. 162—166°C.

Analysis:

$C_8H_{17}NO_2$
calc.: C 63.13%; H 10.01%;
N 8.18%; O 18.69%;
found: C 63.20%; H 9.61%;
N 7.95%; O 19.02%.

The monomethyl 1,1 - cyclohexane - diacetate used as starting material is prepared as follows:

32.8 g. 1,1 - cyclohexane - diacetic anhydride are mixed with 7 g. anhydrous methanol and heated under reflux for 1 hour. After evaporation of the reaction mixture in a vacuum, 37.5 g. monomethyl 1,1 - cyclohexane - diacetate remains behind in the form of a yellowish oil.

Example 2.

Ethyl 1 - aminomethyl - 1 - cyclohexane - acetate.

10 g. of the 1 - aminomethyl - 1 - cyclohexane - acetic acid, prepared according to Example 1, are dissolved in 50 ml. anhydrous ethanol and saturated at 0°C. with gaseous hydrogen chloride. The reaction mixture is left to stand overnight at ambient temperature, then evaporated in a vacuum and the residue recrystallised from ethanol/diethyl ether. Ethyl 1 - aminomethyl - 1 - cyclohexane - acetate is obtained in the form of its hydrochloride; m.p. 161—163°C.

Analysis:

$C_{11}H_{21}ClNO_2$
calc.: C 56.04% H 9.41%;
N 5.94%;
found: C 55.93%; H 9.28%;
N 5.94%.

Example 3.

1 - Aminomethyl - 1 - cycloheptane - acetic acid.

15.9 g. monomethyl - 1,1 - cycloheptane - diacetate are dissolved in 100 ml. anhydrous acetone and, in a manner analogous to that described in Example 1, first mixed with 8.1 g. triethylamine in 30 ml. acetone, thereafter with 9.8 g. ethyl chloroformate in 30 ml. anhydrous acetone and finally with 6.5 g. sodium azide in 20 ml. water. After the reaction has taken place, the reaction mixture is extracted as in Example 1 and the solution obtained of monomethyl 1,1 - cycloheptane - diacetate azide is rearranged in toluene to give the isocyanate. The methyl 1 - isocyanato - methyl - 1 - cycloheptane - acetate obtained is boiled for 3 hours under reflux in 20% hydrochloric acid. Upon evaporation in a vacuum, 1 - aminomethyl - 1 - cycloheptane - acetic acid separates out in the form of its hydrochloride, which is

recrystallised from methanol/acetone/ethyl acetate; m.p. 69—72°C.

Analysis:

$C_{10}H_{20}ClNO_2 \cdot 0.25 H_2O$

calc.: C 53.12%; H 9.13%;
Cl 15.68%; N 6.19%;
O 15.88%
found: C 53.29%; H 9.03%;
Cl 15.73%; N 6.16%;
O 15.77%

The monomethyl 1,1 - cycloheptane - diacetate used as starting material is prepared as follows:

13.7 g. 1,1 - cycloheptane - diacetic anhydride are mixed with 2.36 g. anhydrous methanol in 10 ml. benzene and boiled under reflux for 2 hours. After evaporation, there are obtained 15.9 g. monomethyl 1,1 - cycloheptane - diacetate, which is further worked up directly.

Example 4.

1 - Aminomethyl - 1 - cyclopentane - acetic acid.

Variant A:

17 g. 1,1 - cyclopentane - diacetic acid monoamide are dissolved in 15 ml. water, together with 4 g. sodium hydroxide. The solution obtained is added dropwise at -10°C., while stirring, to a solution of sodium hypobromite, prepared by the dropwise addition of 19 g. bromine to a solution of 24 g. sodium hydroxide in 250 ml. water at -10°C. The reaction mixture is allowed to warm up to ambient temperature, while stirring and thereafter heated to 60°C. for 2 hours.

After acidification with 12N hydrochloric acid, the reaction mixture is extracted three times with 150 ml. amounts of methylene chloride and the aqueous phase evaporated in a vacuum. The crude 1 - aminomethyl - 1 - cyclopentane - acetic acid hydrochloride is obtained by digesting the residue with ethanol and evaporating the ethanolic solution. It is converted into the free amino acid by passing over an ion exchanger in the OH form. After stripping off the solvent and recrystallising the residue from ethanol/diethyl ether, there is obtained pure 1 - aminomethyl - 1 - cyclopentane - acetic acid; m.p. 171—172°C.

Analysis:

$C_8H_{15}NO_2$

calc.: C 61.12%; H 9.62%;
N 8.91%; O 20.25%
found: C 60.78%; H 9.37%;
N 8.93%; O 19.96%.

The 1,1 - cyclopentane - diacetic acid monoamide used as starting material is prepared as follows:

30 g. 1,1 - cyclopentane - diacetic anhydride are mixed, while cooling, with 60 ml. of a 20% aqueous solution of ammonia. After the reaction has taken place, excess ammonia is removed in a vacuum and the solution is acidified with hydrochloric acid and then extracted with methylene chloride. Subsequently, the solvent is stripped off. The 1,1 - cyclopentane - diacetate acid monoamide thus obtained can be further worked up directly.

Variant B:

5.88 g. 1,1 - cyclopentane - diacetic anhydride are introduced, while cooling with ice water, into an ethanolic solution of hydroxylamine, prepared from 2.5 g. crude hydroxylamine benzene-sulphonate and the equivalent amount of sodium ethylate in 15 ml. anhydrous ethanol and subsequent filtration. The reaction mixture is further stirred for 1 hour at ambient temperature, the solution is evaporated in a vacuum and the crude hydroxamic acid taken up in 37 ml. 10% aqueous sodium carbonate solution. While cooling, 4.5 ml. benzene-sulphochloride is added thereto dropwise. The reaction mixture is further stirred for 1 hour at 25°C., mixed with 14 ml. of a 10% aqueous solution of sodium hydroxide and the reaction mixture then heated for 45 minutes to 100°C. After cooling, the solution is acidified with concentrated hydrochloric acid and then evaporated to dryness in a vacuum. The residue is treated with ethanol, filtered and the ethanolic solution concentrated somewhat. 1 - Aminomethyl - 1 - cyclopentane - acetic acid thereby crystallises out as its benzene-sulphonate which, in the manner described in Variant A above, is converted into the free amino acid by means of an ion exchanger.

Example 5.

Sodium 1 - aminomethyl - 1 - cyclohexane - acetate.

An aqueous solution of 1 - aminomethyl - 1 - cyclohexane - acetic acid (Example 1) is mixed with an equimolar amount of a 1 N aqueous solution of sodium hydroxide. Thereafter, the solution is evaporated in a vacuum until the beginning of crystallisation. After the addition of isopropanol, the precipitate obtained is filtered off and dried. The sodium 1 - aminomethyl - 1 - cyclohexane - acetate obtained begins to sinter at about 150°C. and has a melting point of 238°C.

Analysis:

$C_8H_{15}NO_2Na \cdot \frac{1}{2}H_2O$

calc.: C 53.46%; H 8.47%;
found: C 53.48%; H 8.28%.

In the same manner, by reacting a molar aqueous solution of calcium hydroxide with

a solution of 1 - aminomethyl - 1 - cyclohexane - acetic acid, there is obtained the calcium salt.

The analogous ammonium salt is manufactured by reacting an ethanolic solution of 1 - aminomethyl - 1 - cyclohexane - acetic acid with ammonia. After evaporation in a vacuum, the residue is crystallised from methanol/ether. The ammonium salt of 1 - aminomethyl - 1 - cyclohexane - acetic acid thus obtained has a melting point of 145—150°C.

Example 6.

Methyl - 1 - aminomethyl - 1 - cyclohexane - acetate.

In a manner analogous to that described in Example 2, 1 - aminomethyl - 1 - cyclohexane - acetic acid hydrochloride is reacted with methanol in the presence of hydrogen chloride. After evaporation in a vacuum, the residue is recrystallised from methanol/diethyl ether to give pure methyl 1 - aminomethyl - 1 - cyclohexane - acetate; m.p. 150—152°C. (hydrochloride).

Analysis:



calc.: C 53.15%; H 9.13%;

Cl 15.69%; N 6.20%

found: C 53.26%; H 8.68%;

Cl 15.39%; N 6.23%.

Example 7.

n - Butyl 1 - aminomethyl - 1 - cyclohexane - acetate.

A solution of 1 - aminomethyl - 1 - cyclohexane - acetic acid hydrochloride in *n*-butanol is saturated with hydrogen chloride at 0°C. The reaction mixture is then heated to 110°C. for two hours while hydrogen chloride is passed through. The solution thus obtained is then evaporated at 60°C. and the residue is stirred up with hexane, filtered and dried. *n* - Butyl 1 - aminomethyl - 1 - cyclohexane acetate hydrochloride is obtained in the form of a white powder having a melting point of 106—109°C.

Analysis:



calc.: C 58.20%; H 9.96%;

Cl 13.21%; N 5.22%

found: C 58.31%; H 9.96%;

Cl 13.45%; N 5.36%.

Example 8.

Sodium 1 - aminomethyl - 1 - cycloheptane - acetate.

1 - Aminomethyl - 1 - cycloheptane - acetic acid is obtained from the hydrochloride of Example 3 by passing an aqueous solution through a basic ion-exchange resin in the OH form. The solution of the free amino acid is evaporated in a vacuum and the 1 -

aminomethyl - 1 - cycloheptane - acetic acid obtained recrystallised from ethanol; m.p. 180°C.

Analysis:



calc.: C 64.83%; H 10.34%;

N 7.56%

found: C 64.55%; H 10.32%;

N 7.35%.

According to a method described in Example 5, the free amino acid is reacted with a 1 molar aqueous solution of sodium hydroxide to give sodium 1 - aminomethyl - 1 - cycloheptane - acetate, which, after recrystallisation from methanol/isopropanol, sinters above 140°C., with slow decomposition.

The corresponding calcium salt crystallises in the form of colourless platelets from water/acetone. Calcium 1 - aminomethyl - 1 - cycloheptane - acetate sinters above 180°C. without signs of melting.

Example 9.

Methyl 1 - aminomethyl - 1 - cycloheptane - acetate.

In a manner analogous to that described in Example 2, 1 - aminomethyl - 1 - cycloheptane - acetic acid hydrochloride is esterified with methanol in the presence of hydrogen chloride. After working up and crystallising from isopropanol/diethyl ether/hexane, methyl 1 - aminomethyl - 1 - cycloheptane - acetate is obtained as its hydrochloride in the form of colourless crystals having a melting point of 115—116°C.

Analysis:



calc.: C 56.04%; H 9.41%;

Cl 15.04%; N 5.94%

found: C 55.70%; H 9.24%;

Cl 14.94%; N 6.05%.

Example 10.

n - Butyl 1 - aminomethyl - 1 - cycloheptane - acetate - toluene sulphonate.

In a manner analogous to that described in Example 7, 1 - aminomethyl - 1 - cycloheptane - acetic acid hydrochloride is esterified with *n* - butanol in the presence of hydrogen chloride to give *n* - butyl 1 - aminomethyl - 1 - cycloheptane - acetate hydrochloride in the form of a syrup, which is mixed with benzene and an equivalent amount of *p* - toluene - sulphonic acid. The mixture is evaporated to dryness in a vacuum. After crystallisation from chloroform/diethyl ether/hexane, *n* - butyl 1 - aminomethyl - 1 - cycloheptane - acetate *p* - toluene - sulphonate is obtained; m.p. 116—118°C.

Analysis:



calc.: C 60.99%; H 8.53%;
N 3.39%
found: C 60.97%; H 8.68%;
N 3.91%.

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Example 11.

1 - Aminomethyl - 1 - cyclopentane - acetate
benzene - sulphonate.

10 According to the method described in Ex-
ample 1, monomethyl - 1,1 - cyclopentane -
diacetate is subjected to the Curtius re-
arrangement *via* the azide form to give 1 -
aminomethyl - 1 - cyclopentane - acetic acid
15 hydrochloride which has a melting point of
110—120°C. after crystallisation from
ethanol/diethyl ether.

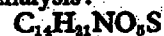
Analysis:



20 calc.: C 49.61%; H 8.33%;
N 7.23%
found: C 49.63%; H 8.12%;
N 7.23%.

25 The benzene-sulphonate of 1 - amino-
methyl - 1 - cyclopentane - acetic acid, which
is obtained by the reaction of the free amino
acid with benzene-sulphonic acid in ethanolic
solution, has a melting point of 171—173°C.

Analysis:



30 calc.: C 53.31%; H 6.71%;
N 4.44%
found: C 53.44%; H 6.77%;
N 4.58%.

Example 12.

35 *n* - Butyl 1 - aminomethyl - 1 - cyclo-
pentane - acetate.

40 According to the method described in
Example 7, 1 - aminomethyl - 1 - cyclo-
pentane - acetic acid hydrochloride is ester-
fied with *n* - butanol to give *n* - butyl - 1 -
aminomethyl - 1 - cyclopentane - acetate
hydrochloride; m.p. 50°C.
anog

45 The corresponding *p* - toluene - sul-
phonate, which is obtained after repeated
evaporation of the benzene solution and by
the addition of an equimolar amount of *p* -
toluene - sulphonic acid and recrystallisation
50 from chloroform/diethyl ether/hexane, has a
melting point of 86—87°C.

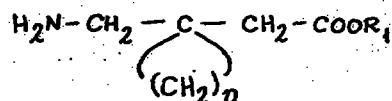
Analysis:



55 calc.: C 59.19%; H 8.11%;
N 3.63%
found: C 59.35%; H 7.99%;
N 3.88%.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:—



wherein R_1 is a hydrogen atom or a lower alkyl radical and n is 4, 5 or 6; and the pharmacologically compatible salts thereof. 60

2. 1 - Aminomethyl - 1 - cyclohexane - acetic acid.

3. Ethyl 1 - aminomethyl - 1 - cyclo- 65
hexane - acetate.

4. 1 - Aminomethyl - 1 - cycloheptane - acetic acid.

5. 1 - Aminomethyl - 1 - cyclopentane - acetic acid. 70

6. Sodium 1 - aminomethyl - 1 - cyclo-
hexane - acetate.

7. Methyl 1 - aminomethyl - 1 - cyclo-
hexane - acetate.

8. *n* - Butyl 1 - aminomethyl - 1 - cylo- 75
hexane - acetate.

9. Sodium 1 - aminomethyl - 1 - cyclo-
heptane - acetate.

10. Methyl 1 - aminomethyl - 1 - cyclo-
heptane - acetate. 80

11. *n* - Butyl 1 - aminomethyl - 1 - cyclo-
heptane - acetate toluene sulphonate.

12. 1 - Aminomethyl - 1 - cyclopentane -
acetate benzene - sulphonate.

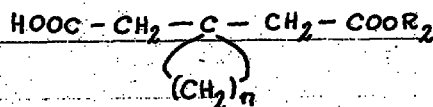
13. Calcium 1 - aminomethyl - 1 - cyclo- 85
hexane - acetate.

14. Ammonium 1 - aminomethyl - 1 -
cyclohexane - acetate.

15. Calcium 1 - aminomethyl - 1 - cyclo- 90
heptane - acetate.

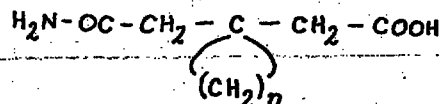
16. *n* - Butyl 1 - aminomethyl - 1 - cylo-
pentane - acetate.

17. Process for the preparation of com-
pounds of the general formula given in
claim 1, wherein a compound of the general 95
formula:—



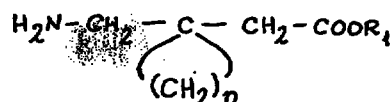
in which R_2 is an alkyl radical containing
up to 8 carbon atoms and n has the same
meaning as in claim 1, is converted, *via* a 100
reactive acid derivative, into an azide which
is then subjected to the Curtius rearrange-
ment.

18. Process for the preparation of com-
pounds of the general formula given in 105
claim 1, wherein a compound of the general
formula:—





calc.: C 60.99%; H 8.53%;
N 3.39%;
found: C 60.97%; H 8.68%;
N 3.91%.



Example 11.

1 - Aminomethyl - 1 - cyclopentane - acetate
benzene - sulphonate.

According to the method described in Example 1, monomethyl - 1,1 - cyclopentane - diacetate is subjected to the Curtius rearrangement *via* the azide form to give 1 - aminomethyl - 1 - cyclopentane - acetic acid hydrochloride which has a melting point of 110–120°C. after crystallisation from ethanol/diethyl ether.

Analysis:



calc.: C 49.61%; H 8.33%;
N 7.23%;
found: C 49.63%; H 8.12%;
N 7.23%.

The benzene-sulphonate of 1 - aminomethyl - 1 - cyclopentane - acetic acid, which is obtained by the reaction of the free amino acid with benzene-sulphonic acid in ethanolic solution, has a melting point of 171–173°C.

Analysis:



calc.: C 53.31%; H 6.71%;
N 4.44%;
found: C 53.44%; H 6.77%;
N 4.58%.

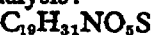
Example 12.

n - Butyl 1 - aminomethyl - 1 - cyclopentane - acetate.

According to the method described in Example 7, 1 - aminomethyl - 1 - cyclopentane - acetic acid hydrochloride is esterified with *n* - butanol to give *n* - butyl - 1 - aminomethyl - 1 - cyclopentane - acetate hydrochloride; m.p. 50°C.

The corresponding *p* - toluene - sulphonate, which is obtained after repeated evaporation of the benzene solution and by the addition of an equimolar amount of *p* - toluene - sulphonic acid and recrystallisation from chloroform/diethyl ether/hexane, has a melting point of 86–87°C.

Analysis:



calc.: C 59.10%; H 8.11%;
N 3.63%;
found: C 59.35%; H 7.99%;
N 3.88%.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:—

wherein R_1 is a hydrogen atom or a lower alkyl radical and n is 4, 5 or 6; and the pharmacologically compatible salts thereof.

2. 1 - Aminomethyl - 1 - cyclohexane - acetic acid.

3. Ethyl 1 - aminomethyl - 1 - cyclohexane - acetate.

4. 1 - Aminomethyl - 1 - cycloheptane - acetic acid.

5. 1 - Aminomethyl - 1 - cyclopentane - acetic acid.

6. Sodium 1 - aminomethyl - 1 - cyclohexane - acetate.

7. Methyl 1 - aminomethyl - 1 - cyclohexane - acetate.

8. *n* - Butyl 1 - aminomethyl - 1 - cyclohexane - acetate.

9. Sodium 1 - aminomethyl - 1 - cycloheptane - acetate.

10. Methyl 1 - aminomethyl - 1 - cycloheptane - acetate.

11. *n* - Butyl 1 - aminomethyl - 1 - cycloheptane - acetate toluene sulphonate.

12. 1 - Aminomethyl - 1 - cyclopentane - acetate benzene - sulphonate.

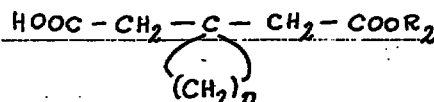
13. Calcium 1 - aminomethyl - 1 - cyclohexane - acetate.

14. Ammonium 1 - aminomethyl - 1 - cyclohexane - acetate.

15. Calcium 1 - aminomethyl - 1 - cycloheptane - acetate.

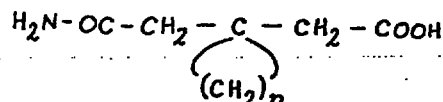
16. *n* - Butyl 1 - aminomethyl - 1 - cyclopentane - acetate.

17. Process for the preparation of compounds of the general formula given in claim 1, wherein a compound of the general formula:—



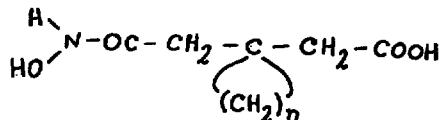
in which R_2 is an alkyl radical containing up to 8 carbon atoms and n has the same meaning as in claim 1, is converted, *via* a reactive acid derivative, into an azide which is then subjected to the Curtius rearrangement.

18. Process for the preparation of compounds of the general formula given in claim 1, wherein a compound of the general formula:—



in which n has the same meaning as in claim 1, is subjected to the Hofmann rearrangement.

- 5 19. Process for the preparation of compounds of the general formula given in claim 1, wherein a compound of the general formula:—



- 10 in which n has the same meaning as in claim 1, is subjected to the Lossen rearrangement.

20. Process for the preparation of com-

pounds of the general formula given in claim 1, substantially as hereinbefore described and exemplified.

- 15 21. Compounds according to claim 1, whenever prepared by the process according to any of claims 17 to 20.

22. Pharmaceutical compositions comprising at least one compound according to claim 1, in admixture with a solid or liquid pharmaceutical diluent or carrier. 20

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