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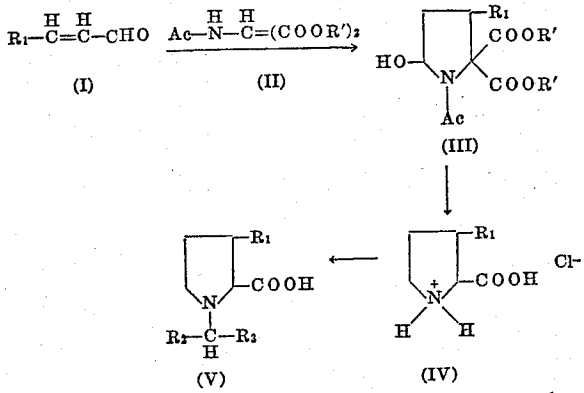
1,3-DIALKYLPROLINES

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This invention is related to a novel composition of matter and is particularly concerned with 1,3-dialkylprolines (V), intermediates thereto, derivatives and quaternary ammonium halide salts thereof, and a process therefor.

The novel products and the process of this invention can be illustratively represented by the following sequence of formulae:

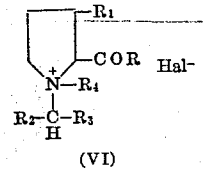


(I) (II) (III) (IV) (V)

wherein R_1 is an alkyl group having from 1 to 12 carbon atoms, inclusive; wherein R′ is an alkyl group having from 1 to 6 carbon atoms, inclusive; wherein R_2 and R_3 are selected from the group of hydrogen and alkyl, in which the alkyl groups together contain up to and including 12 carbon atoms; and wherein Ac is the acyl group of a hydrocarbon carboxylic acid containing from 2 to 12 carbon atoms, inclusive.

In this total synthesis of 1,3-dialkylprolines (V), a mixture is obtained which contains two isomeric 1,3-dialkylprolines.

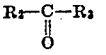
The invention is furthermore concerned with esters and amides of 1,3-dialkylproline and particularly the alkyl halide quaternary ammonium salt of 1,3-dialkylproline acid esters and amides (VI) of the formula



(VI)

wherein R is selected from the group consisting of alkoxy radicals having from 1 to 12 carbon atoms, inclusive, and NH_2—; wherein R_1, R_2 and R_3 have the same significance as hereinabove; wherein R_4 is an alkyl radical having from 1 to 20 carbon atoms, inclusive; and wherein Hal is a halogen atom selected from chlorine, bromine and iodine.

The process of the present invention comprises: treating a selected alkylacrolein (I) with a dialkyl acylamidomalonate (II) wherein the alkyl and acyl groups are defined as above, in the presence of a base to obtain the corresponding N-acyl-2,2-carboalkoxy-3-alkyl-5-hydroxypyrrolidine (III); treating compound III with tin and a mineral acid, e.g., hydrochloric acid, to obtain the corresponding 3-alkylproline hydrochloride (IV); treating compound IV with (1) a base, e.g., silver carbonate to obtain a mixture of 3-alkylprolines as the free amino acids and (2) with a carbonyl compound of the formula



wherein R_2 and R_3 are defined as hereinabove, and then hydrogenating to obtain a mixture of 1,3-dialkylprolines (V).

The alkyl halide quaternary ammonium salts of 1,3-dialkylproline esters and amides of Formula VI are obtained by treating such an amide or ester, prepared as shown in the examples, with an alkyl halide, such as methyl iodide, ethyl iodide, propyl iodide, butyl iodide, hexyl iodide, octyl iodide, decyl iodide, dodecyl iodide, tetradecyl iodide, hexadecyl iodide, octadecyl iodide, eicosyl iodide, methyl bromide and chloride, ethyl bromide and chloride, butyl bromide and chloride, hexyl bromide and chloride, heptyl bromide and chloride, dodecyl bromide and chloride, octadecyl bromide and chloride, eicosyl bromide and chloride, and the like, to give the corresponding methiodide, ethiodide, propyl iodide, butyl iodide, hexyl iodide, octyl iodide, decyl iodide, dodecyl iodide, tetradecyl iodide, hexadecyl iodide, octadecyl iodide, eicosyl iodide, methobromide and chloride, ethobromide and chloride, butyl bromide and chloride, hexyl bromide and chloride, heptyl bromide and chloride, dodecyl bromide and chloride, octadecyl bromide and chloride, eicosyl bromide and chloride, and the like of 1,3-dialkylproline amides and 1,3-dialkylproline esters.

The quaternary ammonium halide salts of Formula VI (particularly when R_4 has more than 10 carbon atoms) are active antimicrobial and wetting agents and can thus be used for cleaning instruments employed in bacteriology and surgery. Moreover, because of their electroconductivity, these compounds can be used for electrocardiographic jellies.

A suitable composition of an electrocardiographic jelly containing the above-indicated salts can be prepared as follows:

	Parts
Glycerol	5
Starch	10
Quaternary ammonium salt	60
Water	100

The jelly is prepared by mixing the starch, glycerol and water, and then adding the selected alkyl halide quaternary salt of the amide or ester of a 1,3-dialkylproline.

The novel 1,3-dialkylprolines per se of Formula V are also useful as buffers and antacids.

The fluosilicic acid salts of 1,3-dialkylprolines (V) are particularly useful for mothproofing according to U.S. Patents 1,915,334 and 2,075,359.

The new 1,3-dialkylprolines can furthermore be converted to 1,3-dialkyl-2-pyrrolidinylpenicillins by condensing the prolines with 6-aminopenicillanic acid as shown in Example 15. These new penicillins have greater stability, particularly against acids and against penicillinase and are thus more effective than penicillin.

The following examples are illustrative of the process and products of the present invention but are not to be construed as limiting.

EXAMPLE 1

N-acetyl-2,2-dicarboethoxy-3-propyl-5-hydroxypyrrolidine

A solution of 1 g. of sodium in 500 ml. of absolute ethanol was cooled to 25° C. and thereto was added 174 g. (0.8 mole) of diethyl acetamidomalonate in one portion. The solution was cooled to 0° C. and thereto was added 116 g. (1.19 moles) of 2-hexene-1-al (1-propylacrolein) dropwise over a period of 30 minutes. The mixture was thereupon stirred at 10° C. for two hours and then at 25° C for eighteen hours. Thereafter was added 1 ml. of acetic acid and the reaction mixture was concentrated in vacuo to about 100 ml. To this solu-

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tion was added ether until crystallization began. The precipitated solids were collected by filtration and recrystallized from ethanol:ether to give N-acetyl-2,2-dicarboethoxy-3-propyl-5-hydroxypyrrolidine of melting point 101–102° C. (yield, 62%).

Analysis.—Calcd. for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.07; H, 8.02; N, 4.72.

EXAMPLE 2

N-acetyl-2,2-dicarboethoxy-3-methyl-5-hydroxypyrrolidine

In the manner given in Example 1, crotonaldehyde and diethylacetamidomalonate were reacted in the presence of potassium ethoxide to give N-acetyl-2,2-dicarboethoxy-3-methyl-5-hydroxypyrrolidine.

EXAMPLE 3

N-hexanoyl-2,2-dicarbopropoxy-3-octyl-5-hydroxypyrrolidine

In the manner given in Example 1, 2-undecene-1-al was reacted with dipropyl hexanoylaminomalonate in the presence of sodium ethoxide to give N-hexanoyl-2,2-dicarbopropoxy-3-octyl-5-hydroxypyrrolidine.

In a manner given in Example 1, other N-acyl-2,2-dicarboalkoxy-3-alkyl-5-hydroxyprrolidines can be prepared by reacting a 1-alkyl substituted acrolein with an acylamidomalonic acid ester in the presence of a base such as potassium or sodium methoxide, ethoxide, propoxide, butoxide or the like. Representative compounds thus prepared include:

N-propionyl - 2,2 - dicarbobutoxy-3-pentyl-5-hydroxypyrrolidine,
N-propionyl - 2,2 - dicarbobutoxy-3-pentyl-5-hydroxypyrrolidine,
N - isobutyryl - 2,2-dicarboethoxy-3-decyl-5-hydroxypyrrolidine,
N - propionyl-2,2-dicarbooctyloxy-3-heptyl-5-hydroxypyrrolidine,
N - hexanoyl - 2,2 - dicarboethoxy-3-octyl-5-hydroxypyrrolidine,
N - octanoyl - 2,2 - dicarbobutoxy-3-nonyl-5-hydroxypyrrolidine,
N - lauroyl - 2,2 - dicarbopropoxy-3-hexyl-5-hydroxypyrrolidine,
N - phenylacetyl - 2,2 - dicarbodecyloxy - 3 - butyl-5-hydroxypyrrolidine,
N - phenylpropionyl - 2,2 - dicarboethoxy - 3 - ethyl-5-hydroxypyrrolidine,

and the like.

EXAMPLE 4

3-propylproline hydrochloride

A mixture of 6.2 g. of granulated tin, 140 ml. of 6 N hydrochloric acid and 6.3 g. of N-acetyl-2,2-dicarboethoxy-3-propyl-5-hydroxypyrrolidine was heated at reflux for one hour. The mixture was then filtered and evaporated to dryness in vacuo. The thus-obtained residue was dissolved in 50 ml. of water and then saturated with hydrogen sulfide gas. The reaction mixture containing tin sulfide was filtered and the filtrate evaporated in vacuo. A viscous oily residue was obtained which was crystallized from isopropanol:ethyl acetate to give 3-propylproline hydrochloride of melting point 165–168° C. and analysis as follows:

Analysis.—Calcd. for $C_8H_{15}NO_2 \cdot HCl$: C, 49.61; H, 8.33; N, 7.23; Cl, 18.31. Found: C, 49.84; H, 8.30; N, 7.49; Cl, 18.09.

EXAMPLE 5

3-methylproline hydrochloride

A mixture of 11.8 g. of granulated tin, 200 ml. of 6 N hydrochloric acid and 10.7 g. of N-acetyl-2,2-dicarboethoxy-3-methyl-5-hydroxypyrrolidine was heated at reflux for 45 minutes and filtered. The filtered compound was evaporated to dryness in vacuo and redissolved in water saturated with hydrogen sulfide. The reaction mixture was filtered and evaporated in vacuo. The viscous oily residue was crystallized from isopropanol:ethyl acetate to give in 18% yield 3-methylproline hydrochloride of melting point 187–190° C.

Aanalysis—Calcd. for $C_6H_{11}NO_2 \cdot HCl$: C, 43.51; H, 7.31; N, 8.46; Cl, 21.41. Found: C, 43.36; H, 7.24; N, 8.29; Cl, 21.04.

EXAMPLE 6

3-octylproline hydrochloride

In the manner given in Example 4, N-hexanoyl-2,2-dicarbopropoxy-3-octyl-5-hydroxypyrrolidine was reacted with tin and hydrochloric acid to give 3-octylproline hydrochloride.

In the manner given in Example 4, other 3-alkylproline hydrochlorides can be produced by reacting N-acyl-2,2-dicarboalkoxy-3-alkyl-5-hydroxypyrrolidine with tin and hydrochloric acid. Representative compounds thus produced include: 3-ethylproline hydrochloride, 3-butylproline hydrochloride, 3-pentylproline hydrochloride, 3-hexylproline hydrochloride, 3-heptylproline hydrochloride, 3-nonylproline hydrochloride, 3-decylproline hydrochloride, 3-undecylproline hydrochloride, 3-dodecylproline hydrochloride, 3-isobutylproline hydrochloride and the like.

EXAMPLE 7

1-methyl-3-propylproline (3-propylhygric acid)

A. 3-PROPYLPROLINE

A mixture of 880 mg. of 3-propylproline hydrochloride, 2 g. of silver carbonate and 10 ml. of water were stirred at room temperature (25° C.) for a period of ½ hour. The mixture was then warmed on a steam bath for 30 minutes and filtered. The filtrate was evaporated under vacuum and the residue crystallized from ethyl alcohol-ethyl acetate to give 600 mg. (85%) of 3-propylproline or melting point 202–203° C.

Analysis—Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.45; H, 9.60; N, 8.95.

B. 1-METHYL-3-PROPYLPROLINE

A mixture of 14 g. (0.89 mole) of 3 propylproline, 11.8 ml. of fomaldehyde, 200 ml. of methanol and 2 g. of 10% palladium-on-carbon catalyst was hydrogenated in a closed vessel (Parr hydrogenator). The reaction mixture was cooled, filtered and the residue evaporated in vacuo and twice recrystallized from ethyl alcohol:ethyl acetate to give 11.6 g. (76%) of 1-methyl-3-propylproline of melting point 202–203° C.

Analysis.—Calcd. for $C_9H_{17}NO_2$: C, 63.12; H, 10.01; N, 8.18. Found: C, 62.65; H, 10.02; N, 8.42.

EXAMPLE 8

1,3-dimethylproline

A. 3-METHYLPROLINE

In the manner given in Example 7–A, 3-methylproline hydrochloride was reacted with silver carbonate to give in 35% yield 3-methylproline melting at 201–203° C. after recrystallization from ethanol:ethyl acetate.

Analysis.—Calcd. for $C_6H_{11}NO_2$: C, 55.79; H, 8.59; N, 10.85. Found: C, 55.16; H, 8.60; N, 10.70.

B. 1,3-DIMETHYLPROLINE

In the manner given in Example 7–B, 3-methylproline was reacted with formaldehyde and hydrogenated in the presence of a palladium-on-carbon catalyst to give in 68% yield, 1,3-dimethylproline of melting point 202–203° C. after recrystallization from ethanol:ethyl acetate.

EXAMPLE 9

1-methyl-3-octylproline

In the manner given in Example 7, 3-octylproline hydrochloride was reacted with silver carbonate to give 3-octylproline.

3-octylproline was thereupon treated with formaldehyde and the mixture hydrogenated in the presence of a palladium-on-charcoal catalyst to give 1-methyl-3-octylproline.

EXAMPLE 10

1-butyl-3-propylproline

In the manner given in Example 7–B, 3-propylproline (Example 7–A) and butyraldehyde are hydrogenated in the presence of a palladium-on-charcoal catalyst in methanol solution to give 1-butyl-3-propylproline.

EXAMPLE 11

1-(1-pentylhexyl)-3-propylproline

In the manner given in Example 7–B, 3-propylproline and undecane-5-one are hydrogenated in the presence of a palladium-on-carbon catalyst to give 1-(1-pentylhexyl)-3-propylproline.

In the manner given in Example 7–A and B, other 1,3-dialkylprolines are produced by the reaction of 3-alkylproline hydrochlorides with silver carbonate and then with a compound of the formula R_2—CO—R_3, in which R_2 and R_3 are alkyl groups or hydrogen having together not more than 12 carbon atoms. Representative compounds thus produced include: 1-methyl-3-pentylproline, 1-methyl-3-hexylproline, 1-methyl-3-dodecylproline, 1-ethyl-3-decylproline, 1 - propyl - 3 - heptylproline, 1 - butyl - 3-octylproline, 1-hexyl-3-nonylproline, 1-dodecyl-3-hexylproline, 1,3-dibutylproline, 1,3-diethylproline, 1-(1-butylpentyl)-3-butylproline, and the like.

EXAMPLE 12

1-methyl-3-propylproline amide

To a stirred mixture of 1.03 g. (0.006 mole) of 1-methyl-3-propylproline, 1.68 ml. (0.006 mole) of triethylamine and 60 ml. of dry acetonitrile at 0° C. was added 0.58 ml. of ethyl chloroformate. The reaction mixture was maintained between 0 and 10° C. for a period of ½ hour and then 6 ml. of concentrated ammonium hydroxide was added. After standing for a period of 18 hours at 25° C. the reaction mixture was evaporated to dryness in vacuo and the resulting residue dissolved in 50 ml. of water. The aqueous solution was made acidic with hydrochloric acid and thereupon extracted with four 50-ml. portions of methylene chloride. The methylene chloride extracts were discarded, the aqueous phase was made basic with sodium hydroxide and then extracted with three 50-ml. portions of methylene chloride. The methylene chloride extracts were combined, evaporated and the residue recrystallized from Skellysolve B hexanes to give 1-methyl-3-propylproline amide of melting point 99–100° C. in 60% yield.

Analysis.—Calcd. for $C_9H_{18}N_2O$: C, 63.49; H, 10.66; N, 16.46. Found: C, 63.60; H, 10.85; N, 16.22.

EXAMPLE 13

1,3-dimethylproline amide

In the manner given in Example 12, 1,3-dimethylproline in acetonitrile was treated with triethylamine, thereupon with ethyl chloroformate, and subsequently with ammonium hydroxide to give 1,3-dimethylproline amide.

EXAMPLE 14

1-methyl-3-octylproline amide

In the manner given in Example 12, 1-methyl-3-octylproline dissolved in dry acetonitrile, was reacted with triethylamine and ethyl chloroformate and subsequently with ammonium hydroxide to give 1-methyl-3-octylproline amide.

In the manner given in Example 12, other 1,3-dialkylproline amides are obtained by reacting 1,3-dialkylproline with triethylamine, ethyl chloroformate, and subsequently treating the mixture with ammonium hydroxide. Representative 1,3-dialkylproline amides thus obtained include: 1-methyl-3-butylproline amide, 1-methyl-3-pentylproline amide, 1-methyl-3-hexylproline amide, 1-methyl-3-heptylproline amide, 1-methyl-3-decylproline amide, 1-methyl - 3 - dodecylproline amide, 1 - ethyl - 3 - octylproline amide, 1,3-dioctylproline amide, 1-butyl-3-nonylproline amide, 1-propyl-3-hexylproline amide, 1,3-dibutylproline amide, 1,3-diethylproline amide, and the like.

EXAMPLE 15

Potassium 6-(3-propylhygramido)penicillanate

A mixture of 3.09 g. of 3-propylhygric acid, 9.5 ml. of tributylamine, 100 ml. of acetonitrile and 40 ml. of acetone was stirred until complete solution had taken place. To this solution, cooled to 0° C., was added 2.05 ml. of isobutyl chloroformate. The reaction mixture was stirred for 30 minutes in an ice bath, then 3.24 g. of 6-aminopenicillanic acid in 50 ml. of water and 1.7 g. sodium bicarbonate was added, and stirring was continued at room temperature for 2 hours. The mixture was evaporated to dryness.

The residue was partitioned between ether and water, and the ether layer was discarded. The aqueous layer was adjusted to pH 6 with dilute hydrochloric acid, extracted several times with ether and the ether solution was dried over sodium sulfate. The addition of a 40% solution of potassium 2-ethyl hexanoate in butyl alcohol precipitated potassium 1-methyl - 3 - propyl - 2 - pyrrolidinylpenicillin [potassium 6-(3-propylhygramido)penicillanate].

EXAMPLE 16

Methyl ester of 1,3-dimethylproline

An excess of diazomethane was added over a 10-minute period to a stirred solution of 1.5 g. of 1,3-dimethylproline in 20 ml. of ethanol. The mixture was thereupon decomposed by the addition of acetic acid, evaporated to dryness, and the resulting residue dissolved with 20 ml. of water. This solution was made basic by the addition of aqueous sodium hydroxide and then extracted with three 25-ml. portions of methylene chloride. The methylene chloride extracts were evaporated to give 500 mg. of crude 1,3-dimethylproline methyl ester.

This material was dissolved in hydrochloric acid, the solution was evaporated and crystallized from ethanol:ether to give the hydrochloric acid salt of the methyl ester of 1,3-dimethylproline having a melting point of 163–165° C.

Analysis.—Calcd. for $C_8H_{15}NO_2 \cdot HCl$: C, 49.61; H, 8.33; N, 7.23. Found: C, 49.60; H, 8.44; N, 6.92.

EXAMPLE 17

Ethyl 3-propylhygrate hydrochloride (1-methyl-3-propylproline ethyl ester hydrochloride)

A solution was prepared containing 1 g. of 1-methyl-3-propylproline in 25 ml. of ethanol. Through this solution was passed dry hydrogen chloride gas for a period of 15 minutes. The solution was thereupon evaporated and the resulting material recrystallized twice from ethanol and water to give ethyl 3-propylhygrate hydrochloride.

Treatment of the hydrochloric acid salt of ethyl 3-propylhygrate with silver carbonate as shown in Example 7–A gives the free ester, ethyl 3-propylhygrate.

In the manner given in Example 17, other esters of 1,3-dialkylprolines and the hydrochlorides can be made by reacting a selected 1,3-dialkylproline in an alkanol having 1 to 12 carbon atoms, inclusive, such as methanol, ethanol, propanol, butanol, pentanol, hexanol, heptanol, octanol, decanol, dodecanol, and the like, with hydrogen chloride to obtain the corresponding alkyl ester of 1,3-dialkylproline hydrochloride, which can be converted with silver carbonate or silver oxide to the corresponding free ester. Representative esters thus obtained include the methyl ester of 1,3-diethylproline, the methyl ester of 1-methyl-3-butylproline, the methyl ester of 1-methyl-3-

pentylproline, the ethyl ester of 1-methyl-3-hexylproline, the butyl ester of 1-methyl-3-decylproline, the octyl ester of 1-methyl-3-heptylproline, the dodecyl ester of 1-ethyl-3-octylproline, and the like.

EXAMPLE 18

Methiodide of ethyl 3-propylhygrate

To 3 g. of ethyl 3-propylhygrate was added with cooling and continuous stirring 4.25 g. of methyl iodide; a vigorous reaction ensued. After additional cooling, 2.5 g. of methyl iodide was added and the mixture was allowed to stand overnight at room temperature. Excess methyl iodide was removed under reduced pressure, and the solid obtained was dissolved in 50 ml. of anhydrous ethanol. The ethanol was removed under reduced pressure and the residue was recrystallized three times from a 1:1 mixture of ethanol:ether to yield crystals of the methiodide of ethyl 3-propylhygrate.

EXAMPLE 19

Methiodide of 1,3-dimethylproline methyl ester

To 2 g. of 1,3-dimethylproline methyl ester was added 2.5 g. of methyl iodide. After standing at room temperature for a period of 22 hours, the reaction mixture was dissolved in 20 ml. of methanol, treated with decolorizing carbon and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue was recrystallized twice from ethyl acetate to give crystals of the methiodide of 1,3-dimethylproline methyl ester.

EXAMPLE 20

Methiodide of 1-methyl-3-propylproline amide (methiodide of 3-propylhygramide)

A solution of 2.5 g. of 1-methyl-3-propylproline amide (3-propylhygramide) in 20 ml. of methanol was treated with 3 ml. of methyl iodide with cooling. After initial vigorous reaction had abated, 20 ml. of methanol and 5 ml. of methyl iodide were added with stirring. Stirring was continued until the exothermic reaction was over, the methiodide of 3-propylhygramide was filtered and washed with methanol. The light yellow filtrate was evaporated to dryness in vacuo and the residue was dissolved in 50 ml. of acetone and seeded with a small amount of crystal, performed in acetone and ethyl acetate. The mixture was then cooled in a refrigerator overnight and the crystals thus obtained were collected by filtration, washed with acetone and ether and dried in vacuo at 40° C. to give the methiodide of 1-methyl-3-propylproline amide (methiodide of 3-propylhygramide).

In the manner given in Examples 18, 19 and 20, alkyl quaternary ammonium salts of the esters and amides of 1,3-dialkylproline can be obtained by reacting alkyl chlorides, bromides or iodides with selected 1,3-dialkylproline esters and amides. Representative compounds thus obtained include: ethiodide, propyl iodide, butyl iodide, pentyl iodide, hexyl iodide, octyl iodide, decyl iodide, dodecyl iodide, tetradecyl iodide, octadecyl iodide, eicosyl iodide, methyl chloride and bromide, ethyl chloride and bromide, propyl chloride and bromide, butyl chloride and bromide, hexyl chloride and bromide, octyl chloride and bromide, decyl chloride and bromide, dodecyl chloride and bromide, tetradecyl bromide and iodide, octadecyl chloride and bromide, eicosyl bromide and iodide of, e.g., the methyl ester of 1-methyl-3-pentylproline, the ethyl ester of 1-methyl-3-hexylproline, the octyl ester of 1-methyl-3-heptylproline, the propyl ester of 1-ethyl-3-decylproline, the butyl ester of 1-octyl-3-dodecylproline, the dodecyl ester of 1,3-dioctylproline, the undecyl ester of 1,3-didodecylproline, the amide of 1,3-dimethylproline, the amide of 1-methyl-3-hexylproline, the amide of 1-ethyl-3-octylproline, the amide of 1-propyl-3-decylproline, the amide of 1-butyl-3-dodecylproline, the amide of 1,3-didecylproline, the amide of 1,3-dioctylproline, the amide of 1,3-dibutylproline, and the like.

We claim:

1. N - acetyl-2,2-dicarboethoxy-3-propyl-5-hydroxypyrrolidine.
2. 1-methyl-3-propylproline amide.
3. 1,3-dimethylproline amide.
4. The methyl ester of 1,3-dimethylproline.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,274,212 September 20, 1966

Barney J. Magerlein et al.

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 3, line 33, for "N-propiony1-2,2-dicarbobutoxy-3-penty1-5-hydroxypyrrolidine" read -- N-butyry1-2,2-dicarbododecyloxy-3-hexy1-5-hydroxypyrrolidine --; column 4, line 38, for "202-203° C." read -- 229-230° C. --; same line 38, for "or" read -- of --; column 8, line 37, strike out "Ibid., Volume 15, Reaction No. 343 (1961)." and insert the same after line 41, same column 8.

Signed and sealed this 5th day of September 1967.

(SEAL)
Attest:

ERNEST W. SWIDER
Attesting Officer

EDWARD J. BRENNER
Commissioner of Patents