

PATENT SPECIFICATION

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(54) THERAPEUTICALLY ACTIVE DERIVATIVES OF N-SUBSTITUTED BUTYRAMIDE

- (71) We, LION HAMIGAKI KABUSHIKI KAISHA of 3-7, Honjo 1-chome, Sumida-ku, Tokyo, Japan, a Japanese body corporate, 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:—
- 10 This invention relates to therapeutically active N-substituted-butyramide derivatives and provides new chemical compounds of this class having the effects of increasing paradoxical sleep and tranquilizing.
- 15 Physiologists recognise two kinds of natural sleep viz., ortho or non-rapid-eye-
- movement (NREM) sleep and para, paradoxical or rapid-eye-movement (REM) sleep. (See, for instance M. Jouvet, "Neurophysiology of the States of Sleep", *Physiol. Review*, Vol. 47, (1967); pp. 117-77). In man and certain other mammals phases of ortho sleep, of para sleep and of wakefulness occur periodically and it is one of the objects of the present invention to provide new pharmaceutical compounds capable of increasing the duration of the phase of para sleep.
- The compounds of the invention are N-substituted- β -carboxymethylacetoxo butyr- amides having the following general formula:—



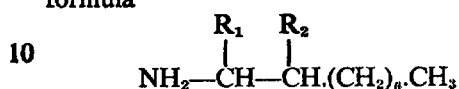
- wherein one of R_1 and R_2 is H and the other is methyl or ethyl, and the symbol n represents an integer from 2 to 5, preferably 3 or 4, and alkali, metal and alkaline earth metal salts thereof. The invention includes processes for producing these compounds and also compositions containing them.
- The compounds of the present invention show useful and unexpected pharmacological action in that they possess the favourable actions mentioned later.
- Generally it is known that the effects of conventional hypnotics are narcotic and decrease the phase of paradoxical sleep and state thereby brought about is essentially state thereby brought about is essentially give abnormal encephalograms, and the different from natural sleep. Thus a compound having hypnotic activity which can produce sleep simulating natural sleep has been looked for. From this point of view the hypnotic effect of the tranquilizers has recently been studied, instead of the classical sleep drugs. But this type of hypnotic has been shown to have muscle relaxing activity on awakening and not to increase the phase of para-sleep.
- The present invention provides new compounds which not only induce sleep simulating natural sleep without any narcotic effect but also actively augment the phase of para-sleep and have a tranquilizing effect without muscle relaxation.
- The present invention also provides compounds of medicinal efficiency that are rapidly absorbed from the gastrointestinal tract so that they have both an immediate effect and security, and can be injected as a water-soluble form.
- It is also an object of the present invention to provide a process by which these compounds with para-sleep augmenting effect (that have never been observed in any conventional medicines) can be easily and economically produced.
- The compounds of the invention show these effects at a small dose and with

[Price 25p]

almost no harmful side effects such as hemolysis, local irritation or gastrointestinal stimulation.

The compounds according to the present invention may be synthesized in the following way:

First, an alkyl-amine of the general formula



in which R_1 , R_2 and n are as defined above, for example 1-methylhexylamine, 1-methylheptylamine or 2-ethyl-hexylamine, is reacted with diketene, for instance in an inactive solvent such as benzene, to give the N-substituted-acetoacetamide. This compound is subjected to reduction, with for example sodium borohydride, or catalytic reduction using for example Raney nickel, to give N-substituted- β -oxybutyramide. This compound is then reacted with succinic anhydride, for instance by heating in pyridine or with succinic acid in an inactive solvent containing a catalyst, for example sulphuric acid, and the corresponding N-substituted- β -carboxymethylacetoxy butyramide is obtained as a crystalline or oily substance which can be converted into its sodium, potassium, calcium or magnesium salts in the usual manner.

One of the compounds according to the invention, that is the calcium salt of N-2-ethylhexyl- β -carboxymethylacetoxy butyramide, is obtained as a white powder which is but slightly hygroscopic. Its pharmaceutical processing is easy. When preparing tablets or capsules a carrier substance such as silicic acid, magnesium aluminosilicate or lactose is added. It is water-soluble and the 5% water solution can be preserved stably at room temperature at least for six months; it is also available as an injection medium.

The effects of the compounds on the sleep and wakefulness of cats are illustrated in the trials described below.

In these trials the calcium salt of 2-ethylhexyl- β -carboxymethylacetoxy butyramide, one of the compounds of the present invention, was orally administered to cats and simultaneous recordings of the electroencephalogram, the electromyogram of the cervical muscle and the movement of eyeball revealed that both total sleep time and para-sleep time were significantly increased after administration of the compound.

In two trials during the period of 3 hours before the administration of 100 mg/kg of this compound in a cat, the total sleep times were 40.5 % and 44.1 % (average 42.3 %), and the para-sleep times were 8.9 % and 7.8 % (average 8.4 %). After the administration, the total sleep times were 65.0 % and

77.1 % (average 71.1 %) and the para-sleep times were 16.7 % and 22.1 % (average 19.4 %). With 150 mg/kg of the compound in the same cat, the total sleep times and the para-sleep times before the administration were 56.1 % and 10.0 % respectively and those after the administration were 78.3 % and 26.1 % respectively. The difference between the para-sleep times before and after the administration in above trials is statistically significant ($P < 0.001$) and also the difference between the total sleep times is significant ($P < 0.05$).

On the other hand, when 30 mg/kg of pentobarbital i.p. or 200 mg/kg of bromvalerylurea was administered orally to the same cat, the phase of para-sleep was never found during the whole provoked sleep of 3 hours. When 3 mg/kg of chlorpromazine was administered orally to the same cats, the total sleep time was 27.5 % and the para-sleep time was 7.8 %, and after the oral administration of 3 mg/kg of nitrazepam, the total sleep time and the para-sleep time were 28.5 % and 5.6 % respectively but severe staggering was observed for 2 days after awakening. Control recordings during the period of 3 hours were repeatedly taken with the same cat for six days and the average total sleep time was 44.9 % (95 % confidence limits: ± 7.2) and the average para-sleep time was 7.4 % (95% confidence limits: ± 2.2).

Twenty-four hour continuous observation tests were performed using three other cats. Three or four day-control tests before the administration revealed that the average total sleep times were 79 %, 79 % and 63 % respectively for each cat, and the average para-sleep times were 14 %, 18 %, and 17 %. During the period of 24 hours after the oral administration of 100 mg/kg of the present above-mentioned compound of the invention, the total sleep times were 82 %, 87 %, and 72 %, and the para-sleep times were 23 %, 21 %, and 21 % for each cat, respectively. The analysis of variance which was carried out with regard to cats and drug administration was statistically significant between the para-sleep time before and after the administration ($P < 0.005$) and also between the total sleep time before and after it ($P < 0.01$). The above results show that the said compound induces the natural sleep of cats, increasing both para-sleep time and total sleep time.

When the same compound was administered to mice, the righting reflex was lost and the ED_{50} was 62.5 mg/kg i.p. and 150 mg/kg orally. The ED_{50} to attain pharmacohypnosis in mice was 400 mg/kg i.p. and 2,000 mg/kg orally. The LD_{50} for mice was 476 mg/kg i.p. and 2,500 mg/kg orally and so the coefficient of safety, i.e. the value of LD_{50} for ED_{50} of righting re-

flex loss, is extremely high. The dosage to attain pharmacohypnosis is about 80 % of the LD₅₀ and this value corresponds to that of the minor tranquillizers. When mice were injected with this compound 100 mg/kg i.p., their motions in a jingle-cage were clearly depressed. In a rotating-cage, their motions were less depressed. When 40 mg/kg or 50 mg/kg of thiopental was administered to mice 15 minutes after the administration of 100 mg/kg i.p. of the present compound, the duration of pharmacohypnosis was prolonged about three times compared with administration of thiopental alone. Conditions Response (CR) in mice effected by buzzer stimulus and electrical shocks, was blocked in 50 % of the mice after administration of this compound 100 mg/kg i.p., although Non Conditioned Response (NCR) was not blocked. This action was more remarkable than that of meprobamate. The fight of *Betta Splendens Regan* (fighting fish) was depressed in water containing 250 ppm of this compound. These results show that this compound belongs to the minor tranquillizers.

The said compound was also found to have an analgesic effect on mice, the ED₅₀ by the writhing method induced by acetic acid in mice was 121 mg/kg i.p., and the potency was about 1/3 that of aminopyrine.

The antagonism against pentetrazol 75 mg/kg s.c. of strychnin 2 mg/kg i.p. was not found after administration of the said compound of the concentration in a dosage of 100 mg/kg i.p. The action of muscle relaxation in mice by the rotating rod method was not found after administration of this compound in a dosage of 100 mg/kg i.p.

The rate of the inhibitory action on respiration of rat brain slice after administration of 1×10^{-3} M of this compound was 27.8 % at 5 mM of potassium ion and 23.6 at 105 mM.

The subacute toxicity to rats has been tested over the period of 3 months by continuous daily administration of 1,000 mg, 400 mg and 200 mg of the said compound per kilogram orally, and 250 mg, 100 mg and 50 mg of this compound per kilogram i.p. The results showed that this compound has no noticeable toxicity, as evidenced by the number of deaths, the rate of increase in bodyweight, the rate of taking food, the clinical chemical tests, the blood pictures and the microscopic tests of organ tissues.

In a pre clinical test on a few human males, the tranquillizing effect was noticeable in the dosage of 10 % 15 mg of the compound per 60 kilograms orally and the effect of inducing natural sleep was noticeable in the dosage of 45 % 60 mg of this compound per 60 kilograms orally.

The invention is further illustrated by the following Examples:

EXAMPLE 1

Calcium salt of N-1-methylhexyl-β-carboxymethylacetoxo butyramide

To a solution of 13.2 grams of 1-methylhexylamine in 20 ml of benzene, was added 9.6 g of diketene in 20 ml of benzene dropwise over a period of 30 min. at 40°C. After distillation of the solvent, the residue was dissolved in ether and washed successively with dilute hydrochloric acid, 2 % sodium bicarbonate solution and water, and then dried with anhydrous sodium sulphate. After distilling off the ether, 20.3 g of N-1-methylhexylacetacetamide boiling at 139—141°C/1.6 mm Hg was obtained. The product forms white crystal melting at 11°C in an ice box. IR_{max} cm⁻¹: 1730, 1650, 1560.

To a solution of 18.6 grams of N-1-methylhexylacetacetamide in 80 ml of methanol, 3.6 g of sodium borohydride was slowly added at 40—45°C. After decomposition with dilute hydrochloric acid, the aqueous residue was extracted with ether. The other extract was washed successively with 2 % sodium bicarbonate solution and water, dried with anhydrous sodium sulphate and then ether removed. By distillation under reduced pressure, 13.2 grams of N-1-methylhexyl-β-oxybutyramide boiling at 147—148°C/1.0 mm Hg was obtained. After recrystallization from ethyl acetate, the product melted at 42°C. IR_{max} cm⁻¹: 1650, 1560.

To a solution of 10.5 grams of N-1-methylhexyl-β-oxybutyramide in 20 ml of pyridine, 9.0 grams of succinic anhydride was added, and the mixture was heated at 105° for 20 minutes. After distilling off the solvent, 60 ml of water was added and the mixture was extracted with ether, the ether layer was washed with 2 % hydrochloric acid and then water and extracted with 50 ml of 10 % sodium bi-carbonate solution. The aqueous layer was separated, washed with ether, and acidified with dilute hydrochloric acid to yield a yellowish oil. It was extracted with ether and the ether layer dried with anhydrous sodium sulphate and decolorized by activated charcoal, to give a colorless viscous oil after removal of the solvent. The product was crystallized in an ice box to give 10.4 grams of N-1-methylhexyl-β-carboxymethylacetoxo butyramide melting at 52°C. IR_{max} cm⁻¹: 1740, 1650, 1560. The amount of 0.05 N-sodium hydroxide solution required to neutralize 60.3 mg of this product: Calcd. for C₁₅H₂₉O₅N. 4.00 ml; Found 3.97 ml.

The effect of the sodium salt of this compounds: ED₅₀ for righting reflex loss in mice was 125 mg/kg. This product affords a solution of the calcium salt by reacting with the calculated amount of calcium hydroxide in water. After distilling the water off and drying under reduced pressure, it

gives a white powder of the calcium salt of ED₅₀ for righting reflex loss in mice: 150 mg/kg orally.

5 EXAMPLE 2

N-1-methylheptyl-β-carboxymethyl-acetoxy butyramide

12.9 grams of 1-methylheptylamine was reacted with 8.4 grams of diketene and 10 19.6 g of N-1-methylheptylacetoacetamide, boiling at 135—137°C/0.2 mm Hg were obtained as crystals. After recrystallization from ethyl acetate, the product melted at 24°C. IRλ_{max} cm⁻¹: 3380, 1730, 1650, 1560.

15 To a solution of 10.0 grams of N-1-methylheptylacetoacetamide in 40 ml of methanol, 1.8 grams of sodium borohydride was added, and the mixture was treated in the same way as in Example 1 to give 8.9 20 grams of N-1-methylheptyl-β-oxybutyramide, boiling at 149—151°C/0.3 mm Hg, as crystals. After recrystallization from ethyl acetate, the product melted at 65°C. IRλ_{max} cm⁻¹: 3340, 1640, 1560.

25 To a solution of 8.1 grams of N-1-methylheptyl-β-oxybutyramide in 20 ml of pyridine, 8.0 grams of succinic anhydride was added, and the mixture was heated at 110°C for 20 minutes. By the same method as in Ex- 30 ample 1, 6.8 grams of N-1-methylheptyl-β-carboxymethylacetoxy butyramide was obtained as crystals. Recrystallization from the mixture of ether and pet. ether afforded crystals melting at 55°C. IRλ_{max} cm⁻¹: 3390, 35 1745, 1720, 1660, 1570.

The amount of 0.05 N-sodium hydroxide solution required to neutralize 65.3 mg of this product: calcd. for C₁₆H₂₉O₅N: 4.03 ml; Found: 4.02 ml. The effect of the sodium salt of this compound on mice: ED₅₀ 40 for righting reflex loss: 75 mg/kg i.p.; 130 mg/kg orally; ED₅₀ for pharmacohypnosis: 600 mg/kg i.p., LD₅₀: 750 mg/kg i.p.

45 EXAMPLE 3

Calcium salt of N-2-ethylhexyl-β-carbox-methylacetoxy butyramide

12.0 grams of 2-ethylhexylamine was reacted with 7.8 grams of diketene, and 17.4 50 grams of N-2-ethylhexylacetoacetamide, boiling 128—130°C/0.3 mm Hg was obtained. IRλ_{max} cm⁻¹: 1730, 1650, 1560. A solution of 39.5 grams of N-2-ethylhexyl-acetoacetamide in 350 ml of methanol was 55 hydrogenated for 18 hours at 75°C in the

presence of Raney nickel. After the catalyst was filtered off, the filtrate was freed from the solvent. By distillation under reduced pressure, 35.5 grams of N-2-ethylhexyl-β-oxybutyramide, boiling at 149— 60 150°C/0.30 mm Hg, was obtained as a colorless viscous oil.

IRλ_{max} cm⁻¹: 3340, 1640, 1560, 1460. Anal. Calcd. for C₁₂H₂₅O₂N: C, 66.93; H, 11.70; N, 6.50; Found: C, 66.91; H, 65 11.70; N, 6.62. The product afforded the p-nitrobenzoate by reacting with p-nitrobenzoylchloride in the presence of pyridine. Recrystallized from alcohol, the p-nitrobenzoate melted at 110°C. Anal. Calcd. for 70 C₁₉H₂₈O₅N₂: C, 62.62; H, 7.74; N, 7.69; Found: C, 62.42; H, 7.68; N, 7.67.

To a solution of 180 grams of N-2-ethylhexyl-β-oxybutyramide in 300 ml of pyridine, 150 grams of succinic anhydride was added, 75 and the mixture was heated at 115° for 30 minutes. By the same method as Example 1, 245 grams of N-2-ethylhexyl-β-carboxymethylacetoxybutyramide was obtained as a 80 colorless viscous oil.

IRλ_{max} cm⁻¹: 1750, 1650, 1570. Anal. Calcd. for C₁₆H₂₉O₅N: C, 60.93; H, 9.27; Found: C, 60.73; H, 9.30. The amount of 0.05 N-sodium hydroxide solution required to neutralize 52.8 mg of this product: Calcd. 85 for C₁₆H₂₉O₅N: 3.35 ml; Found 3.35 ml.

To a solution of 125 grams of N-2-ethylhexyl-β-carboxymethylacetoxybutyramide in 750 ml of 80 % ethanol was added 15 grams of calcium hydroxide and the whole shaken 90 up for 15 minutes. Next, 600 ml of anhydrous ethanol was added and the mixture filtered off. After distilling off the alcohol from the filtrate, the residue was dried under reduced pressure and 130 grams of the 95 calcium salt of N-2-ethylhexyl-β-carboxymethylacetoxybutyramide was obtained in the form of a white powder which was slightly hygroscopic.

IRλ_{max} cm⁻¹: 1740, 1650, 1570. 100

H₂₀ 1 %

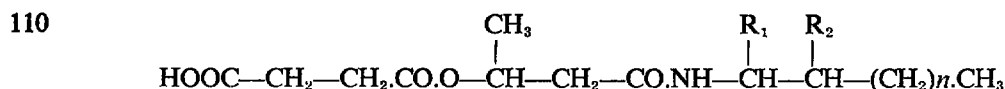
UVA (E) : 192 (290. Anal. Calcd.

max 1 cm

for C₃₂H₅₅O₁₀N₂Ca: C, 57.46; H, 8.40; Ca, 5.99; Found: C, 57.03; H, 8.62; Ca, 6.04. 105

WHAT WE CLAIM IS:—

1. N - substituted - β - carboxymethyloxy butyramide of the general formula



wherein one of R₁ and R₂ is H and the other is methyl or ethyl, and n represents 115 an integer from 2 to 5, inclusive, and the sodium, potassium, calcium and magnesium salts thereof.

2. A compound as claimed in Claim 1 in which n is 3 or 4.

3. N - 2 - ethylhexyl - β - carboxymethyl- 120 acetoxy butyramide of the structural formula

gives a white powder of the calcium salt of ED₅₀ for righting reflex loss in mice: 150 mg/kg orally.

5 EXAMPLE 2

N-1-methylheptyl-β-carboxymethyl-acetoxy butyramide

12.9 grams of 1-methylheptylamine was reacted with 8.4 grams of diketene and 19.6 g of N-1-methylheptylacetoacetamide, boiling at 135–137°C/0.2 mm Hg were obtained as crystals. After recrystallization from ethyl acetate, the product melted at 24°C. IRλ_{max} cm⁻¹: 3380, 1730, 1650, 1560.

To a solution of 10.0 grams of N-1-methylheptylacetoacetamide in 40 ml of methanol, 1.8 grams of sodium borohydride was added, and the mixture was treated in the same way as in Example 1 to give 8.9 grams of N-1-methylheptyl-β-oxybutyramide, boiling at 149–151°C/0.3 mm Hg, as crystals. After recrystallization from ethyl acetate, the product melted at 65°C. IRλ_{max} cm⁻¹: 3340, 1640, 1560.

To a solution of 8.1 grams of N-1-methylheptyl-β-oxybutyramide in 20 ml of pyridine, 8.0 grams of succinic anhydride was added, and the mixture was heated at 110°C for 20 minutes. By the same method as in Example 1, 6.8 grams of N-1-methylheptyl-β-carboxymethylacetoxy butyramide was obtained as crystals. Recrystallization from the mixture of ether and pet. ether afforded crystals melting at 55°C. IRλ_{max} cm⁻¹: 3390, 1745, 1720, 1660, 1570.

The amount of 0.05 N-sodium hydroxide solution required to neutralize 65.3 mg of this product: calcd. for C₁₆H₂₉O₅N: 4.03 ml; Found: 4.02 ml. The effect of the sodium salt of this compound on mice: ED₅₀ for righting reflex loss: 75 mg/kg i.p.; 130 mg/kg orally; ED₅₀ for pharmacohypnosis: 600 mg/kg i.p., LD₅₀: 750 mg/kg i.p.

45 EXAMPLE 3

Calcium salt of N-2-ethylhexyl-β-carboxymethylacetoxy butyramide

12.0 grams of 2-ethylhexylamine was reacted with 7.8 grams of diketene, and 17.4 grams of N-2-ethylhexylacetoacetamide, boiling 128–130°C/0.3 mm Hg was obtained. IRλ_{max} cm⁻¹: 1730, 1650, 1560. A solution of 39.5 grams of N-2-ethylhexylacetoacetamide in 350 ml of methanol was hydrogenated for 18 hours at 75°C in the

presence of Raney nickel. After the catalyst was filtered off, the filtrate was freed from the solvent. By distillation under reduced pressure, 35.5 grams of N-2-ethylhexyl-β-oxybutyramide, boiling at 149–150°C/0.30 mm Hg, was obtained as a colorless viscous oil.

IRλ_{max} cm⁻¹: 3340, 1640, 1560, 1460. Anal. Calcd: for C₁₂H₂₅O₂N: C, 66.93; H, 11.70; N, 6.50; Found: C, 66.91; H, 11.70; N, 6.62. The product afforded the p-nitrobenzoate by reacting with p-nitrobenzoylchloride in the presence of pyridine. Recrystallized from alcohol, the p-nitrobenzoate melted at 110°C. Anal. Calcd. for C₁₆H₂₉O₅N₂: C, 62.62; H, 7.74; N, 7.69; Found: C, 62.42; H, 7.68; N, 7.67.

To a solution of 180 grams of N-2-ethylhexyl-β-oxybutyramide in 300 ml of pyridine, 150 grams of succinic anhydride was added, and the mixture was heated at 115°C for 30 minutes. By the same method as Example 1, 245 grams of N-2-ethylhexyl-β-carboxymethylacetoxybutyramide was obtained as a colourless viscous oil.

IRλ_{max} cm⁻¹: 1750, 1650, 1570. Anal. Calcd. for C₁₆H₂₉O₅N: C, 60.93; H, 9.27; Found: C, 60.73; H, 9.30. The amount of 0.05 N-sodium hydroxide solution required to neutralize 52.8 mg of this product: Calcd. for C₁₆H₂₉O₅N: 3.35 ml; Found 3.35 ml.

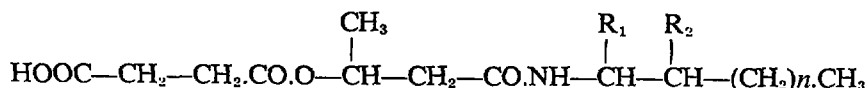
To a solution of 125 grams of N-2-ethylhexyl-β-carboxymethylacetoxybutyramide in 750 ml of 80 % ethanol was added 15 grams of calcium hydroxide and the whole shaken up for 15 minutes. Next, 600 ml of anhydrous ethanol was added and the mixture filtered off. After distilling off the alcohol from the filtrate, the residue was dried under reduced pressure and 130 grams of the calcium salt of N-2-ethylhexyl-β-carboxymethylacetoxybutyramide was obtained in the form of a white powder which was slightly hygroscopic.

IRλ_{max} cm⁻¹: 1740, 1650, 1570. H₂O 1 %

UVλ (E max 1 cm): 192 (290. Anal. Calcd. for C₃₂H₅₉O₁₀N₂Ca: C, 57.46; H, 8.40; Ca, 5.99; Found: C, 57.03; H, 8.62; Ca, 6.04.

WHAT WE CLAIM IS:—

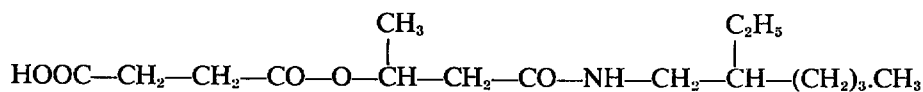
1. N - substituted - β - carboxymethyloxy butyramide of the general formula



wherein one of R₁ and R₂ is H and the other is methyl or ethyl, and n represents an integer from 2 to 5, inclusive, and the sodium, potassium, calcium and magnesium salts thereof.

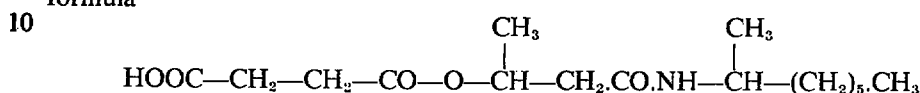
2. A compound as claimed in Claim 1 in which n is 3 or 4.

3. N - 2 - ethylhexyl - β - carboxymethylacetoxy butyramide of the structural formula



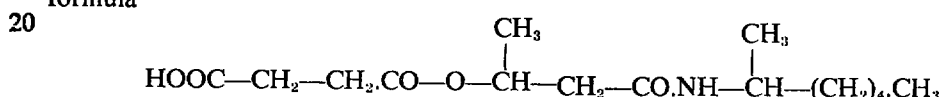
5 or its sodium, potassium or magnesium salt.

4. N - 1 - methylheptyl - β - carboxymethylacetoxy butyramide of the structural formula



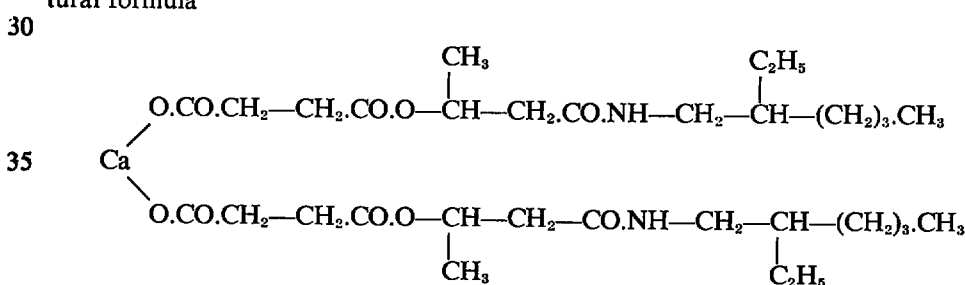
10 or its sodium, potassium, calcium or magnesium salt.

5. N - 1 - methylhexyl - β - carboxymethylacetoxy butyramide of the structural formula

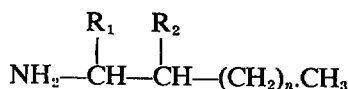


20 or its sodium, potassium, calcium or magnesium salt.

6. Calcium N - 2 - ethylhexyl - β - carboxymethylacetoxy butyramide of the structural formula



35 7. A process for the preparation of an N - substituted - β - carboxymethylacetoxy butyramide as claimed in any of claims 1 to 6 which comprises reacting an alkylamine represented by the general formula



40 50 wherein R_1 , R_2 and n are as defined in claim 1, with diketene thereby producing an N-substituted-acetoacetamide, and thereafter reducing this substance and reacting the product with succinic anhydride, and

55 optionally converting the product so obtained into the sodium, potassium, calcium or magnesium salt.

60 8. A process as claimed in Claim 7 in which the reduction is performed with the aid of sodium borohydride.

9. A process as claimed in Claim 7, in which the reduction is performed catalytically.

10. A process as claimed in Claim 9, in which Raney nickel is used as the catalyst.

11. A process of preparing compound as claimed in claim 1 substantially as described in any of Examples 1, 2 or 3.

12. A tranquillizer composition comprising a compound as claimed in any of claims 1 to 6, together with a diluent or carrier.

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