

PATENT SPECIFICATION

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Int. Cl.:—C 07 c // A 61 k

COMPLETE SPECIFICATION

Acid Amides and a process for the manufacture thereof

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESellschaft, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, 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 relates to novel acid amides and a process for the manufacture thereof; more particularly, the invention is concerned with novel acid amides of β, β -dimethyl - α, γ - dihydroxy - butyric acid, a process for the manufacture thereof, pharmaceutical compositions containing said amides and novel intermediates occurring in said process.

The novel acid amides provided by the invention are compounds of the formula



wherein R is a hydrogen atom or a lower-alkyl group. They have valuable peripheral analgesic activity without undesirable side effects. The preferred compounds are those in which R is a hydrogen atom or the ethyl group; that is to say, N-(*p*-hydroxy-phenyl) β, β - dimethyl - α, γ - dihydroxy - butyric acid amide and N-(*p*-ethoxy-phenyl) β, β - dimethyl - α, γ - dihydroxy - butyric acid amide.

The foregoing novel acid amides may be used in admixture with the customary pharmaceutical excipients such as, for example, maize starch or talc. Other active materials such as 1 - phenyl - 2,3 - dimethyl - 4 - iso-propyl - pyrazolone - (5), caffeine, codeine, codeine phosphate, salicylic acid or active salicylic acid derivatives (e.g. acetyl-salicylic acid) may also be included. It will be appreciated that the resulting pharmaceutical com-

positions, which may be in the form of suspensions, tablets, pills or suppositories form part of the invention.

According to the process provided by the present invention, the novel acid amides aforesaid are manufactured by reacting an aromatic amine of the formula



, wherein X is a lower-alkoxy or acyloxy group or the hydroxy or benzyloxy group with an acid derivative of β, β - dimethyl - α, γ - dihydroxy-butylric acid, and where X is an acyloxy group or the benzyloxy group, converting the same into a hydroxy group.

When the symbol X in the formula for the starting material is a lower-alkoxy group, this group is preferably the ethoxy group (in which case the starting material is *paraphenetidine*).

When using a *p* - (lower alkoxy) - aniline as the amine starting material, the reaction with the acid derivative of β, β -dimethyl- α, γ -dihydroxy-butylric acid results in the corresponding N - [*p* - (lower alkoxy) - phenyl] β, β - dimethyl - α, γ - dihydroxy - butylric acid amide. When *paraphenetidine* is employed, the product is accordingly N-(*p*-ethoxy - phenyl) β, β - dimethyl α, γ - dihydroxy-butylric acid amide.

In order to obtain the N-(*p*-hydroxy-phenyl) β, β - dimethyl - α, γ - dihydroxy-butylric acid amide, a starting material in which X is the hydroxy or benzyloxy group or an acyloxy group (preferably a lower alkanoyloxy group such as acetoxy) should be employed. After the reaction with the acid derivative, the acyloxy group in the reaction product can be converted to the hydroxy group by hydrolysis and the benzyloxy group can be converted to the hydroxy group by hydrogenation, the desired N-(*p*-hydroxy-

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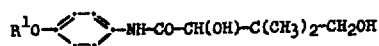
phenyl) β,β - dimethyl - α,γ - dihydroxy-butyric acid amide being obtained.

- The acid derivatives of β,β - dimethyl- α,γ - dihydroxy - butyric acid which can be employed in the process include (a) β,β - dimethyl - α - hydroxy - γ - butyrolactone and (b) β,β - dimethyl - α,γ - dihydroxy-butyryl halides (e.g. the bromide or chloride) in which the free hydroxy groups are protected by acylation, preferably by alkanoylation (i.e. β,β - dimethyl - α,γ - diacyloxy - butyryl halides, preferably β,β - dimethyl - α,γ - dialkanoyloxy - butyryl halides, and most preferably their β,β - dimethyl - α,γ - di(lower alkanoyloxy) - butyryl halide members such as β,β - dimethyl - α,γ - diacetoxy-butyryl chloride).

- Where the acid derivative is a butyryl halide, the X group in the amine starting material should preferably be other than a hydroxy group in order to prevent a competing ester formation. If a hydroxy group is desired in the product the group X in the amine starting material should preferably be an acyloxy group or the benzyloxy group, the conversion being carried out subsequent to the amide formation.

- When β,β - dimethyl - α - hydroxy - γ - butyrolactone is used as the acid derivative, the reaction with the amine starting material is carried out in the presence of an alkaline condensing agent. Alkaline condensing agents include alkali-metal alcoholates (e.g. sodium methylate or potassium ethylate), alkali-metal amides (e.g. sodamide) and alkali-metals (e.g. sodium or potassium metal). It is convenient to carry out the condensation reaction in an organic solvent such as, for example, benzene, acetone or N,N-dimethyl-formamide.

- The intermediates formed in the reaction of an amine starting material in which X is an acyloxy group or the benzyloxy group with the foregoing lactone have the formula



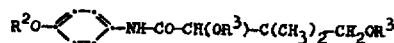
- wherein R^1 is acyl (alkanoyl in the preferred cases and lower-alkanoyl in the especially preferred cases) or benzyl.

- A preferred procedure consists in reacting the lactone with the amine starting material in N,N - dimethyl - formamide in the presence of sodium methylate. The reaction proceeds well while stirring, even at 0°C. Especially good yields of product are obtained when about four mols of amine and about three mols of sodium methylate are used to one mol of lactone. The excess of amine starting material can be regenerated again by working up the mother liquor.

- When a β,β - dimethyl - α,γ - diacyloxy-butyryl halide starting material is reacted with the amine starting material, the reaction is

advantageously carried out in an organic solvent (e.g. benzene, acetone or, preferably, N,N - dimethyl - formamide). The addition of an organic or inorganic acid-binding agent (e.g. pyridine or potassium carbonate) is advisable but not essential. In the absence of such an acid-binding agent as such an excess of the amine must, however, be used. The excess of the amine acts as an acid-binding agent. The reaction, which proceeds exothermically, is conveniently carried out at elevated temperature (e.g. at a temperature in the range of about 20°C to about 140°C).

The intermediates formed in the reaction of the amine starting material with a β,β - dimethyl - α,γ - diacyloxy - butyryl halide have the formula

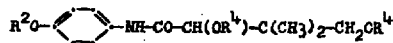


wherein R^2 is a hydrogen atom or a lower-alkyl group or an acyl (preferably alkanoyl and more preferably lower-alkanoyl) or benzyl group and R^3 is an acyl (preferably alkanoyl and more preferably lower-alkanoyl) group. The α - and γ -acyl groups are subsequently split off by hydrolysis (e.g. by treatment with aqueous caustic soda). When R^2 is also an acyl group, this hydrolysis removes this acyl group as well. When R^2 is benzyl, the benzyl group can be removed by hydrogenation.

From the foregoing it can be seen therefore that an important embodiment of the process comprises reacting an amine of the formula



(wherein X has the meaning given earlier) with β,β - dimethyl - α - hydroxy - γ - butyrolactone or a β,β - dimethyl - α,γ - dialkanoyloxy-butyryl halide (preferably one in which lower alkanoyloxy groups are present) to form a compound of the formula



, wherein R^2 has the meaning given earlier and R^4 is an alkanoyl group (a lower alkanoyl group in preferred cases) or a hydrogen atom, and, where R^2 is an acyl group or the benzyl group and/or where R^4 is an alkanoyl group, converting this compound into the required product.

It will be appreciated that N-(p-benzyloxy-phenyl) β,β - dimethyl - α,γ - dihydroxy-butyric acid amide as well as the N[p-(lower-alkoxy) - phenyl] β,β - dimethyl - α,γ - di-

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alkanoyloxy-butyric acid amides formulated hereinbefore are also new compounds and that the invention includes these compounds within its scope. Of these compounds, the preferred are the N - (p - ethoxy - phenyl) β,β - dimethyl - α,γ - dialkanoyloxy - butyric acid amides (especially those in which the alkanoyloxy groups are acetoxy groups).

The following Examples illustrate the process of the invention.

EXAMPLE 1

1000 g of *paraphenetidine* are dissolved in 600 ml of N,N-dimethyl-formamide and treated portionwise with 340 g of sodium methylate. To this is added dropwise, during 8 hours while cooling with ice, a solution of 260 g of D,L α - hydroxy - β,β - dimethyl- γ -butyrolactone in 600 ml of N,N-dimethyl-formamide in such a way that the temperature does not rise above 2°C. Subsequently, it is stirred for a further 20 hours while cooling with ice. Thereafter, the viscous content of the flask is treated with 4—5 kg of finely crushed ice while stirring well. After this, 3-N hydrochloric acid is added slowly thereto while stirring well until Congo paper just becomes blue. After seeding, the solution is again stirred for several more hours at 0°C for completion of crystallisation. The crystalline mass is filtered off under suction, washed with ice-water and ether and dried. 358 g of N - (p - ethoxy - phenyl) β,β - dimethyl - α,γ -dihydroxy-butyric acid amide of melting point 103°—104°C (corrected) are obtained. By extraction of the filtrate with chloroform, concentration of the chloroform solution and recrystallisation of the residue from isopropyl acetate, an additional 48 g of the amide of melting point 103°—104°C are obtained. After recrystallisation of the crude product from isopropyl acetate, 379 g of a pure product of melting point 105°C (corrected) are obtained.

The excess *paraphenetidine* used can be recovered by making the acid-aqueous filtrate obtained above, after extraction thereof with methylene chloride, alkaline by the addition of caustic soda, whereby the separated *paraphenetidine* is isolated by extraction with benzene.

EXAMPLE 2

310 g of D,L β,β -dimethyl- α,γ -diacetoxy-butyric acid chloride (Journ. Am. Chem. Soc., 1940, 62, 2251—2) are added dropwise to a solution of 170 g of *paraphenetidine* in 900 ml of N,N-dimethyl-formamide to which 170 g of anhydrous potassium carbonate had been added, whereby the temperature rises up to 80°C. The reaction mixture is stirred at this temperature for yet a further 2 hours, then cooled down and poured on to ice. After the addition of ether and separation of the ethereal layer, the ether layer is successively washed

with water, dilute hydrochloric acid and once more with water. After drying and concentration of the ethereal phase, 297 g of N-(p-ethoxyphenyl) β,β - dimethyl - α,γ - diacetoxy-butyric acid amide are obtained. This amide is stirred overnight at room temperature in a solution of 91 g of sodium hydroxide in 1200 ml of water. Thereafter, it is filtered off under suction and the residue washed until neutral with ice-cold water. The dried product melts at 105°C after recrystallisation from isopropyl acetate and represents pure N - (p - ethoxy - phenyl) β,β - dimethyl - α,γ -dihydroxy-butyric acid amide.

EXAMPLE 3

170 g of sodium methylate are added portionwise to 800 ml of N,N-dimethyl-formamide. To the resulting solution a solution of 130 g of D,L α - hydroxy - β,β - dimethyl - γ - butyrolactone and 278 g of p-benzyloxy-aniline (melting point 52°—55°C) in 400 ml of N,N-dimethyl-formamide are dropped in during 8 hours while cooling with ice so that the temperature does not rise above 2°C. Thereafter the mixture is stirred for another 20 hours while being cooled with ice. Then the viscous flask contents are treated under good stirring with 2—5 kg of finely divided ice. Thereafter 3-N hydrochloric acid is added slowly with good stirring until the solution is blue to Congo paper. The solution is extracted with methylene chloride, the methylene chloride solution washed with dilute hydrochloric acid and water, dried over anhydrous sodium sulphate and evaporated to dryness. The residue crystallises by triturating with water. The crystallised residue melts at 107°—110°C. The crude product is recrystallised from butyl oxide to yield 275 g of pure N-(p-benzyloxyphenyl) β,β - dimethyl - α,γ - dihydroxy-butyric acid amide of melting point 110°—111°C.

80 g of p - benzyloxy - aniline are recovered from the acid-aqueous solution by treatment with sodium hydroxide solution until alkaline, followed by extraction with methylene chloride.

113 g of the foregoing N-(p-benzyloxyphenyl) β,β - dimethyl - α,γ - dihydroxy-butyric acid amide are dissolved in 100 ml of methanol and hydrogenated after the addition of 12 g of palladium-on-charcoal (5% palladium). The theoretical quantity of hydrogen is taken up in 8 hours. After filtration and evaporation of the solvent, the residue is crystallised from 200 ml of acetonitrile to yield 70 g of N-(p-hydroxyphenyl)- β,β - dimethyl - α,γ - dihydroxy - butyric acid amide of melting point 175°—176°C.

The following Examples illustrate pharmaceutical preparations containing those novel acid amides provided by the invention as set out in the third paragraph of this specification.

EXAMPLE A

An intimate mixture was prepared from 500 g of N - (p - ethoxy - phenyl) β,β - dimethyl- α,γ - dihydroxy - butyric acid amide, 50 g of maize starch and 30 g of talc. Tablets were formed from the mixture, each of said tablets containing 500 mg of active substance (that is to say, the acid amide).

EXAMPLE B

600 g of N - (p - hydroxy - phenyl) β,β - dimethyl - α,γ - dihydroxy - butyric acid amide were intimately mixed with 20 g of codiene phosphate, the resulting mixture was compounded with 600 g sugar syrup (prepared from 384 g of sugar and 216 ml of water) and with 1200 ml of 70% ethanol. The compounded mass was granulated, dried and mixed with 500 g of acetyl-salicylic acid, 100 g of maize starch and 60 g of talc, whereupon tablets were made therefrom, each of said tablets weighing 1.28 g.

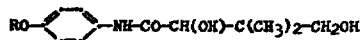
EXAMPLE C

300 g of N - (p - ethoxy - phenyl) β,β - dimethyl - α,γ - dihydroxy - butyric acid amide, 150 g of 1 - phenyl - 2,3 - dimethyl-4 - isopropyl - pyrazolone - (5), 50 g of caffeine, 83.8 g of maize starch, 10 g of talc, 5 g of gelatine and 1.2 g of magnesium stearate were intimately mixed, whereupon tablets each of 600 mg were formed from the mixture.

It will be understood that the terms 'lower alkyl', 'lower alkoxy' and 'lower alkanoyl' are used in the foregoing description and in the claims appended hereto to mean alkyl, alkoxy and alkanoyl groups respectively containing not more than five carbon atoms.

WHAT WE CLAIM IS:—

1) Compounds of the formula



wherein R is a hydrogen atom or a lower-alkyl group.

2) N - (p - ethoxy - phenyl) β,β - dimethyl- α,γ -dihydroxy-butyric acid amide.

3) N - (p - hydroxy - phenyl) β,β - dimethyl- α,γ -dihydroxy-butyric acid amide.

4) A pharmaceutical preparation comprising a compound as set forth in claim 1 in association with a compatible pharmaceutical carrier.

5) A process for the manufacture of the compounds claimed in claim 1, which process comprises reacting an aromatic amine of the formula



, wherein X is a lower-alkoxy or acyloxy group or the hydroxy or benzyloxy group, with an acid derivative of β,β -dimethyl- α,γ -dihydroxy-butyric acid and, where X is an acyloxy group or the benzyloxy group, converting the same into a hydroxy group.

6) A process in accordance with claim 5, wherein *paraphenetidine* is used as the aromatic amine.

7) A process in accordance with claim 5 or claim 6, wherein β,β -dimethyl- α -hydroxy- γ -butyrolactone is used as the acid derivative and wherein the reaction is carried out in the presence of an alkaline condensing agent.

8) A process in accordance with claim 7, wherein sodium methylate is used as the alkaline condensing agent.

9) A process in accordance with any one of claims 5 to 8 inclusive, wherein the reaction is carried out in the presence of an organic solvent.

10) A process in accordance with claim 9, wherein N,N-dimethyl-formamide is used as the organic solvent.

11) A process in accordance with claim 5 or claim 6, wherein a β,β -dimethyl- α,γ -diacyloxy-butyryl halide is used as the acid derivative and the acyl groups are subsequently split off by hydrolysis.

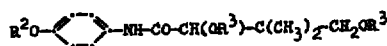
12) A process in accordance with claim 5 or any one of claims 7 to 11 inclusive, wherein p - benzyloxy - aniline is used as the aromatic amine and the benzyloxy group in the product is converted into a hydroxy group by hydrogenation.

13) A process for the manufacture of compounds claimed in claim 1, substantially as described with reference to Examples 1—3.

14) Compounds as claimed in claim 1, when manufactured by the process claimed in any one of claims 5 to 13 inclusive.

15) N - (p - benzyloxy - phenyl) β,β - dimethyl - α,γ - dihydroxy - butyric acid amide.

16) Compounds of the formula



wherein R² is a lower-alkyl group and R³ is an alkanoyl group.

17) N - (p - ethoxy - phenyl) β,β - dimethyl - α,γ - dialkanoyloxy - butyric acid amides.

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EXAMPLE A

An intimate mixture was prepared from 500 g of N - (p - ethoxy - phenyl) β,β - dimethyl- α,γ - dihydroxy - butyric acid amide, 50 g of maize starch and 30 g of talc. Tablets were formed from the mixture, each of said tablets containing 500 mg of active substance (that is to say, the acid amide).

EXAMPLE B

600 g of N - (p - hydroxy - phenyl) β,β - dimethyl - α,γ - dihydroxy - butyric acid amide were intimately mixed with 20 g of codiene phosphate, the resulting mixture was compounded with 600 g sugar syrup (prepared from 384 g of sugar and 216 ml of water) and with 1200 ml of 70% ethanol. The compounded mass was granulated, dried and mixed with 500 g of acetyl-salicylic acid, 100 g of maize starch and 60 g of talc, whereupon tablets were made therefrom, each of said tablets weighing 1.28 g.

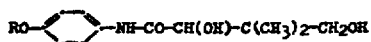
EXAMPLE C

300 g of N - (p - ethoxy - phenyl) β,β - dimethyl - α,γ - dihydroxy - butyric acid amide, 150 g of 1 - phenyl - 2,3 - dimethyl-4 - isopropyl - pyrazolone - (5), 50 g of caffeine, 83.8 g of maize starch, 10 g of talc, 5 g of gelatine and 1.2 g of magnesium stearate were intimately mixed, whereupon tablets each of 600 mg were formed from the mixture.

It will be understood that the terms 'lower alkyl', 'lower alkoxy' and 'lower alkanoyl' are used in the foregoing description and in the claims appended hereto to mean alkyl, alkoxy and alkanoyl groups respectively containing not more than five carbon atoms.

WHAT WE CLAIM IS:—

1) Compounds of the formula



wherein R is a hydrogen atom or a lower-alkyl group.

2) N - (p - ethoxy - phenyl) β,β - dimethyl- α,γ -dihydroxy-butyrac acid amide.

3) N - (p - hydroxy - phenyl) β,β - dimethyl- α,γ -dihydroxy-butyrac acid amide.

4) A pharmaceutical preparation comprising a compound as set forth in claim 1 in association with a compatible pharmaceutical carrier.

5) A process for the manufacture of the compounds claimed in claim 1, which process comprises reacting an aromatic amine of the formula



, wherein X is a lower-alkoxy or acyloxy group or the hydroxy or benzyloxy group, with an acid derivative of β,β -dimethyl- α,γ -dihydroxy-butyrac acid and, where X is an acyloxy group or the benzyloxy group, converting the same into a hydroxy group.

6) A process in accordance with claim 5, wherein *paraphenetidine* is used as the aromatic amine.

7) A process in accordance with claim 5 or claim 6, wherein β,β -dimethyl- α -hydroxy- γ -butyrolactone is used as the acid derivative and wherein the reaction is carried out in the presence of an alkaline condensing agent.

8) A process in accordance with claim 7, wherein sodium methylate is used as the alkaline condensing agent.

9) A process in accordance with any one of claims 5 to 8 inclusive, wherein the reaction is carried out in the presence of an organic solvent.

10) A process in accordance with claim 9, wherein N,N-dimethyl-formamide is used as the organic solvent.

11) A process in accordance with claim 5 or claim 6, wherein a β,β -dimethyl- α,γ -diacyloxy-butyril halide is used as the acid derivative and the acyl groups are subsequently split off by hydrolysis.

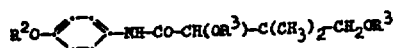
12) A process in accordance with claim 5 or any one of claims 7 to 11 inclusive, wherein p - benzyloxy - aniline is used as the aromatic amine and the benzyloxy group in the product is converted into a hydroxy group by hydrogenation.

13) A process for the manufacture of compounds claimed in claim 1, substantially as described with reference to Examples 1—3.

14) Compounds as claimed in claim 1, when manufactured by the process claimed in any one of claims 5 to 13 inclusive.

15) N - (p - benzyloxy - phenyl) β,β - dimethyl - α,γ - dihydroxy - butyric acid amide.

16) Compounds of the formula



wherein R^2 is a lower-alkyl group and R^3 is an alkanoyl group.

17) N - (p - ethoxy - phenyl) β,β - dimethyl - α,γ - dialkanoyloxy - butyric acid amides.

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18) N - (p - ethoxy - phenyl) β,β - dimethyl - α,γ - diacetoxy - butyric acid amide.

19) A process for the manufacture of the compounds claimed in any one of claims 15 to 18 inclusive, substantially as described.

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