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MALEAMIC ACID DERIVATIVES

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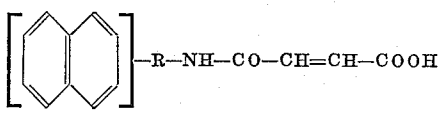
This invention comprises novel derivatives of maleamic acid and in particular those derivatives wherein a hydrogen of the amino group of maleamic acid is replaced by a naphthyl-lower alkyl radical and more particularly by derivatives wherein the lower alkylene chain of the naphthyl-lower alkyl substituent is additionally substituted by one or more groups such as by a lower alkyl, phenyl, benzyl, and the like radicals, or is substituted by any combination of these radicals.

The novel compounds of this invention can be illustrated by the following structural formula:



and includes the alkali metal salts thereof as well as simple ester derivatives, such as esters derived from the low molecular weight alcohols. In the above structure, R is a straight chain alkylene radical having at least one and no more than three carbon atoms in the chain connecting the naphthyl radical and the nitrogen of the amino group of maleamic acid; in other words, R is a methylene, ethylene or propylene radical, each valence of the said alkylene radicals being satisfied by one of the following: (a) hydrogen, (b) a lower alkyl radical having from 1 to 10 carbon atoms, and preferably having up to 6 carbon atoms in a straight or branched chain or alicyclic, such as a methyl, iso- or normal-propyl, iso- or normal-butyl, amyl, hexyl, cyclopentyl, cyclohexyl, and the like, (c) a mononuclear aryl, preferably a phenyl radical, or (d) a mononuclear aryl-lower alkyl radical such as a benzyl radical, for example.

The compounds of this invention posses a variety of properties and are especially useful because they inhibit the excretion of penicillin through the kidney tubules thus providing prolonged blood levels of penicillin. Because of this property the new compounds of this invention are useful as adjuvants for use in conjunction with the administration of penicillin to provide an increase in the blood plasma pencillin concentration with a given dose of penicillin, thereby making possible very high penicillin blood levels, or permitting the use of smaller quantities of penicillin for providing a given blood level, or permitting less frequent administration of penicillin while maintaining a penicillin blood level adequate for bactericidal or bacteriostatic purposes.

Some of the compounds additionally enhance the excretion of uric acid from the body and therefore are useful agents in the treatment of gout or gouty arthritis and in alleviating symptoms of these conditions and of complications associated with gout and gouty arthritis.

Additionally, some of the compounds have been found to inhibit the biosynthesis of cholesterol in liver homogenates in vitro. They have also been found to lower the the incidence and severity of atherosclerotic plaques in the thoracic aorta of estrogen-treated chickens which were treated with these compounds as compared with their estrogen-treated controls, and to lower the plasma level of cholesterol in rats which had been challenged with quantities of saturated fats such as lard, known to produce an increased cholesterol blood level in these animals. Accordingly, these compounds also are potentially useful in lowering blood cholesterol levels in humans which is considered an important function of chemotherapeutic agents in the treatment of atherosclerosis.

The naphthylalkylmaleamic acids or their salts or simple esters can be administered in conventional dosage forms such as in a capsule, pill or tablet either with or without therapeutically inert materials and with or without other therapeutically active substances or in the form of a sterile solution and the like.

While all of the maleamic acid derivatives of this invention possess one or more of the above properties to varying degrees, the compounds having a (1-naphthyl)-lower alkylene or a (2-naphthyl)-lower alkylene radical attached to the amino nitrogen of maleamic acid, and especially 1- or 2-naphthylethylmaleamic acids which also have attached to the ethylene chain a lower alkyl group, and especially a methyl radical, possess one or more of the above described properties to a marked degree.

The maleamic acid derivatives of this invention are easily prepared by bringing together a solution of the selected naphthyl-lower-alkylamine and a solution of maleic anhydride. The reaction between the ingredients occurs quite readily at room temperature accompanied by the precipitation of the maleamic acid derivative from the reaction mixture, which then can be separated by known conventional methods, as by filtration or evaporation of the solvent and the like. Ether has been found to be an effective solvent for the naphthyl-lower-alkylamine as well as for maleic anhydride, although other solvents could be used in its place.

Some of the naphthylalkylamines used in preparing the maleamic acid derivatives of this invention are new compounds which can readily be prepared by one or another of the many well-known methods for preparing naphthylalkylamines. By one such method, a carbonyl compound is converted by means of the Leuckart reaction to the desired naphthylalkylamine. This reaction involves heating the carbonyl compound (i.e., a ketone or an aledhyde) with formamide and formic acid preferably under reflux conditions to form the formamide derivative of the desired naphthylalkylamine. This compound, after hydrolysis with a mineral acid, such as hydrochloric acid, generally is isolated either (a) as an acid addition salt thereof, such as the hydrochloride salt, which may be insoluble in the reaction medium or (b) by treatment of the reaction medium with alkali, such as sodium hydroxide, to obtain the free base, which then is extracted with a solvent, such as ether, and purified by distillation of the base.

Alternatively the selected nitriles can be reacted with a Grignard reagent thus forming the corresponding ketimine. The ketimine then is hydrolyzed to the corresponding carbonyl compound and the latter product converted by means of the Leuckart reaction (supra) to the naphthylalkylamine.

The above and other methods for preparing the amines and the novel maleamic acid derivatives of this invention will be described in more detail by the following examples.

The novel maleamic acid derivatives of this invention, as well as their intermediate naphthylalkylamines, which contain one asymmetric carbon atom in the ethylene or propylene radical will be obtained as racemic mixtures which can be separated into the dextrorotatory and levorotatory isomers by known methods.

The novel maleamic acid derivatives of this invention, as well as the corresponding naphthylalkylamines, which contain two asymmetric carbon atoms in the ethylene or propylene radical will be obtained as diasterioisomers. In this specification and in the claims the diasterioisomer having the higher melting point is considered to be the α-isomer and that having the lower melting point is considered to be the β-isomer. The α-isomer and the β-isomer,

of course, also will be obtained as racemic mixtures which can be separated by known methods.

While greater activity may reside in one or another of the α-isomer or β-isomer or in the dextro- or levorotatory antipode of one or another of these isomers, in general, mixtures of their racemates can be employed for one or another of the uses identified above for which the individual compound may possess the desired property.

The preparation of the novel maleamic acid derivatives of this invention is illustrated by the following examples. It is to be understood, of course, that these examples are illustrative and not limitative of the compounds of this invention and of the methods by which they can be prepared. The examples also illustrate methods for preparing suitable dosage forms of the maleamic acid derivatives of this invention.

EXAMPLE 1

N-[1-(1-naphthyl)-2-propyl]-maleamic acid

1-(1-naphthyl)-2-propylamine (1.85 g., 0.01 mole) is dissolved in ether (20 ml.) and the solution added slowly to an ether solution (30 ml.) of maleic anhydride (0.98 g., 0.01 mole). A solid separates at once. After the reaction mixture has been kept at room temperature for 30 minutes the solid is collected and dried in air at 65° C. to give 2.6 g. of product, M.P. 148–158° C. After crystallization from ethanol there is obtained 1.8 g. of N-[1-(1-naphthyl)-2-propyl]-maleamic acid, M.P. 162.5–163° C.

Analysis.—Calculated for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 72.08; H, 6.20; N, 4.94.

EXAMPLE 2

N-[1-(2-naphthyl)-1-ethyl]-maleamic acid

By replacing 1-(1-naphthyl)-2-propylamine used in Example 1 by 1-(1-naphthyl)ethylamine (5.13 g.) and reacting it with maleic anhydride (2.94 g.) by substantially the same method described in Example 1, there is obtained N-[1-(2-naphthyl)-1-ethyl]-maleic acid which after crystallization from absolute alcohol gives 5.8 g. of product, M.P. 160–161° C.

Analysis.—Calculated for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.73; H, 5.64; N, 5.19.

EXAMPLE 3

N-[1-(1-naphthyl)-1-propyl]-maleamic acid

By replacing 1-(1-naphthyl)-2-propylamine used in Example 1 by 1-(1-naphthyl)-propylamine (5.55 g., 0.03 mole) and reacting it with maleic anhydride (2.94 g., 0.03 mole) by substantially the same method described in Example 1, there is obtained N-[1-(1-naphthyl)-1-propyl]-maleamic acid which after crystallization from alcohol gives 5.3 g. of product, M.P. 170–171° C.

Analysis.—Calculated for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 72.28; H, 6.12; N, 4.94.

EXAMPLE 4

N-[1-(1-naphthyl)-1-butyl]-maleamic acid

By replacing 1-(1-naphthyl)-2-propylamine used in Example 1 by 1-(1-naphthyl)-butylamine (4.97 g., 0.025 mole) and reacting it with maleic anhydride (2.45 g., 0.025 mole) by substantially the same method described in Example 1, there is obtained N-[1-(1-naphthyl)-1-butyl]-maleamic acid which after crystallization from absolute alcohol and from alcohol-water gives 4.78 g. of product, M.P. 152–153° C.

Analysis.—Calculated for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.39; H, 6.30; N, 4.70.

EXAMPLE 5

N-[1-(1-naphthyl)-1-hexyl]-maleamic acid

Step A: Preparation of 1-(1-naphthyl)-1-hexanone.—A Grignard reagent is prepared in ether from normal amyl bromide (33.2 g., 0.22 mole) and magnesium (5.1 g., 0.21 g. atom). To this is added 1-naphthyl cyanide (30.6 g., 0.2 mole) dissolved in dry toluene (300 ml.) The ether is removed by distillation and the residual mixture heated at the boiling point of toluene for 5 hours, cooled and added to a concentrated solution of ammonium chloride (100 ml.). The toluene phase is separated and the aqueous phase extracted with ether. The organic layers are combined and the product, 1-naphthyl amyl ketimine, extracted with 6N sulfuric acid (200 ml.). The acid extract is refluxed for two hours, cooled and extracted with a mixture of ether and benzene (1:1) (250 ml.). The extract is washed with sodium carbonate and saturated sodium chloride solution, dried over sodium sulfate and evaporated to dryness. The residue is distilled to give 10.4 g. of 1-(1-naphthyl)-1-hexanone, B.P. 130–133° C. at 0.4 mm. pressure.

Step B: Preparation of 1-(1-naphthyl)-hexylamine.—A mixture of the ketone prepared in Step A (10.2 g., 0.045 mole), formamide (8.1 g., 0.18 mole) and a few drops of formic acid is placed in a flask equipped with a condenser set for downward distillation. The mixture is heated at 175–180° C. (internal temperature) for 14 hours. Whenever the vapors above the reaction mixture become basic, a few ml. of formic acid is added. The reaction mixture then is extracted with benzene, the benzene evaporated and the residue mixed with concentrated hydrochloric acid (10 ml.). The mixture is refluxed for 12 hours, cooled, diluted with water, made basic with sodium hydroxide and extracted with ether. The ether extract is dried over sodium sulfate and evaporated. The residue is distilled to give 8.2 g. of 1-(1-naphthyl) hexylamine, B.P. 129–142° C. at 0.3 mm. pressure.

Step C: Preparation of N-[1-(1-naphthyl)-1-hexyl]-maleamic acid.—An ether (30 ml.) solution of the amine prepared in Step B (5.68 g., 0.025 mole) is added slowly to an ether (30 ml.) solution of maleic anhydride (2.45 g., 0.025 mole). A clear solution results which gradually deposits a solid. After 16 hours, the precipitate is collected and washed with ether. The solid is crystallized from a mixture of methanol and water to give 4.46 g. of N-[1-(1-naphthyl)-1-hexyl]-maleamic acid, M.P. 136–137° C.

Analysis.—Calculated for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 74.03; H, 7.19; N, 4.30.

EXAMPLE 6

N-[1-(1-naphthyl)-2-methyl-1-propyl]-maleamic acid

Step A: Preparation of 1-(1-naphthyl)2-methylpropylamine.—By replacing the ketone employed in Example 5, Step B, by 1-naphthyl isopropyl ketone (10.8 g., 0.053 mole) and following substantially the same procedure described in Step B of Example 5 there is obtained 7.5 g. of 1-(1-naphthyl)-2-methylpropylamine, B.P. 112–114° C. at 0.2 mm. pressure.

Step B: Preparation of N-[1-(1-naphthyl)-2-methyl-1-propyl]-maleamic acid.—The amine (4.97 g., 0.025 mole) prepared in Step A is reacted with maleic anhydride (2.45 g., 0.025 mole) by substantially the same procedure described in Example 5, Step C, to give N-[1-(1-naphthyl) 2-methyl-1-propyl]-maleamic acid which, after crystallization from a mixture of benzene and hexane, melts at 141–142° C.

Analysis.—Calculated for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.58; H, 6.55; N, 4.69.

EXAMPLE 7

N-[1-(1-naphthyl)-1-amyl]-maleamic acid

Step A: Preparation of 1-(1-naphthyl)-amylamine.—By replacing the ketone used in Example 5, Step B, by 1-(1-naphthyl)-1-pentanone (10.0 g., 0.047 mole), (prepared from butyl magnesium bromide and 1-naphthyl cyanide by the method described in Example 5, Step A) and following substantially the same procedure described in Ex-

ample 5, Step B, there is obtained 7.1 g. of 1-(1-naphthyl) amylamine, B.P. 119–123° C. at 0.1–0.2 mm. pressure.

Step B: Preparation of N-[1-(1-naphthyl)-1-amyl]-maleamic acid.—The amine (6.94 g., 0.03 mole) obtained in Step A is reacted with maleic anhydride (2.94 g., 0.03 mole) by substantially the same method described in Example 5, Step C, to give N-[1-(1-naphthyl) 1-amyl]-maleamic acid which, after crystallization from a mixture of isopropyl alcohol and water, yields 7 g. of product, M.P. 153–154° C.

Analysis.—Calculated for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.19; H, 6.93; N, 4.48.

EXAMPLE 8

N-[α-(1-naphthyl)-hexahydrobenzyl]-maleamic acid

Step A: Preparation of α-(1-naphthyl)-hexhydrobenzylamine.—By replacing the ketone used in Example 5, Step B, by cyclohexy 1-naphthyl ketone (11.2 g., 0.047 mole) and reacting it with formamide (8.5 g., 0.19 mole) by substantially the same method described in Example 5, Step B, there is obtained 8.5 g. of α-(1-naphthyl-hexahydrobenzylamine as a viscous oil, B.P. 151-152° C. at 0.4 mm. pressure.

Step B: Preparation of N-[α-(1-naphthyl)-hexahydrobenzyl]-maleamic acid.—The amine (6.0 g., 0.025 mole) obtained in Step A is reacted with maleic anhydride (2.45 g., 0.025 mole) by substantially the same method described in Example 5, Step C, to give N-[α-(1-naphthyl)-hexahydrobenzyl]-maleamic acid that separates as an oil and then solidifies after standing at room temperature for several hours.

EXAMPLE 9

N-[1-(1-naphthyl)-1-phenyl-2-propyl]-maleamic acid

Step A: Preparation of 1-(1-naphthyl)-1-phenyl-2-propylamine.—By replacing the ketone used in Example 5, Step B, by an equimolecular quantity of 1-(1-naphthyl)-1-phenyl-2-propanone, and following substantially the same procedure described in Example 5, Step B, there is obtained 1-(1-naphthyl)-1-phenyl-2-propylamine.

Step B: Preparation of N-[1-(1-naphthyl)-1-phenyl-2-propyl]-maleamic acid.—By reacting equimolecular quantities of the amine prepared as described in Step A and maleic anhydride by substantially the same procedure described in Example 5, Step C, there is obtained N-[1-(1-naphthyl)-1-phenyl-2-propyl]-maleamic acid.

EXAMPLE 10

N-[1-(1-naphthyl)-3-butyl]-maleamic acid

Step A:Preparation of 1-(2-naphthyl)-3-butylamine.—By replacing the ketone used in Example 5, Step B, by an equimolecular quantity of 1-(1-naphthyl)-3-butanone, and following substantially the same procedure described in Example 5, Step B, there is obtained 1-(1-naphthyl)-3-butylamine.

Step B: Preparation of N-[1-(1-Naphthyl)-3-butyl]-maleamic acid.—Reaction of equimolecular quantities of the above amine and maleic anhydride by substantially the same procedure described in Example 5, Step C, gives N-[1-(1-naphthyl)-3-butyl]-maleamic acid.

EXAMPLE 11

N-[1-(2-naphthyl)-3-butyl]-maleamic acid

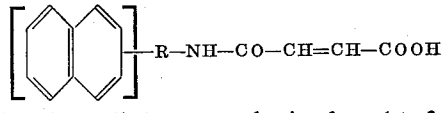
Step A: Preparation of 1-(2-naphthyl)-3-butylamine.—By replacing the ketone used in Example 5, Step B, by an equimolecular quantity of 1-(2-naphthyl)-3-butanone, and following substantially the same procedure described in Example 5, Step B, there is obtained 1-(2-naphthyl)-3-butylamine.

Step B: Preparation of N-[1-(2-naphthyl)-3-butyl]-maleamic acid.—Reaction of equimolecular quantities of the above amine and maleic anhydride by substantially the same procedure described in Example 5, Step C, gives N-[1-(2-naphthyl)-3-butyl]-maleamic acid.

While the above examples describe the preparation of certain illustrative compounds falling within the scope of the generic structure, it is to be understood that the invention is not to be limited by or to these examples nor by the specific reaction conditions described for the preparation of the compounds, but is to be understood to embrace variations and modifications falling within the scope of the appended claims.

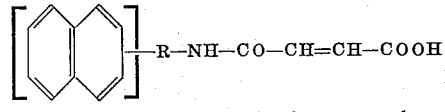
What is claimed is:

1. N-(naphthyl-R)-maleamic acid having the structural formula



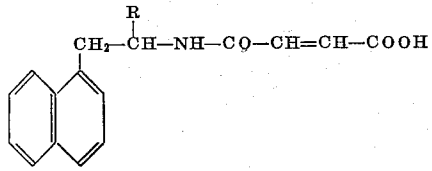
wherein R is an alkylene group having from 1 to 3 carbon atoms linked together in a straight chain between the naphthyl radical and the nitrogen atom of the maleamic acid residue, each remaining valence of said alkylene group being satisfied by a radical selected from the group consisting of hydrogen, lower alkyl, cyclohexyl and phenyl.

2. N-(naphthyl-R)-maleamic acid having the structural formula



wherein R is an alkylene group having two carbons linked together in a straight chain between the naphthyl radical and the nitrogen atom of the maleamic acid residue, the four remaining valences of said alkylene radical being saisfied by only three hydrogen atoms and a lower alkyl group.

3. N-[1-(1-naphthyl)-2-R-2-ethyl]-maleamic acid having the structural formula



wherein R is lower alkyl.

4. N-[1-(1-naphthyl)-2-propyl]-maleamic acid.

5. N-[1-(1-naphthyl)-1-lower alky]-maleamic acid.

6. N-[1-(2-naphthyl)-1-lower alkyl]-maleamic acid.

7. N-(1-naphthyl-2-lower alkyl)-maleamic acid.

8. N-(1-naphthyl-3-lower alkyl)-maleamic acid.

References Cited by the Examiner

UNITED STATES PATENTS

3,018,292 1/1962 Sauers et al. ..... 260—518

OTHER REFERENCES

Frankel et al.: J. Am. Chem. Soc. 75, 331 (1953).

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