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BISMUTH SALTS OF A SUBSTITUTED MALONIC ACID AND PROCESS OF MAKING THEM

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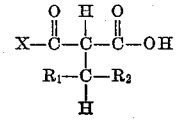
5 Claims. (Cl. 260—447)

This invention relates to the manufacture of oil-soluble, neutral bismuth salts, and it comprises new, normal bismuth salts of substituted malonic acid derivatives having the formula:



wherein X represents a substituent of the class consisting of alkoxy and dialkylamide groups, the alkyl substituent in said groups being a lower alkyl radical and R_1 and R_2 represent lower alkyl groups, said salts having one mol of bismuth combined with 3 mols of said monobasic acid and being neutral, stable compounds of lipoid-like character, soluble in oils and oil solvents; and it further comprises methods of making such normal bismuth salts wherein said monobasic acid derivatives of a substituted malonic acid carrying such branched chain alkyl group are prepared from a corresponding dialkyl ester and the monobasic acids so obtained, or alkali salts thereof, are reacted with a bismuth compound in approximately a molar ratio of 3:1 to produce said neutral, normal bismuth salts; all as more fully hereinafter set forth and as claimed.

Stable and permanent bismuth compounds soluble in oils and oil solvents, insoluble in water and having a substantial content of bismuth are a desideratum.

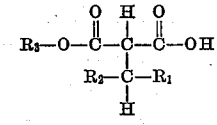
Various basic bismuth salts of certain complex organic acids, which are more or less soluble in oils, are known. Among them are the basic bismuth salts of alpha-carbethoxy-cyclohexyl-acetic acid (the ethyl monoester of cyclohexyl-malonic acid) and of alpha-carbethoxy-beta-methyl nonylic acid (the ethyl monoester of methyl-hexyl-carbin-malonic acid).

In examination of some previously unknown bismuth salts of other malonic ester acids, it has been found that no oil soluble basic salt can be prepared according to the usual methods from the monoesters of secondary butyl-malonic acid or of secondary amyl-malonic acid. Likewise, the neutral bismuth salt of secondary butyl-malonic acid, itself was found to be insoluble in oil. Further, the neutral bismuth salts obtained from the monoesters of normal butyl-malonic acid or of isopropyl-allyl-malonic acid are not soluble in oil.

It comes as an unexpected discovery that the substituted malonic acids with a single free carboxylic group (monobasic acids) of the class represented by the formula given ante, yield neutral, normal bismuth salts having a distinctly lipoid character; these normal bismuth salts having 1 mol of bismuth combined with 3 mols of the said substituted monobasic acids. Our new bismuth salts dissolve in solvents for fats e. g. in organic solvents, fatty oils and other liquid fatty acid esters, whereas they are insoluble in water. Monobasic acids formed by amidating one carboxyl of these malonic acids, in lieu of esterifying, give similar results. The new bismuth compounds are insoluble in water and are of particularly stable character. For therapeutic purposes, this stability is quite important, since their solutions can be readily sterilized by heat. The acids giving these new neutral bismuth compounds are substituted monobasic malonic acids with one carboxyl blocked off with an ester or an amide group and with the methylene carbon of the malonic acid carrying, as a substituent group, a branched chain; a carbon carrying two alkyl groups. They have the general formula, given above; the bismuth carrying three such groups and being a neutral, normal salt of such monobasic acids.

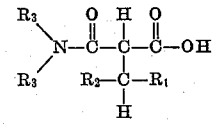
Of our new class of oil-soluble bismuth compounds, the neutral bismuth salts of certain mono-esters or dialkyl amides are particularly interesting. These classes of malonic acid derivatives are as follows:

I. Monoesters:



wherein R_1, R_2 and R_3 represent a lower alkyl group.

II. Amides:



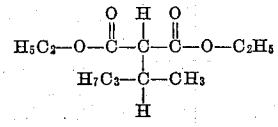
wherein R_1, R_2 and R_3 represent a lower alkyl group.

The neutral bismuth salts obtained from the above malonic acid derivatives wherein R_3 is an alkyl group containing not more than three carbon atoms, such as ethyl or allyl groups, are advantageous. Those in which R_1 and R_2 are methyl, ethyl, propyl, butyl or hexyl groups are also advantageous. All of the above neutral bismuth salts are readily soluble in oil and give stable solutions.

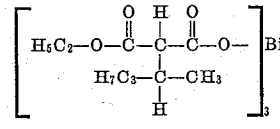
The new oil soluble bismuth compounds can be conveniently prepared by causing a reaction between 3 molecules of such an acid, neutralized with an alkali, and 1 molecule of a bismuth salt, such as the nitrate. Reaction is preferably effected in a polyvalent alcohol, such as glycerine or mannitol. It is also possible to make the new compounds by direct neutralization of the free acid with bismuth oxide or hydroxide. But metathetic reaction of an alkali salt with a bismuth salt in a solvent, generally glycerine, is convenient and advantageous. In purifying and recovering the new compounds, advantage can be taken of their solubility in volatile, non-aqueous liquids, such as ether and benzene.

Example 1

In a specific embodiment of the present invention, starting with the diethyl-ester of propyl methyl carbin malonic acid (the diethyl-ester of unsymmetrical secondary-amyl malonic acid) having the formula



the following procedure may be used to produce a normal bismuth salt having the following formula

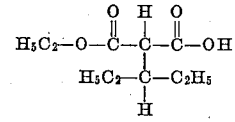


this salt being a neutral bismuth salt of propyl-methyl-carbin-malonic acid monoethyl-ester and containing 25.7 per cent bismuth combined with said monobasic acid.

The said diethyl-ester is first converted into the half-ester (monoethyl-ester of secondary amyl-malonic acid) by partial saponification to give a monobasic acid of the stated general formula. In detail, an alcoholic solution of potash is made, using 56 parts of KOH and 1280 parts of anhydrous or absolute alcohol; both by weight. To this liquid, 230 parts by weight of the diethyl ester are slowly added with agitation. The mixture is allowed to stand at the ordinary temperature for a day and the alcohol distilled off, leaving a crystalline residue of the potassium salt of the half-ester. This is dissolved in water and a little unchanged diethyl-ester removed by shaking out the water solution with benzene. The purified water solution is then acidified with hydrochloric acid in excess. There is an oily separation of the desired half-ester; of propyl-methyl - carbin - malonic acid monoethylester. This is removed, dissolved in ether and dried. When the ether is evaporated, a nearly colorless viscous oil is left. This is dissolved in NaOH solution of N/1 strength, using 121.2 parts (in grams) of the viscous oil in 600 parts by volume (cubic centimeters) of the soda solution. To this liquid there is gradually added, with vigorous stirring, a solution of bismuth nitrate in aqueous glycerine, this solution being prepared in the proportion of 97 parts of crystalline bismuth nitrate, 200 parts of glycerine and 400 parts of water; all by weight. An oily product results and this is dissolved in benzene. The benzene solution is extracted with water in successive portions and is then dried over sodium sulfate. On evaporating the solvent (benzene) under reduced pressure, a neutral bismuth salt under the present invention is obtained as a thick oil. The yield is about 140 parts by weight from the quantities mentioned. This oil represents the neutral bismuth salt of propyl-methyl-carbin-malonic acid monoethyl-ester. It dissolves readily in various non-aqueous organic solvents, in fatty oils and in solvents for fatty oils. It is not soluble in water. It contains 25.7 per cent bismuth (as metal).

Example 2

Diethyl-carbin-malonic acid diethyl-ester (the diethyl-ester of symmetrical secondary amyl-malonic acid) is half saponified to obtain the corresponding monobasic acid which has the following formula:



and which is a colorless oil. In 750 parts by volume of an 8 per cent caustic soda solution are dissolved 303 parts of this diethyl-carbin-malonic acid half-ester. To this solution, which is kept cool and vigorously stirred, is added a solution of 242.6 parts by weight of bismuth nitrate in 75 parts by weight of mannit and 500 parts of water. After completion of the addition, stirring is continued for a short time; until the precipitated bismuth salt has completely balled. The aqueous solution is decanted off and the salt dissolved in ether. The ether solution is shaken out with water until the wash water gives no coloration with sodium sulfide. The dried ethereal solution, on evaporation of the ether, leaves the neutral bismuth salt of diethyl-carbin-malonic acid half-ester as a viscous slightly yellow-colored oil. It is miscible in all proportions with organic solvents and with fatty oils and has the same bismuth content as the product of Example 1, 25.7 per cent.

Example 3

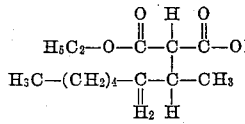
Starting with secondary butyl-malonic acid diethyl-ester, 108 parts by weight are half saponified with 28 parts by weight of caustic potash in 800 parts by volume of alcohol, giving secondary butyl-malonic acid monoethyl ester, a slightly yellow colored oil. Into a cooled solution of 282 parts by weight of this oil in 750 parts by volume of 8 per cent caustic soda solution is introduced a solution of 157.7 parts by weight of bismuth trichloride in a liter of glycerine. Introduction is gradual and stirring vigorous. The further technique is as in Example 1. There is obtained the neutral bismuth salt of secondary butyl-malonic acid ethyl ester, with a bismuth content of 27.1 per cent. In properties, it resembles the products of the previous examples.

Example 4

Isopropyl-malonic acid diethyl ester is half saponified with a molecule of KOH in alcoholic solution, as in Example 1. There results isopropyl-malonic acid mono-ethyl-ester as a nearly colorless, quite mobile oil. To 52.2 parts of this oil dissolved in 300 parts by volume of normal caustic soda solution, is added a solution of 48.5 parts by weight of bismuth nitrate in 300 volumes of a 33 per cent glycerine solution. The oily reaction product is treated like that of Example 2. The yield is 68 parts by weight of a viscous oil which is bismuth-isopropyl-malonic acid ethyl-ester with a bismuth content of 28.6 per cent.

Example 5

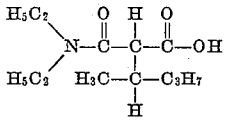
Secondary capryl-malonic acid monoethyl-ester (hexyl-methyl-carbin malonic acid monoethyl-ester) which has the following formula



and is a viscous slightly yellow-colored oil, is produced by the action of 17 parts caustic potash in 500 parts of alcohol upon 163 parts by weight of capryl-malonic-acid diethyl-ester. To 146.4 parts of this yellow oil, dissolved in 500 parts by weight of benzene, are added 55 parts by weight of fine ground bismuth oxide and the mixture digested for several hours under a reflux condenser with vigorous stirring at about 90° C. After the reaction is completed, the benzene solution is freed of the excess bismuth oxide and the benzene completely distilled off in vacuum. There results the neutral bismuth salt of secondary capryl-malonic acid ethyl-ester as a thick, viscous oil with a bismuth content of 22.3 per cent.

Example 6

In the previous examples, a carboxyl of the substituted malonic acid is esterified. The use of an ester group to produce a monobasic acid is, however, not necessary. In another way of securing the monobasic acid of the graphic formula, 230 parts by weight of methyl-propyl-carbin-malonic acid diethyl-ester are heated with 110 parts by weight of diethylamine for several hours under pressure to 130° C. From the mixed products of reaction is distilled out as a fraction, the half-ester of methyl-propyl-carbin-malonic-N, N-diethylamido acid (B. P.$_1$, 110°–115° C.). This is saponified with an alcoholic solution of caustic potash containing 56 parts of potassium hydroxide. The potassium salt obtained by evaporating the alcohol is dissolved in water and by super-saturating with hydrochloric acid, methyl-propyl-carbin-malonic-N, N-diethylamido acid is set free as an oil. This oily monobasic acid has the following formula:



To 229 parts by weight of this oil dissolved in 1000 parts by volume of normal caustic soda solution is gradually added, with vigorous stirring, a solution of bismuth nitrate in glycerine. This nitrate solution is prepared from 162 parts by weight of crystalline bismuth nitrate, 320 parts of glycerine and 700 parts of water. The bismuth compound separates as an oil. This is dissolved in ether, the ethereal solution repeatedly shaken out with water and dried over sodium sulfate. The ether is distilled off finally distilling under reduced pressure. The neutral bismuth salt of methyl-propyl - carbin - malonic - N, N-diethyl-amido acid is obtained as a thick oil with a yield of 244 parts, by weight. The oily salt dissolves very readily in organic solvents and in fatty oils. Its content of bismuth is 23.4 per cent.

A neutral bismuth salt containing 23.4 per cent bismuth is produced as a thick, nearly colorless oil, starting with diethyl-carbin-malonic acid diethyl-ester and diethyl-carbin-malonic-N, N-diethyl-amido acid monomethyl-ester (liquid B. P.$_1$ 109–113° C.) and diethyl-carbin-malonic-N, N-diethyl-amido acid prepared therefrom by saponifying.

Example 7

From 202 parts by weight of isopropyl-malonic acid diethyl ester and 110 parts of diethylamine is prepared the ethyl ester of isopropyl-malonic-N, N-diethyl-amido acid; boiling point, 107°–110° C. The potassium salt is produced by saponification with 1 molecule of potassium hydroxide in alcoholic solution. The alcohol is distilled off, the salt dissolved in ether and on acidifying, the isopropyl-malonic-N, N-diethyl-amido acid is obtained as an oil. This is dissolved in ether and the ethereal solution is dried. When the ether is distilled off, the acid solidifies on standing to a crystalline mass. The melting point is 90–91° C.

To a solution of 150 parts by weight of this acid in 745 parts by volume of a 4 per cent solution of sodium hydroxide is added a solution of 78.8 parts by weight of bismuth trichloride in 50 parts by volume of glycerine, with good stirring. The following technique is as in Example 6. The neutral bismuth salt of the isopropyl-malonic-N, N-diethyl-amido acid is a viscous oil of a light yellow color. It has a bismuth content of 25.8 per cent.

A neutral bismuth salt is obtained in the same way from the ethyl ester of secondary butyl-malonic-N, N-diethyl-amido acid (B. P.$_7$, 145–148° C.) with the aid of amido acid. It is a viscous oil with a bismuth content of 25.1 per cent.

In the foregoing examples for convenience in indicating structure, the old "carbin" terminology is used; one carbon atom being regarded as methane ("carbin") and the substance described as a substituted methane.

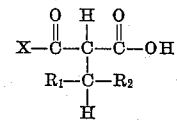
The reason for the unique properties and physical character of the bismuth salts of the acids of the formula given is not clearly apparent. Possibly stereochemical considerations are important. Whatever the cause, the fact exists.

The dialkyl esters of the substituted malonic acids are convenient points of departure in practicing the present invention and in the examples given they are used as source materials. With one equivalent of alkali they can be half saponified to alkali salts of monobasic acids or half-esters which are brought into reaction with ordinary bismuth salts in a 3:1 molecular ratio. Amidated derivatives prepared from dialkyl esters are used in the same way.

The alkyl group in the dialkyl ester and in the half-ester is generally ethyl but methyl and propyl compounds are also useful, giving final bismuth compounds of somewhat different character. For some purposes the difference is advantageous.

What we claim is:

1. In the manufacture of lipoid-like bismuth salts of a substituted malonic acid derivative having the following formula:

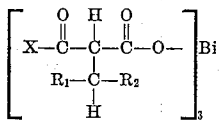


wherein X represents a substituent of the class consisting of alkoxy and dialkylamide groups, the alkyl substituent in said groups being a lower alkyl radical, and R_1 and R_2 represent a lower alkyl group, the process which comprises converting said monobasic acid into the correspond-

ing alkali salt thereof and then reacting said alkali salt of the substituted malonic acid with bismuth nitrate in a 3:1 molar ratio, and recovering the normal bismuth salt of said malonic acid derivative, this being a stable neutral salt soluble in oils and oil solvents.

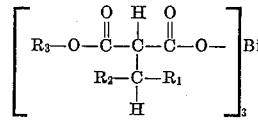
2. The process of claim 1 wherein the alkali salt of monobasic acid is reacted with bismuth nitrate dissolved in aqueous glycerine.

3. As new bismuth salts of lipoid character miscible with oils and oil solvents, the normal bismuth salts of monobasic, substituted malonic acid derivatives, said salts being stable neutral salts having the following formula:



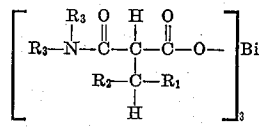
wherein X represents a substituent of the class consisting of alkoxy and dialkylamide groups, the alkyl substituent in said groups being a lower alkyl radical, and R_1 and R_2 represent a lower alkyl group.

4. As new stable bismuth compounds having therapeutic properties, the normal salts of trivalent bismuth with 3 mols of a malonic ester acid derivative, said bismuth salts being neutral, stable compounds having the following formula



wherein R_1, R_2 and R_3 represent a lower alkyl group.

5. As new stable bismuth compounds having therapeutic properties, the neutral normal bismuth salts having the following formula



wherein R_1, R_2 and R_3 represent a lower alkyl group, said salts being soluble in oils and oil solvents.

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