Patented May 27, 1947

2,421,129

UNITED STATES PATENT OFFICE

2,421,129

BETA-ISOBUTYL AMINO-BETA, BETA-DIMETHYL, ETHYL BENZOATE

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No Drawing. Application June 22, 1944, Serial No. 541,662

1 Claim. (Cl. 260—477)

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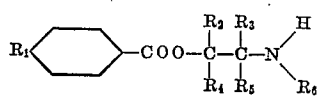
The present invention is concerned primarily with local anesthetics and while more particularly of the type useful for surface anesthesia, has some application also for injection anesthesia.

It is an object of the invention to provide a surface anesthetic of potency considerably greater and of toxicity considerably less than that of cocaine and which has all of the other requisites of a satisfactory surface anesthetic such as solubility in water, stability in water solution to permit use thereof long after it has been prepared and which shall be non-irritating to mucous tissues to which it may be applied, such as nose, throat, mouth or eyes.

The composition of the present invention is an ester of benzoic acid, or lower alkyl derivative thereof, combined with an aliphatic amino alcohol containing two carbon atoms between the nitrogen of the amino group and the oxygen of the alcohol group, the amino group being a secondary amine by virtue of one of the two hydrogen atoms being substituted by a lower alkyl group. According to usual practice it is a water soluble salt of the ester that is preferably employed as the anesthetic rather than the substantially water-insoluble ester base.

Preferably the esters of the present invention are of the general formula (A)



The acid group of this ester may be either benzoic acid or a lower para-alkyl benzoic acid. In other words R_1 may be hydrogen or an alkyl group with not more than three carbon atoms and particularly either methyl, ethyl, propyl or isopropyl.

The groups R_2, R_3, R_4 and R_5 may be either hydrogen or lower alkyl, preferably hydrogen or methyl and ordinarily where, as is desirable, not more than two of the groups R_2, R_3, R_4 and R_5 are alkyls it is preferred to have the same applied to the beta rather than to the alpha carbon, because while pharmacologically speaking

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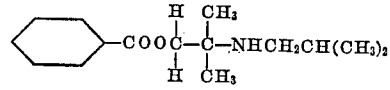
the result is approximately the same, the compound is somewhat less stable where the alkyl groups are on the alpha carbon.

The group R_6 is an alkyl containing not more than eight, and preferably not less than four carbon atoms. With less than four carbons in the alkyl group R_6 the compound tends to be unstable for practical use, and with more than eight carbon atoms, it becomes destructive to the tissue. Accordingly, the alkyl group should be butyl, amyl, hexyl, heptyl or octyl or isomers thereof.

Some hundreds of the esters are defined by the formula A, all of which are new compounds and there are corresponding water-soluble salts thereof when combined with acids. Many of these have been prepared and tested by us, and all have been found to be effective anesthetics, particularly for surface anesthesia, although their utility is by no means uniform.

The greater the loading of the chain with alkyl groups, the greater the anesthetic potency, but the toxicity rises with potency, so that for most purposes, alkyl groups on but one of the two carbon atoms, preferably the beta carbon of the chain, is recommended.

One of the most deseirable compounds of the present invention is the compound beta-(isobutyl amino) beta, beta-dimethyl ethyl benzoate which has been isolated by us in the form of its hydrochloride. The estesr base of that hydrochloride is identified by formula (B) as follows:



Comparative tests of the compounds injected subcutaneously into white mice show that the lethal dose that kills 50 per cent of the animals tested is 100 milligrams per kilogram of body weight for butyn, 150 milligrams for cocaine and 500 milligrams for the hydrochloride of the anesthetic base of the above formula B. Thus, the toxicity of cocaine is more than three and that

of butyn five times as great as that of the hydrochloride of formula B.

Comparative tests were also made for anesthetic potency by instilling the compounds into the cornea of a rabbit's eye. When 0.2 cc. of a ½% solution of either cocaine or butyn was thus instilled the anesthesia lasted thirty minutes. A like quantity of ¼% of the compound of formula B in the form of its hydrochloride, thus instilled, afforded twenty-six minutes of anesthesia. Thus the potency of our new compound based on formula B is practically twice that of either cocaine or butyn.

The compounds of the present invention have thus a decidedly favorable therapeutic index, as compared to that of other surface anesthetics such as cocaine, butyn and the like. Indeed, as compared to cocaine, the composition of the formula B is almost twice as potent, and not more than one-third as toxic, so that its therapeutic index is at least five times that of cocaine, and compares even more favorably with butyn.

The anesthetics embodied by this invention are formed by combination of benzoic acid, or lower alkyl substituted benzoic acid with an amino alcohol. The technology of preparing the component acids and the component amino alcohols is known to those skilled in the art and need therefore not be described here.

The combination of the acid and amino alcohol to give the desired basic ester product may be effected in a number of ways of which two are described as follows:

Method I.—A derivative of the component acid, namely the acid chloride, is allowed to react with one molecular equivalent of the amino alcohol in the presence of water containing one molecular equivalent of alkali. The insoluble product which forms is separated, purified by suitable means, and heated with one molecular equivalent of a concentrated acid such as concentrated hydrochloric acid to form the salt of the anesthetic base such as the hydrochloride.

Method II.—The acid and amino alcohol are allowed to react in the presence of a strong dehydrating acid under heat for a definite period of time. The resulting cooled solution is poured into water and the anesthetic base is isolated therefrom by making the solution alkaline.

A specific example of the application of Method I for the preparation of the hydrochloric acid salt of the anesthetic base of formula B is as follows:

Preparation of beta-(isobutylamino) beta, beta-dimethyl ethyl benzoate (formula B) hydrochloride.—7.3 grams of beta-(isobutylamino) beta, beta-dimethyl ethanol is added to a solution of 3 grams sodium hydroxide in 250 cc. of water. The mixture is stirred rapidly and 7.0 grams of benzoyl chloride, dissolved in 100 ml. of ether is added. After one hour of vigorous stirring the ethereal solution is separated from the water layer and washed with water. The ether is distilled off and the residual oil is treated with 5 cc. of concentrated hydrochloric acid (specific gravity 1.19) and heated for five minutes. On cooling, the mixture solidifies to a white solid. The beta-(isobutylamino) beta, beta-dimethyl ethyl benzoate hydrochloride thus formed is recrystallized from ethyl acetate to give white crystals which melt at 175–6° C.

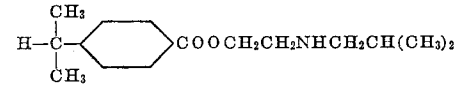
The preparation of another compound within the scope of formula A by Method I is as follows:

Preparation of beta n-hexylamino ethyl benzoate hydrochloride.—7.3 grams of beta n-hexylamino ethanol is added to a solution of 3 grams of

sodium hydroxide in 250 cc. of water. The mixture is stirred rapidly and 7 grams of benzoyl chloride is slowly added. The oily product is dissolved in ether and separated from the water. The ethereal solution is purified by washing with water, followed by dilute hydrochloric acid. The ether is distilled off and the product remains as a residual oil. This is treated with 5 cc. or concentrated hydrochloric acid (specific gravity 1.19) and warmed for five minutes. On cooling the mass solidifies to a white solid. The beta n-hexylamino ethyl benzoate hydrochloride thus formed is purified by re-crystallization from alcohol to give a white crystalline product which melts at 162–3 degrees C.

Examples of the preparation of a compound within the scope of formula A by each method are as follows:

Preparation of beta-isobutylamino ethyl cuminate (para isopropyl benzoate) hydrochloride of the formula.—



By Method I.—9.3 grams of beta isobutylamino ethanol is dissolved in 200 ml. of water containing 3.2 grams of cuminyl chloride. The oily product is separated and purified by washing with water, and dilute hydrochloride acid. The purified oil so obtained is treated with 30 cc. of concentrated sulphuric acid and heated at 110 degrees C. for one hour, after which the solution is cooled and poured into water. The anesthetic is isolated as in the previous examples. The recrystallized product, beta isobutylamino ethyl cuminate hydrochloride melts at 126 degrees C.

By Method II.—8.2 grams of cuminic acid is treated with 11.7 grams of beta isobutylamino ethanol and heated to 90° C. for one hour. The cooled mixture is treated with 25 cc. of concentrated sulphuric acid and the resulting solution is heated at 110° C. for one hour. The cooled mixture is poured into water and the acid solution is made alkaline when the beta isobutylamino ethyl cuminate base separates as an oil. This is separated from the water solution and dissolved in dilute hydrochloric acid. The clear solution is purified by the usual means and the free base is again liberated by the addition of ammonia. This is dried and weighed and dissolved in ethyl acetate and treated with the calculated quantity of dry hydrogen chloride. The resulting white product is filtered and recrystallized to give crystals of beta isobutylamino ethyl cuminate hydrochloride having a melting point of 126° C.

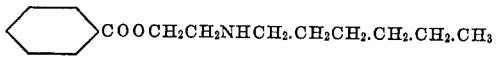
It will be readily understood by those skilled in the art how the foregoing specific examples may be modified to prepare homologous products within the scope of formula A.

In Table I are listed some of the hydrochloride salts of the compounds prepared by us which fall within the scope of our present invention and which are all within the scope of the general formula A. Also included in Table I are the names of the hydrochloride salts, their empirical formulae, their melting points, the percentage of chlorine calculated to be present in those salts and the percentage of chlorine actually found to be present by analysis to serve as a check on the chemical identity of the products listed.

Table 1

	Name	Empirical Formula	Melting Point	Per cent Cl Calculated	Per cent Cl Found
			° C.		
1	Beta n-butylamino ethyl benzoate hydrochloride	$C_{13}H_{20}NO_2Cl$	135	13.75	13.81
2	Beta n-butylamino ethyl para-toluate hydrochloride	$C_{14}H_{22}NO_2Cl$	164–5	13.04	12.84
3	Beta n-butylamino ethyl para-ethyl benzoate hydrochloride	$C_{15}H_{24}NO_2Cl$	144–5	12.40	12.32
4	Beta n-butylamino ethyl cuminate hydrochloride	$C_{16}H_{26}NO_2Cl$	135–6	11.82	11.72
5	Beta isobutylamino ethyl benzoate hydrochloride	$C_{13}H_{20}NO_2Cl$	141–2	13.75	13.74
6	Beta isobutylamino ethyl para-toluate hydrochloride	$C_{14}H_{22}NO_2Cl$	196–7	13.04	12.86
7	Beta isobutylamino ethyl para-ethyl benzoate hydrochloride	$C_{15}H_{24}NO_2Cl$	138	12.40	12.44
8	Beta isobutylamino ethyl cuminate hydrochloride	$C_{16}H_{26}NO_2Cl$	126	11.82	11.70
9	Beta n-amylamino ethyl benzoate hydrochloride	$C_{14}H_{22}NO_2Cl$	151–2	13.04	12.99
10	Beta 2-amylamino ethyl benzoate hydrochloride	$C_{14}H_{22}NO_2Cl$	149	13.04	12.92
11	Beta n-amylamino ethyl cuminate hydrochloride	$C_{17}H_{28}NO_2Cl$	140–2	11.24	11.24
12	Beta n-hexylamino ethyl benzoate hydrochloride	$C_{15}H_{24}NO_2Cl$	162–3	12.40	12.29
13	Beta n-heptylamino ethyl benzoate hydrochloride	$C_{16}H_{26}NO_2Cl$	165–6	11.82	11.92
14	Beta n-octylamino ethyl benzoate hydrochloride	$C_{17}H_{28}NO_2Cl$	161–2	11.24	11.25
15	Beta 2-octylamino ethyl benzoate hydrochloride	$C_{17}H_{28}NO_2Cl$	130–1	11.24	11.42
16	Beta 2-ethylhexylamino ethyl benzoate hydrochloride	$C_{17}H_{28}NO_2Cl$	48–9	11.24	11.05
17	Beta (n-butylamino) beta, beta-dimethyl ethyl benzoate hydrochloride	$C_{15}H_{24}NO_2Cl$	150–1	12.40	12.49
18	Beta (isobutylamino) beta, beta-dimethyl ethyl benzoate hydrochloride	$C_{15}H_{24}NO_2Cl$	175–6	12.40	12.44
19	Beta (n-amylamino) beta, beta-dimethyl ethyl benzoate hydrochloride	$C_{16}H_{26}NO_2Cl$	137–8	11.82	11.91
20	Beta (n-octylamino) beta, beta-dimethyl ethyl benzoate hydrochloride	$C_{19}H_{32}NO_2Cl$	117–9	10.37	10.41
21	Beta (2-octylamino) beta, beta-dimethyl ethyl benzoate hydrochloride	$C_{19}H_{32}NO_2Cl$	118–20	10.37	10.37

Of the compounds listed in the foregoing tabulation, compound 18, the structural formula and the preparation of which have been previously described, is preferred for many uses and its ester base is claimed as one of the species. The ester base of compound 8, the structural formula and preparation of which have also been previously described, is claimed as the second species, and as the third species is claimed the ester base of compound 12, the structural formula of which is:

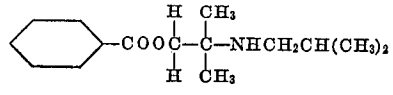


All of the compounds within the scope of formula A are claimed herein generically, regardless whether they be prepared by Method I, by Method II or by any other methods now or hereafter available for the purpose.

As many changes could be made in the above compositions and processes, and many apparently widely different embodiments of this invention could be made without departing from the scope of the claim, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

Having thus described our invention, what we claim as new and desire to secure by Letters Patent of the Untied States is:

As a composition of matter, beta-isobutyl amino beta, beta-dimethyl ethyl benzoate, characterized by high surface anesthetic potency and favorable therapeutic index and having the formula



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