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DIALKYLAMINOPROPANOL ESTERS OF BENZILIC ACID

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7 Claims. (Cl. 260—473)

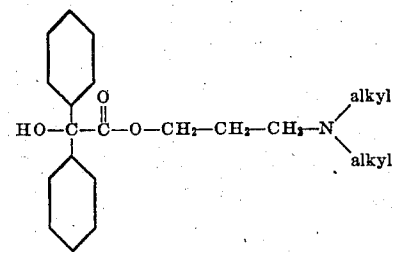
This invention relates to dialkylaminopropanol esters of benzilic acid.

Some of the alkamine esters of the diarylhydroxyacetic acids are of very considerable commercial importance. The exact properties and consequently the uses to which they may be put depend upon the particular acids and the particular aminoalcohols which go to make up the ester. In the present case the dialkylaminopropanol esters of benzilic acid possess particular value as anti-spasmodics and as local anesthetics of long duration.

Many different compounds have been synthesized in the cource of a long search for a local anesthetic which would be a satisfactory substitute for cocaine. Despite its undesirable properties of comparatively low activity, high toxicity, short duration and narcotic characteristics, however, cocaine has still remained the standard against which the new products are measured. Of the many different compounds which have been synthesized, relatively a very few have found commercial acceptance.

In many cases a satisfactory local anesthetic of long duration is highly desirable. For example in cystoscopic work, extended anesthesia is especially desirable. Similarly in spinal anesthesia, long duration is particularly important since in many types of operation the effects of the anesthetic begin to disappear before the operation has been completed. The hydrochloride of β-diethylaminoethyl p-aminobenzoic acid, for example, is very commonly used for spinal anesthesia and, as is well known, is of such comparatively short duration that in many cases repeated injections must be made. Another field in which long duration anesthetics are highly desirable is in connection with treatments of the eye as for painful ulcerations.

The present invention is particularly concerned with the dialkylamino-n-propyl benzilates which may be represented by the formula



Although it is feasible to prepare both the β- and γ-dialkylaminopropyl esters using the same or different alkyl radicals, the present application is primarily concerned with the γ-dialkylaminopropyl esters in which the alkyl radicals are the same, each having 2 to 5 carbon atoms. Typical examples of these compounds are dipropylaminopropyl benzilate and dibutyl-aminopropyl benzilate.

The present invention is not limited to any particular method of producing the desired compounds. Unfortunately however, the presence of the α-hydroxy radical precludes the use, at least on a commercial scale, of the more common methods of preparing esters such as by the reaction of a halide of the acid with the aminoalcohol or by direct esterification of the acid with the aminoalcohol. Our preferred method which produces excellent yields comprises forming an ester of the acid and a lower aliphatic alcohol such as methyl or ethyl alcohol and then carrying out a catalyzed ester interchange with the desired aminoalcohol, preferably removing the replaced alcohol as fast as it is set free. This process is more fully set forth in our copending application, Serial No. 431,822, filed February 21, 1942, of which the present invention is a continuation in part.

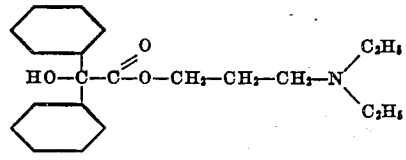
The dialkylaminopropyl benzilates are in general oily compounds which are relatively insoluble in water. Their action is mildly basic

and salts such as the hydrochloride may be readily prepared by dissolving the base in cold anhydrous ether and bubbling dry hydrochloric acid gas therethrough. The hydrochlorides are in general white crystalline solids, generally soluble in water and insoluble in ether. The γ-dibutylaminopropyl benzilate hydrochloride, for example, when purified by recrystallization from an acetone-ether solution occurs as long, silky, white needles melting sharply at 115° C. The hydrochlorides of these bases are suitable for use as local anesthetics in aqueous solution.

The invention will be described in greater detail in conjunction with the following specific examples, which are meant to be merely illustrative and do not in any way limit the invention. The parts are by weight unless otherwise noted.

Example 1

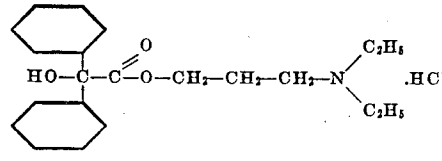
γ-Diethylaminopropyl benzilate



1 part of sodium was dissolved in 170 parts of γ-diethylaminopropyl alcohol and the solution added to 150 parts of ethyl benzilate. The reaction mixture was heated for a period of about 40 hours in an oil bath at 150° C. and then distilled until the temperature reached 200° C. to remove the ethanol and the unreacted aminoalcohol. The residue was dissolved in ether and washed with water to effect a removal of any remaining aminoalcohol and its sodium salt. The ethereal solution was dried over sodium sulfate. After drying the ether was removed and the residue, consisting of ethyl benzilate and γ-diethylaminopropyl benzilate, distilled at a pressure of 5 mm. The fraction distilling between 160° and 210° C. was collected.

Example 2

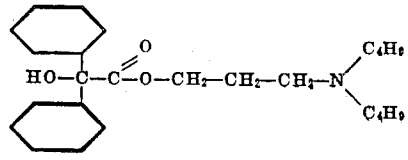
γ-Diethylaminopropyl benzilate hydrochloride



The product of Example 1 was collected and dissolved in anhydrous ether. Dry hydrogen chloride was passed into the cooled solution and the alkamine ester precipitated as the hydrochloride. In the last step an excess of hydrogen chloride was avoided, inasmuch as the hydrochloride is hygroscopic and free hydrogen chloride tends to aggravate this property. The product was filtered and crystallized from acetone. After two recrystallizations the compound melted consistently at 145–6° C.

Example 3

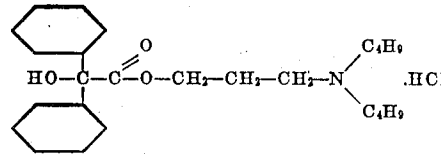
γ-Di-n-butylaminopropyl benzilate



1 part of sodium was dissolved in 415 parts of γ-di-n-butylaminopropanol and mixed with 300 parts of ethyl benzilate. The mixture was heated for 48 hours in an oil bath at a temperature of 160° C. Ethanol boiled gently during the course of the alcoholysis. After cooling, the reaction mixture was diluted with ether and the aminoester and excess aminoalcohol extracted with dilute hydrochloric acid. The aqueous extract was made alkaline with an excess of sodium carbonate, the alkamine ester extracted with ether and washed twice with water. After drying the ethereal extract and removing the ether the residue was distilled at a pressure of 6 mm. The dibutylaminopropanol distilled first at from 99°–105° C. and was recovered. The aminoester distilled from 205°–280° C. This was redistilled at 5 mm. and the fraction distilling between 225° and 230° C. was collected.

Example 4

Hydrochloride of γ-di-n-butylaminopropyl benzilate



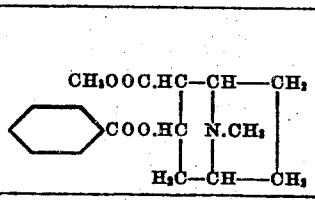
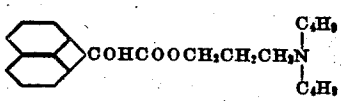
The aminoester obtained in Example 3 was dissolved in anhydrous ether and the solution cooled in an ice bath. Dry hydrogen chloride gas was passed over the surface of the ether while the solution was stirred. The hydrochloride precipitated as an oil which solidified after standing for a few hours in the cold. Recrystallization from an acetone-ether solution gave a pure product in the form of long, silky, white needles that melted at 115° C.

If it is desired to do so, other salts of the bases may be readily prepared. Examples of such salts are the nitrate, sulfate, hydrobromide, phosphate, tartrate, citrate and the like. In some cases it may be desirable to form quaternary salts of the base such as the methiodide and ethobromide. These may be readily prepared, for example, by treating the base in an absolute alcohol solution with a compound such as methyl iodide or ethyl bromide. The quaternary salt may then be precipitated with absolute ether in an approximately quantitative yield. The quaternary compounds have the advantage that they are generally more soluble than a corresponding salt such as the hydrochloride or hydrobromide. It is also an advantage of the quaternary compounds that in most cases the activity of the base as an anesthetic is increased.

That the dialkylaminopropyl benzilates should have this property of producing local anesthesia of long duration particularly in the case of the γ-dibutylpropanol ester was wholly unexpected. The well known β-diethylaminoethanol ester of diphenylacetic acid is active as an anesthetic but it is of relatively short duration, exceeding that of cocaine in corresponding doses by only a few minutes either as a surface anesthetic or as a nerve block. Increasing the number of carbon atoms in the aminoalcohol residue of the diphenylacetic acid esters causes a rapid decrease in their value as anesthetics and increases their toxicity. Further, in the β-dibutylaminoethyl ester of diphenylacetic acid the alkamine radical is large enough so that the base hydrolyzes in solution before there is any perceptible anesthetic activity. On the contrary, increasing the number of carbon atoms in the alkyl radicals of the di-

alkylaminopropyl benzilates increases the anesthetic value very appreciably and the γ-dibutylaminopropyl ester hydrochloride shows no apparent signs of hydrolysis in solution and is extremely active as an anesthetic.

γ-dibutylaminopropyl benzilate hydrochloride itself is of especial interest as a local anesthetic because of its peculiar and unexpected properties. It is active both as a surface anesthetic and as a blocking anesthetic, its activity in either case being very long in duration and characterized by an extremely small minimal anesthetic dose. Its properties as compared with those of cocaine are shown in the following table:

Structural formula	Rabbit cornea			Frog urostyle			Index of anesthetic potency				Therapeutic ratio	
	Minimal anesthetic dose	Duration anesthesia (after 2 per cent)	Irritation	Minimal anesthetic dose	Duration M. A. D.	Dose action for 180 min.	M. L. D. 100 (mouse intraperit.)	Cornea	Urostyle	Toxicity index	Cornea	Urostyle
	*Per cent* 0.5	*Min.* 20	+	*Mgm. per gram* 0.04	*Min.* 30	*Mgm. per gram* 0.18	*Mgm. per gram* 90	1.0	1.0	1.0	1.0	1.0
	0.125	62	+	0.01	180	0.011	75	4.0	4.0	1.2	3.3	3.3

It will be seen that although γ-dibutylaminopropyl benzilate is very slightly more toxic than cocaine it is a much more active compound. For example, as a surface anesthetic the minimal anesthetic dose is only ⅕ that of cocaine and its duration as a surface anesthetic is over three times that of cocaine. Similarly as a nerve block it is over four times as active as is cocaine and the duration of its minimal anesthetic dose is six times that of cocaine. Because of its high activity its therapeutic ratio is nearly three and one-half times that of cocaine, so that coupled with its long period of duration, it is particularly useful as a local anesthetic. Further it is no more irritating than cocaine and is not habit-forming.

We claim:

1. As a new chemical compound, a member selected from the group consisting of the gamma-dialkylamino-n-propyl benzilates and the water-soluble salts thereof, the alkyl groups being identical and each being a straight chain containing from two to four carbon atoms.

2. Gamma - di - n - butylamino-n-propyl benzilate.

3. Water-soluble salts of gamma-di-n-butylamino-n-propyl benzilate.

4. Gamma-di-n-propylamino - n - propyl benzilate.

5. Water-soluble salts of gamma-di-n-propylamino-n-propyl benzilate.

6. Gamma-di-ethylamino-n-propyl benzilate.

7. Water-soluble salts of gamma - di - ethylamino-n-propyl benzilate.

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