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2,423,025

ALKAMINE ESTERS OF DIARYLPROPIONIC ACIDS

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No Drawing. Application March 31, 1942, Serial No. 437,021

10 Claims. (Cl. 260—469)

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This case relates to the alkamine esters of diarylpropionic acids.

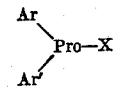
Alkamine esters of the diarylacetic acids are of very considerable commercial importance. The exact properties and consequently the uses to which they may be put depend upon the particular acids and the particular aminoalcohols which go to make up the ester. The dialkylaminoalkanol esters of diarylpropionic acids with which the present case is concerned possess value as anti-spasmodics and as local anesthetics of long duration.

Many different compounds have been synthesized in the course 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 and narcotic character 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 an extended period of anesthesia is especially desirable. Similarly in a spinal anesthesia long duration is particularly important since in many types of operation the effects of the anesthesia begin to disappear before the operation has been completed. The hydrochloride of the β-diethylaminoethyl ester of p-aminobenzoic acid for example, is very commonly used for spinal anesthesia although because of its comparatively short duration repeated injections must be made in many cases. Another field in which local anesthetics of long duration are highly desirable is in connection with treatments of the eye, as for painful ulcerations.

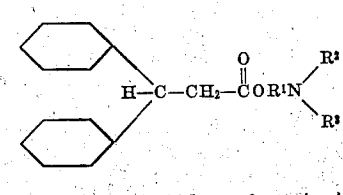
The present invention is particularly concerned with compounds of the general formula

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in which Ar and Ar' are the same or different aryl radicals substituted in a propionic acid represented by Pro and X is the residue of a tertiary amino-alcohol. The aryl radicals may be substituted or unsubstituted such as phenyl, tolyl, naphthyl, ethoxynaphthyl and the like. X may be the residue of any aminoalcohol such as β-diethylaminoethanol, γ-diethylaminopropanol, β-dipropylaminoethanol, δ-dibutylaminobutanol, β-N,N-phenylethylaminoethanol, β-propylaminoethanol, morpholinoethanol, piperidinoethanol and the like, the particular properties of the alkamine ester being dependent upon the particular acid and particular aminoalcohol which go to make up the ester.

While the invention contemplates both the α,α and β,β diarylpropionic acids, in the present application the γ-dialkylaminoalkyldiphenyl propionates of the type formula



in which R^1 is the residue of a straight chain hydrocarbon having two or more carbon atoms and R^2 and R^3 are the same alkyl radicals of from 2 to 5 carbon atoms are of particular interest.

The diarylpropionic acid which forms the basis for these compounds of the present invention may be prepared in any desired manner. For example by a Friedel-Crafts type synthesis, β,β-diphenylpropionic acid may be readily prepared

in good yield by treating cinnamic acid and benzene in the presence of aluminum chloride. The acids may then be converted to their halides in the usual manner, for example β,β-diphenylpropionyl chloride may be made from β,β-diphenylpropionic acid by treatment with thionyl chloride. The acid chloride may then be treated with the desired aminoalcohol to form the alkamine ester.

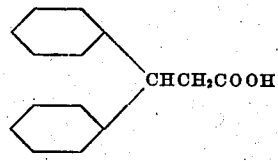
The alkamine esters of the propionic acids in general are oily liquids relatively insoluble in water and soluble in organic solvents such as alcohol or benzene. They have a slightly basic reaction and are most readily usable in the form of a salt, such as the hydrochloride, which is generally a crystalline solid soluble in water and generally soluble in ether.

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 or ethyl acetate 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 in certain respects in that they are more soluble than a corresponding salt such as the hydrochloride or hydrobromide and that they are more easily purified by crystallization than are some of the low melting point salts. It is also an advantage of the quaternary compounds that in most cases the activity of the base as an anesthetic is increased.

The preparation of compounds in the present invention will be more fully illustrated in connection with the following examples which are illustrative and not by way of limitation. All parts are by weight unless otherwise noted.

Example 1

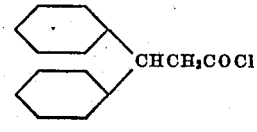
β,β-diphenylpropionic Acid



30 parts of cinnamic acid were dissolved in 160 parts of anhydrous benzene, the mixture cooled to 0° C. and 5 parts of aluminum chloride added every 10 minutes until 40 parts had been used. The reaction mixture was stirred for one hour at 35–40° C., again cooled to 0° C., and a mixture of 100 parts of ice, 100 parts of water, and 50 parts of concentrated hydrochloric acid added cautiously. The benzene was removed from this mixture by a distillation with steam and the remaining diphenylpropionic acid filtered and washed with boiling water to remove cinnamic acid. Crystallization from dilute alcohol gave a pure acid melting at 154° C.

Example 2

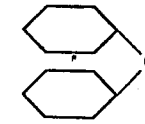
β,β-diphenylpropionyl Chloride



40 parts of β,β-diphenylpropionic acid and 80 parts of thionyl chloride were mixed and gently refluxed for three-quarters of an hour. The excess thionyl chloride was then distilled off. This crude acid chloride was used successfully in the next preparation.

Example 3

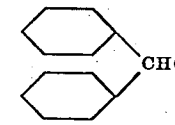
β-diethylaminoethyl β,β-diphenylpropionate



The crude acid chloride of β,β-diphenylpropionic acid obtained in Example 2 was dissolved in 400 parts of anhydrous ether and 38 parts of β-diethylaminoethanol were slowly added with stirring and gentle heating. After the complete addition of the aminoalcohol the mixture was refluxed for 4 hours to insure completion of the reaction. The reaction mixture was then cooled in an ice-bath and the ether extracted repeatedly with dilute hydrochloric acid to remove all the alkamine ester in the form of its hydrochloride. The aqueous solutions were combined and made alkaline with sodium carbonate, thus precipitating the ester as an oil. This was taken up in ether and dried over anhydrous sodium sulfate. The ether was then distilled off and the residue distilled in vacuo at 180–5° C. at 3 mm.

Example 4

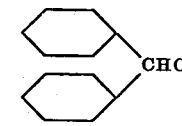
Hydrochloride of β-diethylaminoethyl β,β-diphenylpropionate



The hydrochloride was prepared by dissolving the base as prepared in Example 3 in anhydrous ether and precipitating it with dry hydrogen chloride. The salt crystallized from acetone in long, white needles that melted at 128–9° C.

Example 5

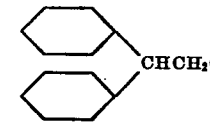
γ-diethylaminopropyl β,β-diphenylpropionate



25 parts of β,β-diphenylpropionic acid were converted into β,β-diphenylpropionyl chloride and dissolved in 300 parts of anhydrous ether. 29 parts of γ-diethylaminopropanol were added slowly with stirring and the mixture was refluxed for one hour. Water was then added and the amines extracted several times with dilute hydrochloric acid, the acid extracts combined, and made alkaline with sodium carbonate whereupon the diethylaminopropyl diphenylpropionate was thrown out as an oil. This was taken up in ether and dried over anhydrous sodium sulfate. The ether was then distilled off and the residue distilled in vacuo. The base boiled at 202–4° C. at 3 mm.

Example 6

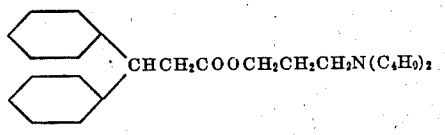
Hydrochloride of γ-diethylaminopropyl β,β-diphenylpropionate



A sample of γ-diethylaminopropyl β,β-diphenylpropionate was converted into its hydrochloride as in Example 4. It was first precipitated from anhydrous, cold ether in the form of an oil, which, after standing overnight, crystallized in white, prismatic needles. It was crystallized from acetone-ether and, thus purified, melted at 85° C.

Example 7

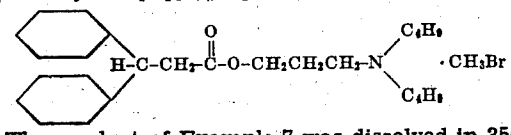
γ-di-n-butylaminopropyl β,β-diphenylpropionate



The acid chloride, prepared from 30 parts of β,β-di-phenylpropionic acid, was dissolved in 350 parts of anhydrous ether and 50 parts of γ-di-n-butylaminopropyl alcohol were added slowly during stirring. During the addition of the amino-alcohol an insoluble oil, presumably the hydrochloride of the aminoalcohol, was precipitated. The mixture was refluxed for about one hour to complete the reaction, cooled, water added and the amines extracted from the ether by means of repeated washing with dilute hydrochloric acid. The combined acid-extracts were made alkaline with solid sodium carbonate and the oily bases were extracted with ether. After washing with water to remove alkali, the ethereal solution was dried over anhydrous sodium sulfate. The ether was then removed and the residual oil, a mixture of the excess aminoalcohol and alkamine ester, was distilled at 3 mm. pressure, the alcohol distilled from 85 to 100° C. and the ester at the more elevated temperature of 225–8° C. as a yellow, very viscous oil.

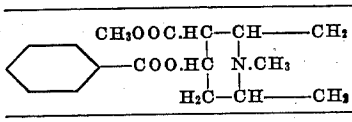
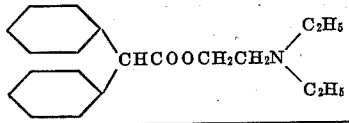
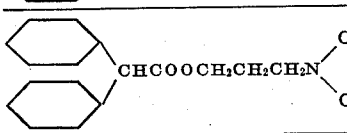
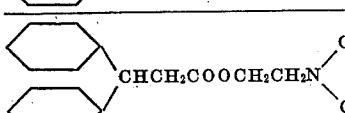
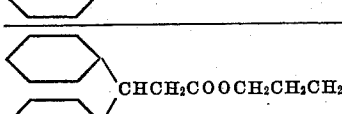
Example 8

γ-di-n-butylaminopropyl β,β-diphenylpropionate methobromide



The product of Example 7 was dissolved in 350 parts of absolute alcohol containing 50 parts of freshly prepared methyl bromide. This mixture was refluxed for 1½ hours at which time it was cooled and about half the alcohol distilled off and absolute ether was added until precipitation stopped. The solid was filtered out and purified by recrystallization from a mixture of acetone and ether.

The local anesthetic properties of the alkamine esters of β,β-diphenylpropionic acid, for example, are particularly notable for their long duration. This is particularly surprising in view of the fact that the lower alkamine esters of diphenylacetic acid, while of good anesthetic properties are of particularly short duration. Increasing the number of carbon atoms in the aminoalcohol radical of the alkamine esters of diphenylacetic acid lowers their anesthetic value and greatly increases their toxicity without causing a satisfactory increase in their duration. On the other hand increasing the number of carbon atoms in the aminoalcohol radical of the alkamine esters of diphenylpropionic acid has very little effect on the activity of the compound as an anesthetic, does not appreciably increase the toxicity and unexpectedly produces a disproportionate increase in the length of their anesthetic duration both as surface anesthetics and as blocking anesthetics. For comparison of their anesthetic value the properties of several alkamine β,β-diphenylpropionates, alkamine diphenylacetates and cocaine are given in the following table:

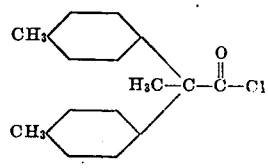
Structural formula	Rabbit cornea			Frog urostyle			Index of anesthetic potency				Therapeutic ratio	
	Minimal anesthetic dose	Duration anesthesia (after 2 per cent)	Irritation	Minimal anesthetic dose	Duration M. A. D.	Dose action for 180 min.	M. L. D. 100 (mouse intraperit.)	Cornea	Urostyle	Toxicity index	Cornea	Urostyle
	*Per cent* 0.5	*Min.* 20	+	*Mgm./gram* 0.04	*Min.* 30	*Mgm./gram* 0.18	*Mgm./gram* 90	1.0	1.0	1.0	1.0	1.0
	0.25	21	+	0.02	40	0.04	300	2.0	2.0	0.3	6.6	6.6
	0.25	13	+	0.02	60	0.04	75	2.0	2.0	1.2	1.7	1.7
	0.25	22	++	0.015	45	0.035	250	2.0	2.7	0.36	5.6	7.5
	0.25	43	++	0.015	120	0.035	150	2.0	2.7	0.6	3.3	4.5

From these figures it will be seen that diethylaminodiphenyl propionate for example, is equal in activity as a surface anesthetic to diethylaminoethyldiphenylacetic acid, is twice as active as cocaine and in similar dosages is approximately twice as persistent. Similarly as a nerve block the propionic acid derivative is more active than the corresponding acetic acid derivatives or cocaine and more than four times as persistent. On this basis it will be seen that γ-diethylaminopropyldiphenyl propionate, for example, has a valuable application as a local anesthetic of long duration. They are less toxic than cocaine, are not habit-forming, and have a therapeutic ratio many times that of cocaine. These alkamine esters therefore are useful as local anesthetics, particularly where long duration is of importance.

Although the β,β substituted propionic acids have been given the greatest amount of attention, the present invention is in no way so limited. The following examples are related to α,α-diaryl propionic acid.

Example 9

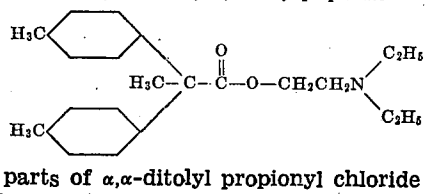
α,α-di-p-tolyl propionyl chloride



200 parts of 95% sulfuric acid were cooled to —20° C. and 52 parts of 67% pyruvic acid slowly added thereto being careful to maintain the temperature below —5° C. 40 parts of oleum (105% sulfuric acid) were added in similar manner keeping the temperature below —5° C. Then maintain the temperature between —10° and —5° C. 78 parts of toluene were added in small portions over a period of ½ hour and this mixture stirred for ¾ of an hour still maintaining the temperature at about —5° C. Finally the mixture was drowned in 400 parts of ice and water, filtered and the crystals washed with ice water. The crystals were dissolved in 200 parts of alcohol and stirred with decolorizing carbon, the carbon filtered out and the product recrystallized by evaporation. The crystals then were mixed with 93 parts of thionyl chloride and refluxed for 1½ hours, the excess thionyl chloride removed by distillation under vacuum and the residue taken up in 250 parts of hexane, the mixture stirred with decolorizing carbon, filtered and cooled. These crystals were collected by filtration, recrystallized twice from hexane and dried over paraffin under a vacuum. The product α,α-di-p-tolyl propionyl chloride melted at 56–57° C.

Example 10

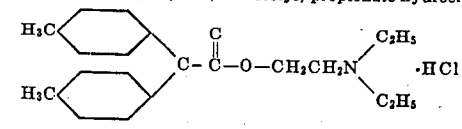
β-diethylaminoethyl α,α-ditolyl propionate



17 parts of α,α-ditolyl propionyl chloride were dissolved in 40 parts of benzene and 16 parts of β-diethylaminoethanol added to the mixture. The mixture was refluxed for 1 hour and then cooled to 20° C. at which temperature the β-diethylaminoethanol hydrochloride which precipitated during the reaction was filtered off. The filtrate was distilled under slightly reduced pressure to remove the residual benzene after which the pressure was reduced to about 1 mm. and the amino ester distilled off at 182–185° C.

Example 11

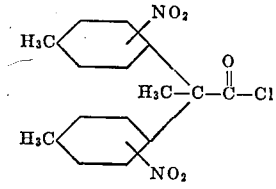
β-diethylaminoethyl α,α-di(aminotolyl) propionate hydrochloride



The ester base produced in Example 10 was dissolved in 75 parts of acetone to which was added 4½ parts of concentrated hydrochloric acid. On stirring and cooling light yellow crystals separated which were purified by recrystallization from acetone-alcohol mixture.

Example 12

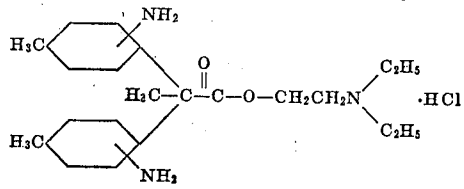
α,α-di(nitrotolyl) propionyl chloride



50 parts of 98% nitric acid and 35 parts of 70% nitric acid were cooled to —5° C. and 20 parts of α,α-di-p-tolyl propionic acid, prepared as in Example 9, were added in 5 part portions, care being taken to keep the temperature below 0° C. The first portions of the α,α-di-p-tolyl propionic acid dissolved but in the latter part of the reaction the α,α-di(nitrotolyl) propionic acid began to crystallize out. The mixture was stirred for ½ hour at 0° C. after all the components were added and then drowned in 100 parts of ice and water, the resulting precipitate filtered off and washed with ice water. The precipitate was recrystallized from glacial acetic acid and refluxed for 1½ hours with 300 parts of thionyl chloride after which the excess thionyl chloride was distilled off, the residue taken up in 25 parts of hexane, stirred with decolorizing carbon, filtered and the filtrate cooled, whereupon the acid chloride separated out and was purified by recrystallization from hexane. The product, α,α-di-(nitrotolyl) propionyl chloride melted at 88–90° C.

Example 13

β-diethylaminoethyl α,α-di(aminotolyl) propionate hydrochloride



24 parts of α,α-di(aminotolyl) propionyl chloride were dissolved in 35 parts of benzene to which mixture was added 16 parts of diethylaminoethanol. The mixture was gradually heated to reflux and held at that point for 30 minutes after which the temperature was lowered to about 20° C. and the precipitated diethylaminoethyl hydrochloride filtered off. To the filtrate were added 15 parts of xylene, 40 parts of iron filings, 10 parts of glacial acetic acid and 40 parts of water. This mixture was refluxed for 2 hours after which the iron sludge was removed and washed with xylene. The washings and filtrate were combined and evaporated to dryness under reduced pressure. The residue was again extracted with xylene and

evaporated under reduced pressure, the final residue being a very viscous amber colored liquid. This liquid was dissolved in 75 parts of acetone and 4.5 parts of concentrated hydrochloric acid added thereto. On stirring and cooling light yellow crystals separated which were collected and then recrystallized from an acetone-alcohol mixture as very light yellow crystals melting at 194–198° C.

We claim:

1. β-diethylaminoethyl β,β-diphenylpropionate.

2. A water-soluble salt of β-diethylaminoethyl β,β-diphenylpropionate.

3. γ-diethylaminopropyl β,β-diphenylpropionate.

4. A water-soluble salt of γ-diethylaminopropyl β,β-diphenylpropionate.

5. γ-di-n-butylaminopropyl β,β-diphenylpropionate.

6. A watersoluble salt of γ-di-n-butylaminopropyl β,β-diphenylpropionate.

7. A compound selected from the group consisting of the β-dialkylaminoethyl and γ-dialkylaminopropyl β,β-diphenylpropionates, the alkyl groups being identical straight-chain containing from 2 to 4 carbon atoms.

8. A water-soluble salt of a compound selected from the group consisting of the β-dialkylaminoethyl and γ-dialkylaminopropyl β,β-diphenylpropionates, the alkyl groups being identical straight-chain containing from 2 to 4 carbon atoms.

9. A γ-dialkylaminopropyl β,β-diphenylpropionate, the alkyl groups being identical straight-chain containing from 2 to 4 carbon atoms.

10. A water-soluble salt of a γ-dialkylaminopropyl β,β-diphenylpropionate, the alkyl groups being identical straight-chain containing from 2 to 4 carbon atoms.

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ARTHUR J. HILL.

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The following references are of record in the file of this patent:

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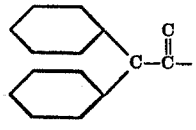
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Certificate of Correction

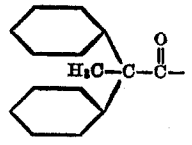
Patent No. 2,423,025. June 24, 1947.

ROGER B. HOLMES ET AL.

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction as follows: Column 8, lines 7 to 11, inclusive, Example 11, for that portion of the formula reading



read



and that the said Letters Patent should be read with this correction therein that the same may conform to the record of the case in the Patent Office.

Signed and sealed this 25th day of May, A. D. 1948.

[SEAL]

THOMAS F. MURPHY,
Assistant Commissioner of Patents.