

1

2,725,399

TERTIARY DIALKYLAMINO PROPANOLS

John Joseph Denton, Somerville, N. J., assignor to American Cyanamid Company, New York, N. Y., a corporation of Maine

No Drawing. Application November 3, 1949,
Serial No. 125,382

3 Claims. (Cl. 260—570.6)

The present invention is concerned with a novel group of synthetic, physiologically-active, basic tertiary alcohols. As such, this application constitutes a continuation-in-part of my copending application Serial No. 691,882, filed August 20, 1946, and now abandoned.

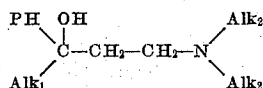
Many different synthetic compounds, pharmacologically-active as anti-spasmodics and local anesthetics, have been synthesized from time to time. The more active and apparently useful of these compounds have, in general, comprised fairly complex molecules containing at least one ester grouping. This grouping was generally considered essential on the basis of analogy to the naturally-occurring extractives which were considered esters of tropic or pseudo-tropic acids.

Unfortunately, for one reason or another, many if not most of these compounds were not wholly satisfactory. Among other factors, the presence of the ester grouping introduces a chemically labile structure which adds to the instability of the molecule. This instability creates difficulty in the laboratory, making the preparation, purification, and handling of the materials extremely difficult. Further, modification may occur in several ways in the animal organism in which the compound is attempted to be used. For example, the compound may break down into other compounds which are ineffectual, or which are irritating, or which may even be highly toxic.

It is, therefore, the principal object of the present invention to develop a series of compounds which are physiologically active, especially as anti-spasmodics. In so doing, it is a further and added object to develop materials which are not subject to the objectionable breakdown which so frequently characterized the more active of the previously-known, synthetic, pharmacologically-active esters.

In the accomplishment of these objects in accordance with the present invention, the surprising fact has been found that the ester grouping previously considered essential in the prior art is quite unnecessary. It has been found in accordance with the present invention that the desirable characteristics are evidenced by a group of basic nitrogenous tertiary alcohols containing no ester grouping.

In particular the present application contemplates the basic tertiary alcohols of the general formula



in which PH, Alk₁ and Alk₂ have the values noted immediately below.

Alk₁ and PH by their location on the molecule may be interchangeable. Alk₁ may be an alkyl radical of from about two to six carbon atoms. Alk₂ is a methyl or ethyl radical. PH may be a phenyl tolyl, xylyl, or a mono- or di- hydroxy, methoxy, chloro- or bromo-substituted phenyl radical.

From the foregoing it will be seen that the compounds of the present invention may vary in scope and structure.

2

Typical illustrative compounds of the type having the structural formula and values noted above are those contained in the following table of compounds in which PH, Alk₁ and Alk₂ have the designated values.

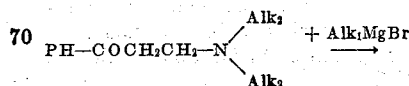
TABLE I

	PH	Alk ₁	$\begin{array}{c} \text{Alk}_2 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{Alk}_2 \end{array}$
10	phenyl	ethyl	dimethylamino.
	Do	do	diethylamino.
	p-tolyl	do	dimethylamino.
	o-tolyl	do	Do.
15	3,4-dimethylphenyl	do	Do.
	2,5-dimethylphenyl	do	Do.
	phenyl	n-propyl	Do.
	Do	isopropyl	Do.
	Do	isoamyl	Do.
	Do	n-butyl	Do.
20	Do	isobutyl	Do.
	Do	n-hexyl	Do.
	p-chlorophenyl	ethyl	diethylamino.
	o-bromophenyl	do	Do.
	4-methoxyphenyl	do	Do.
	2,4-methoxyphenyl	do	Do.
	2,4-dihydroxyphenyl	do	Do.
25	2,5-dimethoxyphenyl	do	Do.

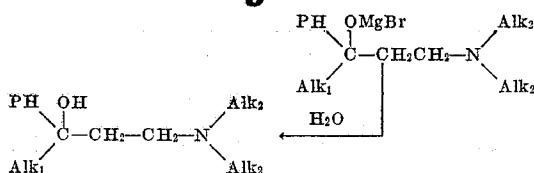
Some of the basic tertiary alcohols of the present invention are crystalline solids. Others, however, are so difficultly crystallizable as to appear to be permanent oils and some appear actually to be permanent oils. The crystalline compounds appear to be free from color when pure. Most of the alcohols are relatively insoluble in water but are readily soluble in ether and in alcohol-ether mixtures.

The alcohols readily form crystalline addition salts, such as the hydrochloride, nitrate, citrate and the like, by reacting the alcohol with the desired acid in the ordinary way in solution. The hydrochlorides, for example, are readily formed and are soluble in aqueous solution. In some cases the water-solubility is so marked that the salts are extremely hygroscopic and in crystalline form must be carefully handled. They possess the markedly useful property in aqueous solution of remaining stable over long periods of time. Quaternary salts such as the methobromide, methiodide, methochloride, ethiodide and ethobromide form readily. Some crystallize with water of crystallization. The quaternary salts appear to have about the same activity as the addition salts and considerably longer action. Some also show mydriatic activity. The salts therefore possess marked utility for pharmacological experiment.

It is surprising that the basic tertiary alcohols of this invention should possess antispasmodic properties in view of the previously considered desirability of the ester grouping. Especially is this a surprising feature in view of the fact that secondary alcohols of similar structure, for example, 3-(1-piperidyl)-1-phenyl-1-propanol and the like possesses no appreciable pharmacological activity either as anesthetics or spasmolytics. According to the present invention, therefore, a novel synthesis has been developed which is general and more effective in operation. This process involves the addition of a suitable Grignard reagent to the proper basic ketone in the presence of a suitable solvent for both. Heating for sufficient time to complete the reaction, followed by hydrolysis produces the desired basic tertiary alcohol. A typical illustration of the reaction may be indicated as follows:



3



Since the first stage in this reaction must be carried out under conditions which are not conducive to hydrolysis, a dialkyl ether, for example, diethyl or dibutyl ether and the like, has been found to be a wholly satisfactory solvent.

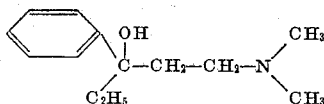
Several precautionary measures should be observed for best operation. Since the first step addition of the Grignard reagent, must be carried out under conditions which are not conducive to hydrolysis, the solvent, whether an ether, a benzene-pyridine mixture or the like, should be essentially anhydrous.

Choice of the particular halogen used in the Grignard reagent may have certain advantages in individual cases. In general, the chloride, bromide and iodide may all be used. In some cases, however, the reagent itself apparently tends to form an insoluble complex with the ketone. In such cases the chloride appears to produce the least insoluble complexes and therefore may be preferable. For a similar reason, in such cases the use of a higher boiling solvent such as dibutyl ether may become preferable in order to utilize increased temperature and thereby improve the solubility.

The amount of Grignard reagent chosen also has an effect on the yield. Apparently this again may be due to the formation of a complex. The latter is believed to form but to break down on hydrolysis. For this reason it appears that some of the reagent is not available for further reaction. In any case a considerable increase over an equimolecular amount of the Grignard reagent ordinarily produces a definitely increased yield. Above about two molecular equivalents, however, further increase in the amount used produces a markedly diminishing return. About two mols of Grignard reagent per mol of ketone appears to be the preferable range.

Preparation of the products of the present invention will be illustrated in conjunction with the following examples, which are to be taken as illustrative only and not by way of limitation. All parts are by weight unless otherwise noted.

EXAMPLE 1

1-dimethylamino-3-phenyl-3-pentanol

To a solution of ethylmagnesium bromide (prepared from 37.5 parts of magnesium turnings, 164 parts ethyl bromide and 750 parts by volume of dibutyl ether) is added a dry solution consisting of 129 parts of omega-dimethylaminopropiophenone and 500 parts by volume of dibutyl ether at a rate such as to keep the temperature of the reaction mixture at 40°–50° C. while it is being stirred rapidly. After the dimethylaminopropiophenone has been added, the mixture is stirred and heated at 40°–50° C. for 1½ hours and then allowed to stand at room temperature until reaction substantially ceases. A solution consisting of 82.1 parts of hydrogen chloride dissolved in 450 parts of water is added slowly to the reaction mixture while it is being stirred vigorously and cooled. The resultant solid is removed by filtration and is redissolved in 600 parts of water. Ammonium hydroxide solution is added until the mixture becomes alkaline. The 1-dimethylamino-3-phenyl-3-pentanol which precipitates is collected on a filter and purified by recrystallization from dilute ethanol. It melts at 45.4°–46.2° C.

4

EXAMPLE 2

1-dimethylamino-3-phenyl-3-pentanol hydrochloride

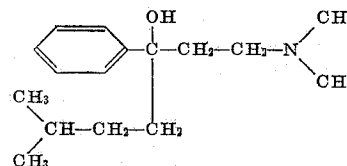
1-dimethylamino-3-phenyl-3-pentanol prepared in accordance with Example 1 is dissolved in diethyl ether. This ether solution is treated with dry hydrogen chloride gas until the mixture becomes acidic to Congo red. The white crystalline product which forms during acidification is collected by filtration and purified by recrystallization to 1-dimethylamino-3-phenyl-3-pentanol hydrochloride melting at 125.2°–125.8° C. (uncorrected) after previous sintering at 124.7° C.

EXAMPLE 3

1-dimethylamino-3-phenyl-3-pentanol ethobromide

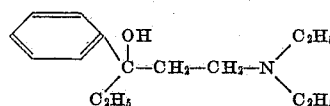
On standing for three days, a solution of 5 parts of 1-dimethylamino-3-phenyl-3-pentanol, 13.6 parts of ethyl bromide, and 20 parts by volume of nitromethane, was diluted with 100 parts by volume of ether. After dilution the mixture deposits the above ethobromide. Recrystallization of this material from an alcohol-ether mixture gives a solid melting at 110.2°–117° C., which on analysis, was found to contain 2.2 percent moisture.

EXAMPLE 4

1-dimethylamino-6-methyl-3-phenyl-3-heptanol

When isoamylmagnesium bromide is substituted for the ethylmagnesium bromide in the procedure for making 1-dimethylamino-3-phenyl-3-pentanol, 1-dimethylamino-6-methyl-3-phenyl-3-heptanol is formed.

EXAMPLE 5

1-diethylamino-3-phenyl-3-pentanol hydrochloride

Substituting omega-diethylaminopropiophenone for the omega-dimethylaminopropiophenone of Example 1 yields 1-diethylamino-3-phenyl-3-pentanol. Converting the latter to the hydrochloride according to the process of Example 2 yields a salt melting at 167.0°–167.5° C.

EXAMPLE 6

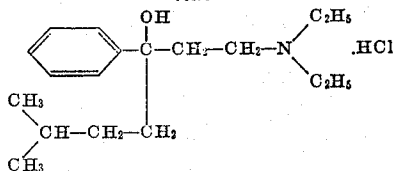
1-diethylamino-3-phenyl-3-pentanol ethobromide

Nine parts of 1-diethylamino-3-phenyl-3-pentanol hydrochloride is dissolved in a minimum amount of water. This solution is made alkaline with dilute caustic, and the free amine which separates is extracted with ether. The ether solution is dried over anhydrous potassium carbonate, filtered, and the ether evaporated. The residue is treated with 50 parts by volume of nitromethane and 15 parts by volume of ethyl bromide. After two days at ordinary temperature, dilution of the solution with 200 parts by volume of ether causes 1-diethylamino-3-phenyl-3-pentanol ethobromide to precipitate. It may be further purified, if desired, by recrystallization from an alcohol-acetone mixture. When pure, it melts at 173.8°–176.0° C.

5

EXAMPLE 7

1-diethylamino-6-methyl-3-phenyl-3-heptanol hydrochloride

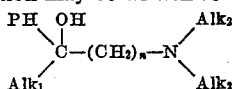


To a solution of isoamylmagnesium chloride (prepared from 68.2 parts of magnesium turnings, 332 parts of isoamyl chloride and 1235 parts by volume of ether), a solution of 300 parts of omegadiethylaminopropiophenone in about 500 parts by volume of ethyl ether is added, with stirring, over a period of about 15 minutes at 5°–35° C. The reaction mixture is stirred at room temperature until the reaction appears to cease. The mixture is then chilled and treated by slowly adding 840 parts by volume of 5N hydrochloric acid. The solid formed is collected on a filter, dried, dissolved in 7000 parts by volume of boiling water, the solution being treated with decolorizing charcoal, filtered, and made alkaline by the addition of ammonium hydroxide. The oil which separates is extracted with ether and the ethereal solution is dried over anhydrous calcium chloride and filtered. When dry hydrogen chloride gas is passed into this ether solution, 1-diethylamino-6-methyl-3-phenyl-3-heptanol hydrochloride precipitates as a white solid. The hydrochloride melts at 206.7°–207.0° C.

From the foregoing examples, the process of preparing the basic tertiary alcohols of the present invention is believed to be clear. In preparing the other compounds of this invention, the procedures of these illustrative examples may be followed. To prepare additional compounds of the present invention requires only substitution of molecularly equivalent amounts of the corresponding aryl ketone and/or the appropriate alkyl Grignard reagent.

The basic tertiary alcohols of this invention may also be prepared by the addition of arylmagnesium halides to alkyl 2-dialkylaminoethyl ketones. The lack of availability of the latter ketones and the difficulty of their preparation, however, make the previously described preparation by the addition of alkylmagnesium halides to aryl 2-dialkylaminoethyl ketones the preferred and more practical method of synthesis.

As was noted above, the compounds of the present invention have a number of desirable properties. However, it is quite surprising that the structure of the alcohols having the desired properties is so specifically limited. For example, a general formula including compounds of the present invention may be written as follows:



When so written n represents the number of carbon atoms separating the $\text{—N(Alk}_2)_2$ grouping and the carbon carrying the alcoholic hydroxyl group. The compounds of the present invention are all those in which n is two. Varying n to alter the separation by one more or one less carbon atom gives compounds having much lower or no activity. This is illustrated, for example, in the following table:

Compound			n	LD ₅₀	ED ₅₀	Antispasmodic Index ¹
PH	Alk ₁	Alk ₂				
phenyl	C ₂ H ₅	C ₂ H ₅	1	175	>1,000	<0.175
Do	C ₂ H ₅	C ₂ H ₅	2	125	100	1.25
Do	C ₂ H ₅	C ₂ H ₅	3	270	1,000	0.27

¹Antispasmodic Index = LD₅₀/ED₅₀, where LD₅₀ is the intraperitoneal dosage in mice in mg./kg. required to kill 50% of the test animals and ED₅₀ is the gamma of compound per hundred ml. of bath required to produce 50% relaxation of a segment of isolated spastic rabbit intestine.

6

Similarly the desired properties seem to reside only in alcohols containing the grouping



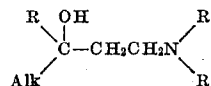
If in this grouping PH is replaced by Alk₁, and Alk₁ and Alk₂ are methyl or ethyl, or as in the present invention, the resultant alcohols again have very little or no antispasmodic activity. The activity of such compounds is not sufficient for pharmacological utilization. This is illustrated in the following table:

Compound		Antispasmodic Activity ¹
Number	Structure	
1		0
2		0
3		55
4		100

¹Relative activity based on activity of compound 4 as one hundred.

I claim:

- 1-diethylamino-3-phenyl-3-pentanol.
- A compound of the group consisting of tertiary amino alcohols of the formula



wherein R is phenyl, Alk is an alkyl of 2 to 6 carbon atoms and



is a lower dialkylamino group and acid addition salts thereof.

- 1-dimethylamino-3-phenyl-3-pentanol.

References Cited in the file of this patent

UNITED STATES PATENTS

828,846	Fourneau	Aug. 14, 1906
1,978,539	Klarer et al.	Oct. 30, 1934
2,282,907	Ter Horst	May 12, 1942
2,411,664	Miescher et al.	Nov. 26, 1946

FOREIGN PATENTS

234,785	Switzerland	Feb. 16, 1945
240,363	Switzerland	May 16, 1946
698,687	France	Feb. 3, 1931

OTHER REFERENCES

Maire: Bull. Soc. Chim. [4] vol. 3 (1908), pp. 280–86.
Campbell: Jour. Amer. Chem. Soc., vol. 60 (1938), pp. 1372–76.