Patented Oct. 12, 1954

2,691,679

UNITED STATES PATENT OFFICE

2,691,679

THERAPEUTIC COMPOUNDS

Howard B. Wright and Marjorie B. Moore, Waukegan, Ill., assignors to Abbott Laboratories, North Chicago, Ill., a corporation of Illinois

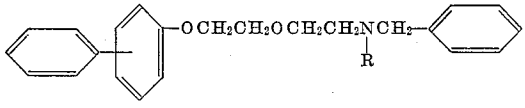
No Drawing. Application June 9, 1951, Serial No. 230,845

3 Claims. (Cl. 260—570.7)

1

The present invention relates to novel chemical compounds having local anesthetic properties, particularly adapted for corneal anesthesia and to a novel process for preparing them. More specifically, these compounds are N-lower-alkylbenzylaminoalkoxyalkyl ethers of phenylphenols and acid-addition salts of the same. In particular, the invention relates to N-lower-alkylbenzylaminoethoxyethyl ethers of phenylphenols and their acid-addition salts.

The compounds of the present invention are N-lower-alkylbenzylaminoethoxyethyl ethers of phenylphenols of the following formula:



wherein the phenyl group of the phenyl ether linkage may be substituted in the ortho, meta, or para positions by the second phenyl group; R is a lower alkyl group containing up to and including four carbon atoms. R includes such groups as methyl, ethyl, isopropyl, secondary butyl, and normal butyl. The invention also includes acid-addition salts of these amines. While the invention encompasses compounds in which the phenyl group attached to the phenoxy group may be in the ortho, meta, or para positions, we have discovered that those compounds having the phenyl group in the ortho position are preferred. Also, compounds in which R is a methyl group are preferred; since compounds wherein R is methyl have enhanced therapeutic properties over those having a lower alkyl group containing more than one carbon atom.

Contemplated in the scope of the invention are acid-addition salts of the above bases. We have discovered that for therapeutic purposes, it is more desirable to administer the compounds in the form of their acid-addition salts. The compounds are usually more water-soluble in the form of their acid-addition salts and produce a more rapid therapeutic effect. Any acid, whether it is organic or inorganic, and which produces a salt without appreciably enhancing the toxicity, is suitable for use. Such acids as phosphoric, sulfuric, hydrochloric, and hydrobromic are satisfactory. Where a retarding effect is desired in obtaining the therapeutic results, salts of other non-toxic acids, such as tannic acids, which are very sparingly soluble in water, may be used. By using the water-insoluble salts, the desired pharmacological effect will be slow in onset and relatively longer in duration. However, the water soluble acid-addition salts are

2

preferred. Of the salts, the inorganic acid salts are most preferred.

Investigators have long sought compounds having local anesthetic properties which will produce anesthesia of long duration. Some compounds have been discovered having properties which make them reasonably desirable as local anesthetics. However, most of these compounds produce either considerable or extreme irritation to mucous surfaces, such as that of the cornea. Such irritation makes these compounds of no practical value for corneal anesthesia because of this undesirable effect. As a result of the research investigation which has resulted in the present invention, we have discovered that N-lower alkyl-benzylaminoethoxyethyl ethers of phenylphenols not only produce anesthesia of unusually long duration but also produce no irritation to the cornea of both animals and humans, even when used in a reasonably concentrated solution. Not only are the compounds of the invention not irritating in moderately concentrated solutions; but, what is even more remarkable, they are active in very dilute solutions. For example, the hydrochloride of β-o-phenylphenoxyethyl β'-N-methylbenzylaminoethyl ether in 0.005% aqueous solution produces anesthesia on the rabbit cornea, lasting for approximately twenty-five minutes in both eyes. In a concentration of 0.05%, the duration was considerably above 200 minutes. What is more important, the solution produced no irritation to the eye. When tests were transferred to the human eye, it was possible to obtain anesthesia for greater than thirty minutes with a very dilute solution without stinging or any irritation. When the concentration was increased, there was still no irritation, however, the duration of anesthesia was increased.

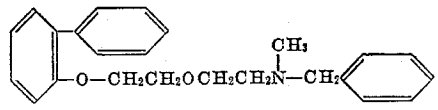
During the investigation which led to the present invention, we prepared and tested a large number of related compounds. However, to our surprise we found the unique local anesthetic and non-irritating properties limited to N-lower-alkyl-benzylaminoethoxyethyl ethers of phenylphenols. For example, when the compound, β-p-methoxyphenoxyethyl β'-N-methylbenzylaminoethyl ether, was tested in a 1% solution, anesthesia was obtained in the rabbit cornea for only about twenty minutes and with a degree of irritation which made the compound unsuitable for corneal anesthesia. With β-p-phenylphenoxyethyl γ'morpholino - n - propyl ether, anesthesia of the rabbit cornea was obtained for approximately seventy-five minutes with a 1% solution. However, the irritation was

to an extreme degree, making the compound completely unsuitable for corneal anesthesia. A similar experience was obtained with other homologues and analogues of compounds related to those of the present invention.

We have discovered novel processes for preparing the bases of the present invention. We have discovered these compounds can be synthesized by joining the elements of the molecule at the oxygen and at the nitrogen linkages. For example, the compounds may be prepared by condensing a β-hydroxyethyl-N-lower alkyl-benzylamine with a β-phenylphenoxyethyl halide, or one may condense a β-phenylphenoxyethoxy ethyl halide with a N-lower-alkyl-benzylamine. Thirdly, the compounds may be prepared by condensing a phenylphenol with a N-lower alkylbenzylaminoethoxyethyl halide. Lastly, one may prepare the compound by alkylating a β-phenylphenoxyethyl β'-aminoethyl ether successively with a benzyl halide and a methyl halide. We prefer the method utilizing the condensation of a β-phenylphenoxyethyl halide with a β-hydroxyethyl N-lower alkylbenzylamine.

In order more clearly to disclose the nature of the present invention, several specific examples illustrating the preparation of typical compounds will hereinafter be described. It should be understood, however, that this is done solely by way of example and is intended neither to delineate the scope of the invention nor limit the ambit of the appended claims.

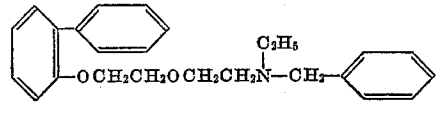
Example I.—β-o-Phenylphenoxyethyl β'-N-methylbenzylaminoethyl ether



About 2.3 g. (0.1 mole) of sodium sand is prepared in 100 cc. of dry xylene, by warming to melt the sodium and stirring vigorously during cooling. Then about 16.5 g. (0.1 mole) of β-hydroxyethyl - N - methylbenzylamine is added dropwise and the mixture stirred and refluxed for 0.5 hours. About 23.2 g. (0.1 mole) of β-o-phenylphenoxyethyl chloride (dissolved in a little xylene) is also added dropwise and the mixture stirred and refluxed for about 6 hours. The mixture is cooled, filtered and the xylene layer extracted with 10% hydrochloric acid. The acid extracts are made basic with a 40% aqueous sodium hydroxide solution and the resulting oil taken up in ether and/or benzene. After drying and distilling, the product has a boiling point 218–220° C. at 1.88 mm. pressure.

The above compound may also be prepared from β - N - methylbenzylaminoethoxyethanol. This intermediate is prepared by adding ethylene oxide to N-(β-hydroxyethyl) -methylbenzylamine. The chloride of the resulting N-methylbenzylaminoethoxyethanol is then prepared by treating this compound with thionyl chloride. The resulting halide is then condensed with an alkali-metal salt of o-phenylphenol to prepare β-o-phenylphenoxyethyl β' - N - methyl - benzylaminoethyl ether.

Example II.—β-o-Phenylphenoxyethyl β'-N-ethylbenzylaminoethyl ether



About 11.8 g. of o-phenylphenoxyethoxy ethyl chloride is refluxed with about 13.5 g. of N-ethylbenzylamine in 100 cc. of dry xylene for about 24 hours. The N-ethylbenzylamine hydrochloride precipitate is filtered, and the xylene filtrate is worked up as in Example I. The product has a boiling point 210–211° C. at 0.45 mm. pressure.

Other compounds according to the invention which are prepared by the processes disclosed are β - m - phenylphenoxyethyl β' - N - methylbenzylaminoethyl ether, β-p-phenylphenoxyethyl β'-N - methylbenzylaminoethyl ether, β - o - phenylphenoxyethyl β' - N - n - propylbenzylaminoethyl ether, β-o-phenylphenoxyethyl β'-N-sec.-butylbenzylaminoethyl ether, and β-o-phenylphenoxyethyl β'-N-n-butylbenzylaminoethyl ether. These compounds exhibit the excellent therapeutic properties of the compounds of the invention.

The acid-addition salts may be prepared by transforming the bases of the invention by treating the bases with the desired acid. Although we have disclosed a number of the acids from which acid-addition salts may be prepared, we prefer the acid-addition salts of the inorganic acids.

The compound, β-o-phenylphenoxyethoxy ethyl chloride, has been used as an intermediate in the preparation of the compound of Example II. This compound may be prepared as follows: About 34 g. of o-phenylphenol and 57 g. of bis (2-chloroethyl) ether are stirred and refluxed with 8 g. of sodium hydroxide in 20 cc. of water for about 7 hours. The mixture is cooled and filtered. Ether (200 cc.) is added to the filtrate and the layers separated. The ether layer is dried, concentrated and the product distilled. The boiling point is 140° C. at 0.1 mm. pressure. The isomers of this compound may be prepared similarly.

The bases of the present invention or their acid-addition salts may be administered in the form of aqeous solutions and as component of the customary ointments and ophthalmic ointments. The compounds may also be dispensed in tablet and capsule form for use in preparing solutions for administration.

Others may readily adapt the invention for use under various conditions of service, by employing one or more of the novel features disclosed, or equivalents thereof. As at present advised with respect to the apparent scope of our invention, we desire to claim the following subject matter.

We claim:

1. The compound β-o-phenylphenoxyethyl β'-N-methylbenzylaminoethyl ether and its acid addition salts.

2. β-o-Phenylphenoxyethyl-β'-N-methylbenzyl aminoethyl ether.

3. β-o-Phenylphenoxyethyl-β'-N-methylbenzylaminoethyl ether hydrochloride.

References Cited in the file of this patent

UNITED STATES PATENTS

Number	Name	Date
2,132,674	Bruson	Oct. 11, 1938
2,170,111	Bruson	Aug. 22, 1939