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ANTI-SPASMODICS SPECIFIC FOR PEPTIC ULCER

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13 Claims. (Cl. 167—65)

This invention relates to an ester of cyclic amino-alcohols and particularly to the benzilic acid ester of N-ethyl-3-hydroxypiperidine, non-toxic onium derivatives thereof, and pharmaceutical compositions of the same.

This application is a continuation-in-part of application Serial No. 217,413, filed March 24, 1951, which is a continuation-in-part of application Serial No. 180,295, filed August 18, 1950, now abandoned.

The reduction of smooth muscle spasm, whether of musculotropic or neurotropic origin, by atropine and by various synthetic compounds related in structure to atropine or papaverine, is well known. While many of those compounds will effectively abolish one or the other type of spasm, they are not capable of relieving both types of muscle spasm. Furthermore, the action of the known compounds is usually accompanied by undesirable side effects such as dilation of the pupil of the eye, dryness of the mouth, large increase in rate of heart beat, hypertension, nausea and vomiting.

Some esters of N-alkyl-4-piperidinol have been found to be active anti-spasmodics or spasmolytics, but such esters have never been put into use. It is well known that changes in the positions of certain substituents on the piperidine ring may produce profound differences in the physiological activity and effects of such compounds, which differences are not predictable. Thus, N-methyl-4-phenyl-4-propionoxypiperidine is a potent analgesic whereas the corresponding N-methyl-2-phenyl-2-propionoxypiperidine has only slight analgesic properties and beta-4-methyl-piperidine-ethyl benzoate has considerable anesthetic action while the 2- and 3-methyl derivatives have no such action. Hence, it will be seen that shifting a group from the 4-position of the piperidine ring may cause complete loss of activity.

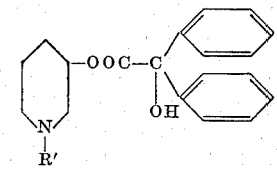
It is, therefore, an object of the present invention to provide a compound for pharmaceutical purposes and having the effect of reducing either involuntary muscle or nervous spasm.

Another object of the invention is to provide a compound having an anti-spasmodic effect in humans, which compound is long lasting in action and which will have only a few undesirable side reactions of minor importance.

A further object of the invention is to provide a series of substituted acetic acid esters of N-lower alkyl-3-piperidinol, in which the lower alkyl has at least two carbons, having longer activity and side reactions both less in number and of lower intensity than other compounds now in use for reducing spasm of human muscle or nerves.

I have found that N-lower alkyl-3-piperidyl benzilate,

in which the lower alkyl has at least two carbons, of the formula



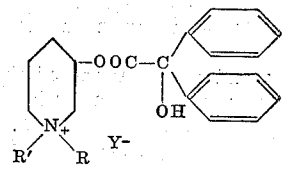
in which R′ represents a lower alkyl of at least two carbons, in the form of non-toxic onium salts are effective antispasmodics in both musculotropic and neurotropic spasms and have long duration of action with fewer undesirable side effects than various other anti-spasmodics now used.

Surprisingly, N-ethyl-3-piperidyl benzilate onium salts have a pronounced and selective action in the stomach, and have been found to be especially effective in the treatment of peptic ulcer, without significantly altering normal tonus or motility of the stomach or intestines. These results are achieved, furthermore, with only infrequent urinary difficulty, constipation, mydriasis and dryness of the mouth. Gastric hypermotility is curbed and gastric secretion and total acid are reduced greatly. Unlike other anti-spasmodics, no tolerance or loss of efficacy to N-ethyl-3-piperidyl benzilate onium salts has been found after long periods of administration.

Such unexpected specific activity in the stomach is even more surprising because the next adjacent homolog N-methyl-3-piperidyl benzilate, as the methyl bromide, does not have this specific activity but, instead, is specific for treating spasm of the colon.

The N-lower alkyl-3-piperidyl benzilate may be prepared by mixing an N-lower alkyl-3-chloro-piperidine and benzilic acid in isopropanol and refluxing the mixture. After filtering and concentrating the reaction mixture in vacuo, it is added to water, acidified and the unreacted acid removed with ether. After neutralizing the aqueous layer, the product is extracted with ether and the solution dried. After removing the ether, the free base is obtained by vacuum distillation.

The onium salts of N-lower alkyl-3-piperidyl benzilate, said lower alkyl having at least two carbons, are readily formed by contacting the free base with a lower alkylating agent in the presence of a suitable solvent such as anhydrous ether. The desired salt forms quickly and generally precipitates from solution. Lower alkylating agents such as methyl bromide, methyl chloride, methyl iodide, the corresponding ethyl halides, and dimethyl sulfate and diethyl sulfate are representative reactants that may be used to form the desired onium salts. Such onium salts may be conveniently represented by the formula



wherein R is a lower alkyl, particularly methyl or ethyl, R′ is a lower alkyl of at least two carbons, and Y is a non-toxic anion, particularly the bromide, chloride, iodide and sulfate anions.

Such N-ethyl-3-piperidyl benzilate onium salts may also be formed by contacting N-methyl-3-piperidyl benzilate as the free base with an ethylating agent, such as ethyl bromide, because it makes no difference whether the N-ethyl group is initially present on the tertiary base or is added when an onium salt is formed.

The following examples illustrate the preparation of the free base and a representative onium salt thereof:

EXAMPLE 1

N-ethyl-3-piperidyl benzilate

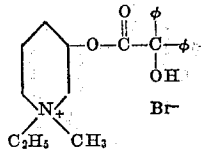
N-ethyl-3-chloropiperidine was prepared according to the method of Fuson and Zirkle described in volume 70, J. Am. Chem. Soc., page 2760.

12.0 grams (0.081 mole) of N-ethyl-3-chloropiperidine was mixed with 18.6 g. (0.081 mole) of benzilic acid and 80 cc. of anhydrous isopropyl alcohol as a solvent. The mixture was refluxed for seventy-two hours. The solution was then filtered and concentrated at 30 mm. of mercury. The concentrate was dissolved in water, acidified with hydrochloric acid and extracted with ether to remove the unreacted benzilic acid.

The aqueous layer was neutralized with sodium bicarbonate and the product was extracted with ether. The ethereal solution of the product was dried with potassium carbonate, the ether was removed by distillation and the residue was distilled at 0.12–0.18 mm. of mercury, the boiling point being 194–198° C. A yield of 16.5 g. (60% of theoretical) of N-ethyl-3-piperidyl-benzilate was obtained.

EXAMPLE 2

N-ethyl-3-piperidyl benzilate methobromide



ϕ=phenyl

34 grams (0.1 mole) of the basic ester, prepared as in Example 1, is dissolved in 75 cc. of isopropyl alcohol and treated with 9.5 g. (0.1 mole) of methyl bromide. The mixture is allowed to stand at room temperature until precipitation is complete. The product is removed by filtration and washed with isopropyl alcohol, yield 33 g., M.P. 175–177° C. On recrystallization from isopropyl alcohol, the M.P. was raised to 179–180° C. dec.

Analysis.—Calcd. for $C_{22}H_{28}BrNO_3$: Br, 18.45; N, 3.23. Found: Br, 18.30; N, 3.23.

The N-ethyl-3-piperidyl benzilate onium salts are highly active compounds orally. The recommended dosage is 5 mg. taken four times a day, i.e., before each meal and before bedtime. However, lower doses such as 2.5 mg. give useful results and higher doses such as 10 mgm. may be administered without adverse side effects.

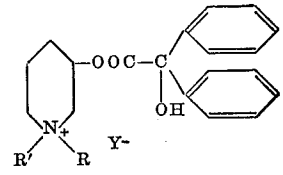
Pharmaceutical formulations are usually prepared of a predetermined amount of an N-ethyl-3-piperidyl benzilate onium salt and made into tablets, capsules, powders and solutions as desired. Carriers such as starch, sugar, talc and water may be used in such formulations. Binders, such as gelatin and lubricants such as sodium stearate may be used to form tablets. Expanders such as sodium bicarbonate may also be included to disintegrate the tablets.

Various changes and modifications of the invention can be made and, to the extent that such variations incorporate the spirit of this invention, they are intended to be included within the scope of the appended claims.

What is claimed is:

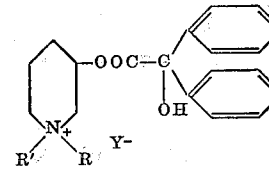
1. A pharmaceutical composition in unit dosage form adapted for human antispasmodic treatment without causing significant dryness of the mouth and dilation of the eye pupil, comprising a member of the group consisting

of N-lower alkyl-3-piperidyl benzilate, said lower alkyl having at least two carbons, and compounds of the formula



wherein R is a lower alkyl group, R′ is a lower alkyl of at least two carbons, and Y is a non-toxic anion, and a pharmaceutical carrier.

2. A pharmaceutical composition in unit dosage form adapted for human antispasmodic treatment without causing significant dryness of the mouth and dilation of the eye pupil, comprising a compound of the formula

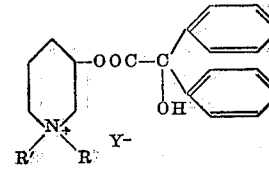


wherein R is a lower alkyl group, R′ is a lower alkyl of at least two carbons, and Y is a non-toxic anion, and a pharmaceutical carrier.

3. A pharmaceutical composition in unit dosage form adapted for human antispasmodic treatment without causing significant dryness of the mouth and dilation of the eye pupil, comprising N-ethyl-3-piperidyl benzilate methobromide and a pharmaceutical carrier.

4. A pharmaceutical composition in unit dosage form adapted for human antispasmodic treatment without causing significant dryness of the mouth and dilation of the eye pupil, comprising an N-ethyl-3-piperidyl benzilate lower alkyl halide in which the halide is a halogen other than fluorine, and a pharmaceutical carrier.

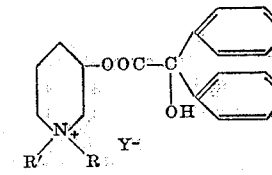
5. The process which comprises administering a compound to a human for its therapeutic antispasmodic effect without causing significant dryness of the mouth and dilation of the eye pupil, said compound being of the formula



wherein R is a lower alkyl group, R′ is a lower alkyl of at least two carbons, and Y is a non-toxic anion.

6. The process which comprises administering N-ethyl-3-piperidyl benzilate methyl bromide to a human for its therapeutic antispasmodic effect without causing significant dryness of the mouth and dilation of the eye pupil.

7. A member of the group consisting of N-lower alkyl-3-piperidyl benzilate, said lower alkyl having a least two carbons, and compounds of the formula



wherein Y is a nontoxic anion, R is a lower alkyl group and R′ is a lower alkyl of at least two carbons.

8. N-ethyl-3-piperidyl benzilate.

9. N-ethyl-3-piperidyl benzilate lower alkyl halide, where the lower alkyl halide is a member selected from

the group consisting of lower alkyl bromide, lower alkyl chloride, and lower alkyl iodide.

10. N-ethyl-3-piperidyl benzilate methyl halide where the methyl halide is a member selected from the group consisting of methyl bromide, methyl chloride, and methyl iodide.

11. N-ethyl-3-piperidyl benzilate methyl chloride.

12. N-ethyl-3-piperidyl benzilate methyl bromide.

13. N-ethyl-3-piperidyl benzilate methyl sulfate.

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