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SALTS OF N-PHENYL-N-(2-PYRIDYLMETHYL)-2-(N-PIPERIDINO)-ETHYLAMINE

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ABSTRACT OF THE DISCLOSURE

Salts of N - phenyl - N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine with a saturated fatty acid having 14 to 22 carbon atoms or with hydroxyphenyl-benzoylbenzoic acid are antitussive agents.

This invention relates to an organic acid salt of a picoline derivative, more particularly, to a pharmaceutically acceptable salt of N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine with an organic acid, the acid being a saturated fatty acid of 14 to 22 carbon atoms or hydroxyphenylbenzoylbenzoic acid.

The salts of the invention are novel compounds and are useful as antitussive drugs. They are crystalline, tasteless, stable, non-hygroscopic and low in toxicity.

As a compound having antitussive action, there has previously been known N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine. However, it is oily and subject to discoloration and, in addition, shows bitterness with some unpleasant after-taste. Its hydrochloride, although crystalline, still shows bitterness. Neither of these is, therefore, suitable for use as a powdery preparation.

The present invention is based upon the discovery that, among salts of N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine was various organic acids, a salt with a saturated fatty acid having 14 to 22 carbon atoms or hydroxyphenylbenzoylbenzoic acid, which salts are easily crystallizable, are suitable for use in pharmaceutical preparations. These salts are non-hygroscopic and sufficiently stable to afford long storage, have no taste and possess low toxicity.

On the other hand, it was also confirmed by the present inventors that salts with a saturated fatty acid having 12 or less carbon atoms (e.g. lauric acid, capric acid, caprylic acid) are not crystalline; salts with a saturated fatty acid having 24 or more carbon atoms (e.g. lignoceric acid) show a hemolytic action; salts with an unsaturated fatty acid (e.g. linoleic acid) are unstable; salts with aliphatic dicarboxylic acids (e.g. maleic acid, fumaric acid, citric acid) have a bitter taste; and salts with a large majority of aromatic carboxylic acid have one or more faults such as being non-crystallizable, unstable and of bitter taste.

A principal object of the present invention is to provide organic acid salts of N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine which have an antitussive effect and the superior characteristics as mentioned above.

Another object of this invention is to provide a method for producing the novel and useful organic acid salts of N - phenyl - N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine.

The new salts of this invention are conveniently prepared by reacting N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine or a mineral acid salts thereof with a saturated fatty acid having 14 to 22 carbon

atoms, hydroxyphenylbenzoylbenzoic acid, or a salt of either of them.

As the fatty acid having 14 to 22 carbon atoms there may be mentioned myristic acid, palmitic acid, stearic acid, arachic acid, behenic acid, and the like. Salts of the fatty acids useful as starting materials are known.

The starting materials to be employed in this invention are N-phenyl-N-(2-pyridylmethyl) - 2 - (N - piperidino)-ethylamine and its mineral acid salts such as the hydrochloride and sulfate. When such a mineral acid salt is employed, the fatty acid or hydroxyphenylbenzoylbenzoic acid is desirably reacted in the form of a suitable salt, such as an alkali or alkaline earth metal salt as, for instance, the salts of sodium potassium, calcium or barium.

The reaction is preferably conducted in a suitable solvent which may be selected from among the organic solvents capable of dissolving the starting material N-phenyl-N - (2 - pyridylmethyl)-2-(N-piperidino)-ethylamine, e.g. lower alcohols, acetone, acetic acid esters, and the like or mixtures of these with organic solvents which are miscible with the first-mentioned solvents, e.g. ether, benzene, petroleum ether, chloroform, or with water. Among these, a mixed solvent of lower alcohol and ethyl ether, as well as acetone, is particularly beneficial.

The reaction usually proceeds at room temperature, but it may be conducted under heating, if required.

When the reaction is complete, crystals of the end product separate out. Therefore, those crystals may be separated from the mother liquor by, for example, filtration in a per se conventional manner. If the end product remains dissolved in the solvent, the product can be isolated by treating the reaction mixture to obtain a concentrated solution and, then, by cooling the solution or by adding a solvent in which the product does not dissolve, so as to precipitate the end product. It is also possible to isolate the end product by the use of ion exchange resin. The reaction proceeds almost quantitatively.

The following experimental data show the properties of the compound of this invention.

EXPERIMENT 1

Stability test

The test was made for examining changes in color and hygroscopicity as to respective compounds.

No. 1 N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine tri-palmitate
No. 2 N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine tri-stearate
No. 3 N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine tri-myristate
No. 4 N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine tri-behenate
No. 5 N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine hydroxyphenylbenzoylbenzoate
No. 6 N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine (control)
No. 7 N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine hydrochloride (control)
No. 8 N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine tri-linoleate (control)

(The above compounds will hereinafter be designated by the respective numbers.)

Conditions: 40° C., 90% relative humidity.

The above samples were allowed to stand under the above conditions and the changes which they underwent with time were observed.

The results are shown in Table 1 (changes in color) and Table 2 (degrees of swelling).

TABLE 1.—CHANGES IN COLOR

Compound	Time (in days) 3	7	10	14	21	28
Compound of this invention:						
No. 1	−	−	−	−	−	−
No. 2	−	−	−	−	−	−
No. 3	−	−	−	−	−	−
No. 4	−	−	−	−	−	−
No. 5	−	−	−	−	−	−
Control:						
No. 6	+	+	+	++	++	+++
No. 7	+	+	+	++	++	+++
No. 8	−	−	−	+	+	++

NOTE: −: no change; +: a slight change; ++: a fair change; +++: a remarkable change.

TABLE 2.—DEGREE OF SWELLING

Compound	Time (in days) 3	7	10	14	21	28
No. 1	−	−	−	−	−	−
No. 2	−	−	−	−	−	−
No. 3	−	−	−	−	−	−
No. 4	−	−	−	−	−	−
No. 5	−	−	−	−	−	−
No. 7 (control)	+	+	+	++	+++	+++

NOTE: −: no change; +: a slight change; ++: a fair change; +++: a remarkable change.

It will be apparent from Tables 1 and 2 that whereas the controls No. 6, 7 and 8 underwent coloration before the 14th day and, the control compound No. 7 underwent swelling at the 3rd day, none of the compounds of this invention underwent coloration or swelling even after the lapse of 28 days.

EXPERIMENT 2

Antitussive test (in dog)

A water suspension of a compound was administered to the stomach of a coughing and non-anesthetized dog (male, weighing 8.5 kg.) through a tube previously put into the stomach, and 50% antitussive dose (AtD_{50}) was calculated by the "Coughing Dog Method" of Y. Kase "Selected Pharmacological Testing Methods," 363 (A. Burger eds.), Marcel Dekker, Inc., New York (1969)]. The results are shown as follows:

TABLE 3

Compound:	AtD_{50} in dog (mg./kg.)
No. 1	38.5 (10.7)
No. 2	41.6 (10.7)
No. 3	35.8 (10.8)
No. 4	47.7 (10.7)
No. 5	22.0 (10.7)
No. 6 (Control)	10.8
Noscapine (Control)	100

Note: Figures in parentheses are the equivalent values as converted to Compound No. 6.

It will be seen from Table 3 that the compounds of this invention are as effective as the starting material No. 6 on an equivalent basis (figures in parentheses above are used for the former), and far superior to the commercial preparations of Noscapine.

EXPERIMENT 3

Sensory test

The powdery compounds were orally administered to ten adults, and the bitterness with some remaining unpleasant taste were evaluated.

TABLE 4

Compound	Number of persons in sensory response −	+	++	+++
Compounds of this invention:				
No. 1	10	0	0	0
No. 2	10	0	0	0
No. 3	10	0	0	0
No. 4	10	0	0	0
No. 5	10	0	0	0
Control:				
No. 6	0	0	0	10
No. 7	0	0	0	10

NOTE: −: no perception at all; +: a slight perception; ++: a fair perception; +++: a remarkable perception.

It will be seen from Table 4 that the compounds of this invention give no bitterness with some remaining unpleasant taste at all, in contrast to the controls which produce extremely remarkable such bitterness.

EXPERIMENT 4

(a) Acute toxicity of compound No. 7

Testing procedure.—Compound No. 7 was administered orally or intravenously to groups each consisting of 10 male mice (ICR–JCL/T strain, 4 weeks of age) and groups each consisting of 10 male rats (SD–JCL/T strain, 6 weeks of age). The animals were placed under observation for 4 days, and 50% lethal dose (LD_{50}) was calculated by the Litchfield-Wilcoxon method.

The results are shown in Table 5.

TABLE 5

LD_{50} (mg./kg.)	I.V.	P.O.
Mice	9.6 (8.6)	195 (175.5)
Rats	8.3 (7.5)	820 (738.0)

NOTE.—I.V. and P.O. signify "intravenous injection" and "oral administration," respectively. Figures in parentheses are the equivalent values as converted to compound No. 6.

(b) Acute toxicity of compound No. 1

Testing procedure.—Compound No. 1 was administered intraperitoneally, subcutaneously or orally to groups each consisting of 10 mice (ICR–JCL/T strain, 4 weeks of age) and groups each consisting of 10 rats (SD–JCL/T strain, 6 weeks of age), and the animals were placed under observation for 7 days, and 50% lethal dose (LD_{50}) was calculated by the Litchfield-Wilcoxon method.

The results are shown in Table 6.

TABLE 6

Route of administration	LD_{50} (mg./kg.) in mouse Male	Female	LD_{50} (mg./kg.) in rat Male	Female
I.P.	300 (87)	290 (84.1)	500 (145)	440 (127.6)
S.C.	660 (191.4)	690 (200.1)	1,200 (348)	1,250 (362.5)
P.O.	700 (203)	750 (217.5)	2,900 (841)	3,000 (870)

NOTE 1.—I.P. signifies "intraperitioneal administration," S.C. "subcutaneous injection" and P.O. "oral administration."

NOTE 2.—Figures in parentheses denote the values as converted to compound No. 6.

It will be apparent from the above Tables 5 and 6 that the compounds of the present invention are less toxic than the compound No. 7.

Pharmaceutical compositions containing the salts of the present invention can be prepared according to any per se conventional method for the preparation of powders, tablets, capsules, syrups or injections.

When the compounds are used as antitussives, a daily dose as converted to free base of about 10 to about 500 milligrams, generally about 50 to about 100 milligrams for adult, is advisable.

The present invention is further illustrated by the following non-limitative examples.

In these examples, "part(s)" means part(s) by weight unless otherwise specified. Part(s) by weight bear the same relation to part(s) by volume as do gram(s) to milliliter(s).

EXAMPLE 1

In 5 parts by volume of ether is dissolved 1.5 parts of N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine, followed by the addition of a solution of 4.2 parts of stearic acid in 60 parts by volume of ether. The mixture is allowed to stand for a while and, then, concentrated whereupon colorless crystals separate. The crystals are recovered by filtration and dried. The procedure yields 4.9 parts of N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine tri-stearate melting at 51°–55° C.

Elementary analysis.—Calculated for

$$C_{19}H_{25}N_3 \cdot 3C_{18}H_{36}O$$

(percent): C, 76.32; H, 11.67; N, 3.66. Found (percent): C, 75.92; H, 11.98; N, 3.69.

EXAMPLE 2

In 5 parts by volume of ethanol is dissolved 4.5 parts of N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino-ethylamine followed by the addition of a solution of 15.9 parts of palmitic acid in 100 parts by volume of ethanol. The mixture is stirred for a while and then concentrated. Upon addition of ether to the concentrate colorless crystals separate. The crystals are recovered by filtration, washed with petroleum ether, and recrystallized from acetone. The procedure yields 14.2 parts of N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine tri-palmitate which melts at 59°–61° C.

Elementary analysis.—Calculated for

$$C_{19}H_{25}N_3 \cdot 3C_{16}H_{32}O_2$$

(percent): C, 75.58; H, 11.46; N, 3.95. Found (percent): C, 75.48; H, 11.42; N, 3.91.

EXAMPLE 3

In 5 parts of volume of ether is dissolved 1.5 parts of N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine, followed by the addition of a solution of 3.3 parts of myristic acid in 30 parts by volume of ether.

After a while, the mixture is concentrated whereupon colorless crystals separate. The crystals are recovered by filtration and dried. The procedure yields 3.6 parts of the desired N - phenyl - N - (2 - pyridylmethyl) - 2 - (N-piperidino)ethylamine trimyristate which melts at 48° to 51° C.

Elementary analysis.—Calculated for

$$C_{19}H_{25}N_3 \cdot 3C_{14}H_{28}O_2$$

(percent): C, 74.72; H, 11.20; N, 4.29. Found (percent): C, 74.64; H, 11.48; N, 4.24.

EXAMPLE 4

In 5 parts by volume of ethanol is dissolved 1.5 part of N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine, followed by the addition of a solution of 5.1 parts of behenic acid in 100 parts by volume of ethanol, the ethanolic solution having been prepared at 50° C. The resulting mixture is stirred at 50° C. for a while and then concentrated, whereupon colorless crystals separate. Petroleum ether is added, whereby 5.2 parts of N-phenyl-N - (2 - pyridylmethyl) - 2 - (N - piperidino) - ethylamine

tri-behenate is obtained. The product melts at 74°–76° C.

Elementary analysis.—Calculated for

$$C_{19}H_{25}N_3 \cdot 3C_{22}H_{44}O_2$$

(percent): C, 77.51; H, 12.01; N, 3.19. Found (percent): C, 77.26; H, 11.86; N, 3.37.

EXAMPLE 5

In 25 parts by volume of ether is dissolved 8.0 parts of N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine, followed by the addition of a solution of 8.1 parts of p-hydroxyphenylbenzoylbenzoic acid in a mixture of 300 parts by volume of ethanol and 100 parts by volume of acetone. The resulting mixture is concentrated, and petroleum ether is added. The resulting crystals are recovered by filtration, whereupon 16.0 parts of the desired N - phenyl - N - (2 - pyridylmethyl) - 2 - (N-piperidino) - ethylamine p - hydroxyphenylbenzoylbenzoate is obtained. The product starts melting in the neighborhood of 90° C. and is completely molten at 115° C.

Elementary analysis.—Calculated for

$$C_{19}H_{25}N_3 \cdot C_{20}H_{14}O_4$$

(percent): C, 76.32; H, 6.41; N, 6.85. Found (percent: C, 76.29; H, 6.51; N, 7.03.

What is claimed is:

1. A pharmaceutically acceptable salt of N-phenyl-N-(2-pyridylmethyl)-2-(N-piperidino)-ethylamine with a saturated fatty acid having 14 to 22 carbon atoms or hydroxyphenylbenzoylbenzoic acid.

2. A compound as in claim 1 said compound being N - phenyl - N - (2 - pyridylmethyl) - 2 - (N - piperidino)-ethylamine tripalmitate.

3. A compound as in claim 1, said compound being N - phenyl - N - (2 - pyridylmethyl) - 2 - (N - piperidino)-ethylamine tristearate.

4. A compound as in claim 1, said compound being N - phenyl - N - (2 - pyridylmethyl) - 2 - (N - piperidino)-ethylamine trimyristate.

5. A compound as in claim 1, said compound being N - phenyl - N - (2 - pyridylmethyl) - 2 - (N - piperidino)-ethylamine tribehenate.

6. A compound as in claim 1, said compound being N - phenyl - N - (2 - pyridylmethyl) - 2 - (N - piperidino)-ethylamine p-hydroxyphenylbenzoylbenzoate.

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