United States Patent Office 2,824,875 Patented Feb. 25, 1958

2,824,875

LOWER ALKYL 4-PHENYL-1-(3-PHENYL-ALKENYL AND -ALKYNYL) PIPERIDINE-4-CARBOXYLATES AND SYNTHESIS THEREOF

Bill Elpern, Delmar, N. Y., assignor to Sterling Drug Inc., New York, N. Y., a corporation of Delaware

No Drawing. Application September 12, 1955 Serial No. 533,894

14 Claims. (Cl. 260—294.3)

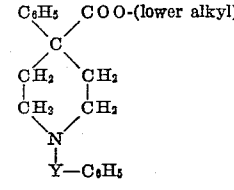
This invention relates to organic compounds and their preparation, and is concerned with an improvement in the substituent attached to the nitrogen atom of the piperidine ring in the class of chemical compounds identified as lower alkyl 4-phenyl-1-(hydrocarbyl)piperidine-4-carboxylates. In particular, it is concerned with lower alkyl 4-phenyl-1-(3-phenyl-alkenyl and -alkynyl)piperidine-4-carboxylates, their acid addition salts, and the preparation of these compounds.

Attempts have been made for some time to develop analgesics having high activity. The highly potent morphine has the disadvantages of causing nausea, vomiting, constipation, and resipratory depression, and for these reasons has been supplanted largely by meperidine, ethyl 4-phenyl-1-methylpiperidine-4-carboxylate, especially in obstetrics where depression of respiration is highly undesirable. Because of the relatively high dose required, meperidine has to be injected in hypertonic concentrations, with a consequent risk of irritation at the site of administration. This limits the choice of concentrations which can be used and restricts undesirably the free choice of optimum dosage. This situation is advantageously modified with the compounds of my invention since they are many times more potent as analgesics than meperidine and thus can be administered in smaller volumes of solution and at higher therapeutic levels of effectiveness without making the solution hypertonic. This reduces any tendency to undesirable accompanying irirtation, and improves the therapeutic usefulness of the medicament.

U. S. Patent 2,167,351 broadly shows lower alkyl 4-aryl-1-(substituted)piperidine-4-carboxylates where the 1-substituent is a monovalent hydrocarbon radical. Included among the specific examples are such compounds having 1-methyl and 1-benzyl substituents, the latter being of primary value as intermediates for the former. The 1-methyl compounds are not known and accepted as effective, morphine-like central analgesics and atropine-like smooth muscle neurospasmolytics in the relief of severe pain. An outstanding example of these 1-methyl compounds is the commercially available meperdine hydrochloride, ethyl 4-phenyl-1-methylpiperidine-4-carboxylate hydrochloride. On the other hand, the intermediate 1-benzyl compounds have been found to have a decidedly lower analgesic activity compared with the 1-methyl compounds. For example, ethyl 4-phenyl-1-benzylpiperidine-4-carboxylate as its hydrochloride has been found to be only approximately one-fourth as effective an analgesic as meperidine hydrochloride when tested by the Bass-Vander Brook modification of the D'Amour-Smith method. This decrease in activity in going from 1-methyl to 1-benzyl would indicate that 1-phenylalkyl substituents are undesirable, and would thus lead investigators away from these compounds and away from compounds such as those of my invention.

I have now prepared lower alkyl 4-phenyl-1-(3-phenyl-alkenyl and -alkynyl)piperidine-4-carboxylates and surprisingly found them to be outstandingly superior as analgesics compared with the corresponding 1-benzyl compounds of U. S. Patent 2,167,351 and, indeed, many times more effective than the corresponding 1-methyl compounds, even meperidine itself. For example, my ethyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate as its hydrochloride salt, when measured as hereinbefore mentioned, is approximately twenty-eight times more effective an analgesic as meperidine hydrochloride, or thus having an analgesic activity approximately one hundred and twelve times that of the corresponding known 1-benzyl homolog. In addition to having this high analgesic activity, my compounds have a relatively low toxicity; for example, said ethyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate hydrochloride is only about twice as toxic [intravenous toxicity in mice when measured by a procedure similar to that described by Hoppe et al., J. Pharm. and Exp. Therap. 95, 502 (1949)] as meperidine hydochloride, so that its therapeutic index compared with meperidine hydrochloride is approximately fourteen.

A preferred subgenera of my compounds are the lower alkyl 4-phenyl-1-(3-phenyl-propenyl and -propynyl)-piperidine-4-carboxylates, which in free base form have the formula



where

$C_6H_5—Y—$

is

$C_6H_5CH=CHCH_2—$
$C_6H_5CH_2CH=CH—$
$C_6H_5C\equiv CCH_2—$

or

$C_6H_5CH_2C\equiv C—$

These unsaturated phenyl-propenyl and phenyl-propynyl compounds, in addition to being useful as analgesic agents, are also useful as intermediates since they can be hydrogenated catalytically to produce the related lower alkyl 4-phenyl-1-(3-phenylpropyl)piperidine-4-carboxylates, which are disclosed and claimed in my copending application, Serial No. 533,889, filed September 12, 1955. Preferred embodiments of this invention are the lower alkyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylates which have been shown by the rat thermal stimulus method to have particularly high analgesic activity.

The lower alkyl 4-phenyl-1-(3-phenyl-propenyl and -propynyl)piperidine-4-carboxylates are prepared by reacting a lower alkyl 4-phenylpiperidine-4-carboxylate with a 3-phenyl-propenylating agent or a 3-phenyl-propynylating agent, said agents being preferably 3-phenyl-propenyl or 3-phenyl-propynyl esters of a strong inorganic acid or an organic sulfonic acid, said ester having the formula, $C_6H_5—Y—An$, where An is an anion of a strong inorganic acid or an organic sulfonic acid, as illustrated hereinabove, and Y is an unsaturated aliphatic divalent hydrocarbon radical having three carbon atoms, as illustrated hereinabove. This reaction is carried out by heating the lower alkyl 4-phenylpiperidine-4-carboxylate with the 3-phenyl-propenyl or 3-phenyl-propynyl ester in the presence or absence of a suitable solvent, but preferably in the presence of a solvent such as a lower alkanol. Specific illustrations of the preparation of these unsaturated compounds are: the preparation of ethyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxlate by heating ethyl 4-phenylpiperdine-4-carboxylate

with 3-phenyl-2-propenyl bromide; and the preparation of ethyl 4-phenyl-1-(3-phenyl-2-propynyl)piperidine-4-carboxylate by heating ethyl 4-phenylpiperidine-4-carboxylate with 3-phenyl-2-propynyl bromide. These preparations were carried out preferably in refluxing n-butanol with stirring in the presence of an alkaline agent such as sodium carbonate to neutralize the hydrogen halide formed by the reaction. The products are isolated in free base form or in the form of their acid addition salts. Catalytic hydrogenation of ethyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate or of ethyl 4-phenyl-1-(3-phenyl-2-propynyl)-piperidine-4-carboxylate using, respectively, one or two molar equivalents of hydrogen yields, in each instance, ethyl 4-phenyl-1-(3-phenylpropyl)piperidine-4-carboxylate.

My new lower alkyl 4-phenyl-1-(3-phenyl-propenyl and -propynyl)piperidine-4-carboxylates are useful in the free base form or in the form of acid addition salts, and these salts are within the purview of the invention. The acids which can be used to prepare acid addition salts are preferably those which produce, when combined with the free base, salts whose anions are relatively innocuous to the animal organism in therapeutic doses of the salts, so that the beneficial physiological properties inherent in the free base are not vitiated by side effects ascribable to the anions. In practicing my invention, I found it convenient to employ the hydrochloride salt. However, other appropriate acid addition salts are those derived from mineral acids such as hydrobromic acid, hydriodic acid, nitric acid, phosphoric acid and sulfuric acid; and organic acids such as acetic acid, citric acid, tartaric acid, lactic acid, quinic acid, methanesulfonic acid, ethanesulfonic acid, and the like, giving the hydrobromide, hydriodide, nitrate, phosphate or acid phosphate sulfate or bisulfate, acetate, citrate or acid citrate, tartrate or bitartrate, lactate, quinate, methanesulfonate and ethanesulfonate salts, respectively.

The following examples will further illustrate the invention without, however, limiting it thereto.

EXAMPLE 1

Lower alkyl 4-phenyl-1-(3-phenyl-propenyl)piperidine-4-carboxylate acid addition salts

The preparation of these compounds is illustrated by the following synthesis of ethyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate hydrochloride: A mixture of 19.1 g. of ethyl 4-phenylpiperidine-4-carboxylate hydrochloride, 14.0 g. of 3-phenyl-2-propenyl bromide (cinnamyl bromide), 100 ml. of n-butanol and 20 g. of anhydrous sodium carbonate was refluxed with stirring for about twenty-three hours. The reaction mixture was allowed to cool, treated with carbon dioxide, and the resulting cloudy solution filtered, yielding a solution of ethyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate in free base form. Hydrogen chloride was bubbled into the filtrate and ether added; the resulting solid was collected and recrystallized once from ethanol-ether (the ethanol containing dilute hydrochloric acid) and three times from water containing hydrochloric acid. The resulting product, ethyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate hydrochloride, melted at 211.2–213.2° C. (corr.).

Analysis.—Calcd. for $C_{23}H_{27}NO_2.HCl$: C, 71.59; H, 7.31; Cl, 9.19. Found: C, 71.32; H, 7.43; Cl, 8.90.

The above-described preparation is also carried out using ethyl 4-phenylpiperidine-4-carboxylate in free base form and only one-half as much sodium carbonate. Alternatively, this preparation can be carried out using other esters such as 3-phenyl-2-propenyl para-toluenesulfonate or iodide in place of 3-phenyl-2-propenyl bromide. Use of 3-phenyl-1-propenyl bromide in the above procedure in place of 3-phenyl-2-propenyl bromide yields ethyl 4-phenyl-1-(3-phenyl-1-propenyl)piperidine-4-carboxylate and its hydrochloride.

Following the above procedure but using methyl 4-phenylpiperidine-4-carboxylate, isopropyl 4-phenylpiperidine-4-carboxylate, n-butyl 4-phenylpiperidine-4-carboxylate, or n-hexyl 4-phenylpiperidine-4-carboxylate in place of ethyl 4-phenylpiperidine-4-carboxylate, there is obtained in the form of the hydrochloride addition salt the following respective compounds: methyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate, isopropyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate, n-butyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate, or n-hexyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate.

Pharmacological evalution of ethyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate hydrochloride in aqueous solution administered intraperitoneally or subcutaneously by the Rat Thermal Stimulus Method of Bass and Vander Brook [J. Am. Pharm. Assoc., Sci. Ed., 41, 569–570 (1952)] has shown that this compound is approximately twenty-eight times as active an analgesic as ethyl 4-phenyl-1-methylpiperidine-4-carboxylate hydrochloride. This compound was found to have an acute toxicity in mice of 16.7 ± 1.1 mg. per kg. when administered intravenously in aqueous solution.

EXAMPLE 2

Lower alkyl 4-phenyl-1-(3-phenyl-propenyl)-piperidine-4-carboxylates

The preparation of these compounds from the corresponding acid addition salts described in Example 1 is illustrated by the following preparation of ethyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate from its hydrochloride salt: A suspension containing 25 g. of ethyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate hydrochloride in 250 ml. of water was made alkaline with 35% sodium hydroxide solution; and the liberated basic product was extracted with benzene (three 150 ml. portions). The combined benzene extracts were washed with water and a saturated aqueous solution of NaCl, and then concentrated in vacuo. The resulting clear oily product solidified and was taken up in ether; the ether solution was dried over anhydrous calcium sulfate, filtered, and the filtrate concentrated to dryness in vacuo to yield the solid product, ethyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate, M. P. 49.7–51.1° C. (corr.).

Analysis.—Calcd. for $C_{23}H_{27}NO_2$: C. 79.10; H, 7.73. Found: C, 79.15; H, 7.97.

EXAMPLE 3

Lower alkyl 4-phenyl-1-(3-phenyl-propynyl)piperidine-4-carboxylates

The preparation of these compounds is illustrated by the synthesis of ethyl 4-phenyl-1-(3-phenyl-2-propynyl)piperidine-4-carboxylate following the procedure given hereinabove in Example 1, using an equivalent quantity of 3-phenyl-2-propynyl bromide in place of 3-phenyl-2-propenyl bromide. The resulting product can be isolated in free base form or in the form of its hydrochloride addition salt.

My lower alkyl 4-phenyl-1-(3-phenyl-propenyl or propynyl)piperidine-4-carboxylates can be formulated in liquid preparations, e. g., aqueous or aqueous-ethanol menstruum, or in solid form, e. g., tablet or powder. The tablet formulation can be prepared using conventional excipients; and the powder can be compounded in capsule form. These preparations can be administered orally or, in the case of the aqueous preparations, intramuscularly or intravenously.

I claim:

1. A compound selected from the group consisting of a lower alkyl 4-phenyl-1-(3-phenyl-propenyl)piperidine-4-carboxylate, a lower alkyl 4-phenyl-1-(3-phenyl-propynyl)piperidine-4-carboxylate; and its acid addition salts.

2. A lower alkyl 4 - phenyl - 1 - (3 - phenyl - 2 - propenyl)piperidine-4-carboxylate.

3. A lower alkyl 4-phenyl-1-(3-phenyl-2-propynyl)piperidine-4-carboxylate.

4. An acid addition salt of a lower alkyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate.

5. An acid addition salt of a lower alkyl 4-phenyl-1-(3-phenyl-2-propynyl)piperidine-4-carboxylate.

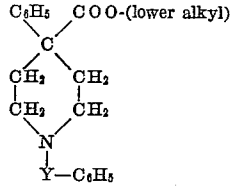
6. Ethyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate.

7. Ethyl 4-phenyl-1-(3-phenyl-2-propynyl)piperidine-4-carboxylate.

8. Ethyl 4-phenyl-1-(3-phenyl-2-propenyl)piperidine-4-carboxylate hydrochloride.

9. Ethyl 4-phenyl-1-(3-phenyl-2-propynyl)piperidine-4-carboxylate hydrochloride.

10. The process of preparing a compound having the formula



where Y is selected from the group consisting of propenyl and propynyl radicals, which comprises reacting a lower

alkyl 4-phenylpiperidine-4-carboxylate with an ester having the formula

$$C_6H_5—Y—An$$

where An is selected from the group consisting of anions of a strong inorganic acid and an organic sulfonic acid.

11. The process of preparing a lower alkyl 4-phenyl-1-(3 - phenyl - 2 - propenyl)piperidine-4-carboxylate which comprises heating a lower alkyl 4-phenylpiperidine-4-carboxylate with a 3-phenyl-2-propenyl halide.

12. The process of preparing ethyl 4 - phenyl - 1 - (3-phenyl - 2 - propenyl)piperidine - 4 - carboxylate which comprises heating ethyl 4 - phenylpiperidine - 4 - carboxylate with 3 - phenyl - 2 - propenyl bromide.

13. The process of preparing a lower alkyl 4 - phenyl-1 - (3 - phenyl-2-propynyl)piperidine-4-carboxylate which comprises heating a lower alkyl 4-phenylpiperidine - 4 - carboxylate with a 3 - phenyl - 2 - propynyl halide.

14. The process of preparing ethyl 4 - phenyl - 1 -(3-phenyl - 2 - propynyl)piperidine - 4 - carboxylate which comprises heating ethyl 4-phenylpiperidine-4-carboxylate with 3-phenyl-2-propynyl bromide.

References Cited in the file of this patent

UNITED STATES PATENTS

2,167,351	Eisleb	July 25, 1939
2,486,795	Kaegi	Nov. 1, 1949

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 2,824,875 February 25, 1958

Bill Elpern

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 1, line 27, for "resipratory" read -- respiratory --; line 51, for "not known" read -- now known --; line 55, for "meperdine" read -- meperidine --; column 2, line 18, for "hydochloride" read -- hydrochloride --; line 72, for "boxlate" read -- boxylate --; column 3, line 35, for "acid phosphate" read -- acid phosphate, --.

Signed and sealed this 22nd day of July 1958.

(SEAL)

Attest:

KARL H. AXLINE
Attesting Officer

ROBERT C. WATSON
Commissioner of Patents