United States Patent Office 2,846,437 Patented Aug. 5, 1958

2,846,437

LOWER ALKYL 4-PHENYL-1-(SUBSTITUTED-ALKYL) PIPERIDINE-4-CARBOXYLATES AND PREPARATION THEREOF

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

No Drawing. Application September 12, 1955 Serial No. 533,890

31 Claims. (Cl. 260—293.4)

The present invention relates to compositions of matter and their preparation, and is concerned with an improvement in the substituent attached to the nitrogen atom or 1-position of the piperidine ring in the class of chemical compounds identified as lower alkyl 4-phenyl-1-(substituted)-piperidine - 4 - carboxylates. In particular, the compounds of this invention are those having a substituted-alkyl radical as the 1-substituent.

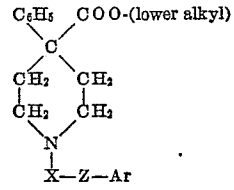
Attempts have been made for some time to develop analgesics having high activity. The highly potent morphine has the disadvantages of causing nausea, vomiting, constipation and respiratory depression, and for these reasons has been supplanted largely by meperidine, ethyl 4-phenyl - 1 - methylpiperidine - 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 irritation, 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 value primarily as intermediates for the former. The 1-methyl compounds are now 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 meperidine 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 is 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 the instant invention.

I have now prepared certain lower alkyl 4-phenyl-1-(substituted-alkyl)piperidine-4-carboxylates and surprisingly found them to be markedly superior as analgesics

compared with the corresponding 1-benzyl compounds of U. S. Patent 2,167,351 and, indeed, more effective than the corresponding 1-methyl compounds, even meperidine itself. For example, my ethyl 4-phenyl-1-(3-phenoxypropyl)piperidine-4-carboxylate as its hydrochloride salt, when measured as hereinbefore mentioned, is approximately twelve times as effective an analgesic as meperidine hydrochloride, or thus having an analgesic activity approximately forty-eight times that of the corresponding known 1-benzyl compound. In addition to having this high analgesic activity, my compounds have a relatively low toxicity; for example, ethyl 4-phenyl-1-(3-phenoxypropyl)piperidine-4-carboxylate is only about two and one-half times as toxic [intravenous toxicity in mice when measured by a procedure similar to that described by Hoppe et al., J. Pharm. & Exp. Therap. 95, 502 (1949)] as meperidine hydrochloride, so that its therapeutic index compared with meperidine hydrochloride is approximately five and one-half.

My compounds in free base form have the formula

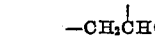


where X is a lower alkylene radical having at least two carbon atoms and having its free valence bonds on different carbon atoms, Z is O, S, SO, SO_2, NH or N(lower alkyl), and Ar is a monocarbocyclic aryl radical having six ring-carbon atoms.

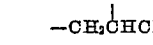
The lower alkyl radicals of the above formula preferably have from one to six carbon atoms inclusive, and include such radicals, as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 2-butyl, n-amyl, n-hexyl, and the like.

The monocarbocyclic aryl radical having six ring-carbon atoms is an aryl radical of the benzene series and includes the unsubstituted phenyl radical and phenyl radicals substituted by substituents such as nitro, amino, (lower alkyl)amino, di-(lower alkyl)amino, (lower alkanoyl)amino, lower alkoxy, lower alkylmercapto, lower alkylsulfonyl, lower alkyl, hydroxy, halo and the like. The substituted-phenyl radicals have preferably from one to three substituents such as those given above; and, furthermore, these substituents can be in any of the available positions of the phenyl nucleus, and where more than one substituent, they can be the same or different and they can be in any of the various position combinations relative to each other. The lower alkyl, (lower alkyl)amino, (lower alkanoyl)amino, lower alkoxy, lower alkylmercapto and lower alkylsulfonyl substituents, and the lower alkyl radicals of said di-(lower alkyl)amino substituent, each have preferably from one to six carbon atoms which can be arranged as straight or branched chains.

The lower alkylene radical designated above as X can have from two to six carbon atoms, and preferably has two to four carbon atoms; such preferred embodiments for X include —CH_2CH_2—, —$CH(CH_3)CH_2$—



—$C(CH_3)_2CH_2$—

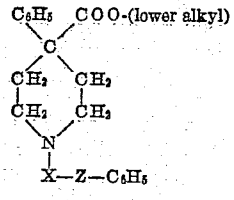


—$CH_2CH_2CH_2$—, —$CH(CH_3)CH_2CH_2$—

—$CH_2CH_2CH_2CH_2$—, and the like.

The compounds of this invention can be prepared by the reaction of a lower alkyl 4-phenylpiperidine-4-carboxylate with an equimolar amount of the appropriate aryl-Z-alkyl ester of a strong inorganic or an organic sulfonic acid. The reaction is generally carried out at a temperature between about 50° C. and 150° C., preferably at reflux, in a lower alkanol solvent. Other methods, such as the reaction of a lower alkyl 4-phenylpiperidine-4-carboxylate with the appropriate aryl-Z-alkanal under catalytic hydrogenation conditions, can be used.

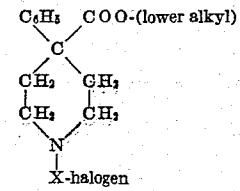
Preferred subgenera of my invention are the compounds having in free base form the formula



where the lower alkyl radical has one to six carbon atoms, X is an alkylene radical having from two to four carbon atoms inclusive and having its free valence bonds on different carbon atoms, and Z is O or S. These preferred embodiments are prepared by reacting a lower alkyl 4-phenylpiperidine-4-carboxylate with a phenyl-Z-alkylating agent, said agent being preferably a phenoxyalkyl or phenylmercaptoalkyl ester of a strong inorganic acid or an organic sulfonic acid, said ester having the formula, C_6H_5—Z—X—An, where An is an anion of a strong inorganic acid or an organic sulfonic acid. Illustrative of the phenoxyalkyl or phenylmercaptoalkyl esters used in the process of my invention are 3-phenoxypropyl bromide, 2-phenylmercaptoethyl chloride, 4-phenoxybutyl iodide, 2-phenoxypropyl sulfate, 3-phenylmercaptopropyl methanesulfonate, 2-phenoxyethyl benzenesulfonate, 2-phenylmercaptobutyl para-toluenesulfonate, and the like. The preferred esters are the phenoxyalkyl halides and phenylmercaptoalkyl halides. The reaction is carried out by heating the lower alkyl 4-phenylpiperidine-4-carboxylate with the appropriate phenoxy-alkylating or phenylmercapto-alkylating agent: for example, ethyl 4-phenyl-1-(3-phenoxypropyl)piperidine-4-carboxylate is obtained by heating ethyl 4-phenylpiperidine-4-carboxylate with 3-phenoxypropyl bromide; and ethyl 4-phenyl-1-(2-phenylmercaptoethyl)piperidine-4-carboxylate is obtained by heating ethyl 4-phenylpiperidine-4-carboxylate with 2-phenylmercaptoethyl chloride. The reaction can be carried out either in the presence or absence of a suitable solvent, but preferably a solvent such as a lower alkanol is used. A preferred procedure is to conduct the reaction 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. Since the preferred intermediate, ethyl 4-phenylpiperidine-4-carboxylate, forms an insoluble carbonate when treated with carbon dioxide, a convenient way of ascertaining whether the reaction is complete or not is merely to treat the reaction mixture with carbon dioxide, the absence of a precipitate indicating completeness of the reaction. The product is isolated in free base form or in the form of an acid addition salt.

An alternative and preferred procedure for preparing the compounds of my invention where Z is NH or N(lower alkyl) consists of introducing stepwise the 1-[(arylamino) alkyl] substituent onto the piperidine nucleus by reacting a lower alkyl 4-phenylpiperidine-4-carboxylate with a hydroxyalkyl halide, HO-X-halogen, to form a lower alkyl 4-phenyl-1-(hydroxyalkyl)piperidine-4-carboxylate; treating this 1-hydroxyalkyl compound with a halogenating agent such as thionyl chloride, phosphorus oxychloride, phosphorus tribromide and the like to yield

the corresponding lower alkyl 4-phenyl-1-(haloalkyl)-piperidine-4-carboxylate having the formula



and then reacting the 1-haloalkyl compound with an amine having the formula Ar—NHR, where R is hydrogen or a lower alkyl radical as defined and illustrated hereinabove. The last step is generally carried out at a temperature between about 50° C. and 150° C., preferably on a steam bath at about 80–100° C. Illustrative of the preparation of these 1-(arylaminoalkyl) compounds are the following preparations: ethyl 4-phenyl-1-[3-(3,4-dimethoxyphenylamino)propyl]piperidine-4-carboxylate by reacting ethyl 4-phenylpiperidine-4-carboxylate with 3-hydroxypropyl chloride, treating the resulting ethyl 4-phenyl-1-(3-hydroxypropyl)piperidine-4-carboxylate with thionyl chloride, and heating the ethyl 4-phenyl-1-(3-chloropropyl)piperidine-4-carboxylate thus formed with 3,4-dimethoxyaniline; and the preparation of ethyl 4-phenyl-1-[2-(N-ethyl-N-phenylamino)ethyl] piperidine-4-carboxylate by reacting ethyl 4-phenylpiperidine-4-carboxylate with 2-hydroxyethyl chloride, reacting the resulting ethyl 4-phenyl-1-(2-hydroxyethyl)piperidine-4-carboxylate with thionyl chloride and reacting the ethyl 4-phenyl-1-(2-chloroethyl)piperidine-4-carboxylate thus formed with N-ethylaniline.

My new lower alkyl 4-phenyl-1-(aryl-Z-alkyl)piperidine-4-carboxylates are useful either 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

(A) *Lower alkyl 4-phenyl-1-(aryloxyalkyl)piperidine-4-carboxylates*

The preparation of these compounds is illustrated by the following synthesis of ethyl 4-phenyl-1-(3-phenoxypropyl)piperidine-4-carboxylate: A mixture of 13.4 g. of ethyl 4-phenylpiperidine-4-carboxylate hydrochloride, 10.8 g. of 3-phenoxypropyl bromide, 100 ml. of dry n-butanol and 20 g. of anhydrous sodium carbonate was refluxed with stirring for twenty-four hours. The reaction mixture was allowed to cool and was filtered. The filtrate was treated with carbon dioxide (either bubbled in or added as the frozen solid) in order to remove any unreacted ethyl 4-phenylpiperidine-4-carboxylate which forms an insoluble carbonate. After filtering off any carbonate precipitate, the filtrate was concentrated in vacuo to yield ethyl 4-phenyl-1-(3-phenoxypropyl)piperi-

dine-4-carboxylate. This product in free base form was converted into its hydrochloride salt by adding 10 ml. of concentrated hydrochloric acid and 50 ml. of water and triturating the mixture to yield the solid salt. Two recrystallizations from water yielded the product, ethyl 4-phenyl-1-(3-phenoxypropyl)piperidine-4-carboxylate hydrochloride as white needles, melting at 179.2-181.7° C. (corr.).

Analysis.—Calcd. for $C_{23}H_{29}NO_3 \cdot HCl$: C, 68.39; H, 7.49; O, 11.88. Found: C, 68.42; H, 7.98; O, 12.14.

Ethyl 4-phenyl-1-(3-phenoxypropyl)piperidine-4-carboxylate in the form of its free base was obtained by dissolving a sample of the above-described hydrochloride in water, treating the aqueous solution with sodium hydroxide solution, extracting the liberated base with ether, drying the ether extract over anhydrous sodium sulfate, evaporating the ether solution slowly to dryness in vacuo, chilling to induce crystallization, and recrystallizing to constant melting point from ethanol-water. The product, ethyl 4-phenyl-1-(3-phenoxypropyl)piperidine-4-carboxylate, melted at 64.8–66.2° C. (corr.).

The above-described preparation can also be carried out using ethyl 4-phenylpiperidine-4-carboxylate in free base form (11.6 g.) and only one-half as much sodium carbonate (10 g.). Alternatively, this preparation is carried out using other esters such as 3-phenoxypropyl paratoluenesulfonate or 3-phenoxypropyl iodide in place of 3-phenoxypropyl bromide.

Following the above procedure but using the appropriate lower alkyl 4-phenylpiperidine-4-carboxylate and using the appropriate aryloxy-alkylating agent, there is obtained the following compounds: methyl 4-phenyl-1-(4-phenoxybutyl)piperidine-4-carboxylate, ethyl 4-phenyl-1-[2-(4-n-butylphenoxy)ethyl]piperidine-4-carboxylate, n-propyl 4 - phenyl - 1 - (3 - phenoxypropyl)piperidine - 4-carboxylate, ethyl 4-phenyl-1-[3-(3,4-dimethoxyphenoxy)-propyl]piperidine-4-carboxylate, isobutyl 4-phenyl-1-(2-phenoxypropyl)piperidine-4-carboxylate, ethyl 4-phenyl-1 - [2 - (4 - ethylmercaptophenoxy)ethyl]piperidine - 4-carboxylate, n-hexyl 4-phenyl-1-(3-phenoxypropyl)piperidine-4-carboxylate, ethyl 4-phenyl-1-[2-(4-ethylsulfonylphenoxy)ethyl]piperidine-4-carboxylate, ethyl 4-phenyl-1-[2 - (4 - nitrophenoxy)ethyl]piperidine - 4 - carboxylate, ethyl 4 - phenyl - 1 - [2 - (4 - dimethylaminophenoxy)-ethyl]piperidine - 4 - carboxylate, ethyl 4 - phenyl - 1-[2 - (4 - n - butylaminophenoxy)ethyl]piperidine - 4-carboxylate, ethyl 4-phenyl-1-[2-(2,4-dichlorophenoxy)-ethyl]piperidine - 4 - carboxylate, ethyl 4 - phenyl - 1-[2 - (3 - hydroxyphenoxy)ethyl]piperidine - 4 - carboxylate, and the like. Ethyl 4-phenyl-1-[2-(4-aminophenoxy)ethyl]piperidine-4-carboxylate is obtained by reducing the corresponding 1-[2-(4-nitrophenoxy)ethyl] compound with a reducing agent effective to reduce nitro groups to amino groups. Ethyl 4-phenyl-1-[2-(4-acetylaminophenoxy)ethyl]piperidine-4-carboxylate is obtained by reacting the corresponding 1-[2-(4-aminophenoxy)-ethyl] compound with acetyl chloride or acetic anhydride.

Pharmacological evaluation of ethyl 4-phenyl-1-(3-phenoxypropyl)piperidine-4-carboxylate hydrochloride in aqueous solution administered intraperitoneally 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 twelve times as active an analgesic as ethyl 4-phenyl-1-methylpiperidine-4-carboxylate hydrochloride. This compound was found to have an acute toxicity (LD_{50}) in mice of 13.7±0.7 mg. per kg. when administered intravenously in aqueous solution.

(B) *Ethyl 4-phenyl-1-(2-phenoxyethyl)piperidine-4-carboxylate*

The preparation of this compound was carried out following the procedure described above in Example 1(A) using 13.5 g. of ethyl 4-phenylpiperidine-4-carboxylate hydrochloride, 10 g. of 2-phenoxyethyl bromide, 100 ml. of n-butanol and 20 g. of anhydrous sodium carbonate. The product in the form of its hydrochloride salt melted at 155.4–157.2° C. (corr.) when recrystallized from water.

Analysis.—Calcd. for $C_{22}H_{27}NO_3 \cdot HCl$: C, 67.79; H, 7.24; O, 12.30. Found: C, 68.05; H, 7.35; O, 12.80.

Ethyl 4-phenyl-1-(2-phenoxyethyl)piperidine-4-carboxylate in free base form was prepared according to the procedure described above in Example 1(A) for the conversion of ethyl 4-phenyl-1-(3-phenoxypropyl)piperidine-4-carboxylate hydrochloride into its free base. The product, ethyl 4-phenyl-1-(2-phenoxyethyl)piperidine-4-carboxylate, melted at 41.3-42.5° C. (corr.).

Pharmacological evaluation of ethyl 4-phenyl-1-(2-phenoxyethyl)piperidine-4-carboxylate hydrochloride in aqueous solution administered intraperitoneally by the Rat Thermal Stimulus Method of Bass and Vander Brook, ibid., has shown that this compound is approximately six times as active an analgesic as ethyl 4-phenyl-1-methylpiperidine-4-carboxylate hydrochloride.

(C) *Ethyl 4-phenyl-1-(4-phenoxybutyl)piperidine-4-carboxylate*

The preparation of this compound was carried out following the procedure described above in Example 1(A) using 13.4 g. of ethyl 4-phenylpiperidine-4-carboxylate hydrochloride, 11.5 g. of 4-phenoxybutyl bromide, 20 g. of anhydrous sodium carbonate and 100 ml. of n-butanol. The product in the form of its hydrochloride salt melted at 158.0–159.6° C. (corr.). A 50% yield was obtained.

Analysis.—Calcd. for $C_{24}H_{31}NO_3 \cdot HCl$: C, 69.00; H, 7.72; Cl, 8.48. Found: C, 68.91; H, 7.33; Cl, 8.22.

Pharmacological evaluation of ethyl 4-phenyl-1-(4-phenoxybutyl)piperidine-4-carboxylate hydrochloride in aqueous solution administered intraperitoneally by the Rat Thermal Stimulus Method of Bass and Vander Brook, ibid., has shown that this compound is approximately three times as active an analgesic as ethyl 4-phenyl-1-methylpiperidine-4-carboxylate.

EXAMPLE 2

(A) *Lower alkyl 4-phenyl-1-(arylmercaptoalkyl)piperidine-4-carboxylates*

The preparation of these compounds is illustrated by the following synthesis of ethyl 4-phenyl-1-(2-phenylmercaptoethyl)piperidine-4-carboxylate: A mixture of 13.5 g. of ethyl 4-phenylpiperidine-4-carboxylate, 8.65 g. of 2-phenylmercaptoethyl chloride, 100 ml. of n-butanol and 15 g. of anhydrous sodium carbonate was refluxed with stirring for twenty-four hours. The reaction mixture was allowed to cool and was filtered. The filtrate was treated with carbon dioxide, allowed to stand overnight, filtered and the filtrate concentrated in vacuo to yield ethyl 4-phenyl-1-(2-phenylmercaptoethyl)piperidine-4-carboxylate. This free base was dissolved in one liter of water containing 6 cc. of concentrated hydrochloric acid and filtered immediately. There separated from the filtrate white crystals which were recrystallized twice from water to yield the product, ethyl 4-phenyl-1-(2-phenylmercaptoethyl)piperidine-4-carboxylate hydrochloride, M. P. 172.6–174.6° C. (corr.).

Analysis.—Calcd. for $C_{22}H_{27}NO_2S.HCl$: S, 7.89; Cl, 8.73. Found: S, 8.20; Cl, 8.83.

Ethyl 4-phenyl-1-(2-phenylmercaptoethyl)piperidine-4-carboxylate in free base form is obtained by dissolving a solution of the above-described hydrochloride in water, treating the aqueous solution with sodium hydroxide solution, extracting the liberated free base with ether, drying the ether solution over anhydrous sodium sulfate, evaporating slowly the ether solution in vacuo, chilling the residual material until crystalline, then recrystallizing this material from ethanol-water. The resulting product is ethyl 4-phenyl-1-(2-phenylmercaptoethyl)piperidine-4-carboxylate.

Following the above procedure for the preparation of

ethyl 4-phenyl-1-(2-phenylmercaptoethyl)piperidine-4-carboxylate 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 and using the appropriate phenylmercaptoalkyl chloride in place of phenylmercaptoethyl chloride, there is obtained methyl 4-phenyl-1-(4-phenylmercaptobutyl)piperidine-4-carboxylate, isopropyl 4-phenyl-1-(2-phenylmercaptopropyl)piperidine-4-carboxylate, n-butyl 4-phenyl-1-(2-phenylmercaptopropyl)piperidine-4-carboxylate, or n-hexyl 4-phenyl-1-(3-phenylmercaptopropyl)piperidine-4-carboxylate, respectively.

(B) *Ethyl 4-phenyl-1-(3-phenylmercaptopropyl)piperidine-4-carboxylate hydrochloride*

This compound was prepared following the procedure described above for Example 2(A) using 13.5 g. of ethyl 4-phenylpiperidine-4-carboxylate, 9.32 g. of 3-phenylmercaptopropyl chloride, 100 ml. of n-butanol and 15 g. of anhydrous sodium carbonate. The product, ethyl 4-phenyl-1-(3-phenylmercaptopropyl)piperidine-4-carboxylate hydrochloride, melted at 126.8–128.6° C. (corr.).

Analysis.—Calcd. for $C_{23}H_{29}NO_2S.HCl$: C, 65.78; H, 7.20; Cl, 8.45. Found: C, 65.90; H, 7.24; Cl, 8.60.

Ethyl 4-phenyl-1-(3-phenylmercaptopropyl)piperidine-4-carboxylate in free base form is obtained following the procedure described above under Example 2(A) for the preparation of ethyl 4-phenyl-1-(2-phenylmercaptoethyl)piperidine-4-carboxylate.

Pharmacological evaluation of ethyl 4-phenyl-1-(3-phenylmercapto)piperidine-4-carboxylate hydrochloride in aqueous solution administered intraperitoneally by the Rat Thermal Stimulus Method of Bass and Vander Brook, ibid., has shown that this compound is approximately five times as active an analgesic as ethyl 4-phenyl-1-methylpiperidine-4-carboxylate hydrochloride.

EXAMPLE 3

(A) *Lower alkyl 4-phenyl-1-(arylsulfonylalkyl)piperidine-4-carboxylates*

The preparation of these compounds is illustrated by the following synthesis of ethyl 4-phenyl-1-(3-phenylsulfonylpropyl)piperidine-4-carboxylate: This compound was prepared following the procedure described in Example 1(A) using 11 g. of 3-phenylsulfonylpropyl chloride, 13.5 g. of ethyl 4-phenylpiperidine-4-carboxylate hydrochloride, 15 g. of anhydrous sodium carbonate and 100 ml. of n-butanol. There was thus obtained 7.4 g. of the product, ethyl 4-phenyl-1-(3-phenylsulfonylpropyl)piperidine-4-carboxylate, M. P. 87.8–89.0° C. (corr.).

Analysis.—Calcd. for $C_{23}H_{29}NO_4S$: C, 66.48; H, 7.03; O, 15.41. Found: C, 66.71, 66.45; H, 7.05, 6.85; O, 15.50.

When ethyl 4-phenyl-1-(3-phenylsulfonylpropyl)piperidine-4-carboxylate is treated with hydrogen chloride, its hydrochloride is formed.

Following the above procedure but using 3-phenylsulfinylpropyl chloride in place of 3-phenylsulfonylpropyl chloride, the product obtained is ethyl 4-phenyl-1-(3-phenylsulfinylpropyl)piperidine-4-carboxylate.

Following the above procedure but using the appropriate lower alkyl 4-phenylpiperidine-4-carboxylate in place of ethyl 4-phenylpiperidine-4-carboxylate and using the appropriate arylsulfonylalkyl chloride, there is obtained the following respective compounds: methyl 4-phenyl-1-(4-phenylsulfonylbutyl)piperidine-4-carboxylate, ethyl 4-phenyl-1-[2-(4-n-butoxyphenylsulfonyl)-ethyl]piperidine-4-carboxylate, ethyl 4-phenyl-1-[3-(4-nitrophenylsulfonyl)propyl]piperidine-4-carboxylate, and the like.

(B) *Ethyl 4-phenyl-1-(2-phenylsulfonylethyl)piperidine-4-carboxylate*

This compound was prepared following the procedure described in Example 3(A) using 18.2 g. of 2-phenylsulfonylethyl chloride, 24.0 g. of ethyl 4-phenylpiperidine-4-carboxylate hydrochloride, 30 g. of anhydrous sodium carbonate and 250 ml. of n-butanol. There was thus obtained 20.4 g. of the product, ethyl 4-phenyl-1-(2-phenylsulfonylethyl)piperidine-4-carboxylate, M. P. 103.0–104.0° C. (corr.).

Analysis.—Calcd. for $C_{22}H_{27}NO_4S$: C, 65.83; H, 6.78; O, 15.94. Found: C, 65.95; H, 6.86; O, 15.70.

EXAMPLE 4

(A) *Lower alkyl 4-phenyl-1-(haloalkyl)piperidine-4-carboxylates*

The preparation of these intermediate compounds is illustrated by the following synthesis of ethyl 4-phenyl-1-(2-chloroethyl)piperidine-4-carboxylate: To a solution containing 5.56 g. of ethyl 4-phenyl-1-(2-hydroxyethyl)-piperidine-4-carboxylate and a drop of pyridine in 400 ml. of benzene was added dropwise over a period of about forty-five minutes 2.95 g. of thionyl chloride. The reaction mixture was heated slightly on a steam bath at the start of the addition of the thionyl chloride and then heated on a steam bath for one and one-half hours after all of the thionyl chloride had been added. The reaction mixture was allowed to cool and the white precipitate that had separated was collected and recrystallized once from absolute ethanol and once from isopropanol, yielding about 4.7 g. of product, ethyl 4-phenyl-1-(2-chloroethyl)piperidine-4-carboxylate as its hydrochloride, M. P. 218.2° C. (corr.) (with decomposition).

Analysis.—Calcd. for $C_{16}H_{22}ClNO_2.HCl$: C, 57.84; H, 6.98; Cl^-, 10.69. Found: C, 57.67; H, 6.82; Cl^-, 10.58.

Following the above procedure but using the appropriate lower alkyl 4-phenyl-1-(hydroxyalkyl)piperidine-4-carboxylate and using the appropriate halogenating agent, there is obtained the following compounds: methyl 4-phenyl-1-(4-chlorobutyl)piperidine-4-carboxylate, ethyl 4-phenyl-1-(3-chloropropyl)piperidine-4-carboxylate, ethyl 4-phenyl-1-(2-bromoethyl)piperidine-4-carboxylate, isobutyl 4-phenyl-1-(2-chloropropyl)piperidine-4-carboxylate, n-hexyl 4-phenyl-1-(3-chloropropyl)-piperidine-4-carboxylate, and the like.

(B) *Lower alkyl 4-phenyl-1-(arylaminoalkyl)piperidine-4-carboxylates*

The preparation of these compounds is illustrated by the following synthesis of ethyl 4-phenyl-1-(2-phenylaminoethyl)piperidine-4-carboxylate: A mixture containing 5.58 g. of aniline, 4.0 g. of anhydrous sodium carbonate and 25 ml. of water was heated on a steam bath at 90° C. To this heated solution was added dropwise with stirring over a period of one and one-half hours 5.0 g. of ethyl 4-phenyl-1-(2-chloroethyl)piperidine-4-carboxylate hydrochloride dissolved in 60 ml. of water. Heating of the reaction mixture was continued on a steam bath for an additional three hours. The reaction mixture was allowed to cool, was filtered, and benzene was added to the organic layer. The organic layer was washed with saturated sodium chloride solution, concentrated in vacuo and distilled in an oil bath at 98° C. at about 40 mm. pressure to remove the unreacted aniline. The residue was dissolved in ether and hydrogen chloride was bubbled into this solution. The precipitate that separated was recrystallized once from absolute ethanol and once from isopropanol, yielding the product, ethyl 4-phenyl-1-(2-phenylaminoethyl)piperidine-4-carboxylate as its dihydrochloride, M. P. 194.2° C.

Analysis.—Calcd. for $C_{22}H_{28}N_2O_2.2HCl$: C, 62.12; H, 7.11; O, 7.53. Found: C, 62.42; H, 7.06; O, 7.50.

Ethyl 4-phenyl-1-(2-phenylaminoethyl)piperi-

dine-4-carboxylate in the form of its free base is obtained by dissolving a sample of the above-described dihydrochloride in water, treating the aqueous solution with sodium hydroxide solution, extracting the liberated base with benzene, drying the benzene extract over anhydrous sodium sulfate and evaporating the benzene solution slowly to dryness in vacuo.

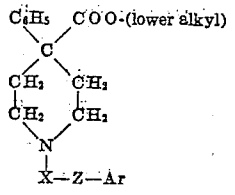
Other lower alkyl 4-phenyl-1-(arylaminoalkyl)piperidine-4-carboxylates that are obtained following the foregoing procedure using the appropriate lower alkyl 4-phenyl-1-(haloalkyl)piperidine-4-carboxylate and the appropriate arylamine are: methyl 4-phenyl-1-[4-(3,4-diethoxyphenylamino)butyl]piperidine-4-carboxylate, ethyl 4-phenyl-1-(3-phenylaminopropyl)piperidine-4-carboxylate, ethyl 4-phenyl-1-[3-(N-ethyl-N-phenylamino)propyl]piperidine-4-carboxylate, ethyl 4-phenyl-1-[2-(4-n-butylaminophenylamino)ethyl]piperidine-4-carboxylate, isobutyl 4-phenyl-1-[2-(4-nitrophenylamino)propyl]piperidine-4-carboxylate, ethyl 4-phenyl-1-[2-(2,4-dibromophenylamino)ethyl]piperidine-4-carboxylate, n-hexyl 4-phenyl-1-[3-(4-isopropylphenylamino)propyl]piperidine-4-carboxylate, and the like.

Pharmacological evaluation of ethyl 4-phenyl-1-(2-phenylaminoethyl)piperidine-4-carboxylate dihydrochloride in aqueous solution administered intraperitoneally by the Rat Thermal Stimulus Method of Bass and Vander Brook, ibid., has shown that this compound is many times more active as an analgesic than ethyl 4-phenyl-1-methylpiperidine-4-carboxylate hydrochloride.

The lower alkyl 4-phenyl-1-(substituted-alkyl)piperidine-4-carboxylates of my invention 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 power can be compounded in capsule form. These preparations can be administered orally, or, in the case of the aqueous preparations, intramuscularly or intravenously.

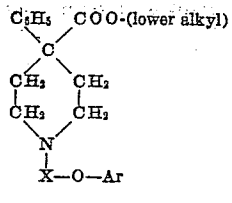
I claim:

1. A composition of matter selected from the group consisting of a compound having the formula



where X is a lower alkylene radical having at least two carbon atoms and having its free valence bonds on different carbon atoms, Z is a member of the group consisting of O, S, SO, SO_2, NH and N (lower alkyl), Ar is a monocarbocyclic aryl radical having six ring-carbon atoms; and its acid addition salts.

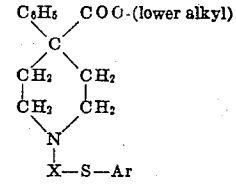
2. A lower alkyl 4-phenyl-1-(aryloxyalkyl)piperidine-4-carboxylate having the formula



where X is a lower alkylene radical having at least two carbon atoms and having its free valence bonds on different carbon atoms, and Ar is a monocarbocyclic aryl radical having six ring-carbon atoms.

3. An acid addition salt of the compound of claim 2.

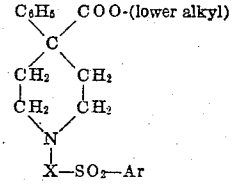
4. A lower alkyl 4-phenyl-1-(arylmercaptoalkyl)piperidine-4-carboxylate having the formula



where X is a lower alkylene radical having at least two carbon atoms and having its free valence bonds on different carbon atoms, and Ar is a monocarbocyclic aryl radical having six ring-carbon atoms.

5. An acid addition salt of the compound of claim 4.

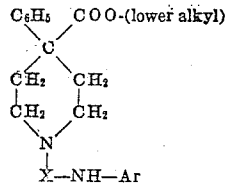
6. A lower alkyl 4-phenyl-1-(arylsulfonylalkyl)piperidine-4-carboxylate having the formula



where X is a lower alkylene radical having at least two carbon atoms and having its free valence bonds on different carbon atoms, and Ar is a monocarbocylic aryl radical having six ring-carbon atoms.

7. An acid addition salt of the compound of claim 6.

8. A lower alkyl 4-phenyl-1-(arylaminoalkyl)piperidine-4-carboxylate having the formula



where X is a lower alkylene radical having at least two carbon atoms and having its free valence bonds on different carbon atoms, and Ar is a monocarbocyclic aryl radical having six ring-carbon atoms.

9. An acid addition salt of the compound of claim 8.

10. Ethyl 4-phenyl-1-(3-phenoxypropyl)piperidine-4-carboxylate.

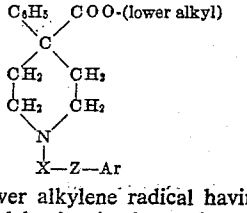
11. Ethyl 4-phenyl-1-(3-phenoxypropyl)piperidine-4-carboxylate hydrochloride.

12. Ethyl 4-phenyl-1-(2-phenoxyethyl)piperidine-4-carboxylate hydrochloride.

13. Ethyl 4-phenyl-1-(2-phenylaminoethyl)piperidine-4-carboxylate.

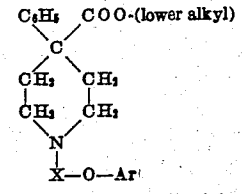
14. Ethyl 4-phenyl-1-(2-phenylaminoethyl)piperidine-4-carboxylate dihydrochloride.

15. The process of preparing a compound having the formula



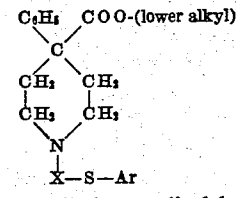
where X is a lower alkylene radical having at least two carbon atoms and having its free valence bonds on different carbon atoms, Z is a member of the group consisting of O, S, SO, SO_2, NH and N(lower alkyl) and Ar is a monocarbocyclic aryl radical having six ring-carbon atoms, which comprises reacting a lower alkyl 4-phenylpiperidine-4-carboxylate with an aryl-Z-alkyl ester of an acid selected from the group consisting of a strong inorganic acid and an organic sulfonic acid.

16. The process of preparing a lower alkyl 4-phenyl-1-(aryloxyalkyl)piperidine - 4 - carboxylate having the formula



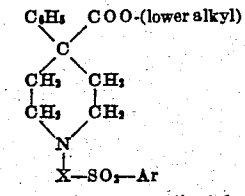
where X is a lower alkylene radical having at least two carbon atoms and having its free valence bonds on different carbon atoms, and Ar is a monocarbocyclic aryl radical having six ring-carbon atoms, which comprises heating a lower alkyl 4-phenylpiperidine-4-carboxylate with an aryloxyalkyl halide.

17. The process of preparing a lower alkyl 4-phenyl-1-(arylmercaptoalkyl)piperidine-4-carboxylate having the formula



where X is a lower alkylene radical having at least two carbon atoms and having its free valence bonds on different carbon atoms, and Ar is a monocarbocyclic aryl radical having six ring-carbon atoms, which comprises heating a lower alkyl 4-phenylpiperidine-4-carboxylate with an arylmercaptoalkyl halide.

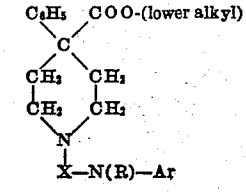
18. The process of preparing a lower alkyl 4-phenyl-1-(arylsulfonylalkyl)piperidine-4-carboxylate having the formula



where X is a lower alkylene radical having at least two carbon atoms and having its free valence bonds on different carbon atoms, and Ar is a monocarbocyclic aryl radical having six ring-carbon atoms, which comprises heating a lower alkyl 4-phenylpiperidine-4-carboxylate with an arylsulfonylalkyl halide.

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

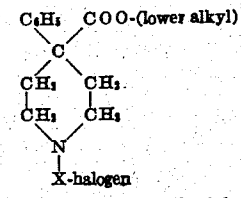
20. The process of preparing a lower alkyl 4-phenyl-1-(arylaminoalkyl)piperidine-4-carboxylate having the formula



where X is a lower alkylene radical having at least two carbon atoms and having its free valence bonds on different carbon atoms, R is selected from the group consisting of hydrogen and a lower alkyl radical and Ar is a monocarbocyclic aryl radical having six ring-carbon atoms, which comprises heating a lower alkyl 4-phenyl-1-(haloalkyl)piperidine-4-carboxylate with an amine having the formula ArNHR.

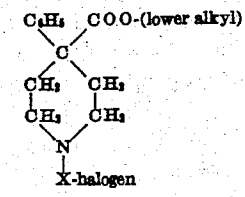
21. The process of preparing ethyl 4-phenyl-1-(2-phenylaminoethyl)piperidine-4-carboxylate which comprises heating ethyl 4-phenyl-1-(2-chloroethyl)piperidine-4-carboxylate with aniline.

22. The process of preparing a lower alkyl 4-phenyl-1-(haloalkyl)piperidine-4-carboxylate having the formula



where X is a lower alkylene radical having at least two carbon atoms and having its free valence bonds on different carbon atoms, which comprises reacting the corresponding lower alkyl 4-phenyl-1-(hydroxyalkyl)piperidine-4-carboxylate with a halogenating agent.

23. A lower alkyl 4-phenyl-1-(haloalkyl)piperidine-4-carboxylate having the formula



where X is a lower alkylene radical having at least two carbon atoms and having its free valence bonds on different carbon atoms.

24. Ethyl 4 - phenyl - 1-(2-phenoxyethyl)piperidine-4-carboxylate.

25. Ethyl 4-phenyl-1-(3-phenylmercaptopropyl)piperidine 4-carboxylate.

26. Ethyl 4-phenyl-1-(3-phenylmercaptopropyl)piperidine-4-carboxylate hydrochloride.

27. Ethyl 4 - phenyl - 1-(2-phenylmercaptoethyl)piperidine-4-carboxylate.

28. Ethyl 4 - phenyl - 1-(2-phenylmercaptoethyl)piperidine-4-carboxylate hydrochloride.

29. Ethyl 4 - phenyl - 1(3-phenylsulfonylpropyl)piperidine-4-carboxylate.

30. Ethyl 4 - phenyl - 1(3-phenylsulfonylpropyl)piperidine-4-carboxylate hydrochloride.

31. Ethyl 4 - phenyl - 1-(3-phenylaminopropyl)piperidine-4-carboxylate.

References Cited in the file of this patent

Thorp: Journal of the Chemical Society of London for 1948, pp. 559–561, May 1948.

Schaumann: Archives of Experimental Pathology and Pharmacology, vol. 196, pp. 109–136, 1940.