

1

3,489,769

1-SUBSTITUTED-3-AROYL-PYRROLIDINES

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16 Claims

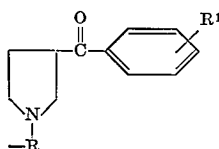
ABSTRACT OF THE DISCLOSURE

The present invention describes 1-substituted -3-arylpyrrolidines which have been shown to be useful in lowering plasma cholesterol levels. The compounds are prepared from 1-substituted-3-cyanopyrrolidines by reaction with aryl magnesium halides.

The present invention relates to certain novel heterocyclic compounds which may be referred to as 3-arylpyrrolidines and is more particularly concerned with 1-substituted-3-arylpyrrolidines, compositions containing the same as active ingredients, and the methods of making and using them.

This application is a continuation-in-part of my co-pending application Ser. No. 570,722, filed Aug. 8, 1966.

The invention is particularly concerned with 1-substituted-3-arylpyrrolidines represented by the following general structural formula:



Formula I

wherein:

R is hydrogen, lower alkyl, aryllower-alkyl, aryloxy, ethoxy, aroyl, lower cycloalkyl, carbethoxy, and ω -alkoxyalkyl,

R¹ is hydrogen, lower alkoxy, trifluoromethyl, halogen having an atomic weight less than 80, and lower alkyl, and acid addition salts thereof.

The compounds of the invention having the foregoing Formula I are generally characterized by important pharmacological activity and are effective as hypocholesterolemic agents and, as such, are particularly useful in lowering plasma cholesterol levels in living animal bodies as demonstrated in rats. Male rats of the Sprague-Dawley strain, weighing between 150–200 grams, were placed in individual cages with raised wire floors and subjected to a 12-hour day with artificial lighting in a room controlled at 75–78° F. The rats remained under these conditions for four days prior to experimentation to adjust to their environment. They were fed a semi-purified basal diet containing 0.375% by weight of the compound being investigated. On the fifth day the rats were randomly selected and divided into two groups. At the end of 21 days and after an overnight fast, the rats were anesthetized with ether and terminally bled from the dorsal aorta into heparinized tubes (Proc. Animal Care Panel 11, 305, 1961). Plasma was extracted according to Dole and Meinertz (J. Biol. Chem. 235, 2995, 1960), and lipids were resolved on a silicic acid column (J. Am. Oil Chem. Soc. 36, 294, 1959) and total cholesterol (Am. J. Clin. Path. 27, 583, 1957) was analyzed (Clin. Chem. 7, 249, 1961). Among the novel compounds of the present invention the preferred compound is Example No. 5, 1-(2-ethoxyethyl)-3-(4-fluorobenzoyl)-pyrrolidine. When test-

2

ed as described hereinabove, the plasma cholesterol level in rats was lowered approximately 50%. The 50% lowering of plasma cholesterol is comparable to that obtained when the known cholesterol lowering agent, ethyl 2-(p-chlorophenoxy)-2-methylpropionate (Atromid-S™), was used as a control drug in the procedure described hereinabove.

It is, accordingly, an object of the present invention to provide new and useful 1-substituted-3-aryl pyrrolidines and methods of making the same. Other objects of the invention will be apparent to one skilled in the art, and still others will become apparent hereinafter.

In the definition of the symbols in the foregoing Formula I and where they appear elsewhere throughout this specification the terms have the following significance.

The term "lower alkyl" as used herein includes straight and branched chain radicals of up to eight carbon atoms inclusive, preferably no more than six carbon atoms, and is exemplified by such groups as methyl, ethyl, propyl, isopropyl, butyl, sec. butyl, tertiary butyl, amyl, isoamyl, hexyl, heptyl, octyl and the like. A "lower-alkoxy" group has the formula —O-lower-alkyl.

The term "lower cycloalkyl" as used herein includes primarily cyclic radicals containing three up to nine carbon atoms inclusive and encompasses such groups as cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, methylcyclohexyl, propylcyclohexyl, ethylcyclopentyl, propylcyclopentyl, dimethylcyclohexyl, cycloheptyl, and cyclo-octyl.

The term "lower alkylene" has the formula —(CH₂)_m— wherein *m* is a positive integer from 1–4 inclusive.

Included in the term "aryllower-alkyl" are lower-alkyl substituted phenyl groups such as benzyl, phenethyl, methylbenzyl, phenpropyl and the like.

An "aryl" radical refers to the phenyl radical alone or to a phenyl radical substituted by any radical or radicals which are not reactive or otherwise interfering under the conditions of reaction, such radicals including lower alkoxy, lower alkyl, trifluoromethyl, halo and the like.

The aryl radicals have preferably no more than one to three substituents such as those given above and, furthermore, these substituents can be in various available positions of the aryl nucleus and, when more than one substituent is present, can be the same or different and can be in various position combinations relative to each other.

An "aryloxy" radical has the formula



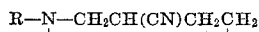
An "aryloxy" radical has the formula —O-aryl.

This invention also includes acid addition salts of the above defined bases formed with nontoxic organic and inorganic acids. Such salts are easily prepared by methods known in the art. When the compounds are to be used as intermediates for preparing other compounds or for any other non-pharmaceutical use, the toxicity or nontoxicity of the salt is immaterial; when the compounds are to be used as pharmaceuticals, they are most conveniently used in the form of nontoxic acid-addition salts. Both toxic and nontoxic salts are therefore within the purview of the invention. The acids which can be used to prepare the preferred nontoxic acid-addition salts are those which produce, when combined with the free bases, salts whose anions are relatively innocuous to the animal organism in therapeutic doses of the salts, so that beneficial physiological properties inherent in the free bases are not vitiated by side effects ascribable to the anions.

The base is reacted with the calculated amount of organic or inorganic acid in aqueous miscible solvent, such as ethanol or isopropanol, with isolation of the salt by concentration and cooling, or the base is reacted with an excess of the acid in aqueous immiscible solvent, such

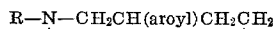
as ethyl ether or isopropyl ether, with the desired salt separating directly. Exemplary of such organic salts are those formed with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, methanesulfonic, acetic, propionic, tartaric, citric, lactic, malic, citraconic, itaconic, hexamic, p-aminobenzoic, glutamic, stearic acid and the like. Exemplary of such inorganic salts are those formed with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

The novel compounds of this invention as represented by Formula I are prepared from 1-R-3-cyanopyrrolidines prepared as described in U.S. Patent 3,318,908. Thus a 1-R-3-cyanopyrrolidine of Formula II, wherein R is lower alkyl, lower



Formula II

cycloalkyl, aryl and phenyllower-alkyl is reacted in a dry inert organic solvent, preferably ether, with an arylmagnesium halide to give a 1-R-3-aroypyrrolidine of Formula III, wherein R is as defined immediately hereinabove.

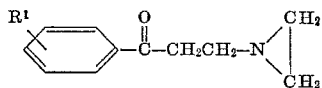


Formula III

Of particular value is the compound of Formula II, wherein R is phenyllower-alkyl as represented by the benzyl group. The 1-benzyl-3-aroypyrrolidine of Formula III prepared from 1-benzyl-3-cyanopyrrolidine and an arylmagnesium halide is reacted with an excess of cyanogen bromide in a dry inert organic solvent, illustratively chloroform, to give a 1-cyano-3-aroypyrrolidine which generally is not isolated, and is hydrolyzed with dilute hydrochloric acid for a period of from about 12 hours to about 16 hours to give a 1-carbamoyl-3-aroypyrrolidine. The latter compound is further hydrolyzed with concentrated hydrochloric acid for a period of from 48 hours to about 72 hours to give a 3-aroypyrrolidine. Alternately, the residual crude material remaining after evaporation of the chloroform solvent following the reaction described above with cyanogen bromide can be hydrolyzed directly to the 3-aroypyrrolidine using concentrated hydrochloric acid.

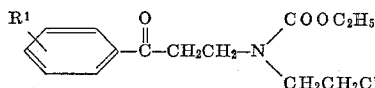
3-aroypyrrolidines can also be prepared by another method as follows:

(1) An ω -dialkylamino propionphenone is reacted with aziridine, the aziridine moiety displacing the dialkylamino group to give an ω -aziridinylpropionphenone of Formula IV.



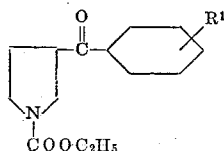
Formula IV

(2) The ω -aziridinylpropionphenone of Formula IV is treated in a dry inert solvent below 20° C. with ethyl chlorocarbonate to give an ω -[N-carbethoxy-N-(2-chloroethyl)amino]-propionphenone of Formula V.



Formula V

(3) The reaction of a compound embraced by Formula V with sodium hydride in dry benzene dimethylformamide solution results in the elimination of the elements of hydrogen chloride with simultaneous formation of the pyrrolidine nucleus to give a 1-carbethoxy-3-aroypyrrolidine of Formula VI.



Formula VI

(4) The 1-carbethoxy-3-aroypyrrolidine of Formula VI is hydrolyzed under acidic conditions to a 3-aroypyrrolidine.

The 3-aroypyrrolidines prepared by the methods described hereinabove constitute novel compounds of Formula I which are especially useful in preparing other novel and useful compounds within the scope of Formula I. Thus, the hydrogen atom of the secondary amine group of the pyrrolidine nucleus exhibits all the reactive properties of a secondary amino group and enters readily into conventional displacement reactions with a variety of reactive compounds, including, for example, alkyl halides, aralkyl halides, N-mono and N,N-disubstituted carbamoyl halides, arylsulfonyl halides, and the like.

Generally speaking, the 3-aroypyrrolidines prepared as described above are reacted with compounds containing reactive halogen atoms in a lower alkanol solvent, illustratively ethanol, containing an alkali metal salt as, for example, sodium carbonate as an acid binder. The reaction is preferably carried out at the reflux temperature of the solvent employed, and following the reaction period the product is extracted into an organic solvent, preferably ether, by acid-base extraction of the concentrated residue of the reaction mixture. After washing and drying, the solvent is evaporated and the product present in the residue is purified by conventional laboratory procedures as, for example, distillation, crystallization, chromatography, and the like.

For specific insight into the type of reactions involved, the intermediates therefor and the manner of carrying them out, and the novel compounds, some of these are specifically set forth in a series of specific examples which follow. It is to be understood the examples are given by way of illustration only and are not to be construed as limiting.

EXAMPLE 1

3-benzoyl-1-ethylpyrrolidine

An ethereal solution of phenylmagnesium bromide was prepared using 61 g. (2.5 mole) of magnesium, 410 g. (2.6 mole) of bromobenzene and 650 ml. of dry ether. The stirred ethereal solution was treated with 248 g. (2.0 mole) of 3-cyano-1-ethylpyrrolidine dissolved in an equal volume of dry ether and following addition the mixture was refluxed six hours. The reaction mixture was decomposed by the careful addition of a solution of 250 g. of ammonium chloride in 750 ml. of water. Following evaporation of the ether, the solution was heated on the steam bath to complete hydrolysis of the ketimine. The product was extracted with ether and then separated from non-basic materials by acid-base extraction. The residual oil was distilled at 97-99° C./0.5 mm. to give 180 g. (44%) of 3-benzoyl-1-ethylpyrrolidine.

Using the process given above in Example 1, the following compounds are prepared from the stated ingredients:

3-benzoyl-1-cyclohexylpyrrolidine is prepared from 1-cyclohexyl-3-cyanopyrrolidine and phenylmagnesium bromide,

3-benzoyl-1-cyclopentylpyrrolidine is prepared from 1-cyclopentyl-3-cyanopyrrolidine and phenylmagnesium bromide,

1-cyclohexyl-3-(m-trifluoromethylbenzoyl)-pyrrolidine is prepared from 1-cyclohexyl-3-cyanopyrrolidine and m-trifluoromethylphenylmagnesium bromide.

EXAMPLE 2

3-benzoyl-1-methylpyrrolidine

To a stirred ether solution of phenylmagnesium bromide prepared from 37.5 g. (1.55 mole) of magnesium, 251 g. (1.60 mole) of bromobenzene and 425 ml. of dry ether was added dropwise a solution of 140 g. (1.27 mole) of 3-cyano-1-methylpyrrolidine in 200 ml. of dry ether. After refluxing two hours, the cooled reaction mixture

5

was treated with a solution of 80 g. of ammonium chloride in 260 ml. of water. The ether was evaporated, the aqueous solution heated one hour to complete hydrolysis of the ketimine and the ketone product extracted with ether. Non-basic materials were separated by acid-base extraction. The residual oil after removal of the ether solvent was distilled in vacuo to give 102 g. (41%) of product at 93–95° C./0.05 mm.

Analysis.—Calculated for $C_{12}H_{15}NO$: N, 7.40. Found: N, 7.57.

EXAMPLE 3

3-benzoyl-1-isopropylpyrrolidine fumarate

To a stirred solution of 2 moles of phenyl magnesium bromide in one liter of ether was added slowly 202 g. (1.46 mole) of 3-cyano-1-isopropylpyrrolidine in 200 ml. of dry ether. After the addition was complete the mixture was stirred and refluxed for three hours and then allowed to stand overnight. To the cooled suspension was then added slowly with stirring 250 g. of ammonium chloride in 750 ml. of water. After the ether was evaporated, the mixture was heated for one hour on a steam bath to insure hydrolysis of ketimine. The ketone was extracted with ether and the combined ether extracts were extracted with 6 N HCl. The acid extracts were made basic with 50% NaOH and the free base was taken up with ether. The ether extracts were washed with water and dried over magnesium sulfate. After the solvent was evaporated, the residual oil was distilled at reduced pressure and the fraction boiling at 98–100° C./0.003 mm. was collected. The light yellow, non-viscous oil weighed 120 g. (38% yield). To a warm solution of 3.7 g. (0.032 mole) of fumaric acid in 150 ml. of isopropanol was added 7.0 g. (0.032 mole) of the free base. The fumarate salt was collected and dried (8.5 g.; M.P. 122–125° C.). After recrystallization from isopropanol the dried fumarate salt (5.0 g.) melted at 125–127° C.

Analysis.—Calculated for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 65.16; H, 6.96; N, 4.05.

EXAMPLE 4

1-methyl-3-(m-methoxybenzoyl)-pyrrolidine

To a stirred Grignard solution prepared from 14.6 g. (0.60 mole) of magnesium, 112 g. (0.60 mole) of m-bromoisole in 250 ml. of ether was added slowly at a rate which maintained gentle refluxing a solution of 60.5 g. (0.55 mole) of 1-methyl-3-cyanopyrrolidine in 50 ml. of dry ether. Stirring was continued for one hour after the addition was complete. To the cooled mixture was then added slowly a solution of 32 g. (0.60 mole) of ammonium chloride in 400 ml. of water. The ether layer was evaporated and the resulting aqueous suspension was heated for one hour on a steam bath to insure hydrolysis of the ketimine. The ketone was extracted with benzene and the combined extracts were extracted with 6 N HCl. After the acid extracts were made basic with 6 N NaOH, the free base was taken up in benzene. The benzene extracts were washed with water and dried over magnesium sulfate. After the solvent was evaporated, the residual oil was distilled at reduced pressure and the fraction boiling at 121–124° C./0.07 mm. was collected. The light yellow, non-viscous oil weighed 30.8 g. (25% yield).

Analysis.—Calculated for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 70.60; H, 7.89; N, 6.41.

EXAMPLE 5

1-(2-ethoxyethyl)-3-(p-fluorobenzoyl)-pyrrolidine oxalate

To a stirred Grignard solution prepared from 11.2 g. (0.46 mole) of magnesium, 80.5 g. (0.46 mole) of p-bromofluorobenzene in 300 ml. of ether was added slowly at a rate which maintained gentle refluxing a solution of 44 g. (0.26 mole) of 1-(2-ethoxyethyl)-3-cyanopyrrolidine in 60 ml. of dry ether. Stirring was continued for

6

one hour after the addition was complete. To the cooled mixture was added slowly a solution of 26.8 g. (0.50 mole) of ammonium chloride in 300 ml. of water. The ether layer was evaporated and the aqueous suspension heated for an hour on a steam bath to insure hydrolysis of the ketimine. The ketone was extracted with ether and the combined extracts were extracted with 6 N HCl. After the acid extracts were made basic with 6 N NaOH the free base which separated was taken up in ether. The ether extracts were washed with water and dried over magnesium sulfate. After the solvent was evaporated, the residual oil was distilled at reduced pressure and the fraction boiling at 130–133° C./0.07 mm. was collected. The light yellow, non-viscous oil weighed 12.9 g. (19% yield). The free base (12.0 g.; 0.044 mole) was added to a solution of 5.6 g. (0.044 mole) of oxalic acid dihydrate in hot isopropanol. The mixture was heated several minutes, filtered and cooled. The crystalline product which separated melted at 141–142° C. and weighed 12.2 g.

EXAMPLE 6

1-benzyl-3-benzoylpyrrolidine hydrochloride hydrate

To a stirred solution of 544 g. (3.0 mole) of phenylmagnesium bromide in 1.5 liters of dry ether was added 279 g. (1.5 mole) of 1-benzyl-3-cyanopyrrolidine in 400 ml. of dry ether at a rate which maintained gentle refluxing. The mixture was stirred for two hours at room temperature after the addition was complete, cooled and treated with 151 g. (3.0 mole) of ammonium chloride in 900 ml. of water. After the ether was evaporated the aqueous suspension was heated on a steam bath for several hours to insure hydrolysis of the ketimine. The mixture was then extracted with ether and the combined extracts were washed with water and dried over magnesium sulfate. The solvent was evaporated and the residual oil distilled at reduced pressure. The light yellow oil boiling at 172–175° C./0.08 mm. weighed 210 g. (53% yield). A portion of the free base (6 g.) was treated with 3 N HCl and the white crystalline hydrochloride which formed was recrystallized from water. The salt weighed 2.6 g. and melted at 116–118.5° C.

Analysis.—Calculated for $C_{18}H_{22}NO_2Cl$: C, 67.59; H, 6.93; N, 4.38. Found: C, 67.85; H, 6.94; N, 4.42.

EXAMPLE 7

1-benzyl-3-(m-trifluoromethylbenzoyl)-pyrrolidine hydrochloride

To a stirred Grignard solution prepared from 32.4 g. (1.3 mole) of magnesium, 300 g. (1.3 mole) of m-bromobenzotrifluoride in 450 ml. of ether was added 186 g. (1.0 mole) of 1-benzyl-3-cyanopyrrolidine in 200 ml. of dry ether at a rate which maintained gentle refluxing. The mixture was stirred at reflux for one hour, cooled and treated with a solution of 70 g. (1.3 mole) of ammonium chloride in 600 ml. of water. After the ether was evaporated, the mixture was heated for one hour on a steam bath to insure hydrolysis of the ketimine. The mixture was extracted with ether and the combined extracts were washed with water, dried over magnesium sulfate and the solvent evaporated. The residual oil was distilled at reduced pressure and the fraction boiling at 165–167° C./0.07 mm. collected. The light yellow oil weighed 123 g. (37% yield). A portion (23 g.) of the product was redistilled slowly and the fraction boiling at 148–150° C./0.04 mm. collected. The oil weighed 16 g. A portion (10 g.) of the oil was dissolved in ether and treated with ethereal hydrogen chloride. The white hydrochloride which formed melted at 158–160° C. and weighed 9.8 g. after it was recrystallized from methyl ethyl ketone.

Analysis.—Calculated for $C_{19}H_{19}NOClF_3$: C, 61.70; H, 5.18; N, 3.79. Found: C, 61.75; H, 5.15; N, 3.99.

EXAMPLE 8

1-benzyl-3-(p-fluorobenzoyl)-pyrrolidine hydrochloride

To the stirred Grignard solution prepared from 42.5 g. (1.76 mole) of magnesium, 308 g. (1.76 mole) of fluorobromobenzene in 700 ml. of ether was added 164 g. (0.88 mole) of 1-benzyl-3-cyanopyrrolidine in 100 ml. of dry ether at a rate which maintained gentle refluxing. The mixture was stirred for one hour at ambient temperature, cooled and treated with a solution of 94 g. (1.8 mole) of ammonium chloride in 500 ml. of water. The resulting suspension was stirred and heated on a steam bath for 16 hours, cooled and treated with 500 g. of 50% NaOH. Toluene was added to the flask and the mixture was heated for one hour on a steam bath to insure hydrolysis of the ketimine. The suspension was filtered and the cake washed with toluene. The organic layer was separated, washed with water and dried over magnesium sulfate. The solvent was evaporated and the residual oil was distilled at reduced pressure. The fraction boiling at 169–170° C./0.5 mm. weighed 103 g. (41% yield). A portion of the free base (7.6 g.) was dissolved in isopropyl ether and treated with ethereal hydrogen chloride. The salt weighed 5.3 g. and melted at 163–165° C. after it was recrystallized from an isopropanol-isopropyl ether mixture.

Analysis.—Calculated for $C_{18}H_{19}ClFNO$: C, 67.60; H, 5.99; N, 4.38. Found: C, 67.82; H, 5.95; N, 4.54.

EXAMPLE 9

3-benzoyl-1-carbamoylpyrrolidine

To a stirred solution of 68.8 g. (0.65 mole) of cyanogen bromide in one liter of chloroform was added 148 g. (0.56 mole) of 1-benzyl-3-benzoylpyrrolidine in 200 ml. of chloroform over a period of five hours. After the addition was complete, the solution was refluxed for one hour and then the solvent was evaporated at reduced pressure. The residual oil was treated with 1600 ml. of 4 N HCl and refluxed for 16 hours. The mixture was cooled and extracted with ether. The aqueous layer was treated with NaOH and then extracted with chloroform. The chloroform was evaporated and the residual oil which crystallized on cooling was recrystallized from ethyl acetate using charcoal. The product weighed 57 g. (58% yield). The material melted at 127.5–128.5° C. after it was recrystallized from the ethyl acetate.

Analysis.—Calculated for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.83. Found: C, 65.83; H, 6.48; N, 12.71.

EXAMPLE 10

1-carbamoyl-3-(p-fluorobenzoyl)-pyrrolidine

To a stirred solution of 44.6 g. (0.43 mole) of cyanogen bromide in 400 ml. of chloroform was added 95 g. (0.33 mole) of 1-benzyl-3-(p-fluorobenzoyl)-pyrrolidine in 100 ml. of chloroform over a period of five hours. After the addition was complete, the solution was refluxed for 1.5 hours and then the solvent was evaporated at reduced pressure. The residual oil was treated with 1600 ml. of 4 N HCl and refluxed for 16 hours. The mixture was cooled and extracted with ether. The aqueous layer was made basic with NaOH and then extracted with chloroform. The chloroform was evaporated in the residual oil crystallized on cooling. The crystalline product weighed 32 g. (41% yield) after it was triturated with ethyl acetate and dried. The product was recrystallized from ethyl acetate-ethanol and the white crystalline material melted at 136.5–137.5° C.

Analysis.—Calculated for $C_{12}H_{13}FN_2O_2$: C, 61.01; H, 5.54; N, 11.86. Found: C, 61.09; H, 5.41; N, 11.61.

EXAMPLE 11

3-(m-trifluoromethylbenzoyl)-pyrrolidine oxalate

To a stirred solution of 44.6 g. (0.043 mole) of cyanogen bromide in 400 ml. of chloroform was added over

a period of four hours, 102 g. (0.31 mole) of 1-benzyl-3-(m-trifluoromethylbenzoyl)-pyrrolidine. After the addition was complete, the mixture was heated at reflux for one hour and then the solvent was evaporated at reduced pressure. An acidic solution of the residual oil in 1200 ml. of 3 N hydrochloric acid was refluxed for 24 hours. The cooled acidic solution was decanted from a dark viscous residue and made basic with 25% sodium hydroxide and the basic solution extracted with benzene. The combined extracts were washed with water, dried over magnesium sulfate and the solvent evaporated. A solution of the residual oil (24 g., 0.1 mole) in isopropyl ether was treated with a solution of 12.6 g. (0.10 mole) of oxalic acid dihydrate in methanol. The crude salt which formed was recrystallized from isopropanol yielding 7.0 g. (7% yield) of product melting at 86–87° C.

Analysis.—Calculated for $C_{14}H_{14}F_3NO_5$: C, 50.45; H, 4.23; N, 4.20. Found: C, 50.33; H, 4.29; N, 4.47.

EXAMPLE 12

3-benzoylpyrrolidine hydrochloride hydrate

A solution of 18 g. of 3-benzoyl-1-carbamoylpyrrolidine in 120 ml. of concentrated HCl was refluxed three days, cooled and made basic with 50% NaOH. The oil which separated was extracted with benzene and the combined extracts were washed with water, dried over magnesium sulfate and the solvent evaporated. The residual oil weighed 8.1 g. (53% yield). A portion of the free base (5.0 g.) was dissolved in isopropanol and treated with ethereal HCl. The salt which formed was recrystallized from an isopropanol-ether mixture. The product weighed 2.5 g. and melted at 59–61° C.

Analysis.—Calculated for $C_{11}H_{16}NO_2Cl$: C, 57.51; H, 7.02; N, 6.10. Found: C, 57.73; H, 6.80; N, 6.22.

EXAMPLE 13

3-(p-fluorobenzoyl)-pyrrolidine oxalate

A mixture of 50 g. of 1-carbamoyl-3-(p-fluorobenzoyl)-pyrrolidine in 400 ml. of conc. HCl was refluxed three days, cooled and made basic with 50% NaOH. The oil which separated was extracted with benzene and the combined extracts were washed with water, dried over magnesium sulfate and the solvent evaporated. The residual oil weighed 19.0 g. (46% yield). A portion (1.9 g., 0.01 mole) of the free base was dissolved in isopropanol and treated with 1.3 g. (0.01 mole) of oxalic acid dihydrate and heated several minutes. The crystalline salt which separated on cooling was recrystallized again from the same solvent. The salt weighed 1.8 g. and melted at 116–119° C. (rapid heating). When the salt was heated slowly it softened at 115–117° C. and melted at 120–124° C.

Analysis.—Calculated for $C_{13}H_{14}FNO_5$: C, 55.12; H, 4.98; N, 4.95. Found: C, 55.40; H, 5.01; N, 4.99.

EXAMPLE 14

1-[3-(p-acetyl-o-methoxyphenoxy)propyl]-3-(p-fluorobenzoyl)-pyrrolidine oxalate

A stirred mixture of 4.8 g. (0.025 mole) of 3-(p-fluorobenzoyl)-pyrrolidine, 7.8 g. (0.027 mole) of 3-(p-acetyl-o-methoxyphenoxy)-propyl bromide, 14 g. of potassium carbonate and 100 ml. of 1-butanol was heated at 75–80° C. for 16 hours, cooled, filtered and the solvent evaporated. The residual oil was taken up in benzene and washed with water. After the solution was dried over magnesium sulfate, the solvent was evaporated. The residual oil was dissolved in isopropanol and treated with 3.2 g. (0.025 mole) of oxalic acid dihydrate, heated for several minutes and the resulting solution filtered. The salt which crystallized on cooling weighed 7.1 g. (61% yield) and melted at 100–103° C.

Analysis.—Calculated for $C_{25}H_{28}FNO_8$: C, 61.34; H, 5.77; N, 2.86. Found: C, 61.86; H, 5.79; N, 2.86.

EXAMPLE 15

1-[2-(p-acetyl-o-methoxyphenoxy)-ethyl]-3-benzoylpyrrolidine oxalate

A stirred mixture of 3.5 g. (0.02 mole) of 3-benzoylpyrrolidine, 5.5 g. (0.02 mole) 2-(p-acetyl-o-methoxyphenoxy)-ethyl bromide, 12 g. of potassium carbonate and 75 ml. of 1-butanol was heated at 75–78° C. for 16 hours, cooled, filtered and the solvent evaporated. The residual oil was dissolved in benzene and chromatographed on 200 g. of 60–100 mesh magnesium silicate, eluting with a benzene-acetone mixture. The product weighed 4.1 g. (56% yield). The free base was dissolved in isopropanol and treated with 2.5 g. (0.02 mole) of oxalic acid dihydrate. The crystalline salt which formed was recrystallized twice from isopropanol. The product weighing 3.4 g. softened at 127° C. and melted at 129–132° C.

Analysis.—Calculated for $C_{24}H_{27}NO_8$: C, 63.01; H, 5.95; N, 3.06. Found: C, 63.01; H, 6.06; N, 3.14.

EXAMPLE 16

1-[3-(p-acetyl-o-methoxyphenoxy)propyl]-3-benzoylpyrrolidine oxalate

A mixture of 3.5 g. (0.02 mole) of 3-benzoylpyrrolidine, 5.7 g. (0.02 mole) of 3-(p-acetyl-o-methoxyphenoxy)-propyl bromide, 12 g. of potassium carbonate and 75 ml. of toluene was refluxed for 16 hours, cooled and treated with 100 ml. of water. The organic layer was separated, washed with cold water and the solvent evaporated. The residual oil was dissolved in benzene and chromatographed on 150 g. of magnesium silicate, eluting with a benzene-acetone mixture. The product weighed 2.0 g. (26% yield). The free base was treated with a solution of 0.7 g. (0.06 mole) of oxalic acid in isopropanol. The salt which separated weighed 2.2 g. and melted at 114–119° C.

Analysis.—Calculated for $C_{25}H_{29}NO_8$: C, 63.68; H, 6.20; N, 2.97. Found: C, 63.47; H, 6.13; N, 3.05.

EXAMPLE 17

1-[3-(p-fluorobenzoyl)-propyl]-3-(p-fluorobenzoyl)-pyrrolidine

A stirred mixture of 3.8 g. (0.020 mole) of 3-(p-fluorobenzoyl)-pyrrolidine, 5.8 g. (0.024 mole) of 2-(3-chloropropyl)-2-(p-fluorophenyl)-1,3-dioxolane, 14.0 g. of potassium carbonate and 75 ml. of 1-butanol was heated at 80° C. for 32 hours and then at reflux for 16 hours. The cooled suspension was filtered and the solvent evaporated at reduced pressure. The residual oil was stirred in a mixture of 100 ml. of 3 N HCl and 100 ml. of ethanol for one hour. After the mixture was made basic with 50% NaOH, the oil in which separated was extracted with benzene and the benzene evaporated. The residual oil (6.1 g.) was chromatographed on 200 g. of 60–100 mesh magnesium silicate, eluting with a benzene-acetone mixture. The product (tan wax) weighed 1.5 g. (21% yield). A portion of the product was molecularly distilled to obtain a pure sample.

Analysis.—Calculated for $C_{21}H_{21}F_2NO_2$: C, 70.57; H, 5.92; N, 3.92. Found: C, 70.81; H, 6.10; N, 3.98.

EXAMPLE 18

 β -Aziridinylpropiofenone

A solution of 35.4 gms. (0.20 mole) of β -dimethylaminopropiofenone in 200 ml. of dimethylformamide was treated with 50 gms. (1.16 mole) of aziridine and the reaction mixture was allowed to stand 48 hours at room temperature while a slow stream of nitrogen was passed through the mixture. The solution was poured into water and the aqueous solution extracted with benzene. The combined benzene extracts were washed with water and dried over magnesium sulfate. An aliquot of the benzene solution was concentrated and the residue

molecularly distilled at 100° C./0.1 mm. The nuclear magnetic resonance spectrum was consistent with the proposed structure.

EXAMPLE 19

1-carbethoxy-3-benzoylpyrrolidine (Method A)

A solution containing approximately 0.20 mole of β -aziridinylpropiofenone in 200 ml. of dry benzene was treated dropwise at 20° C. with 18 gms. (0.17 mole) of ethylchlorocarbonate to give an almost quantitative yield of β -[N-carbethoxy-N-(2-chloroethylamino)]-propiofenone. The course of the preceding reaction was followed by thin layer chromatography.

The benzene solution of β -[N-carbethoxy-N-(2-chloroethylamino)]-propiofenone was treated with 4.8 gms. (0.20 mole) of sodium hydride. No reaction occurred when the benzene solution was refluxed. Dimethylformamide was added to the benzene solution resulting in a vigorous evolution of hydrogen gas. The solution after refluxing for a short period was cooled, poured into water, the benzene layer separated, dried over magnesium sulfate and concentrated to an oil. The oil was chromatographed on 800 gms. of 60–100 mesh magnesium silicate and the product eluted from the column using benzene-acetone solution. The infrared and nuclear magnetic spectra of the product was identical to that of 1-carbethoxy-3-benzoylpyrrolidine prepared by Method B described in Example 20.

EXAMPLE 20

1-carbethoxy-3-benzoylpyrrolidine (Method B)

To a cold stirred mixture (0° C.) of 1.5 gms. (0.008 mole) of 3-benzoylpyrrolidine, 2.2 gms. (0.016 mole) of potassium carbonate and 20 ml. of methylene chloride was added 0.88 gm. (0.008 mole) of ethyl chlorocarbonate. Approximately 10 gms. of ice was added to the reaction mixture which was stirred until the pot temperature reached room temperature. The two phase system was separated and the organic layer was washed with dilute hydrochloric acid, dried over magnesium sulfate and the dried organic solution concentrated to an oil. The oil was purified by chromatography using magnesium silicate, the pure product eluted from the column using benzene-acetone. The pure product weighed 1.0 gm. (50%). The material was molecularly distilled.

Analysis.—Calculated for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.67. Found: C, 67.93; H, 6.99; N, 5.84.

EXAMPLE 21

3-benzoylpyrrolidine hydrochloride hydrate

Ten grams (0.04 mole) of 3-benzoyl-1-carbethoxypyrrolidine was mixed with 25 ml. of absolute ethanol and 25 ml. of concentrated hydrochloric acid and the solution refluxed for 18 hours. The cooled reaction mixture was extracted with ether and the aqueous acid solution was concentrated to an oil. The oil was dissolved in hot acetone and from the cooled acetone solution 5.0 gms. (63%) of the hydrochloride salt was obtained. The salt melted at 59–61°. A mixture melting point with the compound prepared in Example 12 showed no depression.

The present invention also contemplates novel compositions containing the compounds of the invention as active ingredients. In forming the novel compositions of this invention, the active ingredient is incorporated in a suitable carrier, illustratively, a pharmaceutical carrier. Suitable pharmaceutical carriers which are useful in formulating the compositions of this invention include starch, gelatin, glucose, magnesium, carbonate, lactose, malt and the like. Liquid compositions are also within the purview of this invention and suitable liquid pharmaceutical carriers include ethyl alcohol, water, saline, propylene glycol, glycerine, glucose syrup and the like. The physical form of the novel compositions depends in part upon the physical characteristics of the active ingredient. When

11

the active ingredient is a solid, the composition is preferably formulated as a capsule or tablet. When the active ingredient is a liquid, the composition is preferably formulated as a soft gelatin capsule. The preferred composition is a tablet containing the active ingredient in the form of its nontoxic acid-addition salt.

The following are examples of compositions formed in accordance with this invention:

(1) CAPSULES

Capsules of 5 mg., 25 mg., and 50 mg. of active ingredient per capsule are prepared. With the higher amounts of active ingredient, reduction may be made in the amount of lactose.

Typical blend for encapsulation:	Per capsule, mg.
Active ingredient, as salt	5.0
Lactose	296.7
Starch	129.0
Magnesium stearate	4.3
Total	435.0

Additional capsule formulations preferably contain a higher dosage of active ingredient and are as follows:

Ingredients	100 mg. per capsule	250 mg. per capsule	500 mg. per capsule
Active ingredient, as salt	100.0	250.0	500.0
Lactose	231.5	126.5	31.1
Starch	99.2	54.2	13.4
Magnesium stearate	4.3	4.3	5.5
Total	435.0	435.0	550.0

In each case, uniformly blend the selected active ingredient with lactose, starch, and magnesium stearate and encapsulate the blend.

(2) TABLETS

A typical formulation for a tablet containing 5.0 mg. of active ingredient per tablet follows. The formulation may be used for other strengths of active ingredient by adjustment of weight of dicalcium phosphate.

	Per tablet, mg.
(1) Active ingredient, as salt	5.0
(2) Corn starch	13.6
(3) Corn starch (paste)	3.4
(4) Lactose	79.2
(5) Dicalcium phosphate	68.0
(6) Calcium stearate	0.9
Total	170.1

Uniformly blend 1, 2, 4, and 5. Prepare 3 as a 10 percent paste in water. Granulate the blend with starch paste and pass the wet mass through an eight mesh screen. The wet granulation is dried and sized through a twelve mesh screen. The dried granules are blended with the calcium stearate and compressed.

Additional tablet formulations preferably contain a higher dosage of the active ingredient and are as follows:

A. 50 mg. tablet

Ingredients:	Per tablet, mg.
Active ingredient, as salt	50.0
Lactose	90.0
Milo starch	20.0
Corn starch	38.0
Calcium stearate	2.0
Total	200.0

Uniformly blend the active ingredient, lactose, milo starch and the corn starch. This blend is granulated using water as a granulating medium. The wet granules are passed through an eight mesh screen and dried at 140 to 160 degrees Fahrenheit over night. The dried

12

granules are passed through a number ten mesh screen and blended with the proper amount of calcium stearate and this blend is then converted into tablets on a suitable tablet press.

B. 100 mg. tablet

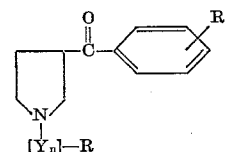
Ingredients:	Per tablet, mg.
Active ingredient, as salt	100.0
Lactose	190.0
Dicalcium phosphate	72.2
Starch	54.0
Milo starch	21.6
Calcium stearate	2.2
Total	540.0

Uniformly blend the active ingredient, lactose, dicalcium phosphate, starch and milo starch. This blend is granulated with water and the wet mass is passed through a number eight mesh screen. The wet granules are dried at 140-160 degrees Fahrenheit over night. The dried granules are passed through a number ten mesh screen. These dried granules are blended with the proper weight of calcium stearate and the lubricated granules are then converted into tablets on a suitable tablet press.

Various modifications and equivalents will be apparent to one skilled in the art and may be made in the compounds, compositions, methods, and procedures of the present invention without departing from the spirit or scope thereof, and it is therefore to be understood that the invention is to be limited only by the scope of the appended claims.

What is claimed:

1. A compound selected from the group having the formula:



wherein;

R is selected from the group consisting of hydrogen, lower alkyl, phenyllower alkyl, p-acetyl-o-methoxyphenoxyethyl, p-acetyl-o-methoxyphenoxypropyl, p-fluorobenzoyl, lower cycloalkyl having three to nine carbon atoms inclusive, 2-ethoxyethyl,

R¹ is selected from the group consisting of hydrogen, lower alkoxy, trifluoromethyl, halogen having an atomic weight less than 80 and lower alkyl, and acid addition salts thereof.

2. A compound of claim 1 which is 3-benzoyl-1-ethylpyrrolidine.

3. A compound of claim 1 which is 3-benzoyl-1-methylpyrrolidine.

4. A compound of claim 1 which is 3-benzoyl-1-isopropylpyrrolidine.

5. A compound of claim 1 which is 1-methyl-3-(m-methoxybenzoyl)-pyrrolidine.

6. A compound of claim 1 which is 1-(2-ethoxyethyl)-3-(p-fluorobenzoyl)-pyrrolidine.

7. A compound of claim 1 which is 1-benzyl-3-benzoylpyrrolidine.

8. A compound of claim 1 which is 1-benzyl-3-(m-trifluoromethylbenzoyl)-pyrrolidine.

9. A compound of claim 1 which is 1-benzyl-3-(p-fluorobenzoyl)-pyrrolidine.

10. A compound of claim 1 which is 1-[3-(p-acetyl-o-methoxyphenoxy)propyl]-3-(p-fluorobenzoyl)-pyrrolidine.

11. A compound of claim 1 which is 1-[2-(p-acetyl-o-methoxyphenoxy)ethyl]-3-benzoylpyrrolidine.

13

12. A compound of claim 1 which is 1-[3-p-acetyl-o-methoxyphenoxy)-propyl]-3-benzoylpyrrolidine.

13. A compound of claim 1 which is 1-[3-(p-fluorobenzoyl)-propyl]-3-(p-fluorobenzoyl)-pyrrolidine.

14. A compound of claim 1 which is 3-benzoylpyrrolidine.

15. A compound of claim 1 which is 3-(p-fluorobenzoyl)-pyrrolidine.

16. A compound of claim 1 which is 3-(m-trifluoromethyl-benzoyl)-pyrrolidine.

14**References Cited****UNITED STATES PATENTS**

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5 ALEX MAZEL, Primary Examiner

J. TOVAR, Assistant Examiner

U.S. Cl. X.R.

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