PATENT SPECIFICATION

NO DRAWINGS

881,893

Date of filing Complete Specification: April 14, 1959.

Application Date: April 22, 1958. *No. 12779/58.*

Complete Specification Published: Nov. 8, 1961.

Index at acceptance:—Class 2(3), B(2: 4A2: H), C1C(1B: 2: 4: 9: 11F: 11G), C1E5K(4: 6), C1E6K(3: 4: 6: 7), C1E7K(4: 6: 7), C1G(2A4: 5A: 5B: 5C: 6A2: 6B5: 6B6), C3A12(A4A: A4C: B3: B4: C1: C6), C3A13A3(A4: B3: F2).

International Classification:—C07c, d.

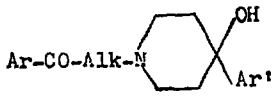
COMPLETE SPECIFICATION

Arylpiperidine Derivatives

I, PAUL ADRIAAN JAN JANSSEN, of Antwerpse Steenweg 16[1], Vosselaar near Turnhout, Belgium, a Citizen of Belgium, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to aroylpiperidine derivatives.

The novel compounds of this invention are 1 - aroyl - alkyl - 4 - arylpiperidin - 4 - ols of the general formula



and the acid addition and quaternary ammonium non-toxic salts thereof, wherein Ar is a halophenyl, methoxyphenyl, ethoxyphenyl, dimethoxyphenyl, thienyl, or monocyclic aromatic hydrocarbon radical containing less than nine carbon atoms, Ar^1 is a halophenyl or monocyclic aromatic hydrocarbon radical containing less than nine carbon atoms, and Alk is a lower alkylene radical containing three to six carbon atoms.

The halophenyl radicals may be fluorophenyl, chlorophenyl, bromophenyl or iodophenyl radicals and the monocyclic aromatic hydrocarbon radicals containing less than nine carbon atoms may suitably be phenyl, tolyl, or xylyl radicals.

The radical Alk may suitably be a trimethylene, propylene, methylpropylene, butylene, tetramethylene, pentamethylene or hexamethylene radical. An especially preferred embodiment of the invention is represented by the compounds in which Alk is a trimethylene radical.

The organic bases of this invention form acid addition and quaternary ammonium non-toxic salts with a variety of inorganic and strong organic acids including sulphuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulphamic, citric, lactic, maleic, malic, succinic, tartaric, cinnamic, acetic, benzoic, gluconic, ascorbic and related acids. They also form quaternary ammonium salts with a variety of organic esters of sulphuric, hydrohalic and aromatic sulphonic acids. Among such esters are methyl chloride and bromide, ethyl chloride, propyl chloride, butyl chloride, isobutyl chloride, benzyl chloride and bromide, phenethyl bromide, naphthylmethyl chloride, dimethyl sulphate, diethyl sulphate, methyl benzene sulphonate, ethyl toluene sulphonate, ethylene chlorohydrin, propylene chlorohydrin, allyl bromide, methallyl bromide and crotyl bromide.

The compounds of this invention can be prepared by the condensation of an aroylalkyl halide of the general formula

Ar—CO—Alk—Halogen

with an appropriately selected 4-arylpiperidin-4-ol. The reaction can be carried out in an inert solvent such as an aromatic hydrocarbon e.g. benzene, toluene, xylene; a lower alkanol, e.g. ethanol, propanol and butanol; or a lower alkanone e.g. acetone, butanone and pentanone. In certain cases the reaction may be usefully accelerated by the use of elevated temperatures.

The aroylalkyl halides used as intermediates can be conveniently prepared by the Friedel-Crafts reaction, including its milder variations employing, for example, γ-chlorobutyryl chloride and benzene or an appropriately substituted benzene such as toluene and xylene, a halogenated benzene such as chlorobenzene, bromobenzene, and fluorobenzene, or an alkoxy benzene such as anisole and phenetole.

[*Price 3s. 6d.*]

A milder catalyst such as stannic chloride can be used rather than aluminium chloride.

These intermediates can also be prepared by treating an ω-haloalkanonitrile with the appropriate aryl magnesium bromide, followed by acid hydrolysis of the adduct.

The 4-arylpiperidine-4-ol intermediates can be prepared by treating the appropriate 4-aryl-1,2,3,6-tetrahydropyridine with hydrogen bromide and then by hydrolysing the resulting 4-aryl-4-bromopiperidine to form the corresponding 4-arylpiperidin-4-ol.

The compounds of this invention have useful pharmacological properties. They are potent depressants of the central nervous system. Specifically, the compounds in which Ar is a thienyl radical exhibit tranquilising and hypnotic effects. The compounds in which Ar is an aryl or substituted aryl group are psychotropic agents. They are also analgesics, antipyretics, and spasmolytic agents.

The compounds which constitute this invention and the processes for their preparation will appear more fully from a consideration of the following Examples. In these Examples quantities are indicated in parts by weight, temperatures are expressed in degrees Centigrade (°C.), and pressures are expressed in millimetres of mercury (mm.).

PREPARATION A

A solution of 71 parts of γ-chlorobutyryl chloride and 63 parts of benzene was added with stirring and cooling to a suspension of 71 parts of aluminium chloride in 310 parts of benzene. After the addition was completed, the cooling bath was removed, and stirring was continued for 30 minutes. The reaction mixture was poured into ice water. The benzene layer was separated, dried over anhydrous sodium sulphate, and filtered. The filtrate was concentrated under reduced pressure to remove the benzene and the residue was distilled to yield γ-chlorobutyrophenone boiling at about 134—137°C. at 5 mm. pressure.

PREPARATION B

To a suspension of 341 parts of aluminium chloride in 1740 parts of carbon disulphide were added 96 parts of fluorobenzene with stirring and cooling. While the temperature was maintained at about 10°C., 141 parts of γ-chlorobutyryl chloride were added. After the addition was completed, the cooling bath was removed and the stirring was continued for 2 hours. The reaction mixture was poured into ice water. The organic layer was separated, washed with water, dried over anhydrous sodium sulphate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was distilled to yield γ-chloro-*p*-fluorobutyrophenone boiling at about 136—142°C. at 6 mm. pressure.

PREPARATION C

A Grignard reagent of *m*-fluorophenylmagnesium bromide was prepared by reacting 6.7 parts of magnesium with 94.5 parts of *m*-bromofluorobenzene in 80 parts of ether. Then 21 parts of γ-cholorobutyronitrile in 64 parts of ether were added and the mixture was refluxed under nitrogen for two hours with stirring. The mixture was then allowed to stand at room temperature for 15 hours and the excess Grignard reagent was decomposed by the addition of 56 parts of concentrated hydrochloric acid and 50 parts of water. The organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was distilled to yield γ-chloro-*m*-fluorobutyrophenone boiling at about 105—125°C. at 2 mm. pressure.

PREPARATION D

A solution of 95 parts of methyl bromide in 356 parts of ether was added portionwise to a refluxing suspension of 24 parts of magnesium in 214 parts of ether. The mixture was refluxed for 2 hours, and 92 parts of *p*-fluoroacetophenone were added in the course of 90 minutes. The refluxing was continued for 3 hours, and the mixture was stirred for 24 hours at room temperature. The Grignard complex was destroyed by the addition of ammonium chloride and 10% hydrochloric acid. The mixture was extracted with ether, and the ether extracts were washed with 10% sulphuric acid and then with water. The extracts were dried over anhydrous calcium chloride, filtered, and concentrated *in vacuo* to remove the solvent. About 0.5 part of hydroquinone was added to the residue which was then heated to a temperature of 100—110°C. under a pressure of 50 mm. The distillate was extracted with ether and the ether extracts were dried over anhydrous calcium chloride and filtered. A small quantity of hydroquinone was added to the ether solution. The solution was fractionated by distillation to yield *p*-fluoro-α-methylstyrene boiling at about 93—94°C. at 80 mm. pressure.

PREPARATION E

A mixture of 856 parts of ammonium chloride and 3000 parts of 36% formaldehyde was stirred and heated to about 60°C. With cooling to maintain this temperature, 944 parts of α-methylstyrene were added slowly. After the addition was completed, the mixture was stirred at room temperature until the temperature of the reaction mixture dropped to about 40°C. After 2000 parts of methanol were added, the stirring was continued for for 20 hours. The methanol was removed *in vacuo* and the residue was diluted with 3000 parts of concentrated hydrochloric acid. For 4 hours, the mixture was heated with stirring at a temperature of 100°C. The mixture was cooled, diluted with 2000 parts of water, and made alkaline with 15 normal sodium hydroxide solution. The reaction mixture was extracted with benzene, and the benzene extracts were dried over anhydrous potassium

carbonate and filtered. The benzene was removed from the filtrate. The remaining residue was distilled *in vacuo* to yield 4-phenyl-1,2,3,6-tetrahydropyridine which boiled at 97—112°C. at 1 mm. pressure.

This base was dissolved in benzene. Dry, gaseous hydrogen chloride was passed through the solution, whereupon there precipitated the hydrochloride which was collected on a filter. The 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride melted at about 199—202°C.

PREPARATION F

While the temperature was being maintained at about 10—20°C., anhydrous hydrogen bromide gas was passed for 7 hours through a solution of 160 parts of 4-phenyl-1,2,3,6-tetrahydropyridine in 500 parts of acetic acid. The mixture was stirred during the addition of the hydrogen bromide gas. The mixture was then allowed to stand at room temperature of 16 hours. The acetic acid and the excess hydrogen bromide were removed *in vacuo* at a bath temperature of less than 40°C. The residue was treated with ether. This solution was cooled, and the product was collected on a filter. The 4-phenyl-4-bromopiperidine hydrobromide was recrystallised from a mixture of acetone and 2-propanol. The compound melted at about 209.5—210.5°C.

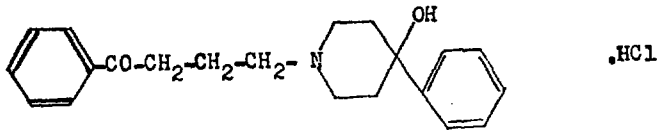
PREPARATION G

A solution of 160 parts of 4-phenyl-4-bromopiperidine hydrobromide in 3000 parts of water was treated with 100 parts of 20% sodium hydroxide solution. The resulting precipitate was recovered by filtration and washed with water. The precipitate was then dissolved in toluene, and the solution was dried over anhydrous potassium carbonate and filtered. The filtrate was cooled to 0°C. The crystalline product thus obtained was collected on a filter to yield 4-phenylpiperidin-4-ol melting at about 159—160°C.

EXAMPLE 1

In a closed reaction vessel a mixture of 8.7 parts of γ-chlorobutyrophenone, 14.2 parts of 4-phenylpiperidin-4-ol, and 0.1 part of potassium iodide in 150 parts of toluene was heated at a temperature of 100—110°C. The contents of the flask were cooled and then filtered. The solid residue was treated with a mixture of water and ether. The ether layer was separated and then added to the filtrate from the original reaction mixture. The combined toluene and ether solution was dried over anhydrous potassium carbonate, filtered, and concentrated to about ¼ of its volume. The solution was cooled. The resulting precipitate was collected on a filter and recrystallised from diisopropyl ether to yield 1 - (γ - benzoylpropyl) - 4 - phenylpiperidin-4 - ol melting at 129—130°C.

The hydrochloride was prepared by treating the above described toluene-ether solution, after drying, with anhydrous hydrogen chloride gas. The precipitated salt was collected on a filter and recrystallised from 2-propanol. In this manner there was obtained 1-(γ-benzoyl-4-phenylpiperidin-4-ol hydrochloride melting at about 182—184°C. The structural formula is



EXAMPLE 2

Substitution of an equimolecular amount of *p*-fluoro-α-methylstyrene for the α-methylstyrene in Preparation E yielded 4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine boiling at about 139—141°C. at 4 mm. pressure.

Substitution of an equimolecular amount of 4 - (*p* - fluorophenyl) - 1,2,3,6 - tetrahydropyridine for the 4-phenyl-1,2,3,6-tetrahydropyridine in Preparation F yielded 4-(*p*-fluorophenyl)-4-bromopiperidine hydrobromide melting at about 143—144°C.

Substitution of an equimolecular amount of 4 - (*p* - fluorophenyl) - 4 - bromopiperidine hydrobromide for the 4-phenyl-4-bromopiperidine hydrobromide in Preparation G yielded 4 - (*p* - fluorophenyl)piperidin - 4-ol melting at about 116.4—117.6°C.

Substitution of 15.6 parts of 4-(*p*-fluorophenyl)-piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 1 yielded 1-(γ-benzoylpropyl) - 4 - (p - fluorophenyl)piperidin - 4 - ol hydrochloride melting at about 188—190.5°C.

EXAMPLE 3

A solution of 192 parts of p-chlorobromobenzene in 124 parts of ether was added dropwise to a suspension of 24 parts of magnesium in 214 parts of ether. The mixture was refluxed for 2 hours. The mixture was cooled to about 5°C., and 39 parts of acetone were added in the course of 2 hours. The mixture was stirred for 24 hours at room temperature, and then decomposed with ammonium chloride solution and 10% hydrochloric acid. The solution was extracted with ether. The ether layer was washed with 10% sulphuric acid and then with water. This solution was dried over anhydrous calcium chloride, filtered, and concentrated *in vacuo*. The residual carbinol was heated *in vacuo* in the presence of 0.5 parts of hydroquinone for 2 hours on an oil bath at a temperature of 100—110°C. The styrene and water were distilled off. The product was

extracted with ether. The ether extract was dried over anhydrous calcium chloride, filtered, and fractionated over hydroquinone, to yield *p*-chloro-α-methylstyrene boiling at about 83—85°C. at 15 mm. pressure.

Substitution of an equimolecular amount of *p*-chloro-α-methylstyrene for the α-methylstyrene in Preparation E yielded 4-(*p*-chlorophenyl-1,2,3,6-tetrahydropyridine boiling at about 157—160°C. at 8 mm. pressure.

Substitution of an equimolecular amount of 4 - (*p* - chlorophenyl) - 1,2,3,6 - tetrahydropyridine for the 4-phenyl-1,2,3,6-tetrahydropyridine in preparation F yielded 4 - (*p*-chlorophenyl) - 4 - bromopiperidine hydrobromide melting at 213—215°C.

Substitution of an equimolecular amount of 4-(*p*-chlorophenyl)-4-bromopiperidine hydrobromide for the 4-phenyl-4-bromopiperidine hydrobromide in Preparation G yielded 4-(*p*-chlorophenyl)piperidin-4-ol melting at about 134.4—136°C.

Substitution of 17 parts of 4-(*p*-chlorophenyl)piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 1 yielded 1-(γ-benzoylpropyl)-4-(*p*-chlorophenyl)piperidin-4-ol melting at 126.6—127.4°C. and 1-(γ-benzoylpropyl) - 4 - (*p* - chlorophenyl) - piperidin - 4-ol hydrochloride melting at about 125—126.8°C.

EXAMPLE 4

Substitution of an equimolecular amount of *p*-methylacetophenone for the p-fluoroacetophenone in Preparation D yielded *p*-methyl-α-methylstyrene boiling at about 72—74°C. at 13 mm. pressure.

Substitution of an equimolecular amount of *p*-methyl-α-methylstyrene for the α-methylstyrene in Preparation E yielded 4-(*p*-tolyl)-1,2,3,6-tetrahydropyridine boiling at about 162—170°C. at 10 mm. pressure.

Substitution of an equimolecular amount of 4-(*p*-tolyl)-1,2,3,6-tetrahydropyridine for the 4-phenyl-1,2,3,6-tetrahydropyridine in Preparation F yielded 4-(*p*-tolyl)-4-bromopiperidine hydrobromide melting at about 190—192°C.

Substitution of an equimolecular amount of 4-(*p*-tolyl)-4-bromopiperidine hydrobromide for the 4-phenyl-4-bromopiperidine hydrobromide in Preparation G yielded 4-(*p*-tolyl-piperidin-4-ol melting at about 136—137°C.

Substitution of 15.3 parts of 4-(*p*-tolyl)-piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 1 yielded 1-(γ-benzoylpropyl)-4-(p-tolyl)piperidin-4-ol melting at 101—102.5° C. and 1-(γ-benzoylpropyl)-4-(*p*-tolyl)piperidin-4-ol hydrochloride melting at about 179.6—181.5°C.

EXAMPLE 5

Substitution of 9.5 parts of δ-chloropentanophenone for the γ-chlorobutyrophenone in Example 1 yielded white, flaky crystals of 1 - (δ - benzoylbutyl) - 4 - phenylpiperidine-4 - ol hydrochloride melting at about 73—75.2°C.

EXAMPLE 6

Substitution of 9.9 parts of γ-chloro-*m*-fluorobutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1-[γ-(*m*-fluorobenzoyl)propyl]-4-phenylpiperidin-4-ol melting at about 119.7—121°C.

EXAMPLE 7

Substitution of 9.9 parts of γ-chloro-*p*-fluorobutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1-[γ-(*p*-fluorobenzoyl)propyl]-4-phenylpiperidin-4-ol melting at 135.6—136.2°C. and 1-[γ-(*p*-fluorobenzoyl)propyl] - 4 - phenylpiperidine - 4 - ol hydrochloride melting at about 204.5—205.5°C.

EXAMPLE 8

Substitution of 15.6 parts of 4-(*p*-fluorophenyl)-piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 7 yielded 1-[γ(*p*-fluorobenzoyl)propyl] - 4 - (*p* - fluorophenyl) - piperidin-4-ol hydrochloride melting at about 201—203.5°C.

EXAMPLE 9

Substitution of 17 parts of 4-(*p*-chlorophenyl)-piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 7 yielded 1 -[γ-(*p*-fluorobenzoyl)propyl] - 4 - (*p* - chlorophenyl) - piperidin-4-ol melting at 148—149.4°C. and 1 - [γ - (*p* - fluorobenzoyl)propyl] - 4 - (*p*-chlorophenyl)piperidin - 4 - ol hydrochloride melting at about 226—227.5°C.

EXAMPLE 10

Substitution of 15.3 parts of 4-(*p*-tolyl)-piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 7 yielded 1-[γ-(*p*-fluorobenzoyl)-propyl] - 4 - (*p* - toylyl)piperidin - 4 - ol hydrochloride melting at about 216—218°C.

EXAMPLE 11

Substitution of an equimolecular amount of *m*-bromochlorobenzene for the *m*-bromofluorobenzene in Preparation C yielded γ,*m*-dichlorobutyrophenone boiling at about 128—135°C. at 2 mm. pressure.

Substitution of 10.3 parts of γ,*m*-dichlorobutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1-[γ-(*m*-chlorobenzoyl) propyl]-4-phenylpiperidin-4-ol hydrochloride melting at about 228.5—229.8°C.

EXAMPLE 12

Substitution of an equimolecular amount of chlorobenzene for the fluorobenzene in Preparation B yielded γ,*p*-dichlorobutyrophenone boiling at about 185—190°C. at 12 mm. pressure.

Substitution of 10.3 parts of γ,*p*-dichlorobutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1-[γ-(*p*-chlorobenzoyl) propyl]-4-phenylpiperidin-4-ol melting at about 130—131.4°C. The hydrochloride melted at about 229.5—230.5°C.

EXAMPLE 13

Substitution of 15.6 parts of 4-(*p*-fluorophenyl)-piperidin-4-ol for the 4-phenylpiper-

idin-4-ol in Example 12 yielded 1-[γ-(*p*-chlorobenzoyl)propyl] - 4 - (*p* - fluorophenyl)-piperidin-4-ol melting at 135—136°C. and 1 - [γ - (*p* - chlorobenzoyl)propyl] - 4 - (*p*-fluorophenyl)piperidin-4-ol hydrochloride melting at about 202.4—204.4°C.

EXAMPLE 14

Substitution of 17 parts of 4-(*p*-chlorophenyl)-piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 12 yielded 1-[γ-(*p*-chlorobenzoyl)propyl] - 4 - (*p* - chlorophenyl)-piperidin-4-ol melting at 154—155°C. and 1 - [γ - (*p* - chlorobenzoyl)propyl] - 4 - (*p*-chlorophenyl)piperidin - 4 - ol hydrochloride melting at about 190.6—192.4°C.

EXAMPLE 15

Substitution of an equimolecular amount of bromobenzene for the fluorobenzene in Preparation D yielded γ-chloro-*p*-bromobutyrophenone boiling at 150—157°C. at 6 mm. pressure.

Substitution of 12.4 parts of γ-chloro-*p*-bromobutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1-[γ-(*p*-bromobenzoyl)propyl] - 4 - phenylpiperidin-4-ol hydrochloride melting at about 234—235.5°C.

EXAMPLE 16

Substitution for an equimolecular amount of *o*-bromotoluene for the *m*-bromofluorobenzene in Preparation C yielded γ-chloro-*o*-methylbutyrophenone boiling at about 140°C. at 7 mm. pressure.

Substitution of 9.4 parts of γ-chloro-*o*-methylbutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1-[γ-(*o*-toluyl) propyl]-4-phenylpiperidin-4-ol hydrochloride melting at about 190—192°C.

EXAMPLE 17

Substitution of an equimolecular amount of *m*-bromotoluene for the *m*-bromofluorobenzene in Preparation C yielded γ-chloro-*m*-methylbutyrophenone boiling at about 128—130°C. at 4 mm. pressure.

Substitution of 9.3 parts of γ-chloro-*m*-methylbutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1-[γ-(*m*-toluyl) propyl]-4-phenylpiperidin-4-ol hydrochloride melting at about 180—181.5°C.

EXAMPLE 18

Substitution of an equimolecular amount of toluene for the fluorobenzene in Preparation B yielded γ-chloro-*p*-methylbutyrophenone melting at 31.5°C.

Substitution of 9.4 parts of γ-chloro-*p*-methylbutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1-[γ-(*p*-toluyl) propyl]-4-phenylpiperidin-4-ol melting at about 122—123.2°C.

EXAMPLE 19

Substitution of 15.6 parts of 4-(*p*-fluorophenyl)-piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 18 yielded 1-[γ-(*p*-toluyl)propyl] - 4 - (*p* - fluorophenyl)piperidin-4-ol melting at about 129—130°C.

EXAMPLE 20

Substitution of 17 parts of 4-(*p*-chlorophenyl)-piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 18 yielded 1-[γ(*p*-toluyl)propyl] - 4 - (*p* - chlorophenyl)piperidin-4-ol melting at about 141—142°C.

EXAMPLE 21

Substitution of 15.3 parts of 4-(*p*-tolyl) piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 18 yielded 1-[γ-(*p*-toluyl(propyl]-4-(*p*-tolyl)piperidin-4-ol melting at about 116—117.4°C.

EXAMPLE 22

Substitution of an equimolecular amount of *m*-xylene for the fluorobenzene in Preparation B yielded γ-chloro-*o,p*-dimethylbutyrophenone boiling at about 140—146°C. at 5 mm. pressure.

Substitution of 10 parts of γ-chloro-*o,p*-dimethyl-butyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1-[γ-(*o,p* - xyloyl)propyl] - 4 - phenylpiperidin-4-ol hydrochloride melting at about 183—185.4°C.

EXAMPLE 23

Substitution of an equimolecular amount of *p*-xylene for the fluorobenzene in Preparation B yielded γ-chloro-2,5-dimethylbutyrophenone boiling at 142—148°C. at 7 mm. pressure.

Substitution of 10 parts of γ-chloro-2,5-dimethylbutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1-[γ-(2,5-xyloyl)propyl]-4-phenylpiperidin-4-ol hydrochloride melting at 176.5—177.5°C.

EXAMPLE 24

Substitution of an equimolecular amount of *o,p*-dimethylacetophenone for the *p*-fluoroacetophenone in Example D yielded *o,p*-dimethyl-α-methylstyrene boiling at about 79—83°C. at 17 mm. pressure.

Substitution of an equimolecular amount of *o,p*-dimethyl-α-methylstyrene for the α-methylstyrene in Preparation E yielded 4(*o,p*-xylyl)-1,2,3,6-tetrahydropyridine. The hydrochloride melted at about 216.8—220°C.

Substitution of an equimolecular amount of 4 - (*o,p* - xylyl) - 1,2,3,6 - tetrahydropyridine for the 4-phenyl-1,2,3,6-tetrahydropyridine in Preparation F yielded white, crystalline 4-(*o,p*-xylyl)-4-bromopiperidine hydrobromide.

Substitution of an equimolecular amount of 4-(*o,p*-xylyl)-4-bromopiperidine hydrobromide for the 4-phenyl-4-bromopiperidine hydrobromide in Preparation G yielded the white, prismatic crystals of 4-(*o,p*-xylyl)piperidin-4-ol.

Substitution of 16.4 parts of 4-(*o,p*-xylyl) piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 23 yielded the colourless needles of 1 - [γ - (2,5 - xyloyl)propyl] - 4 - (*o,p*-xylyl)piperidin-4-ol.

EXAMPLE 25

Substitution of an equimolecular amount of anisole for the fluorobenzene in Preparation B yielded γ-chloro-*p*-methoxybutyrophenone boiling at about 175°C. at 6 mm. pressure.

Substitution of 10.1 parts of γ-chloro-*p*-methoxybutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1-[γ-(*p*-anisoyl) propyl] - 4 - phenylpiperidin - 4 - ol hydrochloride melting at about 221—223°C.

EXAMPLE 26

Substitution of 10.1 parts of γ-chloro-*p*-methoxybutyrophenone for the γ-chlorobutyrophenone in Example 1 and substitution of 15.6 parts of 4-(*p*-fluorophenyl)piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 1 yielded 1 - [γ - (*p* - anisoyl)propyl] - 4-(*p* - fluorophenyl) - piperidin - 4 - ol melting at about 130—131.2°C.

EXAMPLE 27

Substitution of 17 parts of 4-(*p*-chlorophenyl)-piperidin-4-ol for the 4-(*p*-fluorophenyl)piperidin-4-ol in Example 26 yielded 1 - [γ - (*p* - anisoyl)propyl] - 4 - (*p* - chlorophenyl)piperidin-4-ol melting at about 167—168.6°C.

EXAMPLE 28

Substitution of 15.3 parts of 4-(*p*-tolyl) piperidin-4-ol for the 4-(*p*-fluorophenyl) piperidin-4-ol in Example 26 yielded 1-[γ-(*p*-anisoyl)propyl]-4-(*p*-tolyl)piperidin-4-ol melting at about 128.6—129.8°C.

EXAMPLE 29

A mixture of 141 parts of γ-chlorobutyryl chloride and 138.2 parts of 1,3-dimethoxybenzene was dissolved in 1000 parts of nitrobenzene. The solution was cooled to −10°C., and this temperature was maintained while 267 parts of aluminium chloride were added under stirring in the course of about 90 minutes. The reaction mixture was then maintained at 0°C. for 72 hours and then at room temperature for 36 hours. The mixture was poured into a mixture of 300 parts of concentrated hydrochloric acid and 250 parts of ice. After the decomposition was completed, 1100 parts of ether were added. The organic layer was separated, washed with water, washed with 5% sodium hydroxide solution, and washed again with water. The solution was dried over anhydrous sodium sulphate and filtered. The solvents were evaporated *in vacuo*. The residue was treated with diisopropyl ether. Upon cooling, a crystalline product was obtained which was γ - chloro - *o,p* - dimethoxybutyrophenone melting at about 61—62°C.

Substitution of 11.5 parts of γ-chloro-*o,p*-dimethoxybutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1-[γ-(*o,p* - dimethoxybenzoyl)propyl] - 4 - phenylpiperidin - 4 - ol melting at about 109.5—110.5°C.

EXAMPLE 30

Substitution of an equimolecular amount of phenetole for the fluorobenzene in Preparation B yielded γ-chloro-*p*-ethoxybutyrophenone melting at about 50.4—51.8°C.

Substitution of 11 parts of γ-chloro-*p*-ethoxybutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1-[γ(*p*-ethoxybenzoyl)propyl]-4-phenylpiperidin-4-ol melting at about 116—118°C.

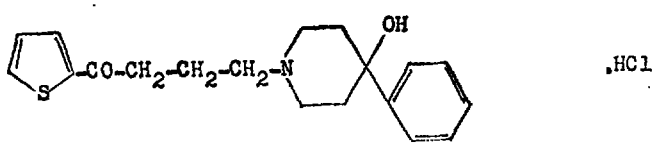
EXAMPLE 31

A mixture of 84 parts of thiophene, 141 parts of γ-chlorobutyryl chloride, and 870 parts of benzene was cooled to about 0°C. While this temperature was maintaiend, 260 parts of stannic chloride were added over a 2 hour period. After the addition was completed, the cooling bath was removed and the stirring was continued for about an hour. The reaction mixture was then poured into a mixture of 60 parts of concentrated hydrochloric acid and 450 parts of ice water. The organic layer was separated, washed with water, dried over anhydrous calcium chloride, and filtered. The filtrate was concentrated under reduced pressure. The residue was distilled to yield 2-(γ-chlorobutyryl)thiophene which boiled at 144—146°C. at 11 mm. of pressure.

A mixture of 9 parts of 2-(γ-chlorobutyryl) thiophene, 14.2 parts of 4-phenylpiperidin-4-ol, and 0.1 parts of potassium iodide in 150 parts of toluene was heated at a temperature of 100—110°C. The mixture was cooled to room temperature and then filtered. The solid residue was triturated with a mixture of water and ether. The ether layer was separated and added to the filtrate from the original reaction mixture. The combined toluene and ether solution was dried over anhydrous potassium carbonate, filtered, and concentrated to about one-fourth of its volume. The solution was cooled, and the resulting product was collected on a filter and recrystallised from diisopropyl ether to yield 1-[γ-(2-thenoyl)propyl]-4-phenylpiperidin-4-ol melting at 112.4—114.2°C.

The hydrochloride can be prepared by passing dry hydrogen chloride gas through the above described toluene-ether solution. The precipitated hydrochloride salt is collected on a filter and recrystallised from 2-propanol. In this manner there was obtained the white, crystalline 1 - [γ - (2 - thenoyl)propyl] - 4-phenylpiperidin-4-ol hydrochloride.

The structural formula was



EXAMPLE 32

Substitution of β-methyl-γ-chlorobutyryl chloride for the γ-chlorobutyryl chloride in Example 31 yielded the colourless needles of 2-(β-methyl-γ-chlorobutyryl)thiophene.

Substitution of 9.7 parts of 2-(β-methyl-γ-chlorobutyryl)-thiophene for the 2-(γ-chlorobutyryl)thiophene in Example 31 yielded 1 - [β - methyl - γ - (2 - thenoyl)propyl] - 4-phenylpiperidin - 4 - ol in white, prismatic crystals.

EXAMPLE 33

Substitution of an equimolecular amount of *p*-fluoro-α-methylstyrene for the α-methylstyrene in Preparation E yielded 4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine boiling at about 139—141°C. at 4 mm. pressure.

Substitution of an equimolecular amount of 4 - (*p* - fluorophenyl) - 1,2,3,6 - tetrahydropyridine for the 4-phenyl-1,2,3,6-tetrahydropyridine in Preparation F yielded 4-(*p*-fluorophenyl)4-bromopiperidine hydrobromide melting at about 143—144°C.

Substitution of an equimolecular amount of 4-(*p*-fluorophenyl)-4-bromopiperidine hydrobromide for the 4-phenyl-4-bromopiperidine hydrobromide in Preparation G yielded 4-(*p*-fluorophenyl)piperidin-4-ol melting at about 116.4—117.6°C.

Substitution of 15.6 parts of 4-(*p*-fluorophenyl)piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 31 yielded 1[γ-(2-thenoyl)propyl] - 4 - (*p* - fluorophenyl) - piperidin-4-ol melting at about 123.8—125.8°C.

EXAMPLE 34

A solution of 192 parts of *p*-chlorobromobenzene in 124 parts of ether was added dropwise to a suspension of 24 parts of magnesium in 214 parts of ether. The mixture was refluxed for 2 hours. The mixture was cooled to about 5°C. and 39 parts of acetone were added in the course of 2 hours. The mixture was stirred for 24 hours at room temperature, and then decomposed with ammonium chloride solution and 10% hydrochloric acid. The solution was extracted with ether. The ether layer was washed with 10% sulphuric acid and then with water. This solution was dried over anhydrous calcium chloride, filtered, and concentrated *in vacuo*. The residual carbinol was heated *in vacuo* in the presence of 0.5 part of hydroquinone for 2 hours on an oil bath at a temperature of 100—110°C. The styrene and water were distilled off. The product was extracted with ether. The ether extract was dried over anhydrous calcium chloride, filtered, and fractionated over hydroquinone to yield *p*-chloro-α-methylstyrene boiling at about 83—85°C. at 15 mm. pressure.

Substitution of an equimolecular amount of *p*-chloro-α-methylstyrene for the α-methylstyrene in Preparation E yielded 4-(*p*-chlorophenyl)-1,2,3,6-tetrahydropyridine boiling at about 157—160°C. at 8 mm. pressure.

Substitution of an equimolecular amount of 4 - (*p* - chlorophenyl) - 1,2,3,6 - tetrahydropyridine for the 4-phenyl-1,2,3,6-tetrahydropyridine in Preparation F yielded 4-(*p*-chlorophenyl)-4-bromopiperidine hydrobromide melting at about 213—215°C.

Substitution of an equimolecular amount of 4-(*p*-chlorophenyl)-4-bromopiperidine hydrobromide for the 4-phenyl-4-bromopiperidine hydrobromide in Preparation G yielded 4-(*p*-chlorophenyl)piperidin-4-ol melting at about 134.4—136°C.

Substitution of 17 parts of 4-(*p*-chlorophenyl)-piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 31 yielded 1-[γ-(2-thenoyl)propyl] - 4 - (*p* - chlorophenyl)-piperidin-4-ol melting at 122—123°C. and 1 - [γ - (2 - thenoyl) - propyl] - 4 - (*p*-chlorophenyl)piperidin - 4 - ol hydrochloride melting at about 212.5—214°C.

EXAMPLE 35

Substitution of an equimolecular amount of α-chloroacetyl chloride for the γ-chlorobutyryl chloride in Example 31 yielded the white, prismatic crystals of 2-(α-chloroacetyl) thiophene.

Substitution of an equimolecular amount of *m*-bromo-acetophenone for the *p*-fluoroacetophenone in Preparation D yielded *m*-bromo-α-methylstyrene boiling at about 99—102°C. at 11 mm. pressure.

Substitution of an equimolecular amount of *m*-bromo-α-methylstyrene for the α-methylstyrene in Preparation E yielded 4(*m*-bromophenyl)-1,2,3,6-tetrahydropyridine. The hydrochloride melted at about 261—267°C.

Substitution of an equimolecular amount of 4 - (*m* - bromophenyl) - 1,2,3,6 - tetrahydropyridine for the 4-phenyl-1,2,3,6-tetrahydropyridine in Preparation F yielded 4-(*m*-bromophenyl)-4-bromopiperidine hydrobromide.

Substitution of an equimolecular amount of 4-(*m*-bromophenyl)-4-bromopiperidine hydrobromide for the 4-phenyl-4-bromopiperidine hydrobromide in Preparation G yielded the pale yellow crystals of 4-(*m*-bromophenyl)-piperidin-4-ol.

Substitution of 8.5 parts of 2-(α-chloroacetyl)-thiophene for the 2-(γ-chlorobutyryl)-thiophene in Example 32 and substitution of 20.5 parts of 4-(*m*-bromophenyl)-piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 32 yielded the colourless needles of 1 - [α - (2 - thenoyl) - methyl] - 4 - (*m*-bromophenyl)piperidin-4-ol.

EXAMPLE 36

Substitution of an equimolecular amount of *p*-methylacetophenone for the *p*-fluoroacetophenone in Preparation D yielded *p*-methyl-α-methylstyrene boiling at about 72—74°C. at 13 mm. pressure.

Substitution of an equimolecular amount of *p*-methyl-α-methylstyrene for the α-methylstyrene in Preparation E yielded 4-(*p*-tolyl)-

1,2,3,6-tetrahydropyridine boiling at about 162—170°C. at 10 mm. pressure.

Substitution of an equimolecular amount of 4 - (*p* - tolyl) - 1,2,3,6 - tetrahydropyridine for the 4-phenyl-1,2,3,6-tetrahydropyridine in Preparation F yielded 4-(*p*-tolyl)-4-bromopiperidine hydrobromide melting at about 190—192°C.

Substitution of an equimolecular amount of 4-(*p*-tolyl)-4-bromopiperidine hydrobromide for the 4-phenyl-4-bromopiperidine hydrobromide in Preparation G yielded 4-(*p*-tolyl)-piperidin-4-ol melting at about 136—137°C.

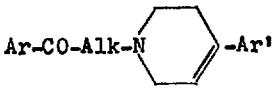
Substitution of 15.3 parts of 4-(*p*-tolyl)-piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 31 yielded 1-[γ-(2-thenoyl)propyl]-4-(*p*-tolyl)piperidin-4-ol hydrochloride melting at about 190—191°C.

EXAMPLE 37

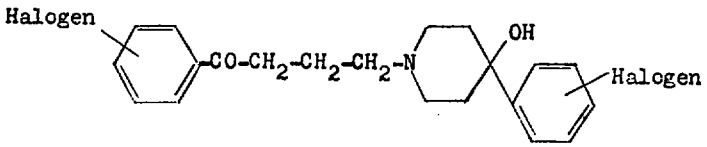
Substitution of an equimolecular amount of δ-chloro-valeryl chloride for the γ-chloro butyryl chloride in Example 31 yielded 2-(δ-chlorovaleryl)thiophene.

Substitution of 9.8 parts of 2-(δ-chloro-valeryl)-thiophene for the 2-(γ-chlorobutyryl) thiophene in Example 31 and substitution of 16.4 parts of 4-(*o*,*p*-xylyl)-piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 31 yielded the white, flaky crystals of 1-[δ-(2-thenoyl)-butyl]-4-(*o*,*p*-xylyl)piperidin-4-ol.

My co-pending Application No. 12780/58 (Serial No. 881,894) of even date herewith claims compounds of the general formula



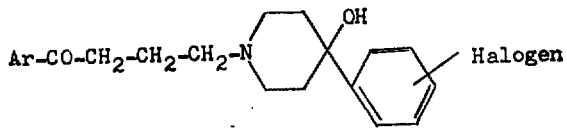
and their acid addition and quaternary ammonium non-toxic salts wherein Ar and Ar^1 are each a halophenyl, methoxyphenyl ethoxyphenyl, dimethoxyphenyl, thienyl, trifluormethylphenyl or monocyclic aromatic hydrocarbon radical containing less than 11 carbon atoms, and wherein Alk is an alkylene radical containing from three to six carbon atoms.



and their acid addition and quaternary ammonium non-toxic salts.

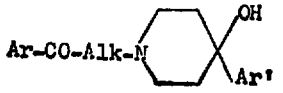
8. 1 - [γ - (*p* - Fluorobenzoyl)propyl] - 4-(*p* - chlorophenyl) - piperidin - 4 - ol.

9. Compounds of the general formula



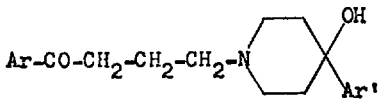
WHAT I CLAIM IS:—

1. Compounds of the general formula



and their acid addition and quaternary ammonium non-toxic salts, wherein Ar is a halophenyl, methoxyphenyl, ethoxyphenyl, dimethoxyphenyl, thienyl, or monocyclic aromatic hydrocarbon radical containing less than nine carbon atoms, Ar^1 is a halophenyl or monocyclic aromatic hydrocarbon radical containing less than nine carbon atoms, and Alk is a lower alkylene radical containing three to six carbon atoms.

2. Compounds of the general formula

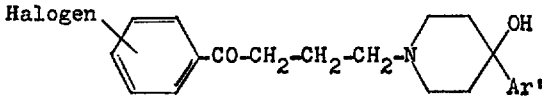


wherein Ar and Ar^1 are monocyclic aromatic hydrocarbon radicals containing less than nine carbon atoms.

3. 1-(γ-Benzoylpropyl)-4-phenylpiperidin-4-ol.

4. 1-(γ-Benzoylpropyl)-4-(*p*-tolyl)piperidin-4-ol.

5. Compounds of the general formula



and their acid addition and quaternary ammonium non-toxic salts, wherein Ar^1 is a monocyclic aromatic hydrocarbon radical containing less than nine carbon atoms.

6. 1 - [γ - (*p* - Fluorobenzoyl)propyl] - 4-(*p* - tolyl) - piperidin - 4 - ol.

7. Compounds of the general formula

and their acid addition and quaternary ammonium non-toxic salts wherein Ar is a monocyclic aromatic hydrocarbon radical containing less than nine carbon atoms.

10. 1 - (γ - Benzoylpropyl) - 4 - (*p* - fluorophenyl)piperidin - 4 - ol.

11. 1 - (γ - Benzoylpropyl) - 4 - (*p* - chlorophenyl)piperidin - 4 - ol.

12. Compounds of the general formula

1,2,3,6-tetrahydropyridine boiling at about 162—170°C. at 10 mm. pressure.

Substitution of an equimolecular amount of 4 - (*p* - tolyl) - 1,2,3,6 - tetrahydropyridine for the 4-phenyl-1,2,3,6-tetrahydropyridine in Preparation F yielded 4-(*p*-tolyl)-4-bromopiperidine hydrobromide melting at about 190—192°C.

Substitution of an equimolecular amount of 4-(*p*-tolyl)-4-bromopiperidine hydrobromide for the 4-phenyl-4-bromopiperidine hydrobromide in Preparation G yielded 4-(*p*-tolyl)-piperidin-4-ol melting at about 136—137°C.

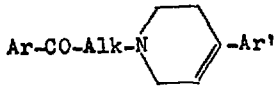
Substitution of 15.3 parts of 4-(*p*-tolyl)-piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 31 yielded 1-[γ-(2-thenoyl)propyl]-4-(*p*-tolyl)piperidin-4-ol hydrochloride melting at about 190—191°C.

EXAMPLE 37

Substitution of an equimolecular amount of δ-chloro-valeryl chloride for the γ-chloro-butyryl chloride in Example 31 yielded 2-(δ-chlorovaleryl)thiophene.

Substitution of 9.8 parts of 2-(δ-chloro-valeryl)-thiophene for the 2-(γ-chlorobutyryl) thiophene in Example 31 and substitution of 16.4 parts of 4-(*o*,*p*-xylyl)-piperidin-4-ol for the 4-phenylpiperidin-4-ol in Example 31 yielded the white, flaky crystals of 1-[δ-(2-thenoyl)-butyl]-4-(*o*,*p*-xylyl)piperidin-4-ol.

My co-pending Application No. 12780/58 (Serial No. 881,894) of even date herewith claims compounds of the general formula

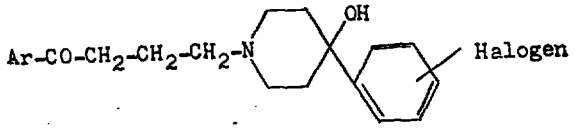


and their acid addition and quaternary ammonium non-toxic salts wherein Ar and Ar^1 are each a halophenyl, methoxyphenyl ethoxyphenyl, dimethoxyphenyl, thienyl, trifluormethylphenyl or monocyclic aromatic hydrocarbon radical containing less than 11 carbon atoms, and wherein Alk is an alkylene radical containing from three to six carbon atoms.

and their acid addition and quaternary ammonium non-toxic salts.

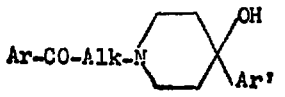
8. 1 - [γ - (*p* - Fluorobenzoyl)propyl] - 4-(*p* - chlorophenyl) - piperidin - 4 - ol.

9. Compounds of the general formula



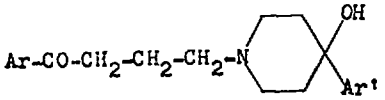
WHAT I CLAIM IS:—

1. Compounds of the general formula



and their acid addition and quaternary ammonium non-toxic salts, wherein Ar is a halophenyl, methoxyphenyl, ethoxyphenyl, dimethoxyphenyl, thienyl, or monocyclic aromatic hydrocarbon radical containing less than nine carbon atoms, Ar^1 is a halophenyl or monocyclic aromatic hydrocarbon radical containing less than nine carbon atoms, and Alk is a lower alkylene radical containing three to six carbon atoms.

2. Compounds of the general formula

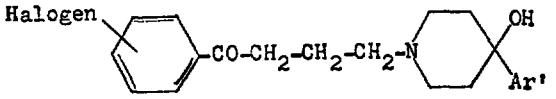


wherein Ar and Ar^1 are monocyclic aromatic hydrocarbon radicals containing less than nine carbon atoms.

3. 1-(γ-Benzoylpropyl)-4-phenylpiperidin-4-ol.

4. 1-(γ-Benzoylpropyl)-4-(*p*-tolyl)piperidin-4-ol.

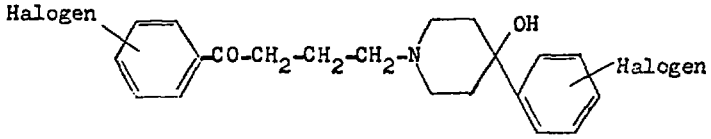
5. Compounds of the general formula



and their acid addition and quaternary ammonium non-toxic salts, wherein Ar^1 is a monocyclic aromatic hydrocarbon radical containing less than nine carbon atoms.

6. 1 - [γ - (*p* - Fluorobenzoyl)propyl] - 4-(*p* - tolyl) - piperidin - 4 - ol.

7. Compounds of the general formula

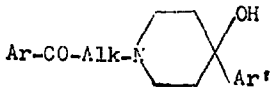


and their acid addition and quaternary ammonium non-toxic salts wherein Ar is a monocyclic aromatic hydrocarbon radical containing less than nine carbon atoms.

10. 1 - (γ - Benzoylpropyl) - 4 - (*p* - fluorophenyl)piperidin - 4 - ol.

11. 1 - (γ - Benzoylpropyl) - 4 - (*p* - chlorophenyl)piperidin - 4 - ol.

12. Compounds of the general formula

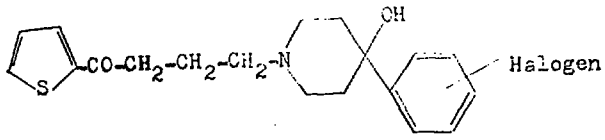


and their acid addition and quaternary ammonium non-toxic salts wherein Ar is a 2-thienyl radical and Ar^1 is a monocyclic aromatic hydrocarbon radical containing less than nine carbon atoms.

13. 1 - [γ - (2 - Thenoyl)propyl] - 4-phenylpiperidin - 4 - ol.

14. 1 - [γ - (2 - Thenoyl)propyl] - 4 - (*p*-tolyl)piperidin - 4 - ol.

15. Compounds of the general formula



16. 1 - [γ - (2 - Thenoyl)propyl)] - 4-(*p* - fluorophenyl) - piperidin - 4 - ol.

17. 1 - [γ - (2 - Thenoyl)propyl] - 4 - (*p*-chlorophenyl) - piperidin - 4 - ol.

18. A process for the preparation of the compounds claimed in any one of the preceding claims which comprises condensing a compound of the general formula

Ar—CO—Alk—Halogen

with at least one equivalent of a compound of the general formula



wherein Ar and Ar^1 have the meanings given in claim 1.

19. A process for the preparation of the compounds claimed in claim 1 substantially as described with reference to any one of Examples 1, 2, 3, 7 to 10, 12 to 15, 17, 18, 22, 23, 25, 31 and 34.

20. A process for the preparation of the compounds claimed in claim 1 substantially as described with reference to any one of Examples 4 to 6, 11, 16, 19 to 21, 24, 26 to 30, 32, 33 and 35 to 37.

ELKINGTON AND FIFE,
Consulting Chemists and Chartered Patent Agents,
Bank Chambers, 329 High Holborn,
London, W.C.1,
Agents for the Applicant.

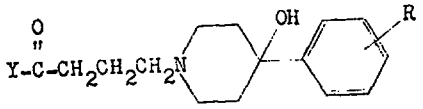
PROVISIONAL SPECIFICATION

Arylpiperidine Derivatives

I, PAUL ADRIAAN JAN JANSSEN, of Antwerpse Steenweg 16¹, Vosselaar near Turnhout, Belgium, a Citizen of Belgium, do hereby declare this invention to be described in the following statement:—

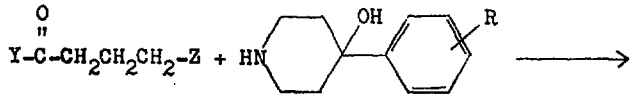
This invention relates to arylpiperidine derivatives.

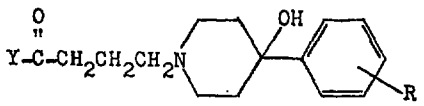
The novel compounds of this invention are 1-aroyl-propyl-4-hydroxy-4-arylpiperidines of the general formula



and their therapeutically useful salts wherein Y is a phenyl, alkylated phenyl, halophenyl, alkoxyphenyl or thienyl radical and R is hydrogen, a halogen atom or a lower alkyl radical.

The compounds of the invention can be made by the condensation of an aroylpropyl halide with a 4-aryl-4-hydroxypiperidine according to the reaction

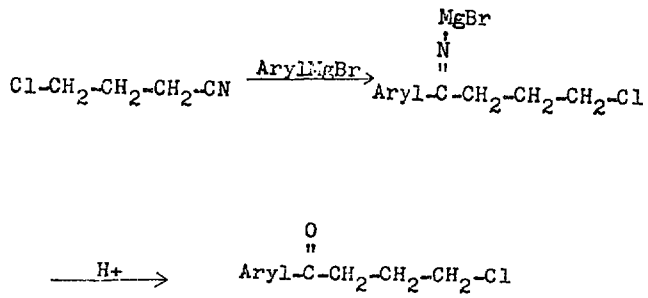




wherein Z is a halogen such as chlorine or bromine and Y and R have the meanings as aforesaid. The reaction is carried out advantageously at elevated temperature and pressure in an inert solvent such as benzene, toluene, xylene, ethanol, butanol, dioxane and methyl isobutyl ketone.

Suitable aroylpropyl halides for use as intermediates for the preparation of compounds of the invention are, for example γ-halobutyrophenones such as γ-chlorobutyrophenone, or γ-bromobutyrophenone; nuclearly alkylated derivatives thereof, such as γ-chlorobutyro 4-methylphenone; nuclearly alkoxylated derivatives thereof or nuclearly halogenated γ-chlorobutyrophenones. These intermediates can be prepared conveniently by the Friedel-Craft reaction employing, for example, γ-chlorobutyryl chloride and benzene or an appropriately substituted benzene such as toluene, *m*-xylene, anisole or phenetole or a halogenated benzene such as chlorobenzene, bromobenzene or fluorobenzene.

Alternatively, these intermediates can be prepared by treating γ-chlorobutyronitrile with the desired aryl magnesium bromide followed by acid hydrolysis according to the reaction



The compounds of the invention have useful pharmacological properties. They are potent central nervous system depressants and in small doses exert a marked tranquilising effect.

The invention is illustrated in greater detail in the following examples. Temperatures are expressed in degrees Centigrade (°C.). Quantities are expressed in parts by weight and parts by volume which bear the same relation one to the other as kilograms to litres.

PREPARATION A

Benzoylpropyl chloride

A solution of 71 parts by weight of γ-chlorobutyryl chloride in 71 parts by volume of anhydrous benzene was added with stirring to a suspension of 71 parts by weight of anhydrous aluminium chloride in 355 parts by volume of anhydrous benzene maintained at 10—15°. After the addition was complete, the cooling bath was removed and stirring continued for an additional 30 minutes The reaction mixture was poured into ice water, the benzene layer separated, dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to remove the benzene and the residue distilled to yield γ-chlorobutyrophenone which boiled at 134—137° at 5 millimetres pressure.

By using equivalent quantities of toluene instead of benzene and otherwise proceeding as described above 4 - methylbenzoylpropyl chloride was obtained which boiled at 100—110° at 4 millimetres pressure.

PREPARATION B

4-Fluorobenzoylpropyl chloride

To a suspension of 341 parts by weight of aluminium chloride in 1375 parts by volume of anhydrous carbon disulphide was added 96 parts by weight of fluorobenzene while stirring and maintaining at 10—15°. Then 141 parts by weight of γ-chlorobutyryl chloride was added slowly while maintaining the temperature at 10°. After the addition was complete the cooling bath was removed and the stirring was continued for about one hour until no more hydrogen chloride was evolved.

Using equivalent quantities of appropriately substituted benzenes and otherwise proceeding as above the following aroylpropyl chlorides were obtained:

$$ArC(=O)-CH_2CH_2CH_2-Cl$$

Ar	b p (m.p.)
4—ClC_6H_4	135—140°/8 mm
4—BrC_6H_4	150—157°/6.5 mm
4—$CH_3OC_6H_4$	175°/6 mm
4—$CH_3CONHC_6H_4$	(147—152°)
2,4-$(CH_3)_2C_6H_3$	130—143°/1 mm
2,5-$(CH_3)_2C_6H_3$	142—145°/6 mm
2,5-$(CH_3O)_2C_6H_3$	150—190°/4 mm (27—30°)

For the 2,4-dimethyl-, 2,5-dimethyl, and 4-acetylamino derivatives the reaction mixture was heated for about half an hour prior to the decomposition with ice water. For subsequent processing according to the syntheses disclosed herein it is not essential that the aroylpropyl chloride be analytically pure.

PREPARATION C

4-tertiary-Butyl-α-methylstyrene

A solution of 95 parts by weight of methyl bromide in 500 parts by volume of anhydrous ether was added dropwise to a refluxing suspension of 24 parts by weight of magnesium in 300 parts by volume of ether. The mixture was refluxed for an additional 2 hours and then 117.5 parts by weight of *p*-tertiary butylacetophenone was added in the course of 90 minutes. The refluxing was continued for an additional 3 hours and then the mixture was stirred overnight at room temperature. The Grignard complex was destroyed by the addition of ammonium chloride and 10% hydrochloric acid. The mixture was extracted with ether, the ether extracts washed with 10% sulphuric acid, then with water and dried over anhydrous calcium chloride. The solution was filtered and concentrated *in vacuo* to remove the solvents. About 0.5 part by weight of hydroquinone was added to the residue which was then heated to a temperature of about 100—110° under a pressure of about 50 millimetres. The distillate, consisting of a mixture of water and 4-tertiary-butyl-α-methylstyrene was extracted with ether and the ether extracts dried over anhydrous calcium chloride. The mixture was separated by filtration, a small quantity of hydroquinone added to the ether solution which was fractionated by distillation to yield 4-tertiary-butyl-α-methylstyrene which boiled at about 98° at 5 millimetres pressure.

Using appropriately substituted acetophenone and otherwise proceeding as described above the following correspondingly substituted α-methylstyrenes were obtained:

$$Y-C(CH_3)=CH_2$$

Y	b.p.	Pressure
3-fluorophenyl	82—84°	50 mm
4-ethylphenyl	60—61°	6
2,4-dimethylphenyl	79—83°	17
2,5-dimethylphenyl	102—105°	30

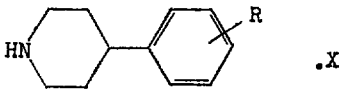
* C L M S *

PREPARATION D

4-Aryl-1,2,3,6-tetrahydropyridines

A mixture of 856 parts by weight of ammonium chloride and 3000 parts by weight of 36% formaldehyde solution was stirred and heated to 60°. At this temperature 944 parts by weight of α-methylstyrene was added slowly with cooling to maintain the temperature. After the addition was complete, the mixture was stirred at room temperature until the temperature of the reaction mixture dropped to 40°. After adding 2000 parts by volume of methanol, the stirring was continued for about 20 hours, then the methanol was removed *in vacuo* and the residue diluted with 2500 parts by volume of concentrated hydrochloric acid. The mixture was heated with stirring to a temperature of about 100° for 4 hours, cooled, diluted with 2000 parts by volume of water and made alkaline by the addition of 15 Normal sodium hydroxide solution. The reaction mixture was extracted with benzene, the benzene extracts dried over anhydrous potassium carbonate, filtered and the benzene removed from the filtrate. The residue remaining was distilled *in vacuo* to yield 4-phenyl-1,2,3,6-tetrahydropyridine which boiled at 97—112° at 1 millimetre pressure. Its hydrochloride melted at 199—202°.

By substituting equivalent quantities of appropriately substituted α-methylstyrene derivatives for the α-methyl styrene used above and otherwise proceeding as described above the following correspondingly substituted 4-phenyl-1,2,3,6-tetrahydropyridines were obtained:



R	X	Melting Point	Boiling Point
4—CH_3	base		b_{10} = 162—170
4—CH_3	HCl	192.4—194	
4—C_2H_5	base	—	B_8 = 150—164
4—C_2H_5	HCl	177.5—179	
2,4-$(CH_3)_2$	HCl	216.8—220	
4—F	base		$b_{4-10.5}$ = 139—141
4—Cl	base	62—63	b_8 = 157—160
4—Cl	HCl	192—194.2	
3—Br	HCl	261—267	
4—Br	HCl	243.5—245	
3—F	base	—	b_8 = 144—145
4-tertiary-butyl	base		b_3 = 150—155
4-tertiary-butyl	HCl	193.5—207	
4—Br	base	35—35.5	b_3 = 162°

PREPARATION E

4-Phenyl-4-bromo-piperidine

A stream of anhydrous gaseous hydrogen bromide was passed for 7 hours through a solution of 160 parts by weight of 4-phenyl-1,2,3,6-tetrahydropyridine in 500 parts by volume of acetic acid while stirring and maintaining the temperature at about 10 to 20°. The reaction mixture was then allowed to stand at room temperature for an additional 16 hours. The acetic acid and excess hydrogen bromide was removed by distillation *in vacuo* at a bath temperature of less than 40° and the residue which remained was treated wih ether and crystallised from a mixture of acetone and isopropanol to yield 4-phenyl-4-bromo-piperidine hydrobromide which melted at 209.5—210.5°.

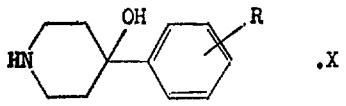
By substituting an equivalent quantity of 4 - *p* - tolyl - 1,2,3,6 - tetrahydropyridine; 4 - *p* - chlorophenyl - 1,2,3,6 - tetrahydropyridine or 4-*p*-fluoro-phenyl-1,2,3,6-tetrahydropyridine for the 4-phenyl-1,2,3,6-tetrahydropyridine and otherwise proceeding as described above 4-*p*-tolyl-4-bromo-piperidine hydrobromide melting at 190—192°; 4-*p*-chlorophenyl - 4 - bromo - piperidine hydrobromide melting at 213—215° and 4-*p*-fluorophenyl - 4 - bromo - piperidine hydrobromide melting at 143—144°, respectively, were obtained.

PREPARATION F

4-Phenyl-4-hydroxypiperidine

A solution of 160 parts by weight of 4-phenyl-4-bromo-piperidine hydrobromide in 3000 parts by volume of water was treated with 80 parts by volume of a 20% sodium hydroxide solution. The precipitate which formed was recovered by filtration, washed with water and pressed as dry as possible on the filter. It was then dissolved in 1500 parts by volume of boiling toluene to which anhydrous potassium carbonate was added to remove the remaining water. The mixture was filtered and the filtrate cooled to 0°. The crystalline residue which was thus obtained recovered by filtration to yield 4-phenyl-4-hydroxy-piperidine which melted at 159—160°. Its hydrochloride melted at 215—216.5°.

By using equivalent quantities of the 4-chlorophenyl, 4-fluorophenyl, and 4-*p*-tolyl analogues and otherwise proceeding as above the following substituted phenyl-4-hydroxy-piperidines were obtained:



R	X	Melting Point
4—F	base	116.4—117.6°
4—F	HCl	191—192.4°
4—Cl	base	134.4—136°
4—Cl	HCl	231—233°
4—CH_3	base	136—137°
4—CH_3	HCl	196—197.4°

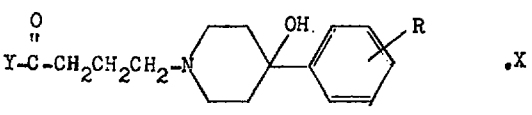
EXAMPLES

1. A mixture of 10.3 parts by weight of 4-fluoro-benzoylpropyl chloride, 11.0 parts by weight of 4-(*p*-chlorophenyl)-4-hydroxypiperidine, 0.2 part by weight of potassium iodide, 23 parts by weight of sodium carbonate dihydrate and 300 parts by volume of methyl isobutyl ketone was refluxed under stirring for 40 hours. The mixture was filtered while still hot, and the filtrate was cooled to −15°C. for some hours. The precipitated white solid was filtered and dried to yield 11 parts by weight (60%) of almost pure 4¹-fluoro-4-{N-[4¹ - hydroxy - 4¹ - (4¹¹ - chloro - phenyl)] piperidino} - butyrophenone.

2. A mixture of 3.7 parts by weight of γ-chlorobutyrophenone, 14.16 parts by weight of 4-phenyl-4-piperidinol, 0.1 part by weight of potassium iodide and 150 parts by volume of toluene was treated in a pressure vessel at 140—150° for 72 hours. After cooling to room temperature the reaction mixture was filtered. The solid residue was treated with a mixture of water and ether and the ethereal layer added to the filtrate from the original reaction mixture. The combined toluene and ether solution was dried over potassium carbonate and concentrated to about ¼ volume. After standing overnight in a cold room the residue was recovered and crystallised from diisopropyl ether to yield γ-(4-phenyl-4-hydroxypiperidino) - butyrophenone which melted at 129—130°.

Alternatively, if desired, salts of γ-(4-phenyl-4-hydroxypiperidino)-butyrophenone can be made by treating the above described toluene-ether solution, after drying, with an appropriate acid. For example, by passing anhydrous hydrogen chloride into the solution for ½ hour, the hydrochloride salt was obtained; m.p. 182—184°.

By using equivalent quantities of the appropriate starting materials and otherwise proceeding as described above in Example 2 the compounds listed below were obtained:



Y	R	X	Melting Point
C_6H_5	H	base	129—130
C_6H_5	H	HCl	182—184
C_6H_5	4—F	HCl	188—190.5
C_6H_5	4—Cl	base	126.6—127.4
C_6H_5	4—Cl	HCl	215—216.8
$4—CH_3—C_6—H_4$	H	base	122—123.2
$2,4—(CH_3)_2—C_6H_3$	H	HCl	183—185.4
$2,5—(CH_3)_2—C_6H_3$	H	HCl	176.5—177.5
$4—CH_3O—3C_6H_4$	H	HCl	221—223
$4—F—C_6H_4$	H	HCl	204.5—205.5
$4—Cl—C_6H_4$	H	base	130—131.4
2-thienyl	H	base	112.4—114.2
$4—F—C_6H_4$	4—F	HCl	201—203.5
$4—F—C_6H_4$	4—Cl	base	142—149.4
„	4—Cl	HCl	226—227.5
C_6H_5	$4—CH_3$	base	101—102.5
C_6H_5	$4—CH_3$	HCl	179.6—181.5
2-thienyl	4—Cl	base	122—123
2-thienyl	4—Cl	HCl	212.5—214
$4—F—C_6H_4$	$4—CH_3$	HCl	216—218
$4—Br—C_6H_4$	H	HCl	234—235.5
$4—Cl—C_6H_4$	4—Cl	HCl	190.6—192.4
$4—Cl—C_6H_4$	4—F	HCl	202.4—204.4

For the purposes of [illegible] therapeutically useful [illegible] are equivalent to the free base. Among such suitable therapeutically useful salts are the hydrohalides, for example the hydrochloride and hydrobromide, sulphate, citrate, malate, maleate, ascorbate, tartrate, acetate and benzoate.

27 AUG 1963 RECEIVED BY HAND

ELKINGTON AND FIFE,
Consulting Chemists and Chartered Patent Agents,
Bank Chambers, 329 High Holborn,
London, W.C.1,
Agents for the Applicant.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1961.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.