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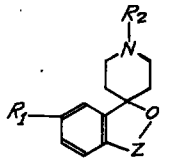


(54) SUBSTITUTED 1,3-DIHYDROSPIRO[ISOBENZOFURAN]S

(71) We, HOECHST AKTIENGESELLSCHAFT, a body corporate organised according to the laws of the Federal Republic of Germany, of 6230 Frankfurt (Main) 80, Postfach 80 03 20, Federal Republic of Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

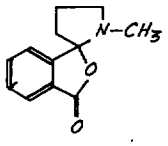
This invention relates to substituted 1,3-dihydrospiro[isobenzofuran]s which are useful as antidepressants, tranquilizers, analgesic agents and as intermediates therefore, to methods for the preparation thereof, and to pharmaceutical preparations comprising these compounds as active ingredients.

To the best of our knowledge, the compounds of this invention have not heretofore been described or suggested. Spiro[phthalanpiperidine]s of the formula



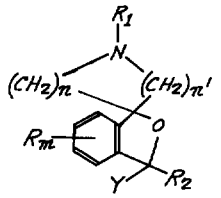
in which

R_1 is hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl, R_2 is hydrogen or benzyl, and Z is $—CH_2—$ or —CO—, described by W. J. Houlihan et al. in U.S. Patent 3,686,186 are outside the scope of the invention. The same applies to the natural product of the formula



described by Y. Inubushi et al. [Chem. and Pharm. Bull, (Japan), *12*, 749 (1964)].

This invention provides a substituted 1,3-dihydrospiro[isobenzofuran] of the general formula I



(I)

in which

R represents a hydrogen atom, an alkyl group having up to 6 carbon atoms, an alkoxy group having up to 6 carbon atoms, a trifluoromethyl group, a halogen atom, or a hydroxy or methylenedioxy group;

R_1 represents a hydrogen atom, an alkyl group having up to 6 carbon atoms, a cycloalkylalkyl group having from 4 to 8 carbon atoms, an alkenyl group having from 3 to 6 carbon atoms, a phenylalkyl group of the formula $(CH_2)_x$—PhR, a diphenylalkyl group of the formula $(CH_2)_m$—$CH(PhR)_2$, a diphenylmethoxyalkyl group of the formula —$(CH_2)_m$—$OCHPh_2$, an alkanoyl group having from 2 to 6 carbon atoms, a phenylalkanoyl group of the formula —$CO(CH_2)_x$—PhR, a benzoyl group of the formula —COPhR, a benzoylalkyl group of the formula —$(CH_2)_m$—COPhR, a phenylhydroxyalkyl group of the formula —$(CH_2)_m$CHOHPhR, an alkoxycarbonyl group having from 2 to 6 carbon atoms, a phenyloxycarbonyl group, or a cycloalkylcarbonyl group having from 4 to 8 carbon atoms, Ph representing a phenyl group;

R_2 represents an alkyl group having up to 6 carbon atoms or a phenyl group of the formula PhRm;

Y represents a hydrogen atom, an alkyl or alkoxy group having up to 6 carbon atoms, a hydroxy or phenyl group;

m, n and n′ which may be the same or different, each represents an integer of from 1 to 3; and

x represents an integer from 1 to 4.

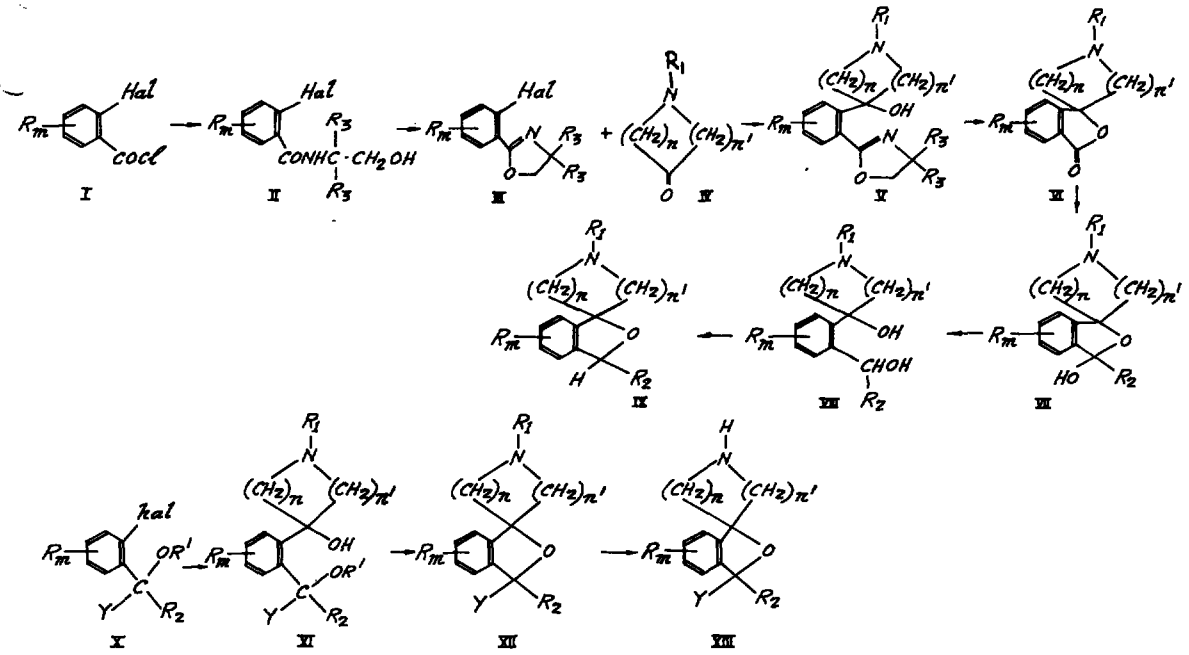
The invention also provides optical antipodes and the acid addition salts thereof, especially the physiologically tolerable acid addition salts.

The compounds that are preferred are those in which R represents a hydrogen atom an alkyl or alkoxy group having up to 3 carbon atoms, a fluorine or chlorine atom, a trifluoromethyl, hydroxy or methylenedioxy group, R_1 represents a hydrogen atom, an alkyl group having up to 6 carbon atoms, a cycloalkylalkyl group having 4 or 5 carbon atoms, an alkenyl group having from 3 to 5 carbon atoms, a phenylalkyl group of the formula —$(CH_2)_m$PhR, a diphenylalkyl group of the formula —$(CH_2)_m$—CH—$(PhR)_2$, an alkanoyl group having from 2 to 4 carbon atoms, a phenylalkanoyl group of the formula —$CO(CH_2)_m$—PhR, a benzoylalkyl group of the formula —$(CH_2)_m$COPhR, a benzoyl group of the formula —COPhR, an alkoxycarbonyl group having 2 or 3 carbon atoms or a cycloalkylcarbonyl group having from 4 to 7 carbon atoms; R_2 represents an alkyl group having up to 3 carbon atoms or a phenyl group of the formula PhR″, R″ being a hydrogen atom, an alkyl or alkoxy group having up to 3 carbon atoms, a halogen atom, or a methylenedioxy or trifluoromethyl group; Y represents a hydrogen atom, an alkyl group having up to 3 carbon atoms, an alkoxy group having up to 4 carbon atoms or a phenyl group of the formula PhR″.

Acids useful for preparing the pharmaceutically acceptable acid addition salts of the invention include inorganic acids for example, hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, and perchloric acids, as well as organic acids, for example, tartaric, citric, acetic, succinic, maleic, fumaric and oxalic acids.

Some compounds within the scope of this invention have greater pharmaceutical activity than others, but those having lower activity, for example those in which Y represents a hydroxy group or R_1 represents an alkanoyl, phenylalkanoyl, benzoyl, alkoxycarbonyl, benzyloxycarbonyl, phenoxycarbonyl, benzyl or substituted benzyl group are nevertheless useful as intermediates for the preparation of the more active compounds.

The invention provides a series of processes for the preparation and interconversion of the compounds of the invention. These processes are defined and described in Methods A to L below, with reference to the following reaction scheme,



Method A

An *o*-halogenobenzoic acid of formula I, in which R represents a hydrogen atom, an alkyl or alkoxy group, a halogen atom or a trifluoromethyl or methylenedioxy group and m is 1 or 2, is converted to the corresponding benzoyl chloride by treatment with a halogenating agent for example, thionyl chloride, phosphorus pentachloride, or oxalyl chloride, preferably at a temperature of 0° to 120°C and for a time of from 0.25 to 24 hours in the presence or absence of a catalyst, for example, dimethylformamide with or without a solvent inert to the reactants, for example, ether, toluene, or dichloromethane. The benzoyl chloride is then allowed to react with 2-aminoethanol which may be substituted by a lower alkyl group in the 2-position, preferably at a temperature of from −20° to 35°C with or without an acid-neutralizing agent, for example, sodium bicarbonate in the presence of a solvent, for example, dichloromethane or benzene to provide an *o*-halogeno-N-(1-hydroxy-2-methyl-2-propyl)benzamide of formula II. It will be readily appreciated by those skilled in the art that the time and temperature necessary to complete the reaction in this and subsequent steps are interrelated and dependent upon the structures and compositions of the reaction components and the solvent.

The *o*-halogeno-N-(1-hydroxy-2-methyl-2-propyl)-benzamide of formula II is cyclized to an *o*-halogenophenyloxazoline of formula III by treatment with a dehydrating agent, for example, thionyl chloride, phosgene, or phosphorus oxychloride, preferably at a temperature of from −20° to 40°C in the presence or absence of a solvent, for example, toluene, pyridine, or chloroform and for a time of 0.5 to 24 hours.

The *o*-halogenophenyloxazoline of formula III is converted to a Grignard reagent under the usual conditions, i.e. by reaction with magnesium, preferably at a temperature of from 25° to 100°C in a solvent, for example, ether or tetrahydrofuran for a time of preferably 0.25 to 24 hours with or without the assistance of an initiator, for example, iodine or 1,2-dibromoethane. Reaction of the Grignard reagent with a cycloazalkanone of formula IV, preferably at a temperature of from −60° to 100°C for a time of 0.25 to 24 hours, provides an oxazolinylphenylcycloazalkanol of formula V.

The oxazolinylphenylcycloazalkanol of formula V is treated with an acid, for example, aqueous hydrochloric or sulphuric acid, preferably at a temperature of from 25° to 125°C, for a time of 10 minutes to 24 hours with or without a solvent, for example, water, ethanol, or acetic acid, to provide a 1,3-dihydrospiro[isobenzofuran-cycloazalkane]-3-one of formula VI.

The 1,3-dihydrospiro[isobenzofuran-cycloazalkane]-3-one of formula VI is allowed to react with an organometallic reagent, for example, alkyl- or aryl-

magnesium halide or an alkyl- or aryllithium under the normal conditions, e.g., at a temperature of from −60° to 100°C with a solvent, for example, hexane, toluene, ether, or tetrahydrofuran, for a time of 10 minutes to 24 hours, to provide a 1,3-dihydro-3-hydroxyspiro[isobenzofuran-cycloazalkane] of formula VII.

The 1,3-dihydro-3-hydroxyspiro[isobenzofuran-cycloazalkane] of formula VII is converted by a reducing agent, for example, lithium aluminium hydride or sodium bis(2-methoxyethoxy)-aluminium hydride, preferably at a temperature of from 0° to 110°C, in a solvent, for example, toluene, ether or tetrahydrofuran and for a time of from 10 minutes to 24 hours to an *o*-hydroxyalkylphenyl-cycloazalkanol of formula VIII.

The *o*-hydroxyalkylphenylcycloazalkanol of formula VIII is treated with an acid, for example, hydrochloric, formic, or *p*-toluenesulphonic acid with or without a solvent, for example, toluene or acetic acid, preferably at a temperature of from 25° to 150°C, advantageously from 25° to 110°C for a time of 5 minutes to 24 hours, advantageously 5 minutes to 3 hours, to provide a 1,3-dihydrospiro[isobenzofuran-cycloazalkane] of formula IX.

Method B

An *o*-halogenobenzyl alcohol of formula X in which R and m are defined as in the description of Method A, Y represents a hydrogen atom or an alkyl group, and R′ represents a hydrogen atom or an alkyl or tetrahydropyranyl group, is converted to the dilithium derivative by treatment with an alkyl lithium of preferably 1 to 6 carbon atoms preferably at a temperature of from −30° to 100° for a time of 10 minutes to 12 hours and in a solvent, for example, ether, hexane, or tetrahydrofuran. Alternatively, an *o*-halogenobenzyl ether X is converted to the lithium derivative or Grignard reagent in the usual manner. The resulting lithium *o*-lithiobenzalkoxide, *o*-lithiobenzyl ether, or Grignard reagent is allowed to react with a cycloazalkanone of formula IV preferably for a time of 0.25 to 24 hours under reaction conditions which are commonly used for this type of reaction, e.g., at a temperature of from −80° to 100°C, preferably from −80° to 20°C, in a solvent, for example, ether, tetrahydrofuran, or hexane to provide an *o*-hydroxy-alkylphenyl-cycloazalkanol or its ether of formula XI.

The *o*-hydroxyalkylphenylcycloazalkanol or its ether of formula XI is then cyclized to a 1,3-dihydrospiro[isobenzofuran-cycloazalkane] of formula XII by acid treatment as in Method A, above.

Method C

An N-benzyl-1,3-dihydrospiro[isobenzofuran-cycloazalkane] of formula XII in which R_1 represents the group CH_2PhR, is hydrogenated preferably at a pressure of 1 to 15 atmospheres with a catalyst, for example, palladium on carbon in a solvent, for example, ethanol, acetic acid, or water in the presence of an acid for example, hydrochloric or perchloric acid at a temperature of from 25° to 100°C until hydrogen uptake ceases, to form the corresponding 1,3-dihydrospiro[isobenzofuran-cycloazalkane] of formula XIII.

Method D

A 1,3-dihydrospiro[isobenzofuran-cycloazalkane] of formula XIII is prepared by treating an N-substituted 1,3-dihydrospiro[isobenzofuran-cycloazalkane] of formula XII with a chloroformate, e.g. an alkyl- or phenylchloroformate, preferably at a temperature of from 25° to 125°C, for 0.25 to 24 hours in a solvent, for example, toluene or benzene to provide the corresponding N-alkoxycarbonyl- or N-phenyloxycarbonyl-1,3-dihydrospiro[isobenzofuran-cycloazalkane], which is then treated with a base, for example, sodium or potassium hydroxide in a solvent, for example, water or ethanol, or with an acid, for example, hydrogen bromide in acetic acid, preferably for 0.25 to 24 hours at a temperature of from 25° to 125°C.

Method E

An N-unsubstituted 1,3-dihydrospiro[isobenzofuran-cycloazalkane] of formula XIII prepared by Method C or D is reacted in known manner with an alkylating or acylating agent, for example, an alkanoyl chloride or an hydride, aroyl chloride or anhydride, aralkanoyl chloride, alkyl halide, alkenyl halide, cycloalkanoyl halide, aralkyl halide or aroylalkyl halide, to provide the corresponding N-alkylated or N-acylated derivative, for example, an N-alkanoyl, N-aroyl, N-

aralkanoyl, N-alkyl, N-alkenyl, N-cycloalkanoyl, N-aralkyl or N-aroylalkyl derivative.

The term "known" is used here and throughout the specification to mean in actual use in the art or described in the literature of the art.

Method F

An N-alkoxycarbonyl-, N-aryloxycarbonyl-, N-alkanoyl-, N-cycloalkylcarbonyl-, N-aroyl-, N-aralkanoyl-1,3-dihydrospiro[isobenzofuran-cycloazalkane] prepared by Methods D or E is reduced with a reagent, for example, lithium aluminium hydride to the corresponding N-alkyl-, N-cycloalkylalkyl-, or N-aralkanyl-1,3-dihydrospiro[isobenzofuran-cycloazalkane].

Method G

An N-substituted-1,3-dihydro-3-hydroxyspiro[isobenzofuran-cycloazalkane] of formula VII is heated with an aliphatic monoalcohol under acid catalysis, for example, in the presence of hydrochloric acid under the normal conditions of this type of reaction, to provide the corresponding ether of formula XII.

Method H

An N-substituted 1,3-dihydrospiro[isobenzofuran-cycloazalkane] of formula XII in which R represents an alkoxy group is heated with an acid, for example, hydrobromic acid or aluminium tribromide, under the normal conditions of hydrolyzing reactions to provide the corresponding hydroxy compound.

Method I

A 1,3-dihydrospiro[isobenzofuran-cycloazalkane] of formula XII where R represents a methoxy group is cleaved to the corresponding compound of formula XII where R represents a hydroxy group by heating with sodium thioethoxide in the presence of a solvent.

Method J

An N-substituted 1,3-dihydrospiro[isobenzofuran-cycloazalkane] of formula XII in which Y represents a hydrogen atom, is treated with an alkyl lithium having up to 6 carbon atoms, preferably in a solvent such as tetrahydrofuran, at a temperature of from –50° to 50°C., for from a few minutes to several hours, to produce the corresponding lithium derivative. The lithium derivative is alkylated *in situ*, preferably at a temperature of from –25° to 50°C., for from several minutes to 24 hours to give the corresponding compound in which Y represents an alkyl group.

Method K

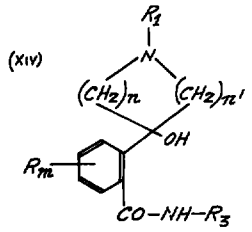
The carbonyl group in the side chain of an N-substituted 1,3-dihydrospiro(isobenzofuran-cycloazalkane) of formula XII wherein R_1 contains a carbonyl group is reduced to form the corresponding N-substituted hydroxy derivative of formula XII.

Method L

An *o*-halogenophenyloxazoline of formula III is reacted with an alkyl lithium, the resulting *o*-lithium-phenyl oxazoline is treated with a cycloazalkanone of formula IV, the resulting 1,3-dihydrospiro(isobenzofuran-cycloazalkane)-3-one of formula V is reacted with an acid, the resulting hydroxy-*o*-oxazolinyl phenyl cycloazalkane of formula VI is reacted with an organometallic reagent, the resulting 3-substituted 1,3-dihydro-3-hydroxy-spiro(isobenzofuran-cycloazalkane) of formula VII is reduced to an *o*-hydroxy-alkylphenyl cycloazalkanol of formula VIII and the azalkanol of formula VIII is treated with an acid to effect cyclization to the corresponding 3-substituted 1,3-dihydrospiro(isobenzofuran-cycloazalkane) of formula IX.

Method M

A compound of formula XIV



wherein R_3 has the meaning given above is reacted with an acid to form a compound of formula VI and/or the compound of formula VI is treated according to method A to form a compound of formula IX.

The compound of the present invention is useful in the treatment of depression in mammals, as demonstrated by their ability to inhibit tetrabenzazine-induced depression in mice [International Journal of Neuropharmacology, *8*, 73 (1969)], s standard assay for useful antidepressant properties. Thus, for instance, the minimum effective dosages (MED) at which the following compounds inhibit ptosis of tetrabenzazine-induced depression in mice are:

	MED, mg/kg
1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine]	0.5
1,3-dihydro-1'methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]	1.0
1,3-dihydro-1'-ethyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]	5.0
1,3-dihydro-1'-methyl-3-(4-methoxyphenyl)spiro[isobenzofuran-1,4'-piperidine]	2.5
1,3-dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,3'-pyrrolidine]	1.6
1,3-dihydro-1'-butyl-3-phenylspiro[isobenzofuran-1,4'piperidine]	10.0
1,3-dihydro-3-p-fluorophenylspiro[isobenzofuran-1,4'-piperidine]	0.5
1,3-dihydro-1'-cyclopropylmethyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]	2.5
1,3-dihydro-3-phenylspiro[isobenzofuran-1,3'-pyrrolidine]	0.3
1'-cyclopropylmethyl-1,3-dihydro-3-phenylspiro[isobenzofuran-1,3'-pyrrolidine] hydrobromide	0.7
1,3-dihydro-3-p-tolylspiro[isobenzofuran-1,4'-piperidine]	0.8
1,3-dihydro-6-fluoro-3-p-fluorophenylspiro[isobenzofuran-1,4'-piperidine]	0.8
1,3-dihydro-6-methoxy-3-phenylspiro[isobenzofuran-1,4'-piperidine]	0.3
1,3-dihydro-3-p-fluorophenyl-1'-methylspiro[isobenzofuran-1,4'-piperidine]	1.4
1,3-dihydro-3-p-methoxyphenylspiro[isobenzofuran-1,4'-piperidine]	2.0
1,3-dihydro-1', 3-dimethyl-3-phenylspiro[isobenzofuran-1,4'-piperidine] hydrobromide	9.5

Compounds of the present invention are further useful as tranquilizers due

to their depressant action on the central nervous system of mammals. This activity is deonstrated in the mouse observation procedure, a standard assay for CNS depressants [Psychopharmacologia, *9*, 259 (1966)]. Thus, for instance, the minimum effective dose (MED) at which 1,3-dihydro-1'-(2-phenylethyl)-3-phenylspiro[isobenzofuran-1,4'-piperidine] displays significant effects on behavior and reflex depression together with muscle relaxation is 20 mg/kg. Similarly, MED's of other compounds are:

	MED, mg/kg
1,3-dihydro-1'-[3-(4-fluorobenzoyl)propyl]-3-phenylspiro[isobenzofuran-1,4'-piperidine]	10.0
1,3-dihydro-1',3-dimethylspiro[isobenzofuran-1,4'-piperidine]	25.0
1,3-dihydro-1'-benzyl-3,5-dimethoxy-3-phenylspiro[isobenzofuran-1,4'-piperidine]	20.0
1,3-dihydro-1'-cyclopropylmethyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]	2.5
1,3-dihydro-1'-propyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]	25.0
1,3-dihydro-1'-benzyl-3-(4-fluorophenyl)spiro[isobenzofuran-1,4'-piperidine]	25.0

The utility of compounds of the present invention as tranquilizers is also demonstrated by their ability to inhibit foot shock-induced rage [Arch. Int. Pharmacodynam. et de Therap., *142*, 30 (1963)] and to antagonize the toxicity of amphetamine in aggregated situations in mice [J. Pharmacol. Exp. Therap., *87*, 214 (1946)]. Thus, at doses of 3 and 10 mg/kg., respectively of 1,3-dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine] and 1,3-dihydro-3-phenylspiro-[isobenzofuran-1,4'-piperidine], 50% of mice are protected from foot-shock-induced rages. Doses of 27,0.9, and 1.0 mg/kg. of 1,3-dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine], 1,3-dihydro-1'-[3-(4-fluorobenzoyl)-propyl]-3-phenylspiro[isobenzofuran-1,4'-piperidine], and 1,3-dihydro-1'-(2-phenethyl)-3-phenylspiro[isobenzofuran-1,4'-piperidine], respectively, antagonize amphetamine toxicity in 50% of mice. These data illustrate that 1,3-dihydrospiro-[isobenzofuran]s of this invention are useful as tranquilizers in mammals when administered in amounts ranging from 0.1 to 50 mg/kg. of body weight per day.

Compounds of the present invention are also useful as analgesic agents due to their ability to alleviate pain in mammals. The analgesic utility of compounds of this invention is demonstrated in the phenyl-o-quinone-induced writhing assay in mice, a standard assay for analgesia [Proc. Soc. Exptl. Biol. Med., *95*, 729 (1957)]. Thus, for instance, an approximately 50% inhibition of writhing is effected by an 8.4 mg/kg. dose of 1,3-dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]. Similarly effective are 14.5 mg/kg. and 10.5 mg/kg. doses of 1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine] and 1,3-dihydro-1'-[3-(4-fluorobenzoyl)propyl]-3-phenylspiro[isobenzofuran-1,4'-piperidine]. Doses of 50 mg/kg of 1,3-dihydro-1'-ethyl-3-phenylspiro[isobenzofuran-1,4'-piperidine], 1,3-dihydro-1',3-dimethyl-3-hydroxyspiro[isobenzofuran-1,4'-piperidine], 1,3-dihydro-3-hydroxy-1'-(2-phenylethyl)-3-phenylspiro(isobenzofuran-1,4'-piperidine], 1,3-dihydro-1',3-dimethylspiro[isobenzofuran-1,4'-piperidine], 1,3-dihydro-3-(4-methoxyphenyl)-1'-methylspiro[isobenzofuran-1,4'-piperidine], and 1,3-dihydro-1'-ethoxycarbonyl-3-phenylspiro[isobenzofuran-1,4'-piperidine] exhibit a 79%, 51%, 56%, 57%, 47%, and 52%, respectively, inhibition of writhing. For comparison, aspirin and propoxyphene hydrochloride, known analgesic agents, effect a 34% and 50% inhibition with doses of 60 mg/kg. and 28 mg/kg., respectively. These data illustrate that the 1,3-dihydrospiro[isobenzofuran]s of this invention are useful for the alleviation of pain in mammals when administered in amounts ranging from 1 to about 50 mg per kg. of body weight per day.

The invention therefore provides a pharmaceutical preparation which comprises a compound of the invention or a physiologically tolerable salt thereof in admixture or conjunction with a pharmaceutically suitable carrier. The

preparation may be in a form suitable for administration orally, intramuscularly, intravenously, subcutaneously, or intraperitoneally. The preparations are preferably in a form suitable for oral administration, for example, gelatin capsules, tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and chewing gum. There preparations generally contain at least 0.5% of active compound, but this may be varied depending upon the particular form and may conveniently be from 7% to 70% of the weight of the unit. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains from 10 to 200 milligrams of active compound.

The carrier in the oral preparation, for example, tablets, pills, capsules and troches, may be one or moe selected from the following: a binder for example gum tragacanth or gelatin; an excipient for example, starch or lactose; a disintegrating agent for example, alginic acid or potato starch; a lubricant for example, magnesium stearate; a sweetening agent for example, peppermint, methyl salicylate, or orange flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier for example, a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or both. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent, and certain preservatives, dyes and colourings, and flavours.

The following Examples illustrate the invention. Temperatures are given in degrees C.

Example 1.

1,3-Dihydro-3-hydroxy-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]

a) A mixture of 400 g. of o-bromobenzoic acid, 230 g. of thionyl chloride, and 1 ml. of dimethylformamide is heated slowly to reflux, and then for one hour under reflux. The excess thionyl chloride is distilled under reduced pressure, and the residue is dissolved in 1 l. of dichloromethane. The resulting solution is added dropwise with stirring to a solution of 520 g. of 2-amino-2-methylpropanol in 1 l. of dichloromethane cooled to 0°, and the mixture is stirred for 2 hours at 0° and filtered. The solid is air dried, stirred for 1 hour in 2 l. of warm water, filtered, washed liberally with water, and air dried to an off-white solid, 2-bromo-N-(1-hydroxy-2-methyl-2-propyl)benzamide, m.p. 142—145°.

b) 254 g. of 2-bromo-N-(1-hydroxy-2-methyl-2-propyl)benzamide are added to 200 ml. of cold (0°) stirred thionyl chloride in the course of 15 minutes. The solution is stirred at 0° for ½ hour and at room temperature for 12 hours, and is then poured into 1.5 l. of ether. The solid which separates is collected, washed with ether, dried, and then added at 0° to 1 l. of 20% aqueous sodium hydroxide. The mixture is extracted with ether, and the ether solution is dried over potassium carbonate and concentrated to an oil. Crystallization from hexane provides colorless crystals, m.p. 39—40°, of 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline.

c) A Grignard reagent is prepared by the drop-wise addition of a solution of 53.3 g. of 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline and 500 ml. of anhydrous tetrahydrofuran to a refluxing stirred mixture of 6.2 g. of magnesium shavings and 100 ml. of tetrahydrofuran. Initiation with iodine crystals is sometimes required. After addition, the mixture is heated under reflux for 2 hours. Then, a solution of 25 ml. of 1-methyl-4-piperidone in 25 ml. of tetrahydrofuran is added dropwise, and the solution is heated under reflux for 2 hours and allowed to cool to room temperature. Approximately 25 ml. of saturated aqueous ammonium chloride is added, the mixture is filtered, and the solid is washed with benzene. The combined organic solution is washed with water and saturated aqueous sodium chloride, dried over potassium carbonate, and concentrated to an oil. Crystallization from ethanol gives colorless crystals, m.p. 162—163°, of 4-[2-(4,4-dimethyl-2-oxazolin-2-yl)-phenyl]-4-hydroxy-1-methylpiperidine.

d) A solution of 6.0 g. of 4-[2-(4,4-dimethyl-2-oxazolin-2-yl)phenyl]-4-hydroxy-1-methylpiperidine and 70 ml. of 3N hydrochloric acid is heated under reflux for 3 hours, cooled to 0°, and made basic with sodium hydroxide. The mixture is extracted with chloroform, and the chloroform solution is dried over potassium carbonate and concentrated to a solid. Recrystallization from benzene provides

colorless crystals, m.p. 147—148°, of 1,3-dihydro-1'-methylspiro[isobenzofuran-1,4'-piperidine]-3-one.

e) A solution of 2.20 g. of 1,3-dihydro-1'-methylspiro[isobenzofuran-1,4'-piperidine]-3-one in 60 ml. of dry tetrahydrofuran is added dropwise in the course of 15 minutes to 12 ml. of cold stirred 2M phenyllithium in benzene-ether. The solution is stirred at 0° for 1 hour and at room temperature for 1 hour, diluted with water, and extracted with benzene. The benzene solution is dried over anhydrous potassium carbonate and concentrated to an oil. Trituration with ether followed by recrystallization from ethanol gives colorless crystals, m.p. 182—183°.

Analysis: Calc. for $C_{19}H_{21}NO_2$: C 77.62%; H 7.17%; N 4.74%
Found: C 77.45%; H 7.34%; N 4.84%

Example 2.

1,3-Dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]

A solution of 8.5 g. of 1,3-dihydro-3-hydroxy-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine], Example 1, in 150 ml. of tetrahydrofuran is added dropwise in 30 minutes to a stirred suspension of 2.0 g. of lithium aluminium hydride in 150 ml. of anhydrous tetrahydrofuran. The mixture is stirred at room temperature for 30 minutes and at 50° for one hour, cooled, diluted cautiously with water, and extracted with chloroform. The chloroform solution is dried over potassium carbonate and concentrated to a solid. Recrystallization from benzene gives colorless crystals, m.p. 190—191° of 4-hydroxy-4-(α-hydroxy-α-phenyl-2-tolyl)-1-methylpiperidine.

A solution of 4.4 g. of 4-hydroxy-4-(α-hydroxy-α-phenyl-2-tolyl)-1-methylpiperidine, 30 ml. of glacial acetic acid, and 7.5 ml. of conc. hydrochloric acid is heated under reflux for 10 minutes, cooled to 0°, diluted with water, made basic with sodium hydroxide, and extracted with chloroform. The chloroform solution is dried over potassium carbonate and concentrated to a solid. Recrystallization from hexane gives colorless crystals, m.p. 123—124°, of 1,3-dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine], (hydrochloride salt, , m.p. 255°).

Analysis: Calc. for $C_{19}H_{21}NO$: C 81.68%; H 7.58%; N 5.01%
Found: C 81.73%; H 7.65%; N 5.02%

Examples 3—22.

In the following odd and even numbered examples, the procedures are the same as in Examples 1 and 2, respectively. The compositions and structures of the starting materials I and IV, of the intermediates II, III, V, VI and VIII, and of the final products VII (odd numbered examples) and IX (even numbered examples) are indicated in Table I and shown in Formulae I—IX of the attached drawing.

TABLE I

Ex	R	m	X	R_1	n	n'	R_2	Y	m.p. °C
1	H	—	Br	CH_3	2	2	Ph	OH	182—3
2	H	—	Br	CH_3	2	2	Ph	H	123—4
3	H	—	Br	CH_2Ph	2	2	Ph	OH	87—90
4	H	—	Br	CH_2Ph	2	2	Ph	H	135—7
5	H	—	Br	CH_2CH_2Ph	2	2	Ph	OH	146—150
6	H	—	Br	CH_2CH_2Ph	2	2	Ph	H	257—61
7	5-CH_3O	1	Br	CH_3	2	2	Ph	OH	208—10
8	5-CH_3O	1	Br	CH_3	2	2	Ph	H	78—80

TABLE 1 (continued)

Ex	R	m	X	R_1	n	n'	R_2	Y	m.p.°C
9	6-CF_3	1	Br	CH_3	2	2	Ph	OH	
10	6-CF_3	1	Br	CH_3	2	2	Ph	H	
11	H	—	Br	CH_3	2	2	Ph-pOCH_3	OH	123—4
12	H	—	Br	CH_3	2	2	Ph-pOCH_3	H	127—8
13	H	—	Br	CH_2Ph	2	2	Ph-pF	OH	60; ·HCl, 178
14	H	—	Br	CH_2Ph	2	2	Ph-pF	H	oil; ·HCl, 235—7
15	5-CH_3O	1	Br	CH_2Ph	2	2	Ph-pF	OH	70
16	5-CH_3O	1	Br	CH_2Ph	2	2	Ph-pF	H	oil
17	H	—	Br	CH_3	2	2	CH_3	OH	157—8
18	H	—	Br	CH_3	2	2	CH_3	H	·oxalate 165—6
19	H	—	Br	CH_2Ph	2	2	CH_3	OH	126—27
20	H	—	Br	CH_2Ph	2	2	CH_3	H	74—6
21	H	—	Br	CH_2Ph	3	1	Ph	OH	oil
22	H	—	Br	CH_2Ph	3	1	Ph	H	82—4

Example 23.

1,3-Dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]

To a cold (–20°) stirred solution of 30 g. of o-bromobenzyhydrol, 85 ml. of anhydrous tetrahydrofuran, and 21 ml. of hexane is added during 1.25 hours 131 ml. of 2.0 M n-butyllithium in hexane. After 3 hours, a solution of 14.8 g. of 1-methyl-4-piperidone in 50 ml. of tetrahydrofuran is added in the course of 10 minutes at –15°. The mixture is stirred at –15° for 2 hours and at room temperature for 15 hours and then treated with saturated aqueous ammonium chloride. The layers are separated, and the solid which precipitates in the organic phase is collected. Recrystallization from toluene provides colorless crystals, m.p. 190—191°, of 4-hydroxy-4-(α-hydroxy-α-phenyl-2-tolyl)-1-methylpiperidine.

A solution of 89 g. of 4-hydroxy-4-(α-hydroxy-α-phenyl-2-tolyl)-1-methylpiperidine and 400 ml. of 88% formic acid is heated under reflux for 2 hours, cooled, diluted with water, made basic with sodium hydroxide, and extracted with chloroform. The chloroform solution is dried over magnesium sulfate, and concentrated to a solid. Recrystallization from hexane gives colorless crystals, m.p. 123—124°, of 1,3-dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine].

Examples 24—43.

The compositions and structures of the compounds XII of Example 23 and of the compounds XII of Examples 24 to 43 prepared in the same manner, as well as the compositions and structures of the starting materials X and of the intermediates XI are indicated in Table II and shown in the attached drawing:

TABLE II

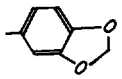
Ex	R	m	X	R_1	n	n'	R_2	Y	m.p. °C
23	H	—	Br	CH_3	2	2	Ph	H	123—4
24	5-CH_3O	—	Br	CH_3	2	2	Ph	H	78—80
25	6-CH_3O	1	Br	CH_3	2	2	Ph	H	82—5
26	5-Cl	1	Br	CH_3	2	2	Ph	H	
27	6-CH_3	1	Br	CH_3	2	2	Ph	H	
28	5,6-OCH_2O	1	Br	CH_3	2	2	Ph	H	
29	5,6-$(CH_3O)_2$	2	Br	CH_3	2	2	Ph	H	165—168
30	H	—	Br	CH_3	2	2	Ph-pOCH_3	H	127—8
31	H	—	Br	CH_3	2	2	Ph-pCl	H	
32	H	—	Br	CH_3	2	2	Ph-pCF_3	H	
33	6-F	1	Br	CH_3	2	2	Ph	H	
34	6-F	1	Br	CH_3	2	2	Ph-pF	H	134—135
35	H	—	Br	CH_3	2	2	Ph-pF	H	126—7
36	H	1	Br	CH_3	2	1	Ph	H	112—13
37	H	1	Br	CH_2Ph	3	2	Ph	H	
38	H	1	Br	CH_3	2	2	CH_3	CH_3	·HCl 250—258, dec.
39	H	1	Br	CH_3	2	2		H	
40	H	1	Br	CH_3	2	2	Ph-m,p$(CH_3O)_2$	H	67—71
41	H	—	Br	CH_3	2	2	Ph-pCH_3	H	135—136
42	H	—	Br	CH_2Ph	3	1	Ph	H	82—84
43	H	—	Br	CH_3	2	2	Ph-mF	H	81—84

TABLE II—Starting Materials

Friedel-Crafts acylation of m-bromoanisole with benzoyl chloride and p-fluorobenzoyl chloride provides 2-bromo-4-methoxybenzophenone, m.p. 83—84°, and 2-bromo-4'-fluoro-4-methoxybenzophenone, m.p. 79—81°, respectively, which are reduced with sodium borohydride to 2-bromo-4-methoxybenzhydrol, b.p. 160° (0.05 mm.), and 2-bromo-4'-fluoro-4-methoxybenzhydrol, a liquid. Acylation of benzene with 2-bromo-5-chlorobenzoyl chloride, 2-bromo-4,5-methylene-dioxybenzoyl chloride, and 2-bromo-4,5-dimethoxybenzoyl chloride provides 2-bromo-5-chlorobenzophenone, 2-bromo-4,5-methylene-dioxybenzophenone, and 2-bromo-4,5-dimethoxybenzophenone, m.p. 76—77°, which are reduced with sodium borohydride to 2-bromo-5-chlorobenzhydrol, 2-bromo-4,5-methylene-dioxybenzhydrol, and 2-bromo-4,5-dimethoxybenzhydrol, m.p. 83—85°. Acylation of anisole with 2-bromobenzoyl chloride provides 2-bromo-4'-methoxybenzophenone, m.p. 93—95°, which is reduced to 2-bromo-4'-methoxybenzhydrol, m.p. 64—65°. Reaction of 2-bromo-4-methylbenzaldehyde and phenylmagnesium bromide provides 2-bromo-4-methylbenzhydrol.

Addition of o-tolylmagnesium bromide, p-chlorophenyl-magnesium bromide,

p-trifluoromethylphenylmagnesium bromide, 3,4-methylenedioxyphenyllithium, 3,4-dimethoxyphenyllithium, p-tolylmagnesium bromide, m-fluorophenylmagnesium bromide, and p-fluorophenylmagnesium bromide to 2-bromobenzaldehyde provide, respectively, 2-bromo-2'-methylbenzhydrol; 2-bromo-4'-chlorobenzhydrol; 2-bromo-4'-trifluoromethylbenzhydrol, b.p. 125° (0.2 mm.), 2-bromo-3',4'-methylenedioxybenzhydrol; 2-bromo-3',4'-dimethoxybenzhydrol; 2-bromo-4'-methylbenzhydrol, b.p. 145° (0.25 mm.); 2-bromo-3'-fluorobenzhydrol; 2-bromo-4'-fluorobenzhydrol, m.p. 77—79°. Also the addition of p-fluorophenylmagnesium bromide to 2-bromo-4-fluorobenzaldehyde provides 2-bromo-4,4'-difluorobenzhydrol, m.p. 78—80°. The 2-bromo-4-fluorobenzaldehyde is prepared by chromium trioxide oxidation of 2-bromo-4-fluorotoluene followed by hydrolysis of the intermediate acetal diacetate.

Friedel-Crafts acylation of 3-bromofluorobenzene with benzoyl chloride or p-fluorobenzyl chloride provide, respectively, 2-bromo-4-fluorobenzophenone, b.p. 111—114° (0.05 mm.), and 2-bromo-4,4'-difluorobenzophenone. These are reduced to 2-bromo-4-fluorobenzhydrol and 2-bromo-4,4'-difluorobenzhydrol, m.p. 78—80°.

Addition of methyllithium to 2-brombenzophenone provides 2-bromophenyl methyl phenyl carbinol. Addition of methyl magnesium iodide to methyl o-bromobenzoate provides 2-bromophenyl dimethyl carbinol.

Example 44.

1,3-Dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]

A solution of 152 g. of 2-bromobenzhydrol, 1 liter of methanol, and 45 ml. of conc. hydrochloric acid is heated under reflux for 24 hours, cooled, stirred with 100 g. of potassium carbonate, filtered, and distilled to provide 2-bromobenzhydryl methyl ether, b.p. 126—128° (0.7 mm.).

To a cold (–60°) stirred solution of 2-bromobenzhydryl methyl ether in 38 ml. of tetrahydrofuran and 14 ml. of hexane is slowly added 53 ml. of 2.1 M n-butyllithium in hexane. After 2 hours, a solution of 10.7 g. of 1-methyl-4-piperidone in 15 ml. of tetrahydrofuran is added dropwise, and the suspension is stirred at –60° for 3 hours and at room temperature for 15 hours. Ice and water are added and the mixture is extracted with chloroform. The chloroform solution is dried over sodium sulfate and concentrated to a mixture of 4-hydroxy-4-(α-methoxy-α-phenyl-2-tolyl)-1-methylpiperidine and benzhydrol methyl ether. This oil is heated under reflux for 30 minutes in 240 ml. of acetic acid containing 60 ml. of hydrochloric acid. Dilution with water and addition of excess sodium hydroxide effects precipitation of a solid. Recrystallization from hexane provides 1,3-dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine], m.p. 123—124°.

Example 45.

1'-Benzyl-1,3-dihydro-3-phenylspiro[isobenzofuran-1,3'-pyrrolidine]

By following the manipulative procedure described above in Example 44, substituting N-benzyl-3-pyrrolidone for 1-methyl-4-piperidone gives a pale yellow oil which crystallizes on standing to give rhombic crystals, m.p. 85—87°, from low boiling petroleum ether.

Analysis: Calc. for $C_{24}H_{23}NO$: C 84.41%; H 6.78%; N 4.10%
Found: C 84.15%; H 6.91%; N 4.13%

Example 46.

1'-Benzyl-1,3-dihydro-3-p-tolylspiro[isobenzofuran-1,4'-piperidine]

A. 2-Bromo-4'-methylbenzhydrol is treated according to the manipulative procedure described above in Example 44 to give 2-bromo-4'-methylbenzhydryl methyl ether, b.p. 125° (0.25 mm.).

B. By following the manipulative procedure described above in Example 45, 2-bromo-4'-methylbenzhydryl methyl ether and 1-benzyl-4-piperidone are reacted to produce a white powder, m.p. 98—99°, from isopropanol.

Analysis: Calc. for $C_{26}H_{27}NO$: C 84.51%; H 7.37%; N 3.79%
Found: C 84.72%; H 7.50%; N 3.79%

Example 47.

1'-Benzyl-1,3-dihydro-3-p-fluorophenyl-6-methoxyspiro[isobenzofuran-1,4'-piperidine]

A. 2-Bromo-4'-fluoro-4-methoxybenzhydrol is treated according to the manipulative procedure described above in Example 44 to give 2-bromo-4'-fluoro-4-methoxybenzhydryl methyl ether as an oil.

B. By following the manipulative procedure described above in Example 45, 2-bromo-4'-fluoro-4-methoxybenzhydryl methyl ether and 1-benzyl-4-piperidone are reacted to produce a white solid, m.p. 86—88°, from heptane.

Analysis: Calc. for $C_{26}H_{26}FNO_2$: C 77.39%; H 6.50%; N 3.47%
Found: C 76.84%; H 6.54%; N 3.46%

Example 48.

1'-Benzyl-1,3-dihydro-6-fluoro-3-p-fluorophenylspiro[isobenzofuran-1,4'-piperidine]

A. 2-Bromo-4,4'-difluorobenzhydrol is treated according to the manipulative procedure described above in Example 44, to give 2-bromo-4,4'-difluorobenzhydryl methyl ether, b.p. 105° (0.50 mm.).

B. By following the manipulative procedure described above in Example 45, 2-bromo-4,4'-difluorobenzhydryl methyl ether and 1-benzyl-4-piperidone are reacted to produce an oil.

Example 49.

1,3-Dihydro-1'-ethoxycarbonyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]

A solution of 7.7 g. of 1'-benzyl-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine] (Example 4), 40 ml. of benzene and 2.5 ml. of ethyl chloroformate is heated under reflux for 18 hours and concentrated to a solid. Recrystallization from cyclohexane provides colorless crystals, m.p. 115—119°.

Analysis: Calc. for $C_{21}H_{23}NO_3$: C 74.75%; H 6.87%; N 4.15%
Found: C 74.55%; H 7.00%; N 4.06%

The compositions and structures of the compounds IX of Examples 50 through 64, tabulated below, are prepared in an analogous manner.

TABLE III

	R_m	R_2	R_1	n,n'	Starting Material	m.p. °C
Example 50	H	CH_3	$COOC_2H_5$	2,2	Example 20	68—70
Example 51	H	Ph-pF	$COOC_2H_5$	2,2	Example 14	104—106
Example 52	H	Ph	COOPh	2,2	Example 2	179—183
Example 53	H	Ph	$COOC_2H_5$	2,1	Example 36	oil
Example 54	H	Ph	$COOC_2H_5$	3,1	Example 22	115—118
Example 55	H	Ph-pCH_3O	$COOC_2H_5$	2,2	Example 30	113—115
Example 56	H	Ph	$COOC_2H_5$	3,2	Example 37	oil
Example 57	6-F	Ph	$COOC_2H_5$	2,2	Example 33	
Example 58	6-CH_3O	Ph	$COOC_2H_5$	2,2	Example 25	178—180
Example 59	5-CH_3O	Ph	COOPh	2,2	Example 24	181—185
Example 60	5-CH_3O	Ph-pF	$COOC_2H_5$	2,2	Example 16	oil
Example 61	H	Ph-pCH_3	$COOC_2H_5$	2,2	Example 46	106—108

TABLE 3 (continued)

	R_m	R_2	R_1	n,n'	Starting Material	m.p.°C
Example 62	6-CH_3O	Ph-pF	$COOC_2H_5$	2,2	Example 47	168—170
Example 63	6-F	Ph-pF	$COOC_2H_5$	2,2	Example 48	123—126
Example 64	H	Ph-m,p $(CH_3O)_2$	COOPh	2,2	Example 40	170—172

Example 65.

1,3-Dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine]

A. A solution of 6.3 g. of 1,3-dihydro-1'-ethoxycarbonyl-3-phenylspiro[isobenzofuran-1,4'-piperidine] (Example 49), 300 ml. of ethanol, and 240 ml. of 20% aqueous potassium hydroxide is heated under reflux for 9 hours, cooled, concentrated to 250 ml., diluted with water, and extracted with chloroform. The chloroform solution is dried over potassium carbonate and concentrated. The residue is recrystallized from cyclohexane to provide colorless crystals, m.p. 119—123°.

Analysis: Calc. for $C_{18}H_{19}NO$: C 81.48%; H 7.22%; N 5.28%
Found: C 81.55%; H 7.56%; N 5.12%

Hydrochloride salt, m.p. 262°.

B. A mixture of 2.9 g. of 1'-benzyl-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine], (Example 4), 0.4 g. of 10% palladium on carbon, 20 ml. of 95% ethanol, and 2 ml. of conc. hydrochloric acid is hydrogenated at 50 p.s.i. and 50°. After hydrogen uptake ceases, the mixture is filtered and the filtrate concentrated. Recrystallization of the residue from cyclohexane provides colorless crystals, m.p. 119—123°.

The compositions and structures of the compounds XIII of Examples 66 through 79, tabulated below, are prepared in analogous manner.

TABLE IV

	R_m	R_2	Y	n,n'	Starting Material	m.p. °C
Example 66	H	CH_3	H	2,2	Example 50	·HCl, 183—184
Example 67	H	Ph-pF	H	2,2	Example 51	98—100
Example 68	H	Ph	H	2,1	Example 53	90—95
Example 69	H	Ph	H	3,1	Example 54	106—110
Example 70	H	Ph-pCH_3O	H	2,2	Example 55	101—103
Example 71	H	Ph	H	3,2	Example 56	·HCl>250
Example 72	6-F	Ph	H	2,2	Example 57	
Example 73	6-CH_3O	Ph	H	2,2	Example 58	·HCl, 204—212
Example 74	5-CH_3O	Ph	H	2,2	Example 59	·HCl, 265—268
Example 75	5-CH_3O	Ph-pF	H	2,2	Example 60	·HCl, 275
Example 76	H	Ph-pCH_3	H	2,2	Example 61	116—117

TABLE 4 (continued)

	R_m	R_2	Y	n,n'	Starting Material	m.p.°C.
Example 77	6-F	Ph-pF	H	2,2	Example 63	111—112
Example 78	H	Ph	OH	2,2	Example 3	183—184
Example 79	H	Ph-m,p $(CH_3O)_2$	H	2,2	Example 64	·HCl, 212—218

Example 80.

1'-Acetyl-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine]

To a cold stirred solution of 6.0 g. of 1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine] (Example 65), 2.4 g. of triethylamine, and 50 ml. of chloroform is added dropwise a solution of 2.0 g. of acetyl chloride and 50 ml. of chloroform. The mixture is stirred for 2 hours at room temperature, washed with water, dried over sodium sulfate, and concentrated. The residue is recrystallized from chloroform to provide colorless crystals, m.p. 128—130°.

Analysis: Calc. for $C_{20}H_{21}NO_2$: C 77.89%; H 6.90%; N 4.55%
Found: C 78.06%; H 6.99%; N 4.43%

The compositions and structures of the compounds IX of Examples 81 through 88, tabulated below, are prepared in analogous manner.

TABLE V

	R_m	R_2	R_1	n,n'	Starting Materials	m.p. °C
Example 81	H	Ph	COC_2H_5	2,2	Example 65	116—119
Example 82	H	Ph	COC_3H_7	2,2	Example 65	110—112
Example 83	H	Ph	$COCH_2Ph$	2,2	Example 65	174—176
Example 84	H	Ph	$COPhCH_3$	2,2	Example 65	172—175
Example 85	H	Ph		2,2	Example 65	133—135
Example 86	H	Ph-pF		2,2	Example 67	149—152
Example 87	H	Ph		2,2	Example 65	127—130
Example 88	H	Ph		3,2	Example 71	oil

Example 89.

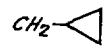
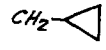
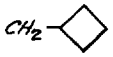
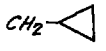
1,3-Dihydro-1'-ethyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]

To a stirred suspension of 0.53 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran is added dropwise a solution of 2.20 g. of 1'-acetyl-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine] (Example 80), in 50 ml. of tetrahydrofuran. The mixture is heated under reflux for 2 hours, cooled, quenched cautiously with water, and extracted with ether. The ether solution is dried over sodium sulfate and concentrated to a solid. Recrystallization from chloroform provides colorless crystals, m.p. 113—115°.

Analysis: Calc. for $C_{20}H_{23}NO$: C 81.87%; H 7.91%; N 4.77%
Found: C 81.76%; H 8.10%; N 4.62%

The compositions and structures of the compounds IX of Examples 90 through 98, tabulated below, are prepared in analogous manner.

TABLE VI

	R_m	R_2	R_1	n,n'	Starting Material	m.p. °C
Example 90	H	Ph	C_3H_7	2,2	Example 81	98—100
Example 91	H	Ph	C_4H_9	2,2	Example 82	102—103
Example 92	H	Ph		2,2	Example 85	97—99
Example 93	H	Ph-pF		2,2	Example 86	·HBr, 233—235
Example 94	H	Ph		2,2	Example 89	119—121
Example 95	H	Ph		3,2	Example 88	·HCl, 203—206
Example 96	H	Ph-pCH_3	CH_3	2,2	Example 61	135—136
Example 97	H	Ph	CH_3	3,2	Example 56	88—89
Example 98	6-CH_3O	Ph-pF	CH_3	2,2	Example 62	·HBr, 235 dec.

Example 99.

1,3-Dihydro-1'-[3-(p-fluorobenzoyl)propyl]-3-phenylspiro[isobenzofuran-1,4'-piperdine]

A stirred mixture of 4.9 g. of 1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine] (Example 65), 4.9 g. of ω-chloro-p-fluorobutyrophenone ethylene ketal, 10 g. of potassium carbonate, and 50 ml. of butanol is heated under reflux for 46 hours and filtered. The filtrate is concentrated to an oil, which is stirred with 50 ml. of 3N hydrochloric acid and 50 ml. of ethanol. The mixture is made basic with sodium hydroxide and extracted with benzene. The benzene solution is dried over sodium sulfate and concentrated. The residue is recrystallized from ether to provide colorless crystals, m.p. 137—138°.

Analysis: Calc. for $C_{28}H_{28}FNO_2$: C 78.30%; H 6.57%; N 3.26%
Found: C 78.28%; H 6.59%; N 3.12%

The compositions and structures of compounds IX of Examples 100 through 111, tabulated below, are prepared in analogous manner. The acid hydrolysis step of Example 99 is omitted when the alkylating agent does not contain a ketal group.

TABLE VII

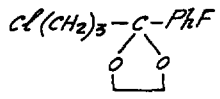
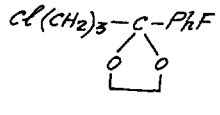
Ex.	R_m	R_2	R_1	n,n'	m.p. °C	Starting Material Ex.	Alkylating Agent
100	H	CH_3	—$(CH_2)_3$CO—PhF	2,2		66	
101	H	Ph	—$(CH_2)_3$CO—PhF	2,1		68	
102	H	Ph	—$(CH_2)_3$CH—$(PhF)_2$	2,2	·HCl, 185—190	65	$Cl(CH_2)_3CH—(PhF)_2$

TABLE VII (continued)

Ex.	R_m	R_2	R_1	n,n'	m.p.°C	Starting Material Ex.	Alkylating Agent
103	H	CH_3	$-(CH_2)_3CH-(PhF)_2$	2,2	167—170	66	$Cl(CH_2)_3CH-(PhF)_2$
104	H	Ph	$-CH_2CH=C(CH_3)_2$	2,2	119—121	65	$BrCH_2CH=C(CH_3)_2$
105	H	Ph	$-CH_2CH=CH_2$	2,2	129—131	65	$BrCH_2CH=CH_2$
106	H	Ph	$-CH_2CH_2O-CH-Ph_2$	2,2	oil	65	$ClCH_2CH_2OCH-Ph_2$
107	H	Ph	$-CH_2CH_2CO-Ph$	2,2		65	$(CH_3)_3\overset{+}{N}CH_2CH_2CO-Ph$
108	H	Ph	i—C_3H_7	2,2	121—124	65	CH_3CHICH_3
109	H	Ph	$(CH_2)_3-Ph$	2,2	89—92	65	$Br(CH_2)_3Ph$
110	H	Ph	$CH_2CH=CHPh$	2,2	142—144	65	$BrCH_2CH=CHPh$
111	H	CH_3		2,2	196—199	66	

Example 112.

1'-Benzyl-1,3-dihydro-3,5-dimethoxy-3-phenylspiro[isobenzofuran-1,4'-piperidine]

A solution of 1'-benzyl-1,3-dihydro-3-hydroxy-5-methoxy-3-phenylspiro[isobenzofuran-1,4'-piperidine] (prepared by method of Example 1), methanol, and a catalytic amount of methanolic hydrogen chloride is heated under reflux, cooled, made basic with sodium hydroxide, and diluted with water. The mixture is extracted with ethyl acetate, and the ethyl acetate solution is dried over sodium sulfate and concentrated to a solid. Recrystallization from acetone-water provides colorless crystals, m.p. 129—133°.

Analysis: Calc. for $C_{27}H_{29}NO_3$: C 78.03%; H 7.05%; N 3.37%
Found: C 78.15%; H 7.12%; N 3.23%

Example 113.

1,3-Dihydro-3-(4-hydroxyphenyl)-1'-methylspiro[isobenzofuran-1,4'-piperidine]

A solution of 3.5 g. of 1,3-dihydro-3-(4-methoxyphenyl)-1'-methylspiro[isobenzofuran-1,4'-piperidine], (Example 12), and 20 ml. of 48% hydrobromic acid is heated under reflux, cooled, diluted with water, neutralized with sodium bicarbonate, and extracted with chloroform. The chloroform solution is dried over magnesium sulfate and concentrated to an oil. Trituration with ether provides crystals, m.p. 132° dec. Recrystallization raises the melting point to 273° dec.

Example 114.

1,3-Dihydro-6-hydroxy-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]

By following the manipulative procedure described above in example 113, 1,3-dihydro-6-methoxy-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine], (Example 25), gives a faintly pink solid, m.p. 207—212°.

Analysis: Calc. for $C_{19}H_{21}NO_2$: C 77.25%; H 7.18%; N 4.74%
Found: C 77.05%; H 7.23%; N 4.74%

Example 115.

1,3-Dihydro-5-hydroxy-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]

By following the manipulative procedure described above in Example 113, 1,3-dihydro-5-methoxy-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine], (Example 24), gives a cream colored solid, m.p. 193—200°.

Analysis: Calc. for $C_{19}H_{21}NO_2$: C 77.25%; H 7.18%; N 4.74%
Found: C 77.00%; H 7.40%; N 4.66%

Example 116.

1,3-Dihydro-6-hydroxy-3-phenylspiro(isobenzofuran-1,4'-piperidine]

A suspension of 2.0 g. of 1,3-dihydro-6-methoxy-3-phenylspiro[isobenzofuran-1,4'-piperidine], (Example 73), and 32 ml. of a 48% hydrobromic acid solution is heated at reflux, effecting the separation of a hydrobromide salt as a crystalline precipitate. The mixture is poured into ice-water with stirring, the precipitate collected by filtration, the filter cake washed with water, and dried. Recrystallization from ethanol gives colorless crystals, m.p. 274—276°, dec.

Analysis: Calc. for $C_{18}H_{19}NO_2 \cdot HBr$: C 59.67%; H 5.58%; N 3.87%; Br 22.06%
Found: C 59.83%; H 5.64%; N 3.95%; Br 21.86%

Example 117.

1,3-Dihydro-1'-(3-hydroxy-3-phenylpropyl)-3-phenylspiro[isobenzofuran-1,4'-piperdine]

A solution of 2.5 g. of 1'-(2-benzoylethyl)-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine], (Example 107), 30 ml. of methanol, and 0.35 g. of sodium borohydride is stirred at room temperature for 4 hours, diluted with water, and extracted with chloroform. The chloroform solution is dried over sodium sulfate and concentrated to provide 1,3-dihydro-1'-(3-hydroxy-3-phenylpropyl)-3-phenylspiro[isobenzofuran-1,4'-piperidine].

Example 118.

1,3-Dihydro-1'-[4-p-fluorophenyl)-4-hydroxybutyl]-3-phenylspiro[isobenzofuran-1,4'-piperidine]

By following the manipulative procedure described above in Example 117, 1,3-dihydro-1'-[3-(p-fluorobenzoyl)-propyl]-3-phenylspiro[isobenzofuran-1,4'-piperidine], (Example 99), produces a yellow oil. The oil is triturated with an ether-petroleum ether mixture to give white crystals which are recrystallized from ethanol to give a white crystalline solid, m.p. 151—154°.

Analysis: Calc. for $C_{28}H_{30}FNO_2$: C 77.93%; H 7.01%; N 3.25%
Found: C 77.78%; H 7.07%; N 3.19%

Example 119.

1,3-Dihydro-3-p-hydroxyphenyl-1'-methylspiro[isobenzofuran-1,4'-piperidine]

A mixture of 1.0 g. of 1,3-dihydro-3-p-methoxyphenyl-1'-methylspiro[isobenzofuran-1,4'-piperidine] (Example 12), 1.0 g. of a 57% sodium hydride dispersion, and dimethylformamide is stirred under nitrogen. To the stirring mixture is rapidly added 2.0 ml. of ethanethiol. The mixture is refluxed under nitrogen for 4 hours, cooled, poured into ice-water, and acidified with 1N hydrochloric acid. The product is collected, dried, and dissolved in boiling dimethyl sulfoxide, and the solution is filtered. Upon cooling small colorless crystals, m.p. 273° dec., separate.

Analysis: Calc. for $C_{19}H_{21}NO_2$: C 77.26%; H 7.17%; N 4.74%
Found: C 76.28%; H 7.33%; N 4.71%

Example 120.

1'-Benzyl-1,3-dihydro-3,3-diphenylspiro[isobenzofuran-1,3'-piperidine]

Reaction of 1'-benzyl-1,3-dihydrospiro[isobenzofuran-1,3'-piperidine]-3-one with a large excess of phenyllithium by the method described in Example 1 provides off-white crystals, m.p. 144—146°.

Analysis: Calc. for $C_{31}H_{29}NO$: C 86.27%; H 6.77%; N 3.25%
Found: C 86.22%; H 7.09%; N 3.21%

Example 121.

(–)-1,3-Dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine]

To a stirred solution of 0.80 g. of 1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine], (Example 65), and 3 ml. of methanol is added a solution of 1.16 g. of di-(p-toluoyl)-d-tartaric acid in 6 ml. of methanol. The solution is concentrated to dryness, and the residue is recrystallized three times from methanol-water to provide colorless crystals. The crystals are dissolved in

methanol and treated with an excess of aqueous sodium hydroxide. The mixture is extracted with ether, and the ether solution is dried over sodium sulfate and concentrated to an oily solid. Recrystallization from cyclohexane provides off-white crystals, m.p. 99—107°, $[\alpha]_D^{25°} = 126.0°$ (c = 1.35, MeOH).

Example 122.

(+)-1,3-Dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine]

The compound, colorless crystals, m.p. 104—112°, $[\alpha]_D^{25°} = +134.4°$ (c = 1.35, MeOH), is prepared from 1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine], (Example 65), and di-(p-toluoyl)-l-tartaric acid by the method described in Example 121, or is alternatively recovered from the aqueous-methanolic mother liquors of Example 121.

Example 123.

1,3-Dihydro-1',3-dimethyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]

A solution of 1.4 g. of 1,3-dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine], (Example 2), in 20 ml. of tetrahydrofuran is cooled to −50° and treated dropwise with 4 ml. of butyllithium in hexane. Stirring is continued for 30 minutes under nitrogen. To the solution is slowly added 900 mg. of dimethylsulfate in 10 ml. of tetrahydrofuran. The mixture is stirred at −10° for 1 hour and overnight at ambient temperature. Ice is added, the mixture is extracted with ether, and the organic solution is concentrated to an oil. The oil is converted to the hydrobromide salt and recrystallized from ethyl acetate to give crystals, m.p. 122—125°.

Analysis: Calc. for $C_{20}H_{23}NO \cdot HBr$: C 64.17%; H 6.46%; N 3.74%; Br 21.35%
Found: C 64.27%; H 6.68%; N 3.42%; Br 20.98%

The compositions and structures of compounds XII of Examples 124 through 126, tabulated below, are prepared from 1,3-dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine], (Example 2), in analogous manner.

TABLE IX

Ex.	R_m	R_2	Y	R_1	n,n'	m.p. °C	Alkylating Agent
124	H	Ph	C_2H_5	CH_3	2,2	107—108	$BrCH_2CH_3$
125	H	Ph	n-C_3H_7	CH_3	2,2	205—206, dec.	$BrCH_2CH_2CH_3$
126	H	Ph	n-C_4H_9	CH_3	2,2	203—204, dec.	$BrCH_2CH_2CH_2CH_3$

Example 127.

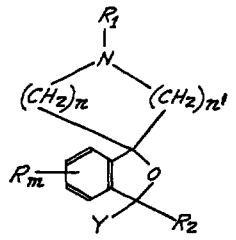
1'-Cyclopropylmethyl-1,3-dihydro-3-phenylspiro[isobenzofuran-1,3'pyrrolidine]

Reaction of 1,3-dihydro-3-phenylspiro[isobenzofuran-1,3'-pyrrolidine] with cyclopropylcarbonyl chloride by the method of Example 80, followed by lithium aluminum hydride reduction by the method of Example 89 provides an amine. The amine is converted to its hydrobromide salt, m.p. 187—190°, from an acetone-ethyl acetate mixture.

Analysis: Calc. for $C_{21}H_{23}NO \cdot HBr$: C 65.28%; H 6.26%; N 3.62%
Found: C 65.08%; H 6.36%; N 3.45%

WHAT WE CLAIM IS:—

1. A compound of the formula (XII)



(XII)

methanol and treated with an excess of aqueous sodium hydroxide. The mixture is extracted with ether, and the ether solution is dried over sodium sulfate and concentrated to an oily solid. Recrystallization from cyclohexane provides off-white crystals, m.p. 99—107°, $[\alpha]_D^{25°} = 126.0°$ (c = 1.35, MeOH).

Example 122.

(+)-1,3-Dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine]

The compound, colorless crystals, m.p. 104—112°, $[\alpha]_D^{25°} = +134.4°$ (c = 1.35, MeOH), is prepared from 1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine], (Example 65), and di-(p-toluoyl)-l-tartaric acid by the method described in Example 121, or is alternatively recovered from the aqueous-methanolic mother liquors of Example 121.

Example 123.

1,3-Dihydro-1',3-dimethyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]

A solution of 1.4 g. of 1,3-dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine], (Example 2), in 20 ml. of tetrahydrofuran is cooled to −50° and treated dropwise with 4 ml. of butyllithium in hexane. Stirring is continued for 30 minutes under nitrogen. To the solution is slowly added 900 mg. of dimethylsulfate in 10 ml. of tetrahydrofuran. The mixture is stirred at −10° for 1 hour and overnight at ambient temperature. Ice is added, the mixture is extracted with ether, and the organic solution is concentrated to an oil. The oil is converted to the hydrobromide salt and recrystallized from ethyl acetate to give crystals, m.p. 122—125°.

Analysis: Calc. for $C_{20}H_{23}NO \cdot HBr$: C 64.17%; H 6.46%; N 3.74%; Br 21.35%
Found: C 64.27%; H 6.68%; N 3.42%; Br 20.98%

The compositions and structures of compounds XII of Examples 124 through 126, tabulated below, are prepared from 1,3-dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine], (Example 2), in analogous manner.

TABLE IX

Ex.	R_m	R_2	Y	R_1	n,n'	m.p. °C	Alkylating Agent
124	H	Ph	C_2H_5	CH_3	2,2	107—108	$BrCH_2CH_3$
125	H	Ph	n-C_3H_7	CH_3	2,2	205—206, dec.	$BrCH_2CH_2CH_3$
126	H	Ph	n-C_4H_9	CH_3	2,2	203—204, dec.	$BrCH_2CH_2CH_2CH_3$

Example 127.

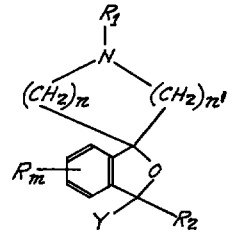
1'-Cyclopropylmethyl-1,3-dihydro-3-phenylspiro[isobenzofuran-1,3'pyrrolidine]

Reaction of 1,3-dihydro-3-phenylspiro[isobenzofuran-1,3'-pyrrolidine] with cyclopropylcarbonyl chloride by the method of Example 80, followed by lithium aluminum hydride reduction by the method of Example 89 provides an amine. The amine is converted to its hydrobromide salt, m.p. 187—190°, from an acetone-ethyl acetate mixture.

Analysis: Calc. for $C_{21}H_{23}NO \cdot HBr$: C 65.28%; H 6.26%; N 3.62%
Found: C 65.08%; H 6.36%; N 3.45%

WHAT WE CLAIM IS:—

1. A compound of the formula (XII)



(XII)

* C L M S *

in which

R represents a hydrogen atom, an alkyl group having up to 6 carbon atoms, an alkoxy group having up to 6 carbon atoms, a trifluoromethyl group, a halogen atom, or a hydroxy or methylenedioxy group,

R_1 represents a hydrogen atom, an alkyl group having up to 6 carbon atoms, a cycloalkylalkyl group having from 4 to 8 carbon atoms, an alkenyl group having from 3 to 6 carbon atoms, a phenylalkyl group of the formula $(CH_2)_x$—PhR, a diphenylalkyl group of the formula $(CH_2)_m$—$CH(PhR)_2$, a diphenylmethoxyalkyl group of the formula —$(CH_2)_m$—$OCHPh_2$, an alkanoyl group having from 2 to 6 carbon atoms, a phenylalkanoyl group of the formula —$CO(CH_2)_x$—PhR, a benzoyl group of the formula —COPhR, a benzoylalkyl group of the formula —$(CH_2)_m$—COPhR, a phenylhydroxyalkyl group of the formula —$(CH_2)_m$CHOHPhR, an alkoxycarbonyl group having from 2 to 6 carbon atoms, a phenyloxycarbonyl group, or a cycloalkylcarbonyl group having from 4 to 8 carbon atoms, Ph representing a phenyl group;

R_2 represents an alkyl group having up to 6 carbon atoms or a phenyl group of the formula PhRm;

Y represents a hydrogen atom, an alkyl or alkoxy group having up to 6 carbon atoms, a hydroxy or phenyl group;

m, n and n' which may be the same or different, each represents an integer of from 1 to 3; and

x represents an integer from 1 to 4, and the optical antipodes thereof.

2. A compound as claimed in claim 1 in which R represents a hydrogen atom, an alkyl or alkoxy group having up to 3 carbon atoms, a trifluoromethyl group, a fluorine or chlorine atom, or a hydroxy or methylenedioxy group;

R_1 represents a hydrogen atom, an alkyl group having up to 6 carbon atoms, a cycloalkylalkyl group having 4 or 5 carbon atoms, an alkenyl group having from 3 to 5 carbon atoms, a phenalkyl group of the formula —$(CH_2)_m$—PhR, a diphenylalkyl group of the formula —$(CH_2)_m$—$CH(PhR)_2$, an alkanoyl group having from 2 to 4 carbon atoms, a phenylalkanoyl group of the formula —$CO(CH_2)_m$—PhR, a benzoylalkyl group of the formula —$(CH_2)_m$—COPhR, a benzoyl group of the formula —COPhR, an alkoxycarbonyl group having 2 or 3 carbon atoms, or a cycloalkylcarbonyl group having from 4 to 7 carbon atoms;

R_2 represents an alkyl group having up to 3 carbon atoms, or a phenyl group of the formula —PhR″, R″ represents a hydrogen atom, an alkyl or alkoxy group having up to 3 carbon atoms, a halogen atom or a methylenedioxy or trifluoromethyl group;

Y represents a hydrogen atom, an alkyl group having up to 3 carbon atoms, an alkoxy group having up to 4 carbon atoms or a phenyl group of the formula —PhR″,

Ph, m, n and n' being as defined in claim 1.

3. 1,3-Dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine].

4. 1,3-Dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine].

5. 1,3-Dihydro-1'-cyclopropylmethyl-3-phenylspiro[isobenzofuran-1,4'-piperidine].

6. 1,3-Dihydro-1'-[3-(p-fluorobenzoyl)propyl]-3-phenylspiro[isobenzofuran--1,4'-piperidine].

7. 1,3-Dihydro-3-(p-fluorophenyl)spiro[isobenzofuran-1,4'-piperidine].

8. 1,3-Dihydro-6-fluoro-1'-methyl-3-(p-fluorophenyl)spiro[isobenzofuran-1',4-piperidine].

9. 1,3-Dihydro-3-phenylspiro[isobenzofuran-1,3'-pyrrolidine].

10. 1,3-Dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,3'-pyrrolidine].

11. 1'-Cyclopropylmethyl-1,3-dihydro-3-phenylspiro[isobenzofuran-1,3'-pyrrolidine].

12. 1,3-Dihydro-3-p-tolylspiro[isobenzofuran-1,4'-piperidine].

13. 1,3-Dihydro-6-fluoro-3-p-fluorophenylspiro[isobenzofuran-1,4'-piperidine].

14. 1,3-Dihydro-6-methoxy-3-phenylspiro[isobenzofuran-1,4'-piperidine].

15. 1,3-Dihydro-3-p-fluorophenyl-1'-methylspiro[isobenzofuran-1,4'-piperidine].

16. 1,3-Dihydro-3-p-methoxyphenylspiro[isobenzofuran-1,4'-piperidine].

17. A compound as claimed in claim 1 and which is described in any one of the Examples herein.

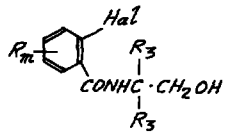
18. An acid addition salt of a compound as claimed in any one of claims 1 to 17.

* C L M S *

19. A physiologically tolerable acid addition salt of a compound as claimed in any one of claims 1 to 17.

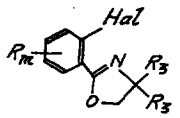
20. A process for the preparation of a compound as claimed in claim 1 which comprises

a) reacting an *o*-halogenobenzoyl chloride with an alkylated or unsubstituted 2-amino-1-ethanol to form the corresponding *o*-halogeno-N-(1-hydroxy-2-ethyl) benzamide of formula II



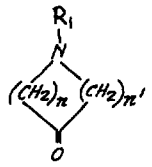
(II)

wherein R_3 represents a hydrogen atom or a lower alkyl group, cyclizing the benzamide to the corresponding *o*-halogeno-phenyl oxazoline of formula III



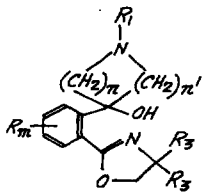
(III)

by treatment with a dehydrating agent, converting the oxazoline to a Grignard reagent by reaction with magnesium, reacting said Grignard reagent with a cycloazalkanone of formula IV



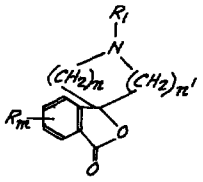
(IV)

to prepare the corresponding hydroxy-*o*-oxazolinyl phenyl cycloazalkane of formula V



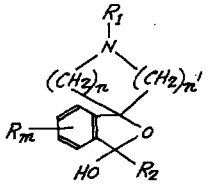
(V)

reacting said azalkane with an acid to form the corresponding 1,3-dihydrospiro-(isobenzofuran-cycloazalkane)-3-one of formula VI



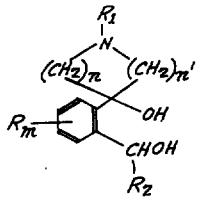
(VI)

reacting said azalkanone with an organometallic reagent to provide a 3-substituted 1,3-dihydro-3-hydroxyspiro-(isobenzofuran-cycloazalkane) of formula VII



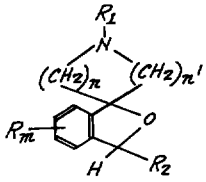
(VII)

reducing said hydroxy-azalkane to an *o*-hydroxyalkylphenyl cycloazalkanol of formula VIII



(VIII)

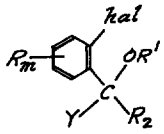
and treating said azalkanol with an acid to effect cyclization to the corresponding 3-substituted 1,3-dihydrospiro-(isobenzofuran-cycloazalkane) of formula IX,



(IX)

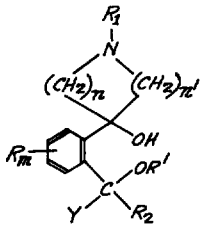
or

b) reacting an *o*-halobenzyl alcohol or an *o*-halobenzyl ether of formula X



(X)

wherein R' represents a hydrogen atom or an alkyl or tetrahydropyranyl group, with an alkyl lithium to form the corresponding lithium *o*-lithiobenzyloxide or *o*-lithiobenzyl alkyl ether, or converting the alkyl ether of formula X into a Grignard reagent, reacting the lithium *o*-lithiobenzyloxide, o-lithiobenzyl alkyl ether or Grignard reagent with a cycloazalkanone of formula IV and treating the corresponding (α-hydroxy-o-tolyl) cycloazalkanol or (α-hydroxy-o-tolyl) cycloazalkyl alkyl ether of formula XI

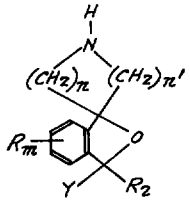


(XI)

thus obained with acid to effect cyclization to the corresponding 1,3-dihydrospiro(isobenzfuran-cycloazalkane) of formula XII, or

c) hydrogenating a 3-substituted N-benzyl-1,3-dihydrospiro(isobenzofuran-cycloazalkane) of the formula XII wherein R_1 stands for the benzyl group to effect cleavage of the benzyl group or

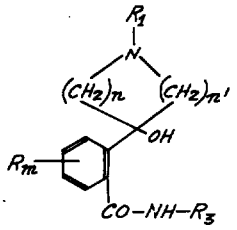
d) reacting an N- and 3-disubstituted 1,3-dihydrospiro(isobenzofuran-cycloazalkane) with a chloroformate to prepare a substituted N-oxycarbonyl-1,3-dihydrospiro(isobenzofuran-cycloazalkane), and treating said cycloazalkane with a base or an acid to form the corresponding N-unsubstituted 1,3-dihydrospiro-(isobenzofuran-cycloazalkane) of formula XIII,



(XIII)

* C L M S *

or
e) alkylating or acylating a 3-substituted 1,3-dihydrospiro(isobenzofuran-cycloazalkane) of formula XIII to provide the corresponding N-alkylated or N-acylated derivative, or
f) reducing an N-acylated 1,3-dihydrospiro(isobenzofuran-cycloazalkane) of formula XII to the corresponding N-alkylated derivative of formula XII or
g) reacting an N-substituted 1,3-dihydro-3-hydroxyspiro(isobenzofuran-cycloazalkane) of formula VII with an aliphatic mono-alcohol in the presence of an acid catalyst to provide the corresponding N-substituted 1,3-dihydro-3-alkoxyspiro(isobenzofuran-cycloazalkane) or formula XII wherein Y represents an alkoxy group, or
h) treating an alkoxy- or benzyloxy substituted 1,3-dihydrospiro(isobenzofuran-cycloazalkane) of formula XII wherein R represents an alkoxy group with an ether-splitting agent to provide the corresponding hydroxy substituted 1,3-dihydrospiro(isobenzofuran-cycloazalkane) wherein R represents a hydroxy group, or
i) treating a 1,3-dihydrospiro(isobenzfuran-cycloazalkane) of formula XII wherein R represents a methoxy group with sodium thioethoxide to give the corresponding hydroxy compound, or
j) treating an N-substituted 1,3-dihydrospiro(isobenzofuran-cycloazalkane) of formula XII wherein Y represents a hydrogen atom with an alkyl lithium to produce the corresponding N-substituted 1,3-dihydro-3-lithiospiro(isobenzofuran-cycloazalkane) and reacting said lithium derivative with an alkylating agent to produce the corresponding N-substituted 1,3-dihydro-3-alkylspiro(isobenzofuran-cycloazalkane) of formula XII, wherein Y represents an alkyl group, or
k) reducing the carbonyl group in the side chain of an N-substituted 1,3-dihydrospiro(isobenzofuran-cycloazalkane) of formula XII wherein R_1 contains a carbonyl group to form the corresponding N-substituted hydroxy derivative of formula XII, or
l) reacting an *o*-halogenophenyloxazoline of formula III with an alkyl lithium, treating the resulting *o*-lithiophenyl oxazoline with a cycloazalkanone of formula IV, reacting the resulting 1,3-dihydrospiro(isobenzofuran-cyclazalkane)-3-one of formula V with an acid, reacting the resulting hydroxy-*o*-oxazolinyl phenyl cycloazalkane of formula VI with an organometallic reagent, reducing the resulting 3-substituted 1,3-dihydro-3-hydroxy-spiro(isobenzofuran-cycloazalkane) of formula VII to an *o*-hydroxyalkylphenyl cycloazalkanol of formula VIII and treating the azalkanol of formula VII with an acid to effect cyclization to the corresponding 3-substituted 1,3-dihydrospiro(isobenzofuran-cycloazalkane) of formula IX, or
m) reacting a compound of formula XIV



(XIV)

wherein R_3 has the meaning given above with an acid to form a compound of formula VI and/or treating the compound of formula VI according to method a) to form a compound of formula IX, wherein in the above mentioned formulae the substituents R, R_1, R_2, Y have the meanings given in claim 1 and wherein hal stands for a halogen atom and wherein m, n and n' have the meanings given in claim 1.

21. A process as claimed in claim 20, conducted substantially as described in any one of the Examples herein.

22. A compound as claimed in claim 1, whenever produced by a process as claimed in claim 20 or claim 21.

23. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 17, claim 19 or claim 22 in admixture or conjunction with a pharmaceutically suitable carrier.

24. A pharmaceutical preparation as claimed in claim 23, in a form suitable for oral administration.

* C L M S *

25. A pharmaceutical preparation as claimed in claim 24, in unit dosage form.

26. A pharmaceutical preparation as claimed in claim 25, which comprises from 10 to 200 mg of the compound per unit dose.

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* C L M S *