

# PATENT SPECIFICATION

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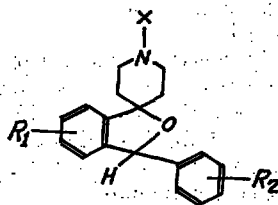
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## (54) 1,3-DIHYDROSPIRO[ISOBENZOFURAN-1,4'-PIPERIDINE]S AND METHODS FOR PREPARING THEM

(71) We, HOECHST AKTIENGESSELLSCHAFT, 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:—

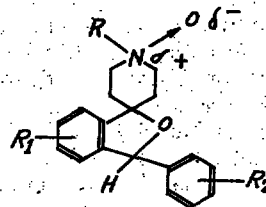
This invention relates to 1,3-dihydrospiro[isobenzofuran-1,4'-piperidine]s.

The invention provides a 1,3-dihydrospiro[isobenzofuran-1,4'-piperidine] of the general formula



(I)

or



(II)

wherein R represents an alkyl group having from 1 to 4 carbon atoms or an unsubstituted or substituted phenalkyl group having from 7 to 9 carbon atoms; X represents a nitroso, amino, mono- or di-alkylamino having from 1 to 5 carbon atoms in each alkyl group, hydroxy or unsubstituted or substituted benzoyloxy group; R<sub>1</sub> represents a hydrogen atom, an alkoxy group having from 1 to 3 carbon atoms or a trifluoromethyl group; and R<sub>2</sub> represents a hydrogen, bromine, fluorine or chlorine atom or an alkoxy group having from 1 to 3 carbon atoms. The invention also provides an acid addition salt of an amino, mono- or di-alkylamino or hydroxy derivative thereof.

There may especially be mentioned compounds of the invention in which R<sub>1</sub> represents a hydrogen atom or a methoxy group and R<sub>2</sub> represents a hydrogen or a fluorine atom or a methoxy group. Preferably X represents a hydroxy group, and F represents an alkyl group having from 1 to 4 carbon atoms, a benzyl group or a phenethyl group.

The substituents R<sub>1</sub> and R<sub>2</sub> may be in any desired position on the rings shown. Preferably R<sub>2</sub> is a para substituent, and preferably R<sub>1</sub> is in the 5 or, more preferably, the 6, position of the isobenzofuran nucleus.

The compounds of the invention may be used as analgesic, anticonvulsant and antidepressant agents, and have relatively low toxicity levels.

Illustrative examples of compounds of the invention are:

5 - methoxy - 1' - nitroso - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine];

1,3 - dihydro - 1' - methyl - 6 - trifluoromethyl - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine] - 1' - oxide;

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

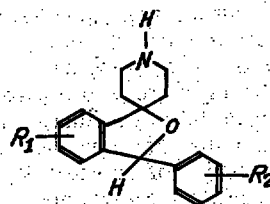
- 1' - ethylamino - 1,3 - dihydro - 6 - methoxy - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine];
- 1' - amylamino - 1,3 - dihydro - 6 - methoxy - 3 - (4 - methoxyphenyl) - spiro - [isobenzofuran - 1,4' - piperidine];
- 1' - butyl - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine] - 1' - oxide;
- 1,3 - dihydro - 1' - phenethyl - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine] - 1' - oxide; and
- 1' - hydroxy - 1,3 - dihydro - 3 - (4 - fluorophenyl) - 5 - methoxyspiro[isobenzofuran - 1,4' - piperidine];
- 1' - benzoyloxy - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine];
- 1' - amino - 1,3 - dihydro - 3 - phenyl - spiro[isobenzofuran - 1,4' - piperidine];
- 1' - hydroxy - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine];
- 1' - benzyl - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4 - piperidine] - 1' - oxide, and
- 1' - (isopropylamino) - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine];
- 1' - hydroxy - 1,3 - dihydro - 3 - (4 - methoxy - phenyl)spiro[isobenzofuran - 1,4' - piperidine];
- 1' - hydroxy - 1,3 - dihydro - 6 - methoxy - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine];
- 1' - hydroxy - 1,3 - dihydro - 3 - (4 - fluoro - phenyl)spiro[isobenzofuran - 1,4' - piperidine];
- 1,3 - dihydro - 1' - methyl - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine] - 1' - oxide.

Preferred salts of the invention are those which are physiologically tolerable. Acids which may be used for preparing physiologically tolerable acid addition salts of the invention include inorganic acids, for example hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, and perchloric acids, and organic acids, for example tartaric, citric, acetic, succinic, malic, and fumaric acids.

The invention also provides a process for preparing a compound of the general formula (I) or (II) or a salt thereof, which comprises one of the three methods described below using as a starting material a piperidine, for example those described in United States Patent No. 3,959,475. While some compounds of the invention are more active pharmaceutically than others, the less active compounds are nevertheless useful as intermediates for the preparation of the more active compounds.

#### Method A

1. A piperidine of the general formula



(III)

wherein R and R<sub>2</sub> have the meanings given above, is N-nitrosated, suitably by a method known to the art, to produce the corresponding nitroso compound of the invention. The process may be carried out, for example, using aqueous acetic acid as solvent. Sodium nitrite is a suitable nitrosating agent. One preferred method of carrying out the N-nitrosation involves the use of aqueous acetic acid as a solvent and sodium nitrite as a nitrosating salt preferably at a reaction temperature of from 0 to 5°C.

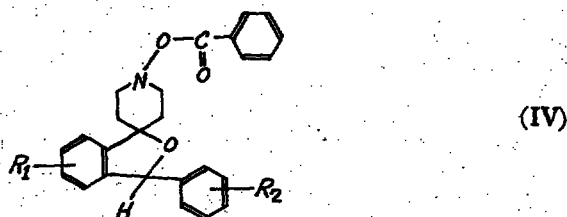
2. The above nitroso compound is then, if desired, converted to the corresponding amino compound, or an acid addition salt thereof, using a reducing agent, for example elemental zinc in an acid medium, preferably at a temperature of from 0 to 110°C (preferably in a solvent, for example aqueous acetic acid). The reaction time is typically from 5 mins to 2 hours. If desired the resulting amino compound may be converted to the corresponding acid addition salt.

3. The above amino compound, or acid addition salt, thereof, is then, if desired, reductively alkylated, the reaction time typically being from a few minutes to 24 hours, preferably at a temperature of from 15 to 100°C., using a suitable alkylating agent and reducing agent in the presence or absence of an organic solvent, to produce the

corresponding secondary or tertiary amine, which is also a compound of the invention or an acid addition salt thereof. The resulting mono- or di-alkylamino compound may be converted into a corresponding acid addition salt, if desired, or *vice versa*. One such method involves the use of a ketone or an aldehyde as the alkylating agent, sodium cyanoborohydride as the reducing agent, and, preferably acetonitrile as the solvent.

#### Method B

1. A piperidine of the general formula (III) is added to a benzoyl peroxide wherein the benzoyl group may be unsubstituted or substituted, preferably dissolved in an organic solvent, for example benzene, and preferably below room temperature. The reaction time is typically from a few minutes to 12 hours, and the reaction temperature is preferably in the range of from 0 to 80°C., for example, about 60°C. A corresponding N-benzoyloxy compound of the invention of the general formula

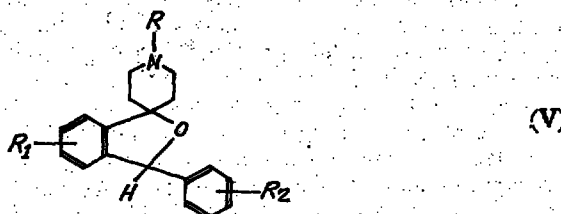


wherein R<sub>1</sub> and R<sub>2</sub> have the meanings given above, may thus be produced.

2. The above N-benzoyloxy compound may, if desired, be converted to the corresponding N-hydroxy compound of the invention, or an acid addition salt thereof, by hydrolysing the benzoyloxy group, preferably by treatment with aqueous sodium hydroxide and ethanol and refluxing the mixture from a few minutes to about two hours and, if desired, converting the resulting compound to the corresponding acid addition salt.

#### Method C

A piperidine of the general formula



wherein R, R<sub>1</sub> and R<sub>2</sub> have the meanings given above is oxidised to the corresponding N-oxide of the invention having the general formula (II), preferably using hydrogen peroxide as the oxidising agent and an organic solvent, preferably glacial acetic acid, at a reaction temperature of about 100°C for from a few minutes to 24 hours, preferably for from a few minutes to two hours. Another suitable oxidising agent is 3-chloro-perbenzoic acid, preferably using chloroform as a solvent.

It will be readily appreciated by those skilled in the art that the time and temperature necessary to complete the reaction in the steps of the above methods are inter-related and dependent upon the structures and compositions of the reactants and the solvent.

The invention also provides a pharmaceutical preparation comprising a compound of the general formula (I) or (II) or a physiologically tolerable salt of the invention, in admixture or conjunction with a pharmaceutically suitable carrier, preferably which contains in the range of from 0.5 to 70% by weight of active ingredient.

Such a preparation may be administered to a patient by any one of various methods, for example, orally as in capsules or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. The free base final products, while effective themselves, may be formulated and administered in the form of their physiologically tolerable addition salts, for purposes of, for example, stability, convenience of crystallisation and increased solubility. The daily dosage is suitably from 0.1 to 50 mg/kg body weight.

The active compounds of the present invention may be administered orally for example with an inert diluent or with an edible carrier, and/or enclosed in gelatin capsules, and/or compressed into tablets. For the purpose of oral therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form, for example, of tablets, troches, dragees, capsules, elixirs, suspensions, syrups, wafers and chewing gum. These preparations preferably contain at least 0.5% of active compound by weight, but the amount may be varied depending upon the particular form and may conveniently be from 4% 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 between 1.0—300 milligrams of active compound.

The tablets, pills, capsules, dragees, troches, may also contain additional ingredients known in the art, for example a binder, for example, micro-crystalline cellulose, gum tragacanth or gelatin; an excipient, for example starch or lactose; a disintegrating agent, for example alginic acid, Primogel or corn starch; a lubricant, for example magnesium stearate or Sterotex; a glidant, for example colloidal silicon dioxide; a sweetening agent, for example sucrose or saccharin; and a flavouring 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 such as a fatty oil. Other dosage unit forms may contain other 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 other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent, and certain preservatives, dyes and colourings, and flavours. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the active compounds of the invention may be incorporated into solutions or suspensions. These preparations should preferably contain at least 0.1% of active compound, more preferably from 0.5 to 30% by weight based on the weight of the preparation. The amount of active compound in such compositions and preparations according to the present invention are prepared so that parenteral dosage units contain preferably between 0.5 to 100 milligrams of active compound.

The solutions or suspensions may also include additional components such as sterile diluents such as water for injection, saline solutions, fixed oils, polyethylene glycols, glycerine, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulphite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparations can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

The analgesic properties of representative compounds of the invention may be demonstrated in the 2-phenyl-1,4-quinone-induced writhing assay in mice, a standard assay for analgesia [Proc. Soc. Exptl. Biol. Med., Vol. 45, 729 (1957)]. Thus, for instance, a 54% inhibition of writhing is effected by a 50 mg/kg of body weight oral dose of 1' - benzoxyloxy - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4 - piperidine]. Similarly, 50 mg/kg of body weight oral doses of 1' - amino - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine], 1' - hydroxy - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine], 1' - benzyl - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine] - 1' - oxide, and 1' - (isopropylamino) - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine] exhibit a 53%, 53%, 48% and 27%, respectively, inhibition of writhing. These data illustrate that a compound of the invention is generally useful for the alleviation of pain in mammals when administered in amounts ranging from, for example, 1 to 50 mg/kg of body weight per day.

The antidepressant activity, in mammals, of representative compounds of the invention may be demonstrated by their ability to inhibit tetrabenzazine-induced depression in mice [International Journal of Neuropsychopharmacology, Vol. 8, 73 (1969)]. A standard assay for useful antidepressant properties, as shown, for example, in Table 1 below. The results are expressed in ED<sub>50</sub>'s (intraperitoneal dose effecting a 50% inhibition of ptosis of tetrabenzazine-induced depression in mice). The doses are in mg/kg of body weight. Table 1 also indicates the relatively low toxicity exhibited by a compound of the invention. The toxicity data is expressed in ALD<sub>50</sub>'s (the acute lethal intraperitoneal dose, mg/kg of body weight, in 50% of the mice tested). This data

was generated by testing groups of four mice at various doses and noting the number of deaths.

TABLE 1

| Compound                                                                       | Antidepressant<br>ED <sub>50</sub> | Toxicity<br>ALD <sub>50</sub> |
|--------------------------------------------------------------------------------|------------------------------------|-------------------------------|
| 1'-hydroxy-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine]            | 1.4                                | 562                           |
| 1'-hydroxy-1,3-dihydro-3-(4-methoxyphenyl)spiro[isobenzofuran-1,4'-piperidine] | 2.6                                | 562                           |
| 1'-hydroxy-1,3-dihydro-6-methoxy-3-phenylspiro[isobenzofuran-1,4'-piperidine]  | 3.2                                | 562                           |
| 1'-hydroxy-1,3-dihydro-3-(4-fluorophenyl)spiro[isobenzofuran-1,4f-piperidine]  | 4.0                                | 316                           |
| 1,3-dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]-1'-oxide    | 6.5                                | 280                           |
| 1'-amino-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine]              | 10.3                               | 100                           |

These data show by way of example the utility of a compound of the invention for the treatment of depression in mammals when administered intraperitoneally in amounts of ranging from, for example, 0.1 to 50 mg/kg of body weight per day.

A compound of the invention may be used as an anti-convulsant agent for mammals, as may be determined by the method of Woodbury, L. A. and Davenport, V.D., in Arch. Int. Pharmacodynam, Vol. 92, (1952) at pages 97-107. For example, 1'-amino-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine] at an intraperitoneal dose of about 5 mg/kg of body weight produced a 50% protection from the effect of a supra maximal electro shock. This datum illustrates the utility of a compound of the invention for the treatment of convulsion in mammals when administered in amounts ranging from, for example, 0.1 to 50 mg/kg of body weight per day.

The following Examples illustrate the invention.

## EXAMPLE 1

A solution of 2.1 g of sodium nitrite in 9 ml of water was added dropwise to a solution of 4.0 g of 1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine] in 15 ml of glacial acetic acid and 6 ml of water at 0°C. The mixture was stirred while maintaining the reaction temperature between 0 and 5°C. Upon completion of the addition, the reaction mixture was allowed to stand for one hour at ambient temperature. Then the reaction mixture was diluted with water, filtered, and the white precipitate was collected, washed with water and cold ethanol and dried. The dried precipitate was recrystallised from ethanol to give very slightly yellow leaflets, mp 159-161°C., of 1'-nitroso-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine].

## Analysis:

Calculated for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: 73.45% C; 6.16% H; 9.52% N  
Found: 73.20% C; 6.11% H; 9.37% N

## EXAMPLE 2

A solution of 7.1 g of 1'-nitroso-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine] (cf Example 1), in 75 ml of glacial acetic acid was added to a stirred suspension of 7.1 g of zinc dust in 50 ml of glacial acetic acid and 50 ml of water whilst the reaction temperature was maintained between 10 and 20°C. The reaction mixture was stirred for 15 minutes at ambient temperature and then at 80°C. for 5 minutes; an additional 4.7 g of zinc dust were introduced and the stirring continued for an additional 10 minutes. The heated mixture was filtered, the precipitate was washed with hot 1N hydrochloric acid and the combined filtrate and washings made basic and extracted with chloroform. The organic solution was dried and the solvent removed, leaving a white crystalline solid, 1'-amino-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine], which is recrystallised from ethanol to give the pure product, mp 143-145°C.

## Analysis:

Calculated for C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O: 77.11% C; 7.19% H; 9.99% N  
Found: 77.04% C; 7.13% H; 9.69% N

## EXAMPLE 3

0.24 g of sodium cyanoborohydride were added to a mixture of 1.4 g of 1'-amino-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine] (cf Example 2), 25 ml of acetonitrile and 2.5 ml of acetone. Five drops of glacial acetic acid were added and then the mixture was warmed briefly and stirred for five hours at ambient temperature under nitrogen whilst maintaining the pH between 6 and 8. The reaction mixture was then diluted with 250 ml of chloroform, washed with 2N hydrochloric acid and 10% aqueous sodium hydroxide solution and dried. The solvent was removed, leaving a pale yellow oil which upon trituration with an ether-petroleum ether mixture gave a white crystalline solid. The solid was recrystallised from ethanol to give fine white crystals, mp 110—112°C., of 1'-(isopropylamino)-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine].

## Analysis:

Calculated for  $C_{21}H_{25}N_2O$ : 78.22% C; 8.13% H; 8.69% N  
 Found: 78.03% C; 8.18% H; 8.73% N

## EXAMPLE 4

5.3 g of 1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine] were added in portions to an ice bath cooled solution of 2.4 g of benzoyl peroxide in 75 ml of benzene. The mixture was allowed to react at 60°C. under nitrogen for two hours and the solvent was removed leaving a semi-crystalline residue which was recrystallised from ethanol to give nearly colourless needles, mp 161—164°C., of 1'-benzoyloxy-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine].

## Analysis:

Calculated for  $C_{25}H_{23}NO_3$ : 77.90% C; 6.01% H; 3.63% N  
 Found: 77.94% C; 6.08% H; 3.64% N

## EXAMPLES 5—7

By following the procedure described above in Example 4, 1,3-dihydro-3-(4-methoxyphenyl)spiro[isobenzofuran-1,4'-piperidine], 1,3-dihydro-6-methoxy-3-phenylspiro[isobenzofuran-1,4'-piperidine], and 1,3-dihydro-3-(4-fluorophenyl)spiro[isobenzofuran-1,4'-piperidine] were each treated to give the corresponding 1'-benzoyloxy compounds tabulated below in Table II.

TABLE II

| Ex. | Empirical Formula                                 | mp<br>C. | %C    | Calculated |      |      | Analysis |      |      |      |
|-----|---------------------------------------------------|----------|-------|------------|------|------|----------|------|------|------|
|     |                                                   |          |       | %H         | %N   | %F   | %C       | %H   | %N   | %F   |
| 5   | C <sub>26</sub> H <sub>25</sub> NO <sub>4</sub>   | 164—166  | 75.16 | 6.06       | 3.37 | —    | 75.15    | 6.22 | 3.34 | —    |
| 6   | C <sub>26</sub> H <sub>25</sub> NO <sub>4</sub>   | 163—167  | 75.16 | 6.06       | 3.37 | —    | 75.11    | 6.17 | 3.36 | —    |
| 7   | C <sub>25</sub> H <sub>22</sub> NO <sub>3</sub> F | 163—166  | 74.42 | 5.50       | 3.47 | 4.71 | 74.58    | 5.65 | 3.51 | 4.85 |

## EXAMPLE 8

A mixture of 2.1 g of 1'-benzoyloxy-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine] (cf Example 4), 24 ml of ethanol and 16 ml of a 10% aqueous sodium hydroxide solution was heated at reflux under nitrogen for 20 minutes. Most of the ethanol was removed *in vacuo* and the residue was diluted with 40 ml of water and the pH adjusted to 6 by the dropwise addition of 2N hydrochloric acid. The aqueous solution was extracted with chloroform, the combined chloroform extracts dried, and the chloroform removed, leaving a pale yellow oil which upon trituration with an ether-petroleum ether mixture gave a white solid. The solid was recrystallised from ethanol to give fine white crystals, mp 184—187°C. of 1'-hydroxy-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine].

## Analysis:

Calculated for  $C_{16}H_{19}NO_2$ : 76.84% C; 6.81% H; 4.98% N  
 Found: 76.63% C; 6.85% H; 4.80% N

## EXAMPLE 9

A mixture of 1.99 g of 1'-benzoyloxy-1,3-dihydro-3-(4-methoxyphenyl)spiro[isobenzofuran-1,4'-piperidine] (cf. Example 5), 24 ml of ethanol and 16 ml of a 10% aqueous sodium hydroxide solution was heated at reflux under nitrogen for 25 minutes.

(17)

Most of the ethanol was removed *in vacuo*, the residue was diluted with 40 ml of water and the pH is adjusted to 9 by addition of 2N hydrochloric acid. The aqueous solution was extracted with chloroform, the combined chloroform extracts dried, and the chloroform removed, leaving a pale beige solid which upon trituration with an ether-petroleum ether mixture leaves a nearly colourless crystalline solid. The solid recrystallised from ethanol to give fine white crystals, mp 183—185°C., of 1'-hydroxy - 1,3 - dihydro - 3 - (4 - methoxyphenyl)spiro[isobenzofuran - 1,4' - piperidine].

## Analysis:

Calculated for  $C_{19}H_{21}NO_3$ : 73.29% C; 6.80% H; 4.50% N  
Found: 73.18% C; 6.82% H; 4.48% N

## EXAMPLE 10

A mixture of 1.3 g of 1'-benzoyloxy-1,3-dihydro-6-methoxy-3-phenylspiro[isobenzofuran-1,4'-piperidine] (cf. Example 6), 18 ml of ethanol and 12 ml of 10% aqueous sodium hydroxide solution was heated at reflux under nitrogen for 20 minutes. Most of the ethanol was removed *in vacuo*, the residue was diluted with 30 ml of water, and the pH adjusted to 8 by addition of 2N hydrochloric acid. The aqueous solution was extracted with chloroform, the combined chloroform extracts dried, and the chloroform removed to give a yellow crystalline solid which upon trituration with an ether-petroleum ether mixture gave a pale yellow crystalline solid. The solid was recrystallised from ethanol to give fluffy white crystals, mp 186—188°C., of 1'-hydroxy - 1,3 - dihydro - 6 - methoxy - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine].

## Analysis:

Calculated for  $C_{19}H_{21}NO_3$ : 73.29% C; 6.80% H; 4.50% N  
Found: 73.41% C; 6.84% H; 4.46% N

## EXAMPLE 11

By following the procedure described above in Example 10, the treatment of a mixture of 1.5 g of 1'-benzoyloxy-1,3-dihydro-3-(4-fluorophenyl)spiro[isobenzofuran-1,4'-piperidine] (cf. Example 7), 18 ml of absolute ethanol, and 12 ml of a 10% aqueous sodium hydroxide solution produced fine white crystals, mp 182—185°C., of 1'-hydroxy - 1,3 - dihydro - 3 - (4 - fluorophenyl)spiro[isobenzofuran - 1,4' - piperidine].

## Analysis:

Calculated for  $C_{18}H_{17}NO_2F$ : 72.22% C; 6.06% H; 4.68% N; 6.35% F  
Found: 72.20% C; 6.09% H; 4.72% N; 6.15% F

## EXAMPLE 12

A solution of 2.8 g of 1,3-dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine], 50 ml of acetic acid and 4 ml of 30% hydrogen peroxide was heated on a steam bath for one hour, diluted with 200 ml of water, concentrated to a total volume of 50 ml, again diluted with 200 ml of water and concentrated to an oil. The oil was then dissolved in chloroform, the chloroform solution washed consecutively with an aqueous sodium bicarbonate solution and water, dried, and the chloroform removed, leaving an oil which upon trituration with ether gave a solid. The solid was recrystallised from acetonitrile to give colourless crystals, mp 166—167°C., of 1,3-dihydro-1'-methyl-3-phenylspiro[isobenzofuran-1,4'-piperidine]-1'-oxide.

## Analysis:

Calculated for  $C_{19}H_{21}NO_2 \cdot H_2O$ : 72.82% C; 7.40% H; 4.41% N  
Found: 72.00% C; 7.44% H; 4.39% N

By following the manipulative procedure outlined above, 1,3-dihydro-1'-methyl-6-trifluoromethyl-3-phenylspiro[isobenzofuran-1,4'-piperidine] was converted to 1,3-dihydro - 1' - methyl - 6 - trifluoromethyl - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine] - 1' - oxide.

## EXAMPLE 13

A solution of 2.0 g of 85% 3-chloroperbenzoic acid in 25 ml of chloroform was added dropwise to a stirring solution, chilled to 0°C. under nitrogen, of 3.6 g of 1' - benzyl - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine] in 15 ml

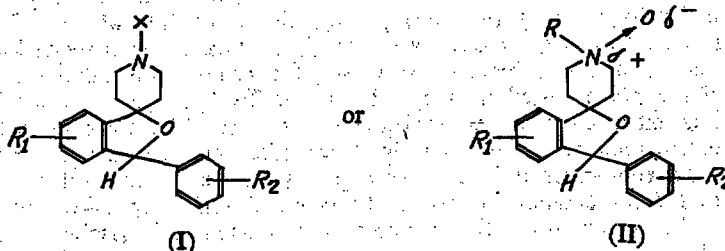
of chloroform. After total addition the resulting solution was stirred for three hours at ambient temperature, diluted with 50 ml of chloroform, washed with a saturated aqueous sodium bicarbonate solution and the chloroform removed *in vacuo*, leaving a very pale yellow oil. The oil was triturated with an ether-petroleum ether mixture to give a white crystalline solid which was recrystallised from acetonitrile to give a somewhat hygroscopic white crystalline solid, mp 147–150°C., of 1'-benzyl-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine]-1'-oxide.

Analysis:

|                                     |           |          |         |
|-------------------------------------|-----------|----------|---------|
| Calculated for $C_{25}H_{25}NO_2$ : | 80.83% C; | 6.78% H; | 3.77% N |
| Found:                              | 80.65% C; | 6.84% H; | 3.73% N |

WHAT WE CLAIM IS:—

1. Compound of the general formula



wherein R represents an alkyl group having from 1 to 4 carbon atoms or an unsubstituted or substituted phenalkyl group having from 7 to 9 carbon atoms, X represents a nitroso, amino, mono- or di-alkylamino having from 1 to 5 carbon atoms in each alkyl group, hydroxy or unsubstituted or substituted benzoyloxy group,  $R_1$  represents a hydrogen atom, an alkoxy group having from 1 to 3 carbon atoms, or a trifluoromethyl group, and  $R_2$  represents a hydrogen, bromine, fluorine or chlorine atom or an alkoxy group having from 1 to 3 carbon atoms.

2. A compound of the general formula (I) as claimed in claim 1, wherein  $R_1$  represents a hydrogen atom or a methoxy group and  $R_2$  represents a hydrogen or a fluorine atom or a methoxy group.

3. A compound of the general formula (I) as claimed in either claim 1 or claim 2, wherein X represents a hydroxy group.

4. A compound of the general formula (II) as claimed in claim 1, wherein R represents an alkyl group having from 1 to 4 carbon atoms, a benzyl group or a phenethyl group,  $R_1$  represents a hydrogen atom or a methoxy group, and  $R_2$  represents a hydrogen or a fluorine atom or a methoxy group.

5. 5 - Methoxy - 1' - nitroso - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine].

6. 1,3 - Dihydro - 1' - methyl - 6 - trifluoromethyl - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine] - 1' - oxide.

7. 1'-Propylamino-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine].

8. 1' - Ethylamino - 1,3 - dihydro - 6 - methoxy - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine].

9. 1 - Amylamino - 1,3 - dihydro - 6 - methoxy - 3 - (4 - methoxyphenyl)spiro - [isobenzofuran - 1,4' - piperidine].

10. 1' - Butyl - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine] - 1' - oxide.

11. 1,3 - Dihydro - 1' - phenethyl - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine] - 1' - oxide.

12. 1' - Hydroxy - 1,3 - dihydro - 3 - (4 - fluorophenyl) - 5 - methoxyspiro - [isobenzofuran - 1,4' - piperidine].

13. 1' - Benzoyloxy - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine].

14. 1' - Amino - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine].

15. 1'-Hydroxy-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine].

16. 1' - Benzyl - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine] - 1' - oxide.

17. 1' - (Isopropylamino) - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine].



**Analysis :**

|                                     |           |          |         |
|-------------------------------------|-----------|----------|---------|
| Calculated for $C_{25}H_{25}NO_2$ : | 80.83% C; | 6.78% H; | 3.77% N |
| Found:                              | 80.65% C; | 6.84% H; | 3.73% N |

1. Compound of the general formula



17. 1' - (Isopropylamino) - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine].

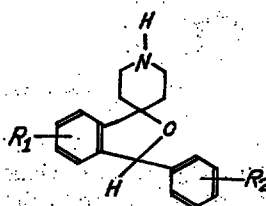


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18. 1' - Hydroxy - 1,3 - dihydro - 3 - (4 - methoxyphenyl)spiro[isobenzofuran - 1,4' - piperidine].
19. 1' - Hydroxy - 1,3 - dihydro - 6 - methoxy - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine].
20. 1' - Hydroxy - 1,3 - dihydro - 3 - (4 - fluorophenyl)spiro[isobenzofuran - 1,4' - piperidine].
21. 1,3 - Dihydro - 1' - methyl - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine] - 1' - oxide.
22. 1' - Nitroso-1,3-dihydro-3-phenylspiro[isobenzofuran-1,4'-piperidine].
23. 1' - Benzoyloxy - 1,3 - dihydro - 3 - (4 - methoxyphenyl)spiro[isobenzofuran - 1,4' - piperidine].
24. 1' - Benzoyloxy - 1,3 - dihydro - 6 - methoxy - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine].
25. 1' - Benzoyloxy - 1,3 - dihydro - 3 - (4 - fluorophenyl)spiro[isobenzofuran - 1,4' - piperidine].
26. 1' - Benzyl - 1,3 - dihydro - 3 - phenylspiro[isobenzofuran - 1,4' - piperidine] - 1' - oxide.
27. An acid addition salt of a compound as claimed in any one of claims 1, 2 and 4, wherein X represents an amino, mono- or di-alkylamino or hydroxy group, or of a compound as claimed in any one of claims 3, 7 to 9, 12, 14, 15 and 17 to 20.
28. A physiologically tolerable acid addition salt of a compound as claimed in any one of claims 1, 2 and 4, wherein X represents an amino, mono- or di-alkylamino or hydroxy group, or of a compound as claimed in any one of claims 3, 7 to 9, 12, 14, 15 and 17 to 20.
29. A process for the production of a compound of the general formula (I) wherein, X represents a nitroso group, as claimed in claim 1, which comprises N-nitrosating a piperidine of the general formula:



(III)

- wherein  $R_1$  and  $R_2$  have the meanings given in claim 1.
30. A process as claimed in claim 29, wherein the nitrosating agent is sodium nitrite.
31. A process as claimed in either claim 29 or claim 30, wherein the reaction is carried out at a temperature in the range of from 0 to 5°C.
32. A process as claimed in any one of claims 29 to 31, wherein aqueous acetic acid is used as a solvent.
33. A process for the production of a compound of the general formula (I) wherein X represents an amino group, as claimed in claim 1, or an acid addition salt thereof, which comprises reducing a compound of the general formula (I) wherein X represents a nitroso group and, if desired, converting the resulting compound into an acid addition salt thereof.
34. A process as claimed in claim 33, wherein the reduction is carried out using elemental zinc and an acid.
35. A process as claimed in either claim 33 or claim 34, wherein the reaction is carried out at a temperature in the range of from 0 to 110°C.
36. A process as claimed in any one of claims 33 to 35, wherein aqueous acetic acid is used as a solvent.
37. A process for the preparation of a compound of the general formula (I), wherein X represents an amino group or an acid addition salt thereof and, if desired, carbon atoms in each alkyl group, as claimed in claim 1, or an acid addition salt thereof, which comprises reductively alkylating a compound of the general formula (I) wherein X represents an amino group or an acid addition salt thereof and, if desired, the resulting mono- or di-alkylamino compound is converted into a corresponding acid addition salt and *vice versa*.
38. A process as claimed in claim 37, wherein the alkylating agent is an aldehyde or a ketone, having from 1 to 5 carbon atoms, and sodium cyanoborohydride is used as a reducing agent.



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39. A process as claimed in any one of claims 37 and 38, wherein acetonitrile is used as a solvent.

40. A process as claimed in any one of claims 37 to 39, wherein the reaction is carried out at a temperature in the range of from 15 to 100°C.

5 41. A process for the preparation of a compound of the general formula (I) wherein X represents an unsubstituted or substituted benzoyloxy group, as claimed in claim 1 which comprises reacting a piperidine of the general formula (III) given in claim 29 with a benzoyl peroxide, the benzoyl group of which may be unsubstituted or substituted.

10 42. A process as claimed in claim 41, carried out in the presence of an organic solvent.

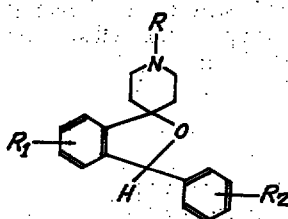
43. A process as claimed in claim 42, wherein the solvent is benzene.

44. A process as claimed in any one of claims 41 to 43, wherein the reaction is carried out at a temperature in the range of from 0 to 80°C.

15 45. A process for the preparation of a compound of the general formula (I), wherein X represents a hydroxyl group, as claimed in claim 1, or an acid addition salt thereof, which comprises hydrolysing a compound of the general formula (I) wherein X represents a benzoyloxy group and, if desired, converting the resulting compound into a corresponding acid addition salt.

20 46. A process as claimed in claim 45, wherein the hydrolysis is carried out using sodium hydroxide and ethanol under reflux.

47. A process for the production of a compound of the general formula (II) as claimed in claim 1, which comprises N-oxidising a piperidine of the general formula



(V)

25 wherein R, R<sub>1</sub> and R<sub>2</sub> have the meanings given in claim 1.

48. A process as claimed in claim 47, wherein the oxidation is performed in the presence of an organic solvent.

49. A process as claimed in claim 48, wherein the oxidising agent is 3-chloro-perbenzoic acid and the solvent is chloroform.

30 50. A process as claimed in claim 48, wherein the oxidising agent is hydrogen peroxide and the solvent is glacial acetic acid.

51. A process for the preparation of a compound of the general formula (I) or (II) as claimed in claim 1, or, where appropriate, an acid addition salt thereof, whenever carried out substantially as described in any one of Examples 1 to 13 herein.

35 52. A compound of the general formula (I) or (II) as claimed in claim 1, or, where appropriate, a physiologically tolerable acid addition salt thereof, whenever prepared by a process as claimed in any one of claims 29 to 51 herein.

40 53. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 26, 28 and 52, in admixture or conjunction with a pharmaceutically suitable carrier.

54. A pharmaceutical preparation as claimed in claim 53, suitable for oral administration.

55. A pharmaceutical preparation as claimed in claim 54, which contains at least 0.5% by weight of the active compound.

45 56. A pharmaceutical preparation as claimed in claim 55, which contains from 4 to 70% by weight of the active compound.

57. A pharmaceutical preparation as claimed in claim 53, suitable for parenteral administration.



(21)

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58. A pharmaceutical preparation as claimed in claim 57, which contains at least 0.1% by weight of the active compound.

59. A pharmaceutical preparation as claimed in claim 58, which contains from 0.5 to 30% by weight of the active compound.

60. A pharmaceutical preparation as claimed in claim 53, which contains from 0.5 to 70% by weight of the active compound.

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