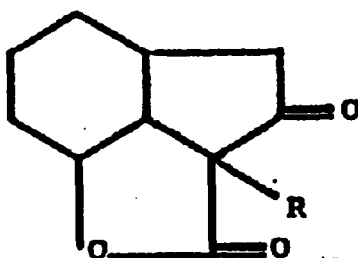


TITLEIndenofuran DerivativesDESCRIPTION

The invention relates to indenofuran derivatives, to a method for their preparation and to pharmaceutical compositions containing them.

The invention provides perhydro-indeno[7,7a,1-bc]furan-2,3-dione derivatives of the general formula I



wherein R represents an unsubstituted benzyl group or a benzyl group ring substituted by one or more straight or branched chain alkyl groups having from 1 to 5 carbon atoms and/or one or more straight or branched chain alkoxy groups having from 1 to 5 carbon atoms and/or one or more hydroxy groups.

The compounds according to the invention are useful as precursors for the synthesis both of Ginkgolides and of related derivatives presenting a PAF-Acether antagonist activity. Most of these compounds present also per se an interesting therapeutic activity in the field of anaphylaxy.

The indenofuran derivatives according to the invention may be prepared by condensing perhydroindeno-[7,7a,1-bc]-furan-2,3-dione (I, R=H) with a compound RX wherein R is as defined above and X represents a halogen

atom. The condensation is carried out under nitrogen circulation at a temperature of from -10°C to 0°C in the presence of an alkali metal hydride. Preferably X represents a bromine atom. The preferred alkali metal hydride is sodium hydride. This process is within the scope of the invention.

Perhydroindeno[7,7a,1-bc]furan-2,3-dione, which is the starting material for the above described process, is a known compound (see J. Am. Chem. Soc. 1984, 106, 5384-5385). We have found that perhydro[7,7a,1-bc]-furan-2,3-dione shares the PAF-Acether antagonist and anti-anaphylactic properties of the compounds of the invention. The invention therefore extends to perhydro[7,7a,1-bc]furan-2,3-dione for use in therapy.

The invention also provides a pharmaceutical composition comprising perhydroindeno[7,7a,1-bc]furan-2,3-dione or an indenofuran derivative according to the invention in admixture with a pharmaceutically acceptable diluent or carrier.

The following Examples illustrate the invention:

EXAMPLE 1

Perhydroindeno[7,7a,1-bc]furan-2,3-dione

200 ml of acetic acid, 10 ml of acetic anhydride and 20.1 g (0.075 mol) of $\text{Mn}(\text{OCH}_2\text{CH}_3)_3 \cdot 2\text{H}_2\text{O}$ were poured, under nitrogen circulation, into a reactor fitted with

warming, cooling and stirring means. The reaction mixture was warmed to 70°C and stirred. After cooling to room temperature, there was added under stirring, 5.5 g (0.03 mol) of 1,2,3,4-tetrahydro-phenylacetoacetic acid. Stirring was maintained for 20 minutes at room temperature, under nitrogen circulation after which the reaction mixture was poured onto ice, then extracted twice with 250 ml of CH₂Cl₂. After washing the organic phases with water, and drying, there was obtained after treatment on a silica gel column (eluent, ethyl acetate): hexane 2:1 by volume).

3 g (yield 55.4 %) of a powder. Elemental analysis showed a very good correspondence with the formula $C_{10}H_{12}O_3$; the structure was confirmed by HPLC.

EXAMPLE 2

2a-(2-Methoxybenzyl)-perhydroindeno[7,7a,1-bc]furan-2,-3-dione

Into the apparatus described in Example 1 were poured 100 ml of tetrahydrofuran and 2.1 g (0.1117 mol) of the compound prepared in Example 1. The mixture was cooled to $-5^{\circ}C$. There was then slowly added, under stirring, 0.735 g (0.0175 mol) of NaH (titre 59%, in oil). Stirring was maintained for 30 minutes. There was then added, dropwise, 5.85 g (0.030 mol) of 2-methoxybenzyl bromide. Under gentle stirring for 3 hours the temperature was allowed to reach $0^{\circ}C$. The reaction mixture was then poured onto 100 ml of iced 1N HCl. After extraction with ethyl acetate, washing with water and drying, the residue was chromatographed on a silica gel column (eluent ethyl acetate:hexane 4:6 by volume). The title compound was thus obtained (yield 23.5 %). This was a white powder melting at $142^{\circ}C$ (Tottoli), elemental analysis of which showed a very good correspondence with the formula $C_{18}H_{20}O_4$.

By the same method were also prepared:

EXAMPLE 3

2a-(2-Ethoxybenzyl)-perhydroindeno[7,7a,1-bc]furan - 2,3-dione

White powder melting at $168^{\circ}C$ (Tottoli), elemental analysis of which showed a very good correspondence with the formula $C_{19}H_{22}O_4$.

EXAMPLE 4

2a-Benzyl-perhydroindeno[7,7a,1-bc]furan - 2,3-dione

White powder melting at 173°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $\text{C}_{17}\text{H}_{18}\text{O}_3$.

EXAMPLE 5

2a-(3-Hydroxybenzyl)-perhydroindeno[7,7a,1-bc]furan - 2,3-dione

White powder melting at 131°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $\text{C}_{17}\text{H}_{18}\text{O}_4$.

EXAMPLE 6

2a-(3-Hydroxy-4-methoxybenzyl)-perhydroindeno[7,7a,-1-bc]furan- 2,3-dione

White powder melting at 107°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $\text{C}_{18}\text{H}_{20}\text{O}_5$.

EXAMPLE 7

2a-(4-t. Butylbenzyl)-perhydroindeno[7,7a,1-bc]furan - 2,3-dione

White powder melting at 187°C (Tottoli), elemental analysis of which showed a very good correspondence with the formula $\text{C}_{21}\text{H}_{26}\text{O}_3$.

TOXICITY

The toxicity was determined per os on rats and mice by the usual methods. DL_{50} was always over 1 g/kg for rats and over 700 mg/kg for mice.

PHARMACOLOGY

The pharmaceutical interest of the compounds of the invention has been established by the following pharmaceutical experiments:

1) Test of passive cutaneous anaphylaxy (PCA) on the rat associated with hyperpermeability to PAF or to histamine

This experiment was conducted as described in 'Fiche Technique' N° 48 of J. Pharm. Paris 1979 10 (1) pages 69-72 (adaptation of the method of BITTEAU E. and HERTZ F.). The method is summarized as follows:

- . Male Sprague-Dawley rats (180-200 g) - six animals per batch. Eight batches were used: one for control, one for each of the example compounds, at the dose of 25 mg/kg.
- . In two sites of the back, previously shaved, were made two injections of an homologous immune-serum (0.1 ml) diluted for a quater.
- . 48 hours later, the rats were submitted to a control and received an intravenous injection of 1 ml of a mixture of ovalbumine (0.5%) and Evans blue (0.5 %), in physiologic serum. As a consequence, the formation of the IgE-antigen complex induced the exudation of plasmatic proteins and the formation of cutaneous wheals, this phenomenon being quantified measuring their surface (S) and their coloration (after extracting for 24 hours in a formamide solution at 65°C): Optical density of the supernatant was determined at 620 nm by a spectrophotometer.
- . The animals were kept fasting for 18 hours before the control. The products were administered, by IP route just before the administration of colorant.
- . Just before the IV injection of colorant, all the animals, including those of control batch, received two intra-dermal injections, in two sites of the back, of PAF (0.025 mcg/0.1 ml) or histamine, opposed

to the injections of immune-serum.

- 30 minutes later, the induced wheals were treated as the wheals obtained with immune-serum.
- The results are appreciated by the percentage of variation of optical density with respect to control.
- The corresponding values appear in the following table.

COMPOUNDS	P A F		HISTAMINE	
	AREA	COLOUR	AREA	COLOUR
EX. 1	*** - 46.4	*** - 50.5	* - 23.5	- 18.7 NS
EX. 2	*** - 57.1	*** - 61.2	- 18.0 NS	- 17.7 NS
EX. 3	** - 39.4	*** - 44.4	* - 26.8	* - 23.4
EX. 4	*** - 43.6	*** - 51.7	** - 36.8	*** - 39.9
EX. 5	** - 36.6	** - 43.8	- 16.2 NS	- 17.9 NS
EX. 6	*** - 50.9	*** - 62.7	*** - 43.9	** - 36.8
EX. 7	** - 42.1	*** - 53.5	- 13.7 NS	- 18.4 NS

NS : not significant
 * : significant
 ** : very significant
 *** : highly significant

2) Anaphylactic bronchoconstriction of a passively sensitized guinea-pig

Passive heterolog sensitizing

Male Hartley guinea-pigs (400-500 g) were sensitized by an intravenous injection (IV) of an antiovalbumin rabbit immune-serum (Cooper Biomedical, U.S.A.). To obtain a satisfactory anaphylactic response, 24 hours later, the following conditions of use were fixed: injection into the penis of a diluted serum (to half concentration : 0.05 ml/100 g).

Bronchoconstriction measure

Guinea-pigs were anesthetized with urethan (2 g/kg IP) then tracheotomized and ventilated by means of a respiratory pump (UGO BASILE): stroke volume 1 ml/100 g, 60 strokes/mn. A pneumothorax was done to abolish spontaneous respiration. The initial resistance was kept constant at 10 cm water pressure according to the method of Konzett and Rossler and the excess of air volume was measured with a bronchospasm transducer (UGO BASILE) connected to a UGO BASILE recorder 'Gemini'. The jugular vein was catheterized for intravenous injections. The anaphylactic shock was induced by an intravenous injection of 0.75 mg/kg of heterolog passive of ovalbumine. Products were given by oral route, 1 hour before the antigenic stimulation in the form of a gummy water suspension at the dose of 25 mg/kg.

Results

The bronchoconstriction induced by ovalbumin was expressed in percentage of maximal bronchoconstriction given by clamping of the trachea. The results are reported in the following table.

EXAMPLES	PERCENTAGE OF REDUCTION OF BRONCHOCONSTRICTION
1	53.2 ***
2	49.8 ***
3	63.7 ***
4	58.3 ***
5	41.4 **
6	55.9 ***
7	48.6 ***

** : very significant
*** : highly significant

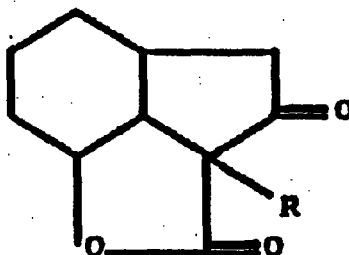
POSODOGY

In human therapy usual doses for per os administration are 0.5 to 1 g per diem, in tablets or gelatine capsules for one month. In IV administration, three weekly injections at 0.05 to 0.2 g in isotonic solution, for one month are recommended.



CLAIMS

1. An indenofuran derivative of the general formula:



wherein R represents an unsubstituted benzyl group or a benzyl group ring substituted by one or more straight or branched chain alkyl groups having from 1 to 5 carbon atoms and/or one or more straight or branched chain alkoxy groups having from 1 to 5 carbon atoms and/or one or more hydroxy groups.

2. 2a-Benzyl-perhydroindeno[7,7a,1-bc]furan-2,3-dione.
3. 2a-(2-Methoxybenzyl)-perhydroindeno[7,7a,1-bc]furan-2,3-dione.
4. 2a-(2-Ethoxybenzyl)-perhydroindeno[7,7a,1-bc]furan-2,3-dione.
5. 2a-(3-Hydroxybenzyl)-perhydroindeno[7,7a,1-bc]furan-2,3-dione.
6. 2a-(3-Hydroxy-4-methoxybenzyl)-perhydroindeno[7,7a,1-bc]furan-2,3-dione.
7. 2a-(4-t-Butylbenzyl)-perhydroindeno[7,7a,1-bc]furan-2,3-dione.



8. A process for the preparation of an indenofuran derivative according to claim 1, the process comprising condensing perhydroindeno[7,7a,1-bc]furan-2,3-dione with a compound RX wherein R is as defined in claim 1 and X represents a halogen atom, under nitrogen circulation at a temperature of from -10°C to 0°C in the presence of an alkali metal hydride.

9. A process according to claim 8 in which perhydro[7,7a,1-bc]furan-2,3-dione is condensed with a compound RBr wherein R is as defined in claim 1.

10. A process according to claim 8 or claim 9 in which the condensation is effected in the presence of sodium hydride.

11. Perhydroindeno[7,7a,1-bc]furan-2,3-dione for use in a method of treatment of the human or animal body by therapy.

12. A pharmaceutical composition comprising a compound according to any of claims 1 to 7 in admixture with a pharmaceutically acceptable diluent or carrier.

13. A pharmaceutical composition comprising perhydroindeno[7,7a,1-bc]furan-2,3-dione in admixture with a pharmaceutically acceptable diluent or carrier.
