PATENT SPECIFICATION (11) 1 589 959

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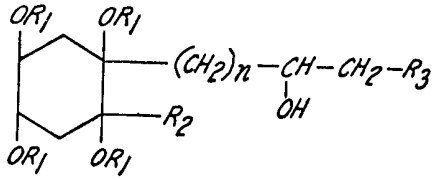
(19) 

(54) CYCLOHEXANETETROL DERIVATIVES

(71) We, E. R. SQUIBB & SONS INC., a corporation organised and existing under the laws of the State of Delaware, United States of America, of Lawrenceville-Princeton Road, Princeton, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method for which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to cyclohexanetetrol derivatives.

Compounds having the formula

I 

and the pharmaceutically acceptable salts thereof are described and claimed in our copending patent application No. 15466/78 (Serial No. 1,589,958). In formula I, and throughout the specification, the symbols are as defined below.

R_1 is alkanoyl having 1 to 7 carbon atoms; acetyl is the preferred alkanoyl group.

R_2 is alkyl; methyl is preferred;

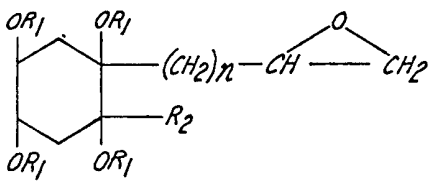
R_3 is alkylamino, dialkylamino, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-aryl-1-piperazinyl, 4-aryl-1,2,3,6-tetrahydro-1-pyridinyl, N-alkyl-N-[(2-pyridinyl)alkyl]-amino, N-alkyl-N-[(3-pyridinyl)alkyl]amino or N-alkyl-N-[(4-pyridinyl)alkyl]amino; and

n is 1, 2 or 3.

The term "aryl", as used throughout the specification, refers to phenyl or phenyl substituted with one or two halogen (fluorine, chlorine, bromine or iodine), alkyl, trifluoromethyl, alkoxy or alkylthio groups.

The terms "alkyl", "alkoxy", and "alkylthio", as used throughout the specification, refer to groups having 1 to 6 carbon atoms.

The compounds of formula I can be prepared by reacting an oxirane compound having the formula

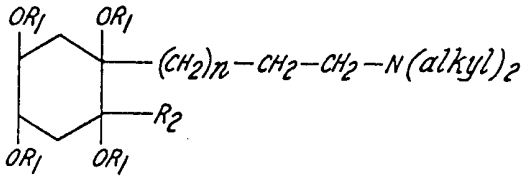
II 

with a nitrogen containing compound having the formula

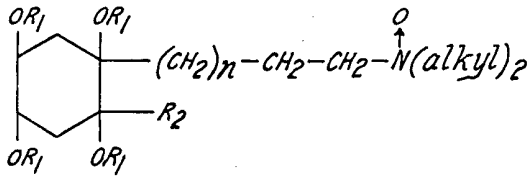
III R_3—H.

Reaction conditions are not critical, but the reaction proceeds more rapidly when carried out with heating in an organic solvent, or mixture of organic solvents, *e.g.*, benzene, glacial acetic acid, ethanol, etc.

The oxirane compounds of formula II are readily obtained from a corresponding cyclohexanetetrol derivative having the formula

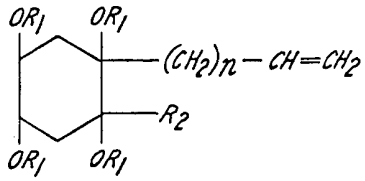
IV 

Compounds of formula IV are known; see, for example, United States patent 3,936,465 issued February 3, 1976. Oxidation of a compound of formula IV yields the corresponding N-oxide having the formula

V 

Exemplary of the oxidizing agents which may be used are the peracids, *e.g.*, *m*-chloroperbenzoic acid.

Vacuum pyrolysis of an N-oxide of formula V yields an olefin having the formula

VI 

Oxidation of an olefin of formula VI yields the corresponding oxirane compound of formula II. Exemplary of the oxidizing agents which may be used are the peracids, *e.g.*, *m*-chloroperbenzoic acid.

The oxirane compounds of formula II and the olefins of formula VI are the subject of the present invention.

The compounds of formula I can be converted to their pharmaceutically acceptable acid-addition salts with both organic and inorganic acids using methods well known in the art. Exemplary salts are hydrohalides (*e.g.*, hydrochloride and hydrobromide), nitrate, phosphate, borate, acetate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate and the like.

Formula I includes all stereoisomers and mixtures thereof. Particular stereoisomers are prepared by utilizing as the starting material the compound of formula IV with the corresponding stereoisomerism. The preferred stereoisomers are those in which the OR_1 groups are all axial.

The compounds of formula I, and the pharmaceutically acceptable salts thereof, are useful as hypotensive agents in mammals, *e.g.*, domestic animals such as dogs and cats. Daily doses of from 5 to 50 milligrams per kilogram of animal body weight, preferably about 5 to 25 milligrams per kilogram of animal body weight, can be administered in single or divided doses. Both oral and parenteral administration are specifically contemplated.

Example 1.

1,2: 1,4: 4,5-trans-1-Methyl-2-(2-oxiranylethyl)-1,2,4,5-cyclohexanetetrol tetraacetate ester

A) 1,2: 1,4: 4,5-*trans*-1-[4-(Dimethylamino)butyl]-2-methyl-1,2,4,5-cyclohexanetetrol, tetraacetate ester, N-oxide

A solution of 8.5 g of 1,2: 1,4: 4,5-*trans*-1-[4-(dimethylamino)butyl]-2-methyl-1,2,4,5-cyclohexanetetrol, tetraacetate ester in 200 ml of chloroform is cooled in an ice bath and 4.4 g of 85% *m*-chloroperbenzoic acid is added. The mixture is warmed to room temperature over 5 hours. The solution is partially evaporated *in vacuo* to one-third its volume and chromatographed on 400 g of neutral Alumina III (wet-packed in chloroform). The column is eluted with 600 ml of chloroform to remove any forerun and then the N-oxide product is eluted with 650 ml of 20% methanolic chloroform to give 10.4 g of oil. Crystallization from ethyl acetate give 7.45 g of a hydroscopic white solid, melting point 128—130°C.

B) 1,2: 1,4: 4,5-*trans*-1-Methyl-2-(3-butenyl)-1,2,4,5-cyclohexanetetrol, tetraacetate ester

An amount of 6.4 g of the above N-oxide is heated in a vacuum distillation set-up under 30 mm Hg vacuum with nitrogen bleed until all the solid is melted and vigorous evolution of volatile side products cease. The vacuum is then improved to 2—3 mm Hg and the product distilled as a pale yellow liquid which crystallizes on standing to give 4.55 g of the olefin as a white solid; boiling point of distillate 180—200°C (mainly 195°C), at 2—3 mm Hg.

C) 1,2: 1,4: 4,5-*trans*-1-Methyl-2-(2-oxiranylethyl)-1,2,4,5-cyclohexanetetrol tetraacetate ester

A solution of 2.0 g of the above tetraacetate-olefin and 1.05 g of 85% *m*-chloroperbenzoic acid in 50 ml of chloroform is prepared at 0°C and stirred for about 16 hours at room temperature. The solution is then suction filtered through 30 g of neutral Alumina III. The alumina is washed with 100 ml of chloroform and the combined filtrate evaporated *in vacuo* to give a colorless oil, which solidifies on standing to give 1.85 g of the epoxide product as a white solid.

Examples 2 and 3.

Following the procedure of Example 1, but substituting the compound listed in column I for 1,2: 1,4: 4,5-*trans*-1-[4-(dimethyl-amino)butyl]-2-methyl-1,2,4,5-cyclohexanetetrol, tetraacetate ester, yields the compound listed in column II with the compound listed in column III being prepared as an intermediate

	Column I	Column II
2	1,2: 1,4: 4,5-*trans*-1-[3-(dimethylamino)propyl]-2-methyl-1,2,4,5-cyclohexanetetrol, tetraacetate ester	1,2: 1,4: 4,5-*trans*-1-methyl-2-[oxiranylmethyl]-1,2,4,5-cyclohexanetetrol, 1,2,4,5-tetraacetate ester
3	1,2: 1,4: 4,5-*trans*-1-[5-(dimethylamino)pentyl]-2-methyl-1,2,4,5-cyclohexanetetrol, tetraacetate ester	1,2: 1,4: 4,5-*trans*-1-methyl-1-[3-oxiranylpropyl]-1,2,4,5-cyclohexanetetrol, 1,2,4,5-tetraacetate ester

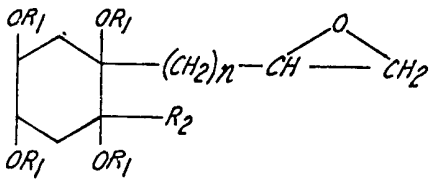
Column III

1,2 : 1,4 : 4,5-*trans*-1-methyl-2-[2-propenyl]-1,2,4,5-cyclohexanetetrol, 1,2,4,5-tetraacetate ester.

1,2 : 1,4 : 4,5-*trans*-1-methyl-2-[4-pentenyl]-1,2,4,5-cyclohexanetetrol, 1,2,4,5-tetraacetate ester.

WHAT WE CLAIM IS:—

1. A compound having the formula



wherein R_1 is alkanoyl having 1 to 7 carbon atoms; R_2 is alkyl having 1 to 6 carbon atoms; and n is 1, 2 or 3.

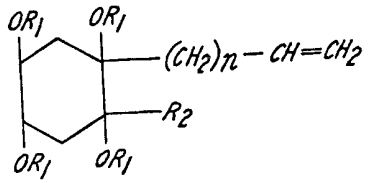
2. A compound in accordance with claim 1 wherein R_1 is acetyl and R_2 is methyl.

3. A compound in accordance with claim 2 wherein n is 1.

4. A compound in accordance with claim 2 wherein n is 2.

5. A compound in accordance with claim 2 wherein n is 3.

6. A compound having the formula



wherein R_1 is alkanoyl having 1 to 7 carbon atoms; R_2 is alkyl having 1 to 6 carbon atoms; and n is 1, 2 or 3.

7. A compound in accordance with claim 6 wherein R_1 is acetyl and R_2 is methyl.

8. A compound in accordance with claim 7 wherein n is 1.

9. A compound in accordance with claim 7 wherein n is 2.

10. A compound in accordance with claim 7 wherein n is 3.

11. A compound in accordance with claim 1 as named in any of the Examples.

12. A compound in accordance with claim 6 as named in any of the Examples.

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