PATENT SPECIFICATION (11) 1 589 958

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(21) Application No. 15466/78 (22) Filed 19 April 1978

(31) Convention Application No. 795465

(32) Filed 10 May 1977 in

(33) United States of America (US)

(44) Complete Specification published 20 May 1981

(51) INT CL³ C07C 93/24 A61K 31/22 31/44 31/495 C07D 211/70 213/36 295/08

(52) Index at acceptance

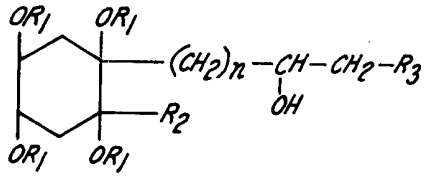
C2C 1530 1531 1626 215 220 221 225 226 227 22Y 246 250 251 252 25Y 29X 29Y 30Y 311 313 314 31Y 322 323 32Y 334 338 360 362 364 366 368 36Y 373 37Y 456 45Y 464 502 50Y 613 620 623 624 648 650 652 658 662 66X 694 802 80Y AA BG BL LQ LZ QT

(72) Inventors RITA THERESA FOX and
FREDERIC PETER HAUCK

(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 provides compounds having the formula



I

and the pharmaceutically acceptable salts thereof; such compounds have been found to have cardio-vascular activity. 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;

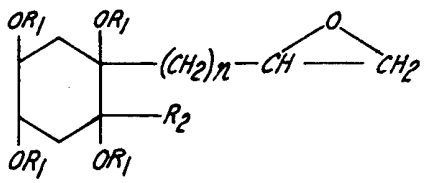
R_3 is alkylamino, dialkylamino, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-aryl-1-piperazinyl, 4-aryl-1,2,3,6-tetrahydro-1-pyridinyl, N-alkyl-N-[(2-pyridinyl)alkyl]amino, N-alkyl-N-[(3-pyridinyl)alkyl]amino or N-alkyl-N-[(4-pyridinyl)alkyl]amino; and

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 this invention can be prepared by reacting an oxirane compound having the formula



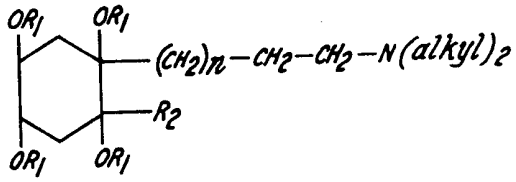
II

with a nitrogen containing compound having the formula

$$R_3—H \qquad \text{III}$$

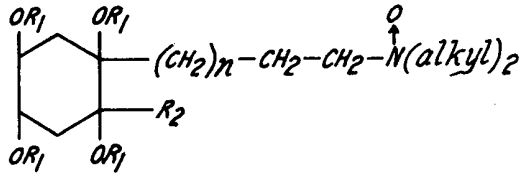
Reaction conditions are not critical, but the reaction proceeds more rapidly when carried out with heating in an organic solvent, or mixture of organic solvents, *e.g.*, benzene, glacial acetic acid, ethanol, etc.

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



IV

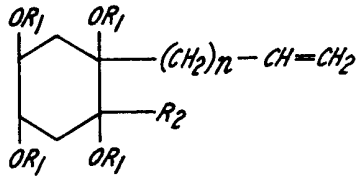
Compounds of formula IV are known; see, for example, United States patent 3,936,465 issued February 3, 1976. Oxidation of a compound of formula IV yields the corresponding N-oxide having the formula



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 novel intermediates which are useful in the preparation of the compounds of formula I, and as such, are the subject of our copending patent application No. 6086/80 (Serial No. 1,589,959).

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 - [4 - (Dimethylamino) - 3 - hydroxybutyl] - 2 - methyl - 1,2,4,5 - cyclohexanetetrol, 1,2,4,5 - 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 temparature. 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.

D) 1,2:1,4:4,5 - *trans* - 1 - [4 - (Dimethylamino) - 3 - hydroxybutyl] - 2 - methyl - 1,2,4,5 - cyclohexanetetrol, 1,2,4,5-tetraacetate ester

An amount of 20 ml of 3.87 M dimethylamine in benzene is added to a solution of 2.0 g of the tetraacetate-epoxide in 80 ml of benzene in a Parr bomb. The bomb is heated for about 16 hours at 100°±5°C. The bomb is cooled to room temperature and the solution evaporated *in vacuo* to give 2.3 g of oil. An acid-base extraction gives 1.65 g of basic material. Crystallization from 10 ml 1:1 ethyl acetatehexane yields 564 mg of the title compound, melting point 94—105°C.

Anal. Calc'd. for $C_{21}H_{45}NO_9$ (445.5 g/m): C, 56.61; H, 7.92; N, 3.14
Found: C, 56.50, H, 7.86; N, 3.21

Example 2

1,2:1,4:4,5 - *trans* - 1 - [3 - Hydroxy - 4 - [4 - (2 - methoxyphenyl) - 1 - piperazinyl]butyl] - 2 - methyl - 1,2,4,5 - cyclohexanetetrol, 1,2,4,5 - tetraacetate ester, hydrochloride (1:1)

A solution of 1.4 g of 1 - (2 - methoxyphenyl)piperazine and 3.0 g of 1,2:1,4:4,5 - *trans* - 1 - methyl - 2 - (oxiranylethyl) - 1,2,4,5 - cyclohexanetetrol, tetraacetate ester in 50 ml of absolute ethanol and 20 ml of benzene is stirred for about 16 hours at 55°C. The solvent is removed *in vacuo*, and the 4.5 g of residue is dissolved in ether and treated with an anhydrous solution of hydrogen chloride in isopropanol to yield a solid. The solid is collected, washed with ether and dried *in vacuo*. [The ether solution is washed (dilute hydrochloric acid, water and a saturated solution of sodium chloride), dried and evaporated *in vacuo* to give 0.55 g of recovered epoxide starting material.] The hydrochloride salt does not recrystallize. It is dissolved in water, made alkaline with cold concentrated ammonium hydroxide and extracted with chloroform to give 3.5 g of an oil-foam mixture. Crystallization from ether gives 2.6 g of the free base as a solid.

Conversion of the free base to the mono-hydrochloride salt, and recrystallization from ethyl acetate-methanol gives 2.0 g of the title compound as a crystalline solid, melting point 213—217°C.

Anal. Calc'd. for $C_{30}H_{40}N_2O_{10}$. HCl: C, 57.27; H, 7.21; N, 4.45; Cl, 5.64
Found: C, 57.26; H, 7.50; N, 4.32; Cl, 5.66

Example 3

1,2:1,4:4,5 - *trans* - 1 - [3 - Hydroxy - 4 - [methyl[2 - (2 - pyridinyl)ethyl] - amino]butyl] - 2 - methyl - 1,2,4,5 - cyclohexanetetrol, tetraacetate ester, hydrochloride (1:2)

A solution of 1.7 g of 1,2:1,4:4,5 - *trans* - 1 - methyl - 2 - (oxiranylethyl) - 1,2,4,5 - cyclohexanetetrol, tetraacetate ester (prepared as described in Example 1C) and 0.58 g of 2 - (β - methylaminoethyl)pyridine in benzene and absolute ethanol (15:37.5) is stirred at 57°C for about 16 hours. The solvent is removed *in vacuo* and the 2.25 g of residue is chromatographed on 100 g of neutral Alumina III. Elution with 800 ml of 25—45% ethyl acetate-hexane gives 0.4 g of forerun (mainly epoxide). Elution with 800 ml of 50—60% ethyl acetate-hexane and 600 ml of 5% methanol-ethyl acetate gives 1.1 g of the desired product as an oil. This material is dissolved in ether and converted to the dihydrochloride salt. Two recrystallizations from methanol-ethyl acetate give 0.82 g of the title compound, melting point 186—187.5°C.

Anal. Calc'd. for $C_{27}H_{40}N_2O_9$. HCl (573.1/609.6 g/m)
C, 53.20; H, 6.95; N, 4.60; Cl, 11.63
Found: C, 53.07; H, 7.05; N, 4.53; Cl, 11.55

Example 4

1,2:1,4:4,5 - *trans* - 1 - [3 - Hydroxy - 4 - (3,6 - dihydro - 4 - phenyl - 1 - (2H) - pyridinyl)butyl] - 2 - methyl - 1,2,4,5 - cyclohexanetetrol, tetraacetate ester

A solution of 1.65 g of 1,2:1,4:4,5 - *trans* - 1 - methyl - 2 - (2 - oxiranylethyl) - 1,2,4,5 - cyclohexanetetrol, tetraacetate esters (prepared as described in Example 1C) and 0.69 g of 4 - phenyl - 1,2,3,6 - tetrahydropyridine in benzene-absolute ethanol (15:37.5) is stirred at 57°C for about 16 hours. The solution is evaporated *in vacuo* and the residue crystallized from ether-hexane to give 1.1 g of solid. An additional 0.6 g is obtained from the next two crops. The 1.7 g of combined solid is recrystallized from ethyl acetate-hexane to give 0.80 g of the title compound, melting point 142—147°C.

Anal. Calc'd. For $C_{30}H_{41}NO_9$ (559.67 g/m): C, 64.38; H, 7.38; N, 2.50
Found: C, 64.33; H, 7.47; N, 2.43

Examples 5—18

Following the procedure of Example 1, but substituting the compound listed in column I for dimethylamine, yields the compound listed in column II.

	Column I	Column II
5	methylamine	1,2:1,4:4,5-*trans*-1-[4-(methyl-amino)-3-hydroxybutyl]-2-methyl-1,2,4,5-cyclohexanetetrol, 1,2,4,5-tetraacetate ester
6	1-piperazine	1,2:1,4:4,5-*trans*-1-[3-hydroxy-4-(1-piperazinyl)butyl]-2-methyl-1,2,4,5-cyclohexanetetrol, 1,2,4,5-tetracetate ester
7	1-methylpiperazine	1,2:1,4:4,5-*trans*-1-[3-hydroxy-4-(4-methyl-1-piperazinyl)butyl]-2-methyl-1,2,4,5-cyclohexanetetrol, 1,2,4,5-tetraacetate ester
8	1-phenylpiperazine	1,2:1,4:4,5-*trans*-1-[3-hydroxy-4-(4-phenyl-1-piperazinyl)butyl]-2-methyl-1,2,4,5-cyclohexanetetrol, 1,2,4,5-tetraacetate ester

	Column I	Column II
9	1-(2-methylphenyl)-piperazine	1,2:1,4:4,5-*trans*-1-[3-hydroxy-4-[4-(2-methylphenyl)-1-piperazinyl]-butyl]-2-methyl-1,2,4,5-cyclohexanetetrol, 1,2,4,5-tetraacetate ester
10	1-[3-(trifluoromethyl)-phenyl]piperazine	1,2:1,4:4,5-*trans*-1-[3-hydroxy-4-[4-[3-(trifluoromethyl)phenyl]-1-piperazinyl]butyl]-2-methyl-1,2,4,5-cyclohexanetetrol, 1,2,4,5-tetra-acetate ester
11	1-[2-(methylthio)-phenyl]piperazine	1,2:1,4:4,5-*trans*-1-[3-hydroxy-4-[4-[2-(methylthio)phenyl]-1-piperazinyl]butyl]-2-methyl-1,2,4,5-cyclohexanetetrol, 1,2,4,5-tetra-acetate ester
12	1-(4-chlorophenyl)-piperazine	1,2:1,4:4,5-*trans*-1-[4-(4-chlorophenyl)-1-piperazinyl]-3-hydroxybutyl]-2-methyl-1,2,4,5-cyclohexanetetrol, 1,2,4,5-tetraacetate ester
13	3-(β-methylamino-ethyl)pyridine	1,2:1,4:4,5-*trans*-1-[3-hydroxy-4-[methyl[2-(3-pyridinyl)ethyl]amino]-butyl]-2-methyl-1,2,4,5-cyclohexanetetrol, tetraacetate ester
14	4-(γ-methylamino-propyl)pyridine	1,2:1,4:4,5-*trans*-1-[3-hydroxy-4-[methyl[3-(4-pyridinyl)propyl]-amino]butyl]-2-methyl-1,2,4,5-cyclohexanetetrol, tetraacetate ester
15	4-(2-ethylphenyl)-1,2,3,6-tetrahydro-pyridine	1,2:1,4:4,5-*trans*-1-[3-hydroxy-4-[3,6-dihydro-4-[(2-ethylphenyl)-1(2*H*)-pyridinyl]butyl]-2-methyl-1,2,4,5-cyclohexanetetrol, tetra-acetate ester
16	4-(2-ethylthio phenyl)-1,2,3,6-tetra-hydro-pyridine	1,2:1,4:4,5-*trans*-1-[3-hydroxy-4-[3,6-dihydro-4-[(2-ethylthiophenyl)-1(2*H*)-pyridinyl]butyl]-2-methyl-1,2,4,5-cyclohexanetetrol, tetra-acetate ester
17	4-(3-trifluoro-methyl-phenyl)-1,2,3,6-tetra-hydro-pyridine	1,2:1,4:4,5-*trans*-1-[3-hydroxy-4-[3,6-dihydro-4-[(3-trifluoromethyl-phenyl)-1(2*H*)-pyridinyl]butyl]-2-methy-1,2,4,5-cyclohexanetetrol, tetraacetate ester
18	4-(4-bromophenyl)-1,2,3,6-tetrahydro-pyridine	1,2:1,4:4,5-*trans*-1-[3-hydroxy-4-[3,6-dihydro-4-[(4-bromophenyl)-1(2*H*)-pyridinyl]butyl]-2-methyl-1,2,4,5-cyclohexanetetrol, tetra-acetate ester

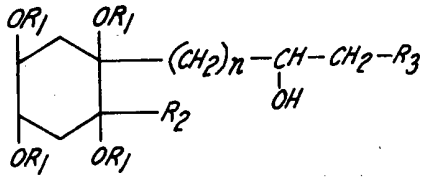
Examples 19—20

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.

	Column I	Column II
19	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-[3-(dimethylamino)-2-hydroxypropyl]-2-methyl-1,2,4,5-cyclohexanetetrol, 1,2,4,5-tetraacetate ester
20	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-[5-(dimethylamino)-4-hydroxypentyl]-2-methyl-1,2,4,5-cyclohexanetetrol, 1,2,4,5-tetraacetate ester

WHAT WE CLAIM IS:—

1. A compound having the formula



or a pharmaceutically acceptable salt thereof, wherein R_1 is alkanoyl having 1 to 7 carbon atoms; R_2 is alkyl; R_3 is alkyl-amino, 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; wherein aryl is phenyl or phenyl substituted with one or two halogen, alkyl, trifluoromethyl, alkoxy or alkyl-thio groups and wherein alkyl, alkoxy and alkylthio are groups having 1 to 6 carbon atoms.

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 in accordance with claim 2 wherein R_3 is alkylamino or dialkylamino.

7. A compound in accordance with claim 6 wherein R_3 is dialkylamino.

8. A compound in accordance with claim 2 wherein R_3 is 1-piperazinyl, 4-alkyl-1-piperazinyl, or 4-aryl-1-piperazinyl.

9. A compound is accordance with claim 8 wherein R_3 is 4-aryl-1-piperazinyl.

10. A compound in accordance with claim 2 wherein R_3 is 4-aryl-1,2,3,6-tetrahydropyridinyl.

11. A compound in accordance with claim 2 wherein R_3 is N-alkyl-N-[(2-pyridinyl)alkyl]amino, N-alkyl-N-[(3-pyridinyl)alkyl]amino or N-alkyl-N-[(4-pyridinyl)alkyl]amino.

12. A compound in accordance with claim 11 wherein R_3 is N-alkyl-N-[2-(2-pyridinyl)ethyl]amino.

13. 1,2:1,4:4,5 - *trans* - 1 - [4 - dimethylamino) - 3 - hydroxybutyl] - 2 - methyl - 1,2,4,5 - cyclohexanetetrol, 1,2,4,5-tetraacetate ester.

14. 1,2:1,4:4,5 - *trans* - 1 - [3 - hydroxy - 4 - [4 - (2 - methoxyphenyl) - 1 - piperazinyl]butyl] - 2 - methyl - 1,2,4,5 - cyclohexanetetrol, 1,2,4,5 - tetraacetate ester, hydrochloride (1:1).

15. 1,2:1,4:4,5 - *trans* - 1 - [3 - hydroxy - 4 - [methyl[2 - (2 - pyridinyl)ethyl]amino]butyl] - 2 - methyl - 1,2,4,5 - cyclohexanetetrol, tetraacetate ester, hydrochloride (1:2).

16 1,2:1,4:4,5 - *trans* - 1 - [3 - hydroxy - 4 - (3,6 - dihydro - 4 - phenyl - 1(2*H*) - pyridinyl)butyl] - 2 - methyl - 1,2,4,5 - cyclohexanetetrol, tetraacetate ester.

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

For the Applicants
D. YOUNG &CO.,
Chartered Patent Agents,
9 &10 Staple Inn,
London, WC1V 7RD.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1981
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.