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3,542,820

α,ω - ALKANEDIOLPHOSPHORYLALKANOLAMINE DERIVATIVES AND PROCESS FOR PREPARING THEREOF

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Int. Cl. C07f 9/08
U.S. Cl. 260—403 3 Claims

ABSTRACT OF THE DISCLOSURE

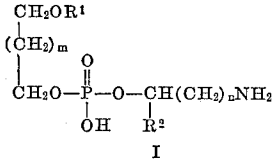
There are disclosed alkanediolphosphorylalkanolamine derivatives of the formula

$$R^1OCH_2—(CH_2)_m—CH_2O—PO(OH)—OCHR^2—(CH_2)_n—NH_2$$

in which R^1 represents a carboxylic acyl group containing 18 to 20 carbon atoms and three or four double bonds, *m* represents the integers zero, one or two, *n* represents the integers one or two, and R^2 represents a hydrogen atom or the methyl group. Those compounds possess antihypertensive activities, and methods for their preparation and use are also disclosed.

This invention relates to new alkanediolphosphorylalkanolamine derivatives and to a process used for their synthesis.

More specificaly, this invention relates to alkanediolphosphorylalkanolamine derivatives of Formula I,



I

in which R^1 represents a carboxylic acyl group containing 18 to 20 carbon atoms and three or four double bonds, such as, for example, an octadeca-6,9,12-trienoyl, octadeca - 9,12,15 - trienoyl, octadeca-6,9,12,15-tetraenoyl, eicosa - 8,11,14 - trienoyl or an eicosa-5,8,11,14-tetraenoyl group; *m* represents the integers zero, one or two; *n* represents the integers one or two; and R^2 represents a hydrogen atom or a lower alkyl group, such as, for example, a methyl group.

The alkanediolphosphorylalkanolamine derivatives of this invention have been found to possess pharmacological properties which render them useful as medicinal agents. More particularly, these derivatives exhibit utility as antihypertensive agents when tested in standard pharmacological tests. For example, when these derivatives are administered to renal hypertensive rats, obtained by the method of A. Grollman, Proc. Soc. Exptl. Biol. Med., 57, 102 (1944), reduction of blood pressure toward normal levels is observed. This fall in blood pressure is readily measured by the method of H. Kersten et al., J. Lab. Clin. Med., 32 1090 (1947).

When the compounds of this invention of Formula I are employed as antihyptertensive agents in warm-blooded animals, e.g. rats, alone or in combination with pharmacologically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice. For example, they may be administered orally in solid form containing such excipients as starch, milk sugar, certain types of clay and so forth.

They may also be administered orally in the form of solutions or they may be injected parenterally. For parenteral administration they may be used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic.

The dosage of the present therapeutic agents will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects and preferably at a level that is in a range of from about 0.3 mg. to about 100 mg. per kilo per day, although as aforementioned variations will occur. However, a dosage level that is in the range of from about 3 mg. to about 10 mg. per kilo per day is most satisfactory. Such doses may be administered once or twice a day, as required.

A noteworthy aspect of this invention is the discovery that a minimum of three double bonds must be present in the acyl group of the alkanediolphosphorylalkanolamines of Formula I before said compounds exhibit antihyptertensive activity. For example, 1-octadeca-9,12-dienoyl - 1,3, - propanediol - 3 - phosphoryl-2-ethanolamine (containing two double bonds in the acyl group) (I;

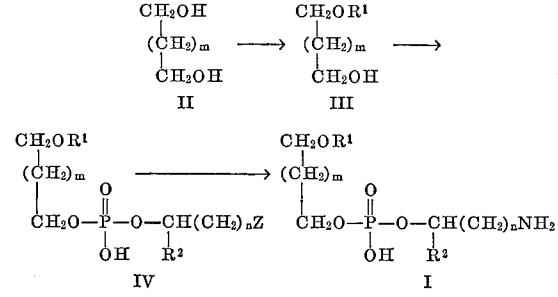
$$R^1=CH_3(CH_2)_3(CH_2—CH=CH)_2(CH_2)_7CO$$

m=1, *n*=1 and R^2=H) when administered by injection at a daily dose of 1 to 10 mg./kg. for five days does not show an antihypertensive effect in renal hyptertensive rats according to the method of Kersten et al., cited above; whereas, 1 -octadeca - 9,12,15 - trienoyl-1,3 - propanediol-3-phosphoryl-2-ethanolamine (containing three double bonds in the acyl group) [I;

$$R^1=CH_3(CH_2—CH=CH)_3(CH_2)_7CO$$

m=1, *n*=1 and R^2=H], a compound of this invention, exhibits a profound antihypertensive effect at these dose levels. 1 - octadeca - 9,12 - dienoyl-1,3-propanediol-3-phosphoryl-2-ethanolamine is prepared by the same process described below, for the compounds of this invention except that octadeca-9,12-dienoyl chloride, described by C. F. H. Allen et al., Org. Syntheses, 37, 66(1957), is used as the acylating agent.

More specifically, I prefer to prepare the alkanediolphosphorylalkanolamine derivatives of this invention by the process illustrated by the following formulae:



II III

IV I

in which R^1, R^2, *m* and *n* are as defined above and Z represents a primary amino group coupled with an amine-protecting group, such as, preferably a tert-butyloxycarbonyl group or some other amine-protecting group, for example, such as those described by E. Schröder and K. Lübke in "The Peptides," vol. I, Academic Press, New York, 1965, pp. 3–51.

The starting material of Formula II is 1,2-ethanediol, 1,3-propanediol or 1,4-butanediol, described in "Rodd's Chemistry of Carbon Compounds," second edition, S. Coffey, Editor, Elsevier Publishing Company, New York, 1965, pp. 11–14.

In employing the process illustrated above for the preparation of the compounds of this invention of Formula I, an excess, preferably five- to fifteen-fold, of the starting material of Formula II, is treated with an acylating agent, such as, for example, an appropriate acid chloride, in the presence of an acid acceptor, preferably pyridine, to afford the monoacylated derivative of Formula III in which R^1 is as defined above.

The preferred acylating agents for the above reactions are the corresponding acid chlorides, prepared from the appropriate acids, according to the method used by W. Stoffel and H. D. Pruss, J. Lipid Res., 8, 196 (1967) for the preparation of octadeca-6,9,12-trienoyl chloride. Such acids are octadeca-6,9,12-trienoic acid, described by J. M. Osbond and J. C. Wickers, Chem. and Ind., 1287 (1959); octadeca-9,12,15-trienoic acid, described by S. S. Nigam and B. C. L. Weedon, Chem. and Ind., 155 (1955); octadeca-6,9,12,15-tetraenoic acid, described by M. Matic, Biochem. J., 68, 692 (1958); eicosa-8,11,14-trienoic acid, described by W. Stoffel, Ann. Chem., 673, 26 (1964); and eicosa-5,8,11,14-tetraenoic acid, described by J. M. Osbond and J. C. Wickers, cited above.

The monoacylated derivative of Formula III is condensed with phosphorus oxychloride in the presence of an organic base, preferably quinoline, followed by treatment with an appropriate hydroxyalkylcarbamic acid tert-butyl ester, described below, to afford the phosphoric acid ester of Formula IV in which R^1, R^2, m and n are as defined above and Z represents a primary amino group coupled with a tert-butyloxycarbonyl group.

The appropriate hydroxyalkylcarbamic acid tert-butyl esters preferred in the above reaction are 2-hydroxyethylcarbamic acid tert-butyl ester, described by F. J. M. Daemen et al., Rec. Trav. Chim., 82, 487 (1963), 3-hydroxypropylcarbamic acid tert-butyl ester, 2-hydroxypropylcarbamic acid tert-butyl ester and 3-hydroxybutylcarbamic acid tert-butyl ester. The latter three esters may be readily prepared according to the procedure of F. J. M. Daemen et al., cited above, used for the preparation of the former ester. When employing this procedure for this purpose, an equivalent amount of 3-amino-1-propanol, described by L. Henry, Chem. Ber., 33, 3169 (1900), 1-amino-2-propanol, described by P. A. Levene and J. Scheidegger, J. Biol. Chem., 60, 172 (1924) and 4-amino-2-butanol, described by R. Robinson and H. Suginome, in J. Chem. Soc., 304 (1932), is used instead of ethanolamine to obtain the corresponding hydroxyalkylcarbamic acid tert-butyl ester, respectively.

Finally, the phosphoric acid esters of Formula IV are readily converted to the alkanediolphosphorylalkanolamine derivatives of Formula I by conventional methods such as those described by E. Schroder and K. Lubke, cited above, see page 39; the use of hydrogen chloride in ether solution is a preferred conventional method.

The following examples will illustrate this invention.

EXAMPLE 1

To a cold solution of 5.0 g. of 1,3-propanediol in 50 ml. of dry chloroform, 5.0 g. of octadeca-9,12,15-trienoyl chloride and 20 ml. of pyridine are added. The mixture is allowed to stand at room temperature for 18 hours. The solution is diluted with chloroform, washed with 2 N hydrochloric acid and water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness to yield 5.8 g. of an oil. The residual oil is subjected to chromatography on silica gel. Elution with benzene affords a small amount of the diacylated derivative, 1,3-dioctadeca-9,12,15-trienoyl-1,3-propanediol. Subsequent elution with 2% ethyl acetate in benzene affords the desired monoacylated derivative, 1-octadeca-9,12,15-trienoyl-1,3-propanediol (III, $R^1=CH_3(CH_2—CH=CH)_3(CH_2)_7CO$)

$\gamma_{max.}^{CHCl_3}$ 3400, 1745 and 1670 cm.$^{-1}$.

In the same manner, but using an equivalent amount of the acid chlorides, octadeca-6,9,12-trienoyl chloride, octadeca-6,9,12,15-tetraenoyl chloride, eicosa-8,11,14-trienoyl chloride or eicosa-5,8,11,14-tetraenoyl chloride instead of octadeca-9,12,15-trienoyl chloride, the corresponding monoacylated derivatives, 1-octadeca-6,9,12-trienoyl-, 1-octadeca-6,9,12,15-tetraenoyl-, 1-eicosa-8,11,14-trienoyl- and -eicosa-5,8,11,14-tetraenoyl-1,3-propanediol, are obtained. These monoacylated derivatives are readily characterized by their infrared spectra which show absorption bands similar to those reported above for 1-octadeca-9,12,15-trienoyl-1,3-propanediol.

In the same manner, but using an equivalent amount of 1,2-ethanediol or 1,4-butanediol, instead of 1,3-propanediol, together with the appropriate acid chloride, the monoacylated derivatives, 1-octadeca-6,9,12-trienoyl-, 1-octadeca-9,12,15-trienoyl-, 1-octadeca-6,9,12,15-tetraenoyl-, 1-eicosa-8,11,14-trienoyl-, 1-eicosa-5,8,11,14-tetraenoyl-1,2-ethanediol and -1,4-butanediol, are obtained. These monoacylated derivatives are readily characterized by their infrared spectra which show absorption bands similar to those reported above for 1-octadeca-9,12,15-trienoyl-1,3-propanediol.

EXAMPLE 2

To 1.288 g. of freshly distilled phosphorus oxychloride, in 50 ml. of dry chloroform, cooled to 10°, a solution of 2.79 g. of 1-octadeca-9,12,15-trienoyl-1,3-propanediol, prepared as described in Example 1 and 1.18 g. of quinoline in 50 ml. of dry chloroform are added over a period of 30 minutes. The reaction mixture is kept at 25° for two hours after which it is again cooled to 0° and a solution of 1.18 g. of 2-hydroxyethylcarbamic acid tert-butyl ester and 1.2 g. of pyridine in 50 ml. of dry chloroform are added over a period of 30 minutes. The reaction mixture is allowed to stand at room temperature for 24 hours. Water (0.6 ml.) is added and the reaction mixture is stirred for one hour, washed with cold 2 N hydrochloric acid and water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residual oil, the phosphoric acid ester, 1-octadeca-9,12,15 - trienoyl - 1,3-propanediol-3-phosphoryl-N-(tert-butyloxycarbonyl)-ethanolamine [IV;

$R^1=CH_3(CH_2—CH=CH)_3(CH_2)_7CO$

$m=1$, $n=1$, $R^2=H$ and $Z=NHCOOC(CH_3)_3$],

$\gamma_{max.}^{CHCl_3}$ 3400–3500, 1745, 1700 and 1695 cm.$^{-1}$, shows essentially one spot on thin layer chromatography

(SiO_2—$CHCl_3$:CH_3OH:H_2O::95:35:6)

This phosphoric acid ester is dissolved in 50 ml. of dry chloroform and treated with a stream of dry hydrogen chloride for two hours. The solvent is then removed under reduced pressure. The oily residue is dissolved in a mixture of ethanol:ether:water::4:2:1 and passed through a column of IR45 (OH^- cycle) ion exchange resin. Evaporation of the filtrate yields an oil which is subjected to chromatography on 60 g. of silica gel. Elution with 2–5 percent methanol in chloroform yield the desired alkanediolphosphorylalkanolamine, 1 - octadeca - 9,12,15-trienoyl - 1,3-propanediol-3-phosphoryl-2-ethanolamine (I; $R^1=CH_3(CH_2—CH=CH)_3(CH_2)_7CO$, $m=1$, $n=1$ and $R^2=H$),

$\gamma_{max.}^{CHCl_3}$ 3400–3500, 1745 and 1650 cm.$^{-1}$.

In the same manner, but using an equivalent amount of the hydroxyalkylcarbamic acid tert-butyl esters, 3-hy-

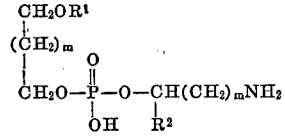
droxypropyl-, 2-hydroxypropyl- and 3-hydroxybutyl-carbamic acid tert-butyl ester, described above, instead of 2-hydroxyethylcarbamic acid tert-butyl ester, the corresponding alkanediolphosphorylalkanolamines, 1-octadeca-9,12,15-trienoyl - 1,3-propanediol - 3-phosphoryl - 3-hydroxypropylamines, -2-hydroxypropylamine and -3-hydroxybutylamine, are obtained, respectively. These alkanediolphosphorylalkanolamines are readily characterized by their infrared spectra which show absorption bands similar to those reported above for 1-octadeca-9,12,15-trienoyl-1,3-propanediol-3-phosphoryl-2-ethanolamine.

In the same manner, but using an equivalent amount of the appropriate monoacylated derivative prepared as described in Example 1, 1-octadeca-6,9,12-trienoyl-, 1-octadeca - 6,9,12,15-tetraenoyl-, 1-eicosa-8,11,14-trienoyl- or 1 - eicosa-5,8,11,14-tetraenoyl-1,3-propanediol instead of octadeca-9,12,15-trienoyl-1,3-propanediol, together with the appropriate hydroxyalkylcarbamic acid tert-butyl ester, the corresponding alkanediolphosphorylalkanolamines, 1-octadeca-6,9,12-trienoyl-, octadeca-6,9,12,15-tetraenoyl-, eicosa-8,11,14-trienoyl-, eicosa-5,8,11,14-tetraenoyl-1,3-propanediol-3-phosphoryl-2-ethanolamines, -3-hydroxypropylamines, -2-hydroxypropylamines and -3-hydroxybutylamines, are obtained. These alkanediolphosphorylalkanolamines are readily characterized by their infrared spectra which show absorption bands similar to those reported above for 1-octadeca-9,12,15-trienoyl-1,3-propanediol-3-phosphoryl-2-ethanolamine.

In the same manner, but using an equivalent amount of 1,2-ethanediol or 1,4-butanediol instead of 1,3-propanediol, together with the appropriate monoacyl derivative prepared as described in Example 1, and the appropriate hydroxyalkylcarbamic acid tert-butyl ester, described above, the alkanediolphosphorylalkanolamines, 1-octadeca-6,9,12-trienoyl-, 1-octadeca-9,12,15-trienoyl-, 1-octadeca-6,9,12,15-tetraenoyl-, 1-eicosa - 8,11,14-trienoyl-, 1-eicosa-5,8,11,14-tetraenoyl - 1,2-ethanediol-2-phosphoryl- and -1,4-butanediol - 4-phosphoryl - 2-ethanolamines, 3-hydroxypropylamines, -2-hydroxypropylamines and -3-hydroxybutylamines, are obtained. These alkanediolphosphoryalkanolamines are readily characterized by their infrared spectra which show absorption bands similar to those reported above for 1-octadeca - 9,12,15-trienoyl-,1,3-propanediol-3-phosphoryl-2-ethanolamine.

I claim:

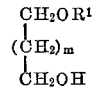
1. A compound selected from those of the formula



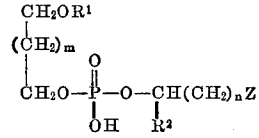
wherein R^1 represents a carboxylic acyl group containing from eighteen to twenty carbon atoms and three or four double bonds; *m* represents an integer selected from the group which consists of 0, 1 and 2; *n* represents an integer selected from the group which consists of 1 and 2; and R^2 is selected from the group which consists of hydrogen and lower alkyl.

2. 1-octadeca - 9,12,15-trienoyl - 1,3-propanediol - 3-phosphoryl-2-ethanolamine.

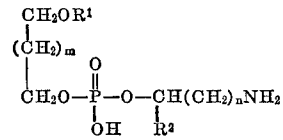
3. The process which comprises treating a compound selected from the group which consists of 1,2-ethanediol, 1,3-propanediol and 1,4-butanediol with an acylating agent in the presence of an acid acceptor, thereby securing a monoacylated compound of the formula



wherein R^1 represents a carboxylic acyl group containing from eighteen to twenty carbon atoms and having three or four double bonds, and *m* is an integer selected from 0, 1 and 2; condensing said monoacylated compound first with phosphorus oxychloride in the presence of an organic base, and then treating the reaction mixture with a hydroalkylcarbamic acid tert-butyl ester, thereby securing a compound of the formula



wherein R^1 and *m* are as above defined, *n* is an integer selected from the group which consists of 1 and 2, R^2 is selected from the group consisting of hydrogen and lower alkyl, and Z represents a primary amino group coupled with a tert-butyloxycarbonyl group; and treating said last-named compound with hydrogen chloride under substantially anhydrous conditions, thereby securing a compound of the formula



wherein R^1, *m*, *n* and R^2 are as above defined.

References Cited

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3,162,668	12/1964	Reed et al.	260—403 X

CHARLES B. PARKER, Primary Examiner

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U.S. Cl. X.R.

260—405.5; 424—211

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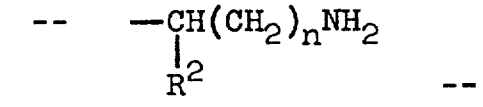
UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,542,820 Dated November 24, 1970

Inventor(s) Sumanas Rakhit

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

In Column 5, lines 50-53, in the right hand portion of the claimed formula, the subscript "m" should be -- n -- whereby said portion of the formula should read:



Signed and sealed this 13th day of April 1971.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

WILLIAM E. SCHUYLER,
Commissioner of Pate