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5,6,8,9 - TETRAHYDRO - 1,3 - BENZOXAZACYCYLOUNDECANE - 2,4,7(3H) - TRIONES AND THEIR PREPARATION

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No Drawing. Filed June 20, 1968, Ser. No. 738,421

Int. Cl. C07d 87/54

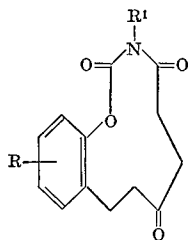
U.S. Cl. 260—239.3

6 Claims

ABSTRACT OF THE DISCLOSURE

There are disclosed herein 5,6,8,9-tetrahydro-1,3-benzoxazacycloundecane - 2,4,7(3H) - triones and its corresponding 3-methyl derivative as well as the 11-methoxy derivatives of both the above compounds and the intermediates used in their preparation, viz, 3,4,5,6-tetrahydro-2(1H)-benzo(h)quinolone, its 1-methyl derivative, and the 8-methoxy derivatives of both those compounds. The compounds possess anti-inflammatory activity, and a process for their preparation as well as methods for using them are also disclosed.

The present invention relates to macrocyclic imides which may be represented by Formula I.



in which R represents hydrogen or the methoxyl group and R¹ represents hydrogen or the methyl group. The compounds of this invention may be regarded as imides and are designated as benzoxazacycloundecane derivatives.

The new and novel macrocyclic imides of this invention have been found to possess interesting pharmacological properties. More particularly, these compounds have exhibited utility as anti-inflammatory agents in standard pharmacological tests, for example, in the rat paw edema test described by Winter et al. in *Proc. Soc. Exp. Biol. Med.*, vol. 111, p. 544 (1962).

When the compounds of this invention are employed as anti-inflammatory agents in warm-blooded animals, for example, in rats, alone or in combination in pharmacologically acceptable carriers, the proportion of the latter is determined by the solubility and the chemical nature of the compound, by the chosen route of administration, and by standard pharmacological practice. For example, the compounds of this invention may be administered orally in solid form together with suitable excipients such as starch, lactose, certain types of clay, and similar products. They may also be administered orally in the form of solutions or suspensions, or they may be injected parenterally. For parenteral administration they may be used in the form of sterile solutions which may also contain other solutes, for example enough salt or glucose to make the solutions isotonic.

In practical use the new pharmacologically active macrocyclic imides may be utilized at various dosages and frequencies of administration, both depending upon the manner of administration employed and other controlling

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factors. Generally it is preferred to begin by the use of relatively small dosages of the particular pharmacologically active compound utilized, these dosages initially being substantially less than optimal dosages. Thereafter the dosage may be increased by small increments until more satisfactory treatment results are secured, and 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 20 mg. to about 200 mg. per kilogram body weight. When using them as anti-inflammatory agents single oral doses of 50 to 100 mg. per kilogram body weight are preferred. Such dosages may be administered from 1 to 3 times per day, as required.

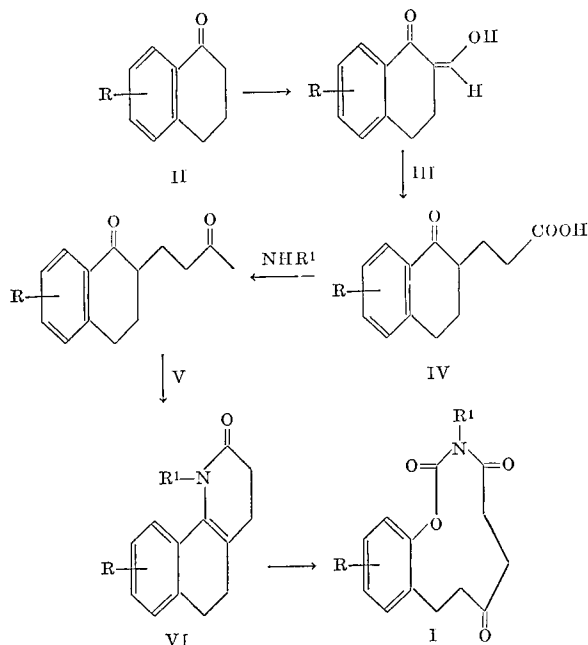
The compounds of this invention are particularly distinguished by possessing a low order of toxicity.

We prefer to prepare the compounds of this invention by reacting a suitably substituted tetralone of Formula II in which R is as defined above with ethyl formate in the presence of an alkali metal hydride such as, for example, sodium hydride, in an inert solvent such as, for example, benzene or tetrahydrofuran, preferably at room temperature, to yield the corresponding 2-hydroxymethylene derivative of Formula III in which R is as defined above. The latter compound is treated with a lower alkyl ester of acrylic acid such as for example, ethyl acrylate (commercial grade) in the presence of an organic base, preferably triethylamine, in a lower alkanol preferably methanol. This treatment is carried out by stirring for 1 to 5 days at temperatures between room temperatures to about 50° C., preferably for 60 hours at 35° C., to obtain the corresponding 1,2,3,4-tetrahydro-1-oxo-2-naphthalenepropionic acid lower alkyl ester, viz, the ethyl ester if ethyl acrylate has been employed. This ester is hydrolyzed under mild alkaline conditions, preferably with methanolic potassium hydroxide, to yield the corresponding 1,2,3,4-tetrahydro-1-oxo-2-naphthalenepropionic acid of Formula IV, in which R is as defined above. The unsubstituted acid (IV, R=H) is identical with the compound described by Bachmann et al. in *J. Am. Chem. Soc.*, vol. 22, p. 2533 (1950), and the methoxylated derivative (IV, R=OCH₃) is identical with the compound described by Akhrem et al. in *Izvest. Akad. Nauk. S.S.S.R. Otdel. Khim. Nauk.* 1960, 1637, cited in *Chem. Abs.* vol. 55, p. 8366a.

The above compounds are treated with an acid halide such as, for example, thionyl chloride or preferably oxalyl chloride, to yield the corresponding acid halide, preferably the chloride, of 1-(2H)-naphthalenone-2-propionic acid. Treatment of said acid chloride in an inert solvent, preferably benzene, in the presence of a suitable amine, preferably ammonia or methylamine, yields the corresponding 1-(2H)-naphthalenone-2-propionamides of Formula V in which R and R¹ are as defined above.

These amides are then subjected to cyclisation under dehydrating conditions, by treatment with a strong acid at an elevated temperature, preferably by treatment under reflux with perchloric or p-toluenesulfonic acid in an aromatic solvent, for example, in benzene, toluene or xylene, with a concomitant removal of water by azeotropic distillation. In this manner there are obtained correspondingly substituted cyclic en-amides of Formula VI in which R and R¹ are as defined above and which may correctly be designated as derivatives of 1,3,4,5,6-penta-hydro-2-oxo-benzo(h)-quinoline. Treatment of said last-named compounds with an organic per-acid, preferably with m-chloroperbenzoic acid yields the correspondingly substituted macrocyclic imide of Formula I in which R and R¹ are as defined above, and which may be designated as derivatives of 5,6,8,9-tetrahydro-1,3-benzoxazacy-

clouddecane-2,4,7(3H), trione. The following examples and formulae, in which R and R¹ are as defined above will illustrate this invention.



EXAMPLE 1

A mixture of 3,4-dihydro-6-methoxy - 1(2H)-naphthalenone (5.0 g.) dry benzene (100.0 ml.), ethyl formate (10.0 ml.) and sodium hydride suspension (3.0 g.) is stirred under nitrogen for three days at room temperature. Methanol (10 ml.) is added, the reaction mixture taken up in ether and extracted twice with 2 N potassium hydroxide solution. The basic layer is acidified with 10% sulfuric acid and extracted with ether. 3,4-dihydro-2-hydroxymethylene-6-methoxy-1(2H)-naphthalenone is obtained after evaporation of the solvent and is used without purification in the following step. A mixture of the above compound (5.5 g.), methanol (20.0 ml.), ethyl acrylate (3.5 g.) and triethylamine (1.0 ml.) is stirred for 60 hours at 35° C. The reaction mixture is taken up in ether and washed with 1 l. of 30% sodium carbonate solution and then with water. After drying of the ether layer and evaporation of the ether the residue is filtered through a 30-fold amount of neutral alumina (Act. II) with petroleum ether—benzene 1:1. The eluate is crystallized from acetone-hexane, to yield 1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-naphthalenepropionic acid ethyl ester with M.P. 57 to 58° C.

Said last-named compound (13.5 g.) is dissolved in 220 ml. methanol, 14.5 g. potassium hydroxide are added and the mixture is refluxed for two hours. The reaction mixture is taken up in ether and extracted with 2 N potassium hydroxide solution. The basic layer is cooled in an ice bath and carefully acidified with concentrated sulfuric acid. The precipitate is filtered off, washed with water and recrystallized from acetone-hexane, to yield 1,2,3,4-tetrahydro-6-methoxy-1-oxo - 2 - naphthalenepropionic acid with M.P. 134 to 135° C.

In the same manner, by using 3,4-dihydro-1(2H)-naphthalenone as starting material and proceeding as above, 1,2,3,4 - tetrahydro-1-oxo-2-naphthalenepropionic acid is obtained with M.P. 108 to 110° C.

EXAMPLE 2

To a solution of 1,2,3,4-tetrahydro - 1 - oxo-2-naphthalenepropionic acids (1.0 g.) in ethanol (70 ml.) a solution of sodium (1.15 g.) in ethanol (80 ml.) is added. The solvent is completely removed and the residue flashed with dry benzene (3 times). The dried sodium salt is sus-

pended in dry benzene (150 ml.) and a few drops of pyridine are added. The mixture is cooled in an ice bath, and oxalyl chloride (18 ml.) is added dropwise. The mixture is allowed to reach room temperature and is stirred for 45 minutes, filtered, and the solvent is evaporated.

The residual acid chloride

($\nu_{\text{max.}}^{\text{CHCl}_3}$ 1762 cm.⁻¹, 11.2 g.)

is dissolved in dry benzene (55 ml.) and methylamine is introduced for an half hour. The clear solution is diluted with benzene, washed with water, dried and the solvent is removed to yield 1,2,3,4-tetrahydro-N-methyl - 1 - oxo-2-naphthalenepropionamide with M.P. 93 to 94° C. after crystallization from methanol-ether.

In the same manner, but using ammonia instead of methylamine 1,2,3,4 - tetrahydro-1-oxo-2-naphthalenepropionamide is obtained with M.P. 147 to 148° C. after crystallization from chloroform-ether.

Again in the same manner, by using 1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-naphthalenepropionic acid as starting material and using methylamine as above, 1,2,3,4-tetrahydro-6-methoxy-N-methyl-1-oxo - 2 - naphthalenepropionamide is obtained with M.P. 139 to 140° C. after crystallization from methanol-ether, and in the same manner, when using ammonia instead of methylamine, 1,2,3,4-tetrahydro-6-methoxy-1-oxo-2 - naphthalenepropionamide is obtained.

EXAMPLE 3

A solution of 1,2,3,4 - tetrahydro - 1 - oxo - 2 - naphthalenepropionamide (0.924 g.) obtained as described in Example 2 in dry toluene (80 ml.) is refluxed with a Dean-Stark water separator in the presence of p-toluenesulfonic acid (0.151 g.) for 2 hours. The mixture is passed through a column of neutral alumina (Act. II, 20 g.), eluted with benzene and the solvent removed to yield 3,4,5,6 - tetrahydro - 2(1H) - benzo(h)quinolone with M.P. 181 to 183° C. after crystallization from chloroform-ether.

In the same manner, by using the corresponding N-methyl-propionamide, obtained as described in Example 2, as the starting material and proceeding as above, 3,4,5,6 - tetrahydro - 1 - methyl - 2(1H) - benzo(h)quinolone is obtained with M.P. 113–115° C. after crystallization from chloroform-hexane.

Again in the same manner, by using the corresponding 6-methoxylated derivatives, obtained as described in Example 2, as starting materials, 3,4,5,6 - tetrahydro-8-methoxy 1 - methyl - 2(1H) - benzo(h)quinolone, M.P. 78 to 80° C. after crystallization from methanol-ether-hexane, and 3,4,5,6 - tetrahydro - 8 - methoxy - 2(1H) - benzo(h)quinolone are respectively obtained.

EXAMPLE 4

To a suspension of m-chloroperbenzoic acid (9.5 g.) in methylene chloride a solution of 3,4,5,6 - tetrahydro-2(1H) - benzo(h)quinolone (3.9 g.), obtained as described in Example 3, in methylene chloride (40 ml.) is added at such a rate so as to maintain gentle reflux. The mixture is stirred for one hour at room temperature and filtered. The residue is washed with ether, refluxed with benzene (70 ml.) for 15 minutes and filtered hot to remove residual benzoic acid, to yield 5,6,8,8 - tetrahydro-1,3 - benzoxazacycloundecane - 2,4,7(3H) - trione with M.P. 136 to 137° C. after crystallization from benzene.

In the same manner, but using 3,4,5,6 - tetrahydro-1-methyl-2(1H)-benzo(h)quinolone, obtained as described in Example 3, as starting material, 5,6,8,9 - tetrahydro-3 - methyl - 1,3 - benzoxazacycloundecane - 2,4,7(3H) - trione is obtained with M.P. 139 to 140° C. after crystallization from methanol-ether.

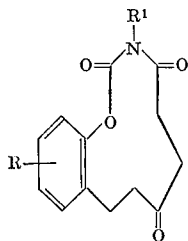
Again in the same manner, but using as starting materials the 8-methoxylated benzo(h)quinolone derivatives obtained as described in Example 3, 5,6,8,9-tetrahydro-11 - methoxy - 3 - methyl - 1,3-benzoxazacycloundecane-

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2,4,7(3H)-trione, M.P. 169 to 171° C., and 5,6,8,9-tetrahydro - 11 - methoxy - 1,3 - benzoxazacycloundecane-2,4,7(3H)-trione are respectively obtained.

We claim:

1. A compound selected from those of the formula



wherein R represents hydrogen or the methoxyl group, and R¹ represents hydrogen or the methyl group.

2. A compound as described in claim 1 which is: 5,6,8,9 - tetrahydro - 1,3 - benzoxazacycloundecane-2,4,7(3H)-trione.

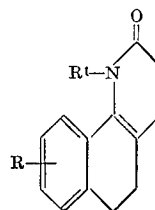
3. A compound as described in claim 1 which is: 5,6,8,9 - tetrahydro - 3 - methyl - 1,3 - benzoxazacycloundecane-2,4,7(3H)-trione.

4. A compound as described in claim 1 which is: 5,6,8,9 - tetrahydro - 11 - methoxy - 3 - methyl - 1,3 - benzoxazacycloundecane-2,4,7(3H)-trione.

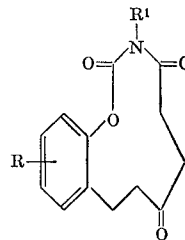
5. A compound as described in claim 1 which is: 5,6,8,9 - tetrahydro - 11 - methoxy - 1,3 - benzoxazacycloundecane-2,4,7(3H)-trione.

6. The process which comprises treating a compound of the formula

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10 wherein R is selected from the group consisting of hydrogen and methoxy, and R¹ is selected from the group consisting of hydrogen and methyl, with an organic peracid, thereby securing a compound of the formula



25 R and R¹ being as above identified.

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U.S. Cl. X.R.

424—244; 260—289