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LACTONES OF 1,12 - DIMETHYL - 6,10 - DIHYDROXY - 9 - OXO - 1,2,3,4,9,10,11,12 - OCTAHYDROPHENANTHRENE - 1 - CARBOXYLIC ACID

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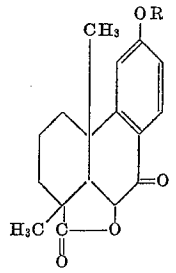
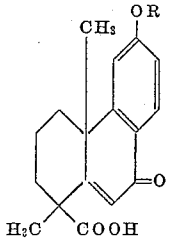
5 Claims. (Cl. 260—343.3)

This invention pertains to a new group of lactones related to 1,12-dimethyl-6,10-dihydroxy-9-oxo-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid and lower alkyl ethers thereof. It is specifically concerned with lactones having the structural formula



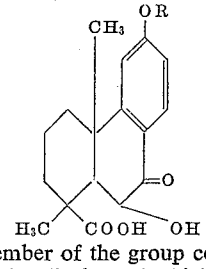
wherein R is a member of the group consisting of hydrogen and lower alkyl radicals. Among the lower alkyl radicals which R represents are methyl, ethyl, straight and branched-chain propyl, butyl, amyl and hexyl.

From the standpoint of chemical structure, the lactones which comprise this invention are isomeric with, and for some purposes are equivalent to, the unsaturated carboxylic acids to which they are related by a process of tautomerization. These unsaturated carboxylic acids can be represented by the structural formula



wherein R is a member of the group consisting of hydrogen and lower alkyl radicals.

For some purposes the lactones which comprise this invention are also equivalent to the hydroxy carboxylic acids which can be represented by the structural formula



wherein R is a member of the group consisting of hydrogen and lower alkyl radicals, and which are related to the lactones by a process of intramolecular dehydration.

Although for certain applications, such as reactions involving transesterifications, the latter two structural species may play an important role, I have found that

the lactonic forms of these compounds are more stable under normal condtions and I have developed methods for preparing these lactones in good yield and in high states of purity.

A suitable starting material for preparing the compounds of this invention is an alkyl O-alkylpodocarpate, such as methyl O-methylpodocarpate. An oxo group is first introduced into the 9-position by means of a controlled oxidation with chromium trioxide. When this 9-oxo derivative is brominated in a halogenated hydrocarbon solvent with a selective brominating agent such as N-bromosuccinimide, a bromine atom is introduced into the 10-position. When the resulting methyl ester of 1,12-dimethyl - 6 - methoxy-9-oxo-10-bromo-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid is heated with a nitrogenous base such as 2,4,6-trimethylpyridine, ring closure occurs with the loss of the elements of methyl bromine and the formation of the desired lactone.

In an alternative method for the preparation of the lactones which comprise this invention, an O-alkylpodocarpic acid such as O-methylpodocarpic acid is converted to the 9-oxo derivative with chromium trioxide, and the resulting 1,12-dimethyl-6-methoxy-9-oxo-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid is treated with N-bromosuccinimide. While an intermediate 10-bromo derivative is believed to exist in this reaction mixture, elimination of the bromine atom as hydrogen bromide and ring closure occur spontaneously, with the result that the lactone can be isolated directly from the mixture.

In preparing the lactone of this invention wherein R is hydrogen, that is, the lactone of 1,12-dimethyl-6,10-dihydroxy - 9 - oxo - 1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid, it is preferred to dealkylate a corresponding 6-alkoxy derivative by such means as heating it with a mixture of glacial acetic acid and hydrobromic acid.

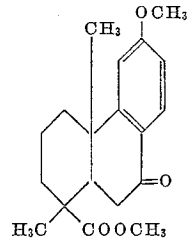
The compounds which constitute this invention have valuable hormonal and anti-inflammatory properties. Specifically, they have been found to inhibit the hyperemia that is associated with states of inflammation of the iris. The claimed compounds are also useful as intermediates in chemical syntheses.

My invention will appear in greater detail from the following examples. However, it is not to be construed as limited thereby in spirit or in scope. In these examples temperatures are given in degrees centigrade and quantities of materials are given in parts by weight.

Example 1

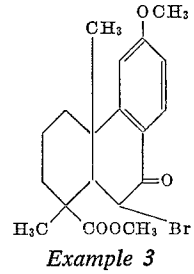
A solution of 100 parts of methyl O-methylpodocarpate in 1050 parts of hot glacial acetic acid is stirred and cooled to 17° C. and treated at that temperature, by slow addition, with 72 parts of chromium trioxide in 166 parts of 80% acetic acid in the course of 30 minutes. Stirring is continued for another 10 minutes after which the mixture is stored at 5° C. for 3 days and then at room temperature for 2 days. It is then poured with stirring into 1000 parts of ice-cold water and extracted with ether. The ether extract is washed with 10% aqueous sodium hydroxide until the washings are no longer colored and then with water to neutrality. The washed ether solution is dried over anhydrous calcium sulfate, filtered and stripped of solvent under vacuum. The slightly yellow solid residue is recrystallized twice from aqueous ethanol to yield clusters of beautiful white prisms melting at about 122–124° C. A 1% solution in absolute alcohol gives a specific rotation of +124°. The infrared spectrum exhibits strong bands at 5.82, 6.02, 6.28, 6.39, and 6.76 microns. The ultraviolet spectrum shows a peak at 227 millimicrons with a molecular extinction coefficient of 13,000 and a peak at 276 millimicrons with a molecular extinction coefficient of 15,800. The methyl ester of

1,12-dimethyl - 6 - methoxy-9-oxo-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid has the structural formula



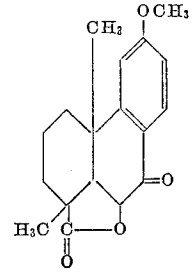
Example 2

A mixture of 4.9 parts of the methyl ester of 1,12-dimethyl - 6 - methoxy-9-oxo-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid and 2.8 parts of N-bromosuccinimide in 80 parts of anhydrous carbon tetrachloride is allowed to stand, with occasional stirring, at room temperature for 30 hours. This reaction is promoted by light, and for good results it is advisable to expose the mixture to sunlight for a substantial portion of the reaction time. At the end of this period of time the succinimide formed in the reaction is removed by filtration; it amounts to about 1.3 parts. The solvent is removed from the filtrate by a vacuum distillation, leaving a residual yellow oil which gradually crystallizes. This brominated derivative is purified by recrystallization from aqueous methanol. In this manner it is obtained as well-formed needles which, after thorough drying, melt at about 142–144.5° C. This methyl ester of 1,12-dimethyl-6-methoxy-9-oxo-10-bromo-1,2,3,4,9,10,11,12 - octahydrophenanthrene-1-carboxylic acid has the structural formula



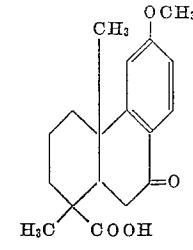
Example 3

A mixture of 3.0 parts of the methyl ester of 1,12-dimethyl - 6 - methoxy-9-oxo-10-bromo-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid, and 23 parts of 2,4,6-trimethylpyridine is heated under reflux for a period of 2 hours. The mixture is then poured, with stirring, into 200 parts of water, and the resulting suspension is acidified with dilute hydrochloric acid. The almost colorless precipitate which remains is collected on a filter. For purification, it is recrystallized from a mixture of benzene and petroleum ether. Another good method of purification is by sublimation in a vacuum. The purified material melts at 198–200.5° C. and exhibits a specific rotation of about +85°. Ultraviolet absorption maxima are observed at 231 and 291 millimicrons. Infrared absorption maxima appear at 5.67, 6.93, 6.25, and 6.39 microns. This compound is the lactone of 1,12-dimethyl - 6 - methoxy-9-oxo-10-hydroxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid and it has the following structural formula



Example 4

A solution of 90 parts of O-methylpodocarpic acid and 1070 parts of glacial acetic acid is stirred and maintained at 15–18° C. while a solution of 65.4 parts of chromium trioxide in a mixture of 32 parts of water and 134 parts of glacial acetic acid is added in the course of 30 minutes. The reaction mixture is stirred at 5–10° C. and then stored at 8–10° C. for 3 days. After further storage at room temperature for 2 days, 40 parts of 95% ethanol are added slowly with good mixing in order to decompose any unreacted chromium trioxide. The entire reaction mixture is stirred into 3000 parts of warm water and then extracted exhaustively with ether. The combined ether extracts are washed with dilute hydrochloric acid until the washings are no longer colored and then with water to neutrality. The solution is dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to yield a light yellow, viscous oil. The product is decolorized by boiling a methanolic solution with activated charcoal. The 1,12-dimethyl-6-methoxy-9-oxo-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid crystallizes from aqueous methanol in small, colorless, gleaming prisms which melt at about 183–185° C. The infrared spectrum shows well-defined bands at 2.83, 5.90, 5.98, 6.27, and 7.82 microns. The ultraviolet absorption spectrum has peaks at 226 and 276 millimicrons with molecular extinction coefficients of 13,600 and 15,700. respectively. The compound has the structural formula



Example 5

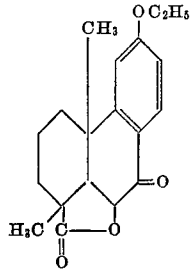
A slurry prepared from 4.00 parts of 1,12-dimethyl-6-methoxy-9-oxo-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid, 2.52 parts of N-bromosuccinimide and 320 parts of anhydrous carbon tetrachloride is allowed to stand, with occasional stirring, for 30 hours at room temperature. This reaction is promoted by light, and for good results it is advisable to expose the mixture to sunlight for a substantial portion of the reaction time. The precipitated material, which consists largely of succinimide, is collected on a filter and the desired reaction product is recovered from the filtrate after removal of the solvent by a vacuum distillation. The residual material, by recrystallization from aqueous methanol, gives the same purified lactone of 1,12-dimethyl-6-methoxy-9-oxo-10-hydroxy - 1,2,3,4,9,10,11,12 - octahydrophenanthrene - 1 - carboxylic acid that is obtained by the procedure of Example 3. When the residue obtained by evaporation of the crystallization liquors is extracted with dilute sodium hydroxide solution, the fraction which remains undissolved by this treatment yields more of the pure lactone when it is recrystallized from aqueous methanol.

Example 6

To a solution of 400 parts of methyl podocarpate and 120 parts of sodium hydroxide in 1100 parts of water and 1600 parts of 95% ethanol are added all at once 330 parts of diethyl sulfate. The reactants are quickly mixed and then allowed to stand until a thick white precipitate forms. This precipitate is collected on a filter, washed with dilute ethanol, and recrystallized from methanol to yield methyl O-ethylpodocarpate as thin, colorless needles melting at about 144–147.5° C.

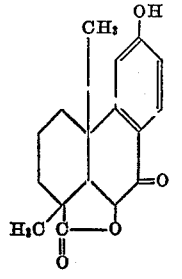
A stirred solution of 100 parts of methyl O-ethylpodocarpate in 1000 parts of hot glacial acetic acid is cooled to 15° C. and treated at that temperature with 68

parts of chromium trioxide in 156 parts of 80% acetic acid in the course of 30 minutes. Stirring is continued for a few more minutes after which the mixture is maintained at 10° C. for 2 days and then at room temperature for 2 days. It is then poured, with stirring, into 1000 parts of ice and water and extracted with ether. This extract is washed with 10% aqueous potassium hydroxide until the washings are colorless and then with water to neutrality. The ether solution is dried over anhydrous calcium sulfate, filtered and concentrated in vacuo. When the residual methyl ester of 1,12-dimethyl-6-ethoxy-9-oxo-1,2,3,4,9,10,11,12 - octahydrophenanthrene-1-carboxylic acid is treated with N-bromosuccinimide by the procedure of Example 2, and the resultant methyl ester of 1,12-dimethyl-6-ethoxy-9-oxo-10-bromo-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid is treated with boiling 2,4,6-trimethylpyridine by the procedure of Example 3, there is obtained the lactone of 1,12-dimethyl-6-ethoxy-9-oxo-10-hydroxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid. This compound has the following structural formula



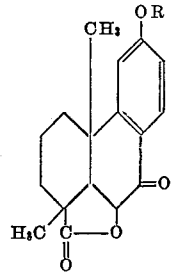
Example 7

A mixture of 5 parts of the lactone of 1,12-dimethyl-6-methoxy-9 - oxo - 10 - hydroxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-1-carboxylic acid, 37 parts of glacial acetic acid and 30 parts of 48% hydrobromic acid is heated under reflux for a period of 1 hour. The reaction mixture is then cooled and poured, with stirring, into about 350 parts of water. The insoluble material is washed by decantation with several portions of fresh water and it is then extracted with mixtures of chloroform and ether. The organic solution is washed with dilute potassium bicarbonate solution and then with several portions of water. All aqueous washings are discarded. When the organic phase is dried, filtered and evaporated to dryness there is obtained a crystallizate of a lactone of 1,12-dimethyl-6,10-dihydroxy-9-oxo-1,2,3,4,9,10,11,12-octahydrophenanthrene - 1 - carboxylic acid in which the hydroxyl group participating in lactone formation is that occupying the 10-position. This compound has the following structural formula



I claim:

1. A compound having the structural formula



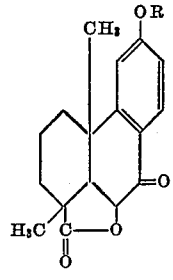
wherein R is a member of the group consisting of hydrogen and lower alkyl radicals.

2. The lactone of 1,12-dimethyl-6-methoxy-9-oxo-10-hydroxy - 1,2,3,4,9,10,11,12 - octahydrophenanthrene - 1-carboxylic acid.

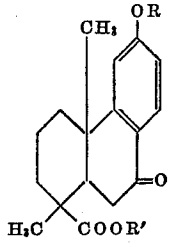
3. The lactone of 1,12-dimethyl-6-ethoxy-9-oxo-10-hydroxy - 1,2,3,4,9,10,11,12 - octahydrophenanthrene - 1-carboxylic acid.

4. The lactone of 1,12-dimethyl-6,10-dihydroxy-9-oxo-1,2,3,4,9,10,11,12 - octahydrophenanthrene - 1 - carboxylic acid.

5. In a process for preparing a compound having the structural formula



wherein R is a member of the group consisting of hydrogen and lower alkyl radicals, the steps which comprise dissolving a compound having the structural formula



wherein R and R' are each members of the group consisting of hydrogen and lower alkyl radicals, in a halogenated hydrocarbon solvent, mixing the solution thus obtained with N-bromosuccinimide, and allowing it to stand in the presence of light.

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