United States Patent Office 2,705,712 Patented Apr. 5, 1955

2,705,712

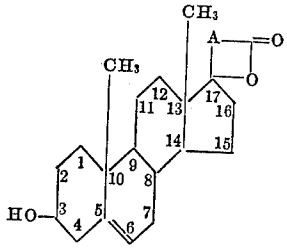
CYCLOPENTANOPHENANTHRENE LACTONES

John A. Cella, Skokie, Ill., assignor to G. D. Searle & Co., Chicago, Ill., a corporation of Illinois

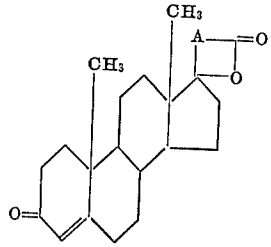
No Drawing. Application September 21, 1953, Serial No. 381,514

5 Claims. (Cl. 260—239.57)

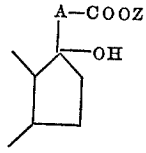
The present invention relates to γ-lactones and alkali metal salts of 3'-[17-(polyhydro-17-hydroxy-15H-cyclopenta[a]phenanthrene)]-acrylic and -propionic acids, and to processes for the preparation of these lactones and salts from 17-ethynlpolyhydro-17-hydroxy-cyclopenta[a]phenathrenes. More particularly, this invention relates to compounds of the formula



and congeneric 3-oxo compounds of the formula



A in each of the foregoing formulas being an ethylene (—CH_2CH_2—) or vinylene (—CH=CH—) radical. Equivalent to the preceding lactones for the purposes of this invention are salts of the corresponding hydroxy acids derived by hydrolytic cleavage of the anhydro ring in the manner shown



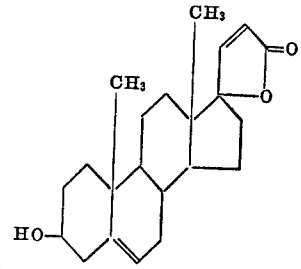
upon treatment of the appropriate parent lactone with alkali, Z in the foregoing part-formula being an alkali metal and A having the meaning assigned above.

The compounds of this invention are valuable in medicine as cardio-regulatory agents. Their capacity for exercising a depressant effect on the heart muscle commends this use in the treatment of auricular fibrillation and flutter, paroxysmal tachycardia, and divers other cardiac dysfunctions associated with rhythm changes of the heart caused by disturbances in the regular automaticity or conductance pattern of its best. Moreover, the subject compounds manifest a relatively unilateral pressor activity of value, for example, in the compensation of hypotension accompanying administration of spinal and various general anesthetics.

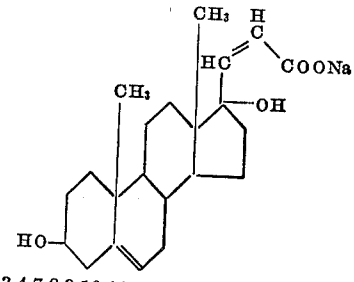
Additionally, the compounds of the present invention, being possessed of a potent myotrophic activity uncomplicated by the capacity for testoid stimulation which characterizes and delimits the anabolic utility of testosterone and other naturally-occurring substances known to increase muscle strength and mass, are uniquely adapted

to use in the care of premature infants, the management of convalescence from acute illness and surgical procedures, and for long-term administration to patients with chronic debilitating disease.

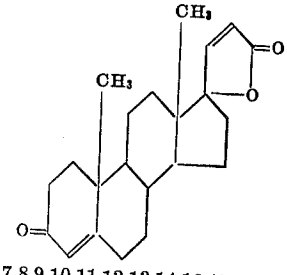
Among the compounds contemplated by the present invention are those formulated and named as follows:



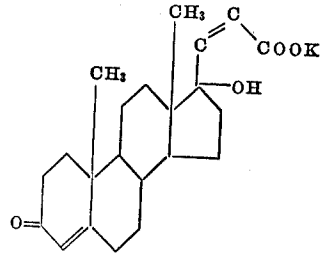
3'-[17-(1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-3,17-dihydroxy - 10,13 - dimethyl - 15H - cyclopenta[a]phenanthrene)]-acrylic acid γ-lactone.



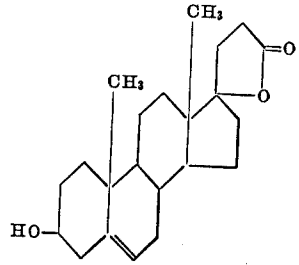
3'-[17-(1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-3,17-dihydroxy - 10,13 - dimethyl - 15H - cyclopenta[a]phenanthrene)]-acrylic acid sodium salt.



3'-[17-(1,2,3,6,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-17-hydroxy - 10,13 - dimethyl-3-oxo-15H-cyclopenta[a]phenanthrene)]-acrylic acid γ-lactone.

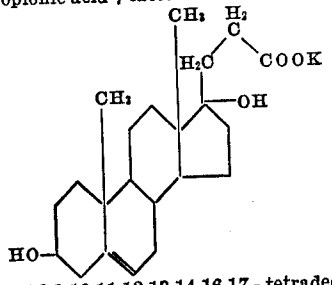


3'-[17-(1,2,3,6,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-17-hydroxy - 10,13 - dimethyl-3-oxo-15H-cyclopenta[a]phenanthrene)]-acrylic acid potassium salt.

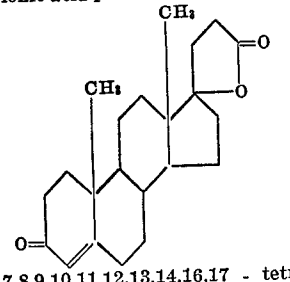


3'-[17-(1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-3,17-

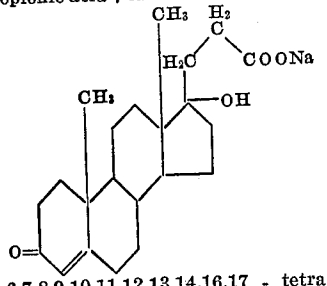
dihydroxy - 10,13 - dimethyl - 15H - cyclopenta[a]phenanthrene)]-propionic acid γ-lactone.



3'-[17-(1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-3,17-dihydroxy - 10,13 - dimethyl - 15H - cyclopenta[a]phenanthrene)]-propionic acid potassium salt.



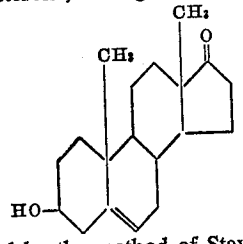
3'-[17-(1,2,3,6,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-17-hydroxy - 10,13 - dimethyl-3-oxo-15H-cyclopenta[a]phenanthrene)]-propionic acid γ-lactone.



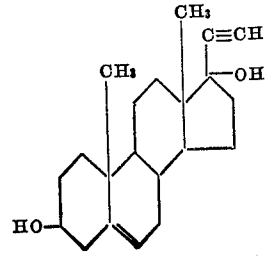
3'-[17-(1,2,3,6,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-17-hydroxy - 10,13 - dimethyl-3-oxo-15H-cyclopenta[a]phenanthrene)]-propionic acid sodium salt.

The compounds to which this invention relates are soluble in alcohol, as also in propylene glycol. They may be administered in solid form as tablets or capsules; dissolved or suspended in aqueous alcohol, they may be given parenterally.

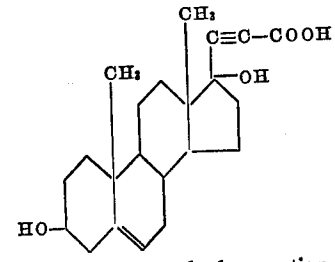
The subject compounds may be prepared in accordance with the following procedures: A 1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro - 3-hydroxy-10,13-dimethyl-17-oxo-15H-cyclopenta[a]phenanthrene, for example, dehydroepiandrosterone, having the formula



may be converted by the method of Stavely, "Journal of the American Chemical Society," 61, 79–80 (1939), using acetylene in the presence of potassium and tert. amyl alcohol as condensing agents, to a 17-ethynyl-1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro - 3,17-dihydroxy - 10,13-dimethyl-15H-cyclopenta[a]phenanthrene, of the formula



The ethynyl compound, in turn, may be carboxylated after the general method of Haynes and Jones, "Journal of the Chemical Society," 1946, 503–506, whereby the Grignard reagent and carbon dioxide enable the preparation of a 17-carboxyethynyl-1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro - 3,17 - dihydroxy-10,13-dimethyl-15H-cyclopenta[a]phenanthrene, the formula of which is



The latter compound, upon hydrogenation in the presence of a catalyst such as palladium on calcium carbonate, or the equivalent, is reduced and, in acid medium, subsequently cyclized to 3'-[17-(1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro - 3,17-dihydroxy-10,13-dimethyl-15H-cyclopenta[a]phenanthrene)]-acrylic acid γ-lactone, one of the compounds of this invention. Oppenauer oxidation of this 3-hydroxy lactone, using aluminum isopropoxide, affords another compound of the present invention, namely, 3'-[17-(1,2,3,6,7,8,9,10,11,12,13,14,16,17 - tetradecahydro - 17-hydroxy-10,13-dimethyl-3-oxo - 15H - cyclopenta[a]phenanthrene)]-acrylic acid γ-lactone. Alternatively, the 3-hydroxy lactone above may be hydrogenated in the presence of a catalyst such as palladium on carbon powder to give the 3'-[17-(1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro - 3,17-dihydroxy-10,13 - dimethyl - 15H-cyclopenta[a]phenanthrene)]-propionic acid γ-lactone of this invention. This lactone may be subjected to Oppenauer oxidation to yield still another of the subject compounds, to wit, 3'-[17-(1,2,3,6,7,8,9,10,11,12,13,14,16,17 - tetradecahydro - 17-hydroxy-10,13-dimethyl - 3-oxo-15H-cyclopenta[a]phenanthrene)]-propionic acid γ-lactone.

The 17 - carboxyethynyl - 1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro - 3,17-dihydroxy-10,13-dimethyl-15H-cyclopenta[a]phenanthrene, which serves as an intermediate for the preparation of compounds of this invention, may be converted by Oppenauer oxidation to a 17 - carboxyethynyl - 1,2,3,6,7,8,9,10,11,12,13,14,16,17-tetradecahydro - 17 - hydroxy-10,13-dimethyl-3-oxo-15H-cyclopenta[a]phenanthrene, which, like the claimed compounds, is a therapeutically valuable material.

The following examples will illustrate in detail certain of the processes and products of this invention. However, the invention is not to be construed as limited thereby, either in spirit or in scope, since it will be apparent to those skilled in the art of organic synthesis that many modifications, both of materials and of methods, may be practiced without departing from the purpose and intent of this disclosure. In the examples hereinafter detailed, temperatures are given in degrees centigrade (° C.) and relative amounts of materials in parts by weight, except as otherwise noted.

Example 1

A. *17 - carboxyethynyl-1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-3,17-dihydroxy-10,13-dimethyl-15H-cyclopenta[a]phenanthrene.*—The Grignard reagent of 17-ethynyl-5-androsten-3β,17β-diol is prepared by adding a solution of 15 parts of the ethynyl compound in approximately 260 parts of dimethoxyethane to a solution of ethyl magnesium bromide prepared by interaction of 7.2 parts of magnesium and 33 parts of ethyl bromide, in 215 parts of ether. The reactants are maintained at approximately 40° C. until the evolution of ethane gas formed in process effectively ceases—which is usually after from 2 to 4 hours. Next, the reaction mixture is treated in a bomb at room temperature for 36 hours with 200 parts of solid carbon dioxide. Excess carbon dioxide is then vented and the heterogeneous contents of the bomb thereupon acidified to pH 5. The resultant three-phase mixture is filtered, and the precipitate thus recovered is extracted with several 100 cc. portions of hot dioxane. The insoluble residue (which is the magnesium bromide salt of the desired product) is then taken up in 50 volumes of an acidified 50–50 mixture of dioxane and

water at the boiling point. On cooling, long needles of 17 - carboxyethynyl - 1,2,3,4,7,8,9,10,11,12,13,14,16,17-tetradecahydro - 3,17-dihydroxy-10,13-dimethyl-15H-cyclopenta[a]phenanthrene separate as a monohydrate. Vacuum drying results in loss of water of hydration. The anhydrous product melts with decomposition, at 234-235° C., and shows $[\alpha]_D$—132.5° (in dioxane).

B. *3' - [17 - (1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro - 3,17 - dihydroxy-10,13-dimethyl-15H-cyclopenta[a]phenanthrene)]-acrylic acid γ-lactone.*—A solution of 1 part of the diol of the preceding Part A in 45 parts of dioxane containing 5 parts of pyridine is agitated with hydrogen at room temperature and atmospheric pressure in the presence of 0.1 part of 5% palladium supported on calcium carbonate. When one equivalent of hydrogen has been absorbed, the reduction is stopped and the reaction mixture thereupon filtered to remove catalyst. The bulk of the solvent is stripped in vacuo, and the oily residue is then treated with sufficient 1% aqueous hydrochloric acid to induce crystallization. The solid product thus obtained is filtered off and then crystallized from 20–30 volumes of 80% aqueous methyl alcohol. The purified material, 3'-[17-(1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-3,17-dihydroxy-10,13-dimethyl-15H - cyclopenta[a]phenanthrene)]-acrylic acid γ-lactone, shows M. P. 197.5–201° C., $[\alpha]_D$+2° (in chloroform).

Example 2

3'-[17-(1,2,3,6,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-17-hydroxy - 10,13 - dimethyl - 3 - oxo - 15H - cyclopenta[a]phenanthrene)]-acrylic acid γ-lactone.—The 3-hydroxy lactone of the preceding Example 1B may be converted to the corresponding 3-oxo compound by Oppenauer oxidation according to the following procedure: 4 parts of the starting 3-hydroxy lactone is dissolved in a mixture of 220 parts of dry toluene and 24 parts of cyclohexanone. This solution is refluxed for 1 hour with approximately one-third its volume of 10% aluminum isopropoxide in dry toluene. The reaction mixture is hydrolyzed by addition of a saturated aqueous solution of Rochelle salts, then steam distilled to remove solvent. The distalland is extracted with chloroform to remove the oil precipitated therein, and the chloroform extract is then dried and finally evaporated to dryness. The residue is purified by chromatographic adsorption on silica gel, using benzene and ethyl acetate as developing solvents. The material thus obtained is further purified by chrystallization from a 50–50 mixture of ethyl acetate and cyclohexane. The 3'-[17-(1,2,3,6,7,8,9,10,11,12,13,14,16,17-tetradecahydro-17-hydroxy - 10,13 - dimethyl-3-oxo-15H-cyclopenta[a]phenanthrene)]-acrylic acid γ-lactone prepared in this manner shows M. P. 153.5–154.5° C., $[\alpha]_D$+203.5° (in chloroform).

Example 3

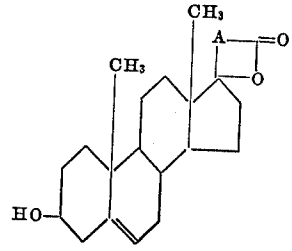
3'-[17-(1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-3,17-dihydroxy-10,13-dimethyl - 15H - cyclopenta [a] phenanthrene)]-propionic acid γ-lactone.—A solution of 1 part of the 3-hydroxy lactone of Example 1B in 50 volumes of alcohol is hydrogenated at atmospheric pressure and room temperature in the presence of 0.1 part of 5% palladium supported on carbon powder. When one equivalent of hydrogen has been absorbed, the reduction is stopped; and the reaction mixture is then filtered to remove the catalyst. The filtrate is evaporated to dryness, following which the residue is crystallized from approximately 40 volumes of 70% aqueous methyl alcohol. Recrystallization from approximately 15 volumes of a mixture consisting of 90 parts of cyclohexane and 10 parts of methyl ethyl ketone yields the desired 3'-[17-(1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecohydro-3,17-dihydroxy-10,13-dimethyl - 15H - cyclopenta[a]phenanthrene)]-propionic acid γ-lactone as a pure product. The material shows M. P. 187–189° C.

Example 4

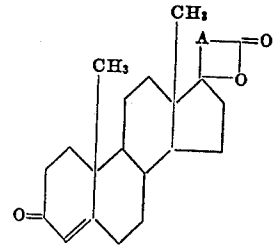
3'-[17-(1,2,3,6,7,8,9,10,11,12,13,14,16,17-tetradecahydro-17-hydroxy-10,13-dimethyl-3-oxo - 15H - cyclopenta [a]phenanthrene)]-propionic acid γ-lactone.—A solution of 1 part of the 3-hydroxy lactone of the preceding Example 3 in a mixture of 45 parts of dry toluene and 9 parts of cyclohexanone is refluxed for 20 minutes with one-eighth its volume of 20% aluminum isopropoxide in dry toluene. A saturated aqueous solution of Rochelle salts is added to hydrolyze the reaction product, whereupon the materials are steam distilled to remove solvent. The oily product precipitated in the distilland is extracted with ether; and the ether extract is washed, dried over anhydrous sodium sulfate, and evaporated to dryness in a stream of air, in that order. Chromatographic purification of the residue on silica gel, using benzene and ethyl acetate as developing solvents, affords the desired 3'-[17-(1,2,3,6,7,8,9,10,11,12,13,14,16,17-tetradecahydro-17-hydroxy-10,13-dimethyl-3-oxo -15H- cyclopenta [a]phenanthrene)]-propionic acid γ-lactone, which is crystallized from a mixture consisting of 2 parts of ethyl acetate and 3 parts of petroleum ether. The product shows M. P. 148–149° C.

I claim:

1. A compound selected from the group consisting of compounds of the formula

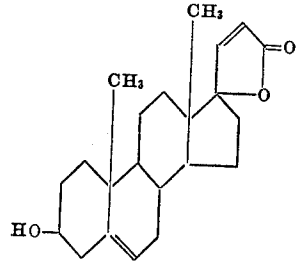


and congeneric 3-oxo compounds of the formula

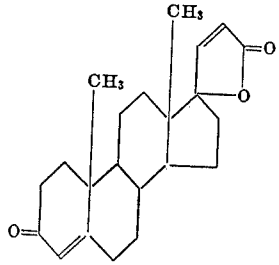


A in each of the foregoing formulas being selected from the group consisting of ethylene and vinylene radicals.

2. 3' - [17- (1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-3,17-dihydroxy - 10,13 - dimethyl-15H-cyclopenta[a]phenanthrene)]-acrylic acid γ-lactone, having the formula

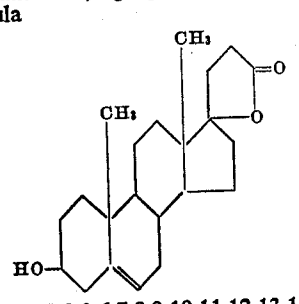


3. 3' - [17 - (1,2,3,6,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-17-hydroxy-10,13-dimethyl -3- oxo-15H-cyclopenta[a]phenanthrene)]-acrylic acid γ-lactone, having the formula



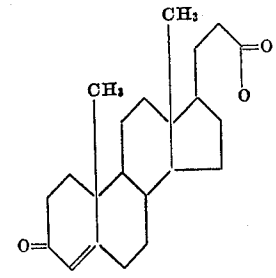
4. 3' - [17 - (1,2,3,4,7,8,9,10,11,12,13,14,16,17 - tetradecahydro - 3,17 - hydroxy - 10,13 - dimethyl-15H-cyclo-

penta[a]phenanthrene)]-propionic acid γ-lactone, having the formula



5. 3' - [17 - (1,2,3,6,7,8,9,10,11,12,13,14,16,17 - tetradecahydro-17-hydroxy-10,13-dimethyl-3-oxo-15H - cyclo-

penta[a]phenanthrene)]-propionic acid γ-lactone, having the formula



No references cited.