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PHENANTHRENE DERIVATIVES

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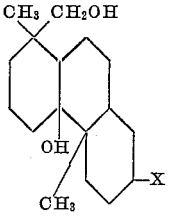
8 Claims. (Cl. 260—99)

The present invention relates to new triols that can be prepared from hydrogenated rosin and, more specifically, to triols obtained by the reduction of oxidation products of the lactone of hydroxytetrahydroabietic acid.

It is well known that a crystalline lactone can be obtained from partially hydrogenated rosin, i. e., a rosin containing a dihydroabietic acid, by treatment of the partially hydrogenated rosin with sulfuric acid. This lactone is commonly called "the lactone of hydroxytetrahydroabietic acid" and is characterized by a melting point of 131–132° C. and $[\alpha]_D$—3°. The structure of this lactone has been recently established. It has been shown that the angular methyl group is at the 4b position and the alcoholic oxygen at the 4a position, the angular methyl group having shifted during lactonization from the 4a position which it has in dihydroabietic acid to the 4b position. The lactone is extremely stable and does not readily undergo such reactions as hydrolysis, etc., which break the lactone ring. The lactone of hydroxytetrahydroabietic acid can, however, be oxidized by various means to produce products that are oxygenated in the 7 position. Thus, for example, there can be produced by oxidation products in which the isopropyl group at the 7 position of the lactone is replaced by an acetyl, ketonic oxygen or hydroxyisopropyl group.

In accordance with this invention, it has been found that the above-described oxidation products of the lactone of hydroxytetrahydroabietic acid can be reduced by means of an alkali metal aluminum hydride to produce a group of trialcohols having the formula



wherein X is a radical selected from the group consisting of hydroxy, 1-hydroxyethyl and 1-hydroxyisopropyl radicals. For convenience, these compounds hereinafter will be referred to, respectively, as the 7-hydroxy, the 7-hydroxyethyl and the 7-hydroxyisopropyl triols.

The preparation of the compounds of the invention involves first an oxidation of the lactone of hydroxytetrahydroabietic acid. A preferred method is one in which the lactone is oxidized by anhydrous chromium trioxide, and from the oxidation product there is isolated the lactone of 7-acetyl-4a-hydroxy-1,4b-dimethyl-perhydrophenanthrene-1-carboxylic acid and the lactone of 4a-hydroxy-1,4b-dimethyl-7-oxoperhydrophenanthrene-1-carboxylic acid. The 7-acetyl lactone is then reduced with an alkali metal aluminum hydride to form 4a-hydroxy-7(1-hydroxyethyl)-1-hydroxymethyl-1,4b-dimethyl-perhydrophenanthrene (the 7-hydroxyethyl triol) and the 7-oxolactone is reduced with an alkali metal aluminum hydride to form 4a,7-dihydroxy-1-hydroxymethyl-1,4b-dimethyl-perhydrophenanthrene (the 7-hydroxy triol. In order to obtain the 7-hydroxyisopropyl triol, the 7-acetyl lactone is reacted with a Grignard reagent to form the 14-hydroxy lactone which is then reduced by means of an alkali metal aluminum hydride to form 4a-hydroxy-7(1-hydroxyisopropyl)-1a-hydroxymethyl-1,4b-dimethyl-perhydrophenanthrene (the 7-hydroxyisopropyl triol).

In another method of preparing the compounds of the invention wherein X of the above formula is hydroxy or 1-hydroxyisopropyl, the lactone of hydroxytetrahydroabietic acid is oxidized by elemental oxygen, and from the oxidation product there is isolated both the 7-oxolactone and the 14-hydroxy lactone. The 7-oxolactone can be reduced as above to form the 7-hydroxy triol of the invention whereas the 14-hydroxy lactone can be reduced by means of an alkali metal aluminum hydride to form directly the 7-hydroxyisopropyl triol of the invention.

From the preceding description, it is seen that the process of preparing the compounds of the invention involves the common step of reducing, by means of an alkali metal aluminum hydride, a compound selected from the group consisting of the 7-acetyl, 14-hydroxy and 7-oxo derivatives of the lactone of hydroxytetrahydroabietic acid.

In order to illustrate the invention, the following examples are presented. Parts and percentages are by weight unless otherwise specified.

Example 1

There was prepared a solution of 30.4 parts of the lactone of hydroxytetrahydroabietic acid in approximately 425 parts of acetic acid and 490 parts of acetic anhydride. To this solution there was added 33.3 parts of solid chromium trioxide over a period of 7 hours, and the resulting solution was stirred at room temperature overnight. The resulting dark green solution was poured into 8000 parts of ice water containing 100 parts of sodium acetate and stirred for 3 hours. The resulting precipitate was removed by ether extraction and the ether extract was then washed with water until clear. Evaporation of the ether yielded 23 parts of a solid material.

The solid material was dissolved in 160 parts of absolute ethanol containing 20 parts of Girard's reagent (trimethylaminoacethydrazide hydrochloride) and 21 parts of acetic acid and boiled under reflux for 2 hours. The solution was cooled, poured into 1800 parts of ice water containing 12 parts of sodium hydroxide, and then extracted with ether. The aqueous layer from the extraction was again extracted with fresh ether and then acidified with 150 parts of concentrated hydrochloric acid. All of the ether extracts were combined, washed with water until neutral, dried and evaporated to yield 12.4 parts of a nonketonic residue which was discarded. The acidified aqueous layer was extracted with fresh water and the extract washed until neutral, dried and evaporated to dryness to yield 8.74 parts of a ketonic fraction. The

ketonic fraction was dissolved in 20 parts of benzene and chromatographed on a column of basic alumina. The alumina was then eluted with various solvents to obtain seventeen fractions as follows:

Fraction	Eluting Solvent	Wt. of Solvent (parts)	Wt. of Residue (parts)
1	Benzene	45	
2	do	45	
3	do	45	
4	do	45	0.90
5	do	45	
6	do	45	
7	do	45	
8	do	440	1.13
9	do	879	1.20
10	do	879	0.45
11	do	879	0.35
12	do	2,300	0.59
13	CH_2Cl_2	1,335	2.04
14	CH_2Cl_2	1,335	0.41
15	CH_2Cl_2	2,670	0.10
16	Ether	720	nil
17	Ether—MeOH	1,500	nil
			7.17

Fractions 1–11 were mixed and recrystallized from isooctane to yield 3.75 parts of a crystalline material believed to be the 7-acetyl derivative of the starting lactone. This was confirmed by a positive iodoform test and an infrared absorption spectrum which indicated the presence of the expected groups. *Analysis.*—Found: C, 74.94; H, 9.46. Calculated for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27.

Fractions 13 and 14 were combined and recrystallized from isopropyl ether which yielded 1.8 parts of a material melting at 150–152° C. This material was identified as the 7-oxo derivative of the starting lactone. *Analysis.*—Found: C, 73.97; H, 8.84. Calculated for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75.

Example 2

Approximately 3 parts of lithium aluminum hydride was suspended in 175 parts of ether in a reaction vessel equipped with stirrer, dropping funnel and condenser plus drying tube. To this suspension there was slowly added 2.7 parts of the 7-acetyl lactone (prepared in Example 1) dissolved in a mixture of 50 parts of ether and 125 parts of tetrahydrofuran. The reaction was stirred for 6 hours.

To destroy excess lithium aluminum hydride, approximately 11 parts of ethyl acetate was slowly added to the reaction mixture. The lithium aluminum complex was next hydrolyzed by slowly adding approximately 65 parts of 20% sulfuric acid and stirring for 2 hours. The mixture was then extracted with ether and the ether extract was washed with water until neutral. The resulting ether solution was dried over sodium sulfate and evaporated to give 2.15 parts of crystalline product.

Recrystallization from isooctane yielded two crops of crystals. These were identified as A (M. P. 207–213° C.) and B (M. P. 181–183° C.).

Recrystallization of A from isopropyl ether raised the melting point from 218 to 220° C. and analysis of this fraction gave: C, 73.74; H, 11.26.

Recrystallization of B from isopropyl ether brought the melting point to 184–186° C. Analysis of this fraction gave: C, 73.17; H, 11.13. The calculated values for $C_{19}H_{34}O_3$ (the 7-hydroxyethyl triol) are: C, 73.50; H, 11.04. The two fractions of crystals thus represent two epimers in which the hydroxyl group and the hydrogen attached to the 1 carbon atom of the 1-hydroxyethyl radical are reversed in position.

Example 3

There was prepared a solution of 1.7 parts of the 7-oxolactone (obtained in Example 1) in approximately 10 parts of dry tetrahydrofuran and this solution was added slowly to a suspension of 3 parts of lithium aluminum hydride in approximately 175 parts of ether. The reaction mixture was stirred at room temperature for 44 hours.

To destroy excess lithium aluminum hydride there was slowly added about 12.5 parts of ethyl acetate. The lithium aluminum complex was next hydrolyzed by the slow addition of 20 parts of water followed by stirring for 2 hours. A white lithium salt was filtered from the solution. The reaction mixture was next extracted with ether and the ether extract was washed with water, dried over sodium sulfate, and evaporated to yield 1.72 parts of a white powder.

Crystallization of the white powder from isopropyl ether gave 1.3 parts of white crystals, M. P. 169–170° C. *Analysis.*—Found: C, 71.96, H, 10.79. Calculated for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. The product of this example was thus identified as the 7-hydroxy triol of the invention.

Example 4

In a reaction vessel equipped with a stirrer and dry ice trap there was placed 60.8 parts of the lactone of hydroxy-tetrahydroabietic acid and 60 drops of a solution of cobalt naphthenate in petroleum naphtha (analyzing 6% cobalt) as a catalyst. Oxygen was introduced into the reaction vessel with continuous stirring for 10 hours while the reaction was kept at a temperature of 140° C. Total oxygen consumed in this time amounted to 54.4 mole per cent of the lactone.

Approximately 5 parts of liquid, principally water, was found in the dry ice trap. There remained in the reaction vessel 62.8 parts of oxidate.

The 62.8 parts of oxidate obtained as above was dissolved in 132 parts of benzene and chromatographed on a column of acid alumina. The alumina was eluted with various solvents to give 13 fractions as follows:

Fraction	Eluting Solvent	Wt. of Solvent (parts)	Wt. of Residue (parts)
1	Benzene	1,320	0.00
2	do	790	38.30
3	do	880	5.75
4	do	1,320	2.07
5	do	2,200	0.86
6	do	2,640	0.85
7	Benzene: CH_2Cl_2 (1:1)	3,330	1.42
8	do	3,330	3.73
9	do	3,330	0.59
10	CH_2Cl_2	8,040	0.26
11	CH_2Cl_2: Ether (1:1)	6,020	0.00
12	Ether	4,200	0.00
13	Methanol	4,750	1.14
			54.97

Fractions 6 through 9 were crystalline, noncarbonyl fractions which were recrystallized from acetone to yield pure 14-hydroxy lactone of hydroxytetrahydroabietic acid, M. P. 180.5–181.5° C., plus mother liquor. From many such oxidations, chromatographic separations, and recrystallizations of the corresponding fractions, 7.8 parts of mother liquor accrued.

In another reaction vessel, 7.8 parts of the mother liquor obtained as above was dissolved in 140 parts of dry ether and added slowly to a well-stirred suspension of 4 parts of lithium aluminum hydride in 175 parts of dry ether. Stirring was continued at room temperature for 68 hours. At the end of this time, the excess lithium aluminum hydride was destroyed by adding approximately 16 parts of ethyl acetate with stirring.

The lithium aluminum complex was next hydrolyzed by slowly adding approximately 65 parts of 20% sulfuric acid. The resulting ether layer was extracted, washed with water and dried over sodium sulfate. The ether was next evaporated yielding 8.28 parts of an oil which crystallized on standing. Upon recrystallization from ethyl acetate there was obtained 1.6 parts of white crystals melting at 195–200° C. This product was identified as the 7-hydroxyisopropyl triol. *Analysis.*—Calculated for $C_{20}H_{36}O_3$: C, 74.02; H, 11.18. Found: C, 74.13; H, 11.23.

Example 5

A methyl Grignard reagent was prepared by reaction of 0.16 part magnesium, 0.94 part methyl iodide and 17.5 parts of dry ether. One half part of the 7-acetyl lactone prepared as in Example 1 was dissolved in 20 parts of ether and added to the Grignard reagent at room temperature. After stirring overnight at room temperature, there was added 25 parts of a saturated aqueous solution of ammonium chloride and stirring was continued for an additional 20 minutes. The resulting ether layer was separated, washed with water and dried over sodium sulfate. Upon evaporation of the ether there was obtained 0.47 part of a product which was recrystallized twice from acetone to obtain 0.09 part of crystals melting at 175–177° C. This product was found to be identical with the 14-hydroxy lactone prepared as an intermediate in Example 4.

The 14-hydroxy lactone was next reduced with lithium aluminum hydride by the procedure of Example 4 to yield a product identical with the ultimate product of Example 4, i. e., the 7-hydroxyisopropyl triol.

As seen from the preceding examples, the process of preparing the compounds of the invention involves the common step of reducing with an alkali metal aluminum hydride a product resulting from the oxidation of the lactone of hydroxytetrahydroabietic acid. The reduction is generally carried out in solution. Any inert organic solvent can be used as a medium for the reaction, provided that it is a solvent for either one or both of the reactants. Suitable solvents that can be used are diethyl ether, di-n-butyl ether, dioxane, tetrahydrofuran, diethyl carbitol, benzene, hexane, toluene, etc. The reaction should be carried out under anhydrous conditions in order to avoid hydrolysis of the hydride and consequent reduction in yields. Any alkali metal aluminum hydride, such as sodium, lithium, etc., aluminum hydrides can be used for the reduction but lithium aluminum hydride is preferred. The amount of alkali metal aluminum hydride is preferably within the ratio of from 0.5 to about 10 moles, more preferably from about 1 to about 5 moles, per mole of the compound to be reduced. In general, the reaction is carried out at a temperature of from 0° C. to 50° C. and preferably at a temperature of from about 15° C. to about 35° C.

The alkali metal aluminum complex which is formed as an intermediate in the reaction is hydrolyzed by the addition of water, an acid or a base. Suitable acids for this purpose are the mineral acids, such as sulfuric acid, phosphoric acid, etc., but an alkali metal hydroxide, such as sodium or potassium hydroxide, may be used with equivalent results. The concentration of the hydrolytic agent can be varied over a wide range since water alone can be used but, in general, if an acid or base is used, concentration will be within the range of from about 5% to about 25% by weight of the compound to be reduced. The hydrolysis takes place readily at room temperature. Elevated temperatures are not required but may be used.

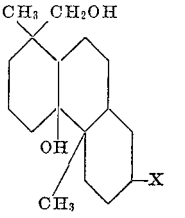
The method by which the triols of the invention are separated from the reaction mixture will, of course, depend upon the type of solvent used for carrying out the reaction. If a water-immiscible solvent is used for the reduction, in which solvent the triol is soluble, the triol will then be present in the organic phase and can be separated from that phase by removal of the solvent. It can also be separated from the reaction mixture by extraction with a suitable water-immiscible solvent, such as, for example, ethyl benzene, toluene, hexane, etc. Each of them is a crystalline solid and can be purified by crystallization procedures.

The new triols produced in accordance with the invention can be esterified by reaction with an acyl anhydride or an acyl halide as, for example, acetic anhydride, propionic anhydride, phthalic anhydride, ketene, acetyl chloride, benzoyl chloride, etc. Thus, it is possible to produce any aliphatic, cycloaliphatic, araliphatic or aromatic acid ester of these important new alcohols. The esterification reaction is generally carried out in an organic solvent that is a solvent for the triol to be esterified. The temperature employed can be varied over a wide range and depends upon the acylating agent used.

The triols of the invention have a variety of useful applications. For example, they are valuable ingredients of delayed tack adhesives. This is evidenced by the fact that when each of the triols is admixed in equal amount with neoprene in hydrocarbon solution air-dried films of each mixture are free from tack. However, when the films are fluxed on a hot plate and strips of paper pressed thereon, the strips of paper adhere firmly upon cooling of the films. The triols are also useful intermediates in the synthesis of compounds similar to constituents of the erythrophleum alkaloids.

What I claim and desire to protect by Letters Patent is:

1. A composition of matter having the formula



wherein X is a radical selected from the group consisting of hydroxy, 1-hydroxyethyl and 1-hydroxyisopropyl radicals.

2. 4a-hydroxy-7(1-hydroxyethyl)-1-hydroxymethyl-1,-4b-dimethylperhydrophenanthrene.

3. 4a,7-dihydroxy-1-hydroxymethyl-1,4b-dimethylperhydrophenanthrene.

4. 4a-hydroxy - 7 - (1-hydroxyisopropyl) - 1 - hydroxymethyl-1,4b-dimethylperhydrophenanthrene.

5. The method of preparing the composition of claim 1 which comprises reducing with an alkali metal aluminum hydride a compound selected from the group consisting of the 7-acetyl, 14-hydroxy and 7-oxo derivatives of the lactone of hydroxytetrahydroabietic acid.

6. The method of preparing the compound of claim 2 which comprises reducing with an alkali metal aluminum hydride the lactone of 7-acetyl-4a-hydroxy-1,4b-dimethylperhydrophenanthrene-1-carboxylic acid.

7. The method of preparing the compound of claim 3 which comprises reducing with an alkali metal aluminum hydride the lactone of 4a-hydroxy-1,4b-dimethyl-7-oxoperhydrophenanthrene-1-carboxylic acid.

8. The method of producing the compound of claim 4 which comprises reducing with an alkali metal aluminum hydride the lactone of 4a-hydroxy-7-(1-hydroxyisopropyl) - 1,4b - dimethylperhydrophenanthrene-1-carboxylic acid.

No reference cited.