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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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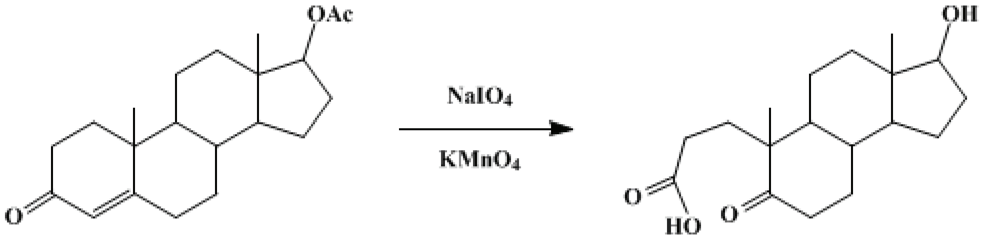
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.055.0067

Organic Syntheses, Coll. Vol. 6, p.690 (1988); Vol. 55, p.67 (1976).

17β-HYDROXY-5-OXO-3,5-*seco*-4-NORANDROSTANE-3-CARBOXYLIC ACID

[1*H*-Benz[*e*]indene-6-propanoic acid, dodecahydro-3-hydroxy-3*a*,6-dimethyl-7-oxo-]



Submitted by L. Milewich[1] and L. R. Axelrod.
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1. Procedure

A 3-l., three-necked, round-bottomed flask fitted with an efficient mechanical stirrer, a 100-ml. dropping funnel, and a 500-ml. dropping funnel is charged with a solution of 10.0 g. (0.0303 mole) of testosterone acetate [17β-(acetyloxy)-androst-4-en-3-one] (Note 1) in 600 ml. of *tert*-butyl alcohol and a solution of 5.6 g. (0.041 mole) of anhydrous potassium carbonate in 150 ml. of water. To the flask are added 100 ml. of a solution prepared from 40.0 g. (0.187 mole) of sodium metaperiodate (Note 2) in 500 ml. of water, and 10 ml. of a solution prepared from 0.8 g. (0.005 mole) of potassium permanganate in 100 ml. of water. Stirring is begun, and the remaining portions of these solutions are transferred to the appropriate dropping funnels. The metaperiodate solution is added over a period of about 30 minutes, and the permanganate solution is added as needed to maintain a pink color (Note 3). Stirring is continued for an additional 1.5 hours (Note 4) before a solution of 20.0 g. of sodium bisulfite in 40 ml. of water is slowly added (Note 5). After stirring for 20 minutes the suspension is filtered through a 10-g. pad of Celite® filter aid (Note 6) on a coarse sintered-glass filter, and the residual cake is washed with two 50-ml. portions of *tert*-butyl alcohol. The filtrates are combined and concentrated by distillation (Note 7) to a volume of about 200 ml. After cooling, 25 ml. of 10% sulfuric acid is added. The resulting mixture is extracted with three 300-ml. portions of diethyl ether. The combined ethereal extracts are washed, first with two 50-ml. portions of water, twice with solutions prepared from 5.0 g. of sodium bisulfite in 20 ml. of water, and finally twice with 50 ml. of water. Crushed ice is added to the ethereal layer, and the mixture is extracted with three 70-ml. portions of 10% aqueous sodium hydroxide. The aqueous layers are combined and washed with 50 ml. of ether. The aqueous layer is transferred to a 2-l. separatory funnel, crushed ice is added, and 300 ml. of 10% sulfuric acid is introduced carefully. The separatory funnel is shaken gently, and the product separates as a gum or stringy mass (Note 8). The mixture is extracted with four 200-ml. portions of dichloromethane, and the extracts are combined and washed with three 15-ml. portions of water. The organic layer is dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The resulting material is triturated with 50 ml. of acetone, and after a brief heating period crystals begin to separate. The mixture is cooled and filtered, yielding 6.0–6.5 g. (63–70%) of 17β-hydroxy-5-oxo-3,5-*seco*-4-norandrostane-3-carboxylic acid, m.p. 204–205° (Note 9). Additional product can be obtained from the filtrate by concentration and cooling.

2. Notes

1. Testosterone acetate was obtained from Steraloids, Inc.
2. Sodium metaperiodate was purchased from J. T. Baker Chemical Company.
3. During these additions the temperature of the reaction mixture rises to about 35°.
4. At this point the reaction mixture has a pH of about 5.2.
5. When the bisulfite solution is added, the solution acquires a deep brown color and iodine fumes

develop.
6. The product was purchased from Johns-Manville Corporation.
7. Evaporation is carried out under reduced pressure with a bath temperature of 75°. A deep iodine-colored fraction distills first, followed by a colorless distillate.
8. The checkers found it convenient to separate the aqueous phase from the sticky amorphous mass and later dissolve the product in the dichloromethane solution that was used for the extractions.
9. The reported melting points are 206.5–207°,[2] 204–205.5°,[3] 200–202°,[4] 204–206°,[5] and 192°.[6] The product has the following spectral properties; IR (KBr) cm.$^{-1}$: 3390, 1717, 1700, and 1056; ^{1}H NMR ($CDCl_3$), δ: 0.82 (C_{18}-CH_3), 1.14 (C_{19}-CH_3), and additional broad absorptions; $[\alpha]^{28}_{D}$ +36°.

3. Discussion

17β-Hydroxy-5-oxo-3,5-*seco*-4-norandrostane-3-carboxylic acid has been prepared by ozonolysis of testosterone[2,3,4] or testosterone acetate, followed by alkaline hydrolysis,[5] and by the oxidation of testosterone acetate with ruthenium tetroxide.[6]

The present procedure corresponds to the method[7] described earlier for the synthesis of 5-oxo-3,5-*seco*-4-norcholestane-3-carboxylic acid and is useful for preparing large quantities of the title compound.

References and Notes

1. Southwest Foundation for Research and Education, Division of Biological Growth and Development, Department of Biochemistry, San Antonio, Texas 78284. [Present address: Department of Obstetrics and Gynecology, The University of Texas, Health Science Center at Dallas, Dallas, Texas 75235.]
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

potassium permanganate (7722-64-7)

sodium sulfate (7757-82-6)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

acetone (67-64-1)

dichloromethane (75-09-2)

tert-butyl alcohol (75-65-0)

ruthenium tetroxide (20427-56-9)

sodium metaperiodate (7790-28-5)

testosterone acetate,
17β-(acetyloxy)-androst-4-en-3-one

4-norandrostane-3-carboxylic acid

testosterone

17β-Hydroxy-5-oxo-3,5-seco-4-norandrostane-3-carboxylic acid

1H-Benz[e]indene-6-propanoic acid, dodecahydro-3-hydroxy-3a,6-dimethyl-7-oxo-

5-oxo-3,5-seco-4-norcholestane-3-carboxylic acid