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Working with Hazardous Chemicals

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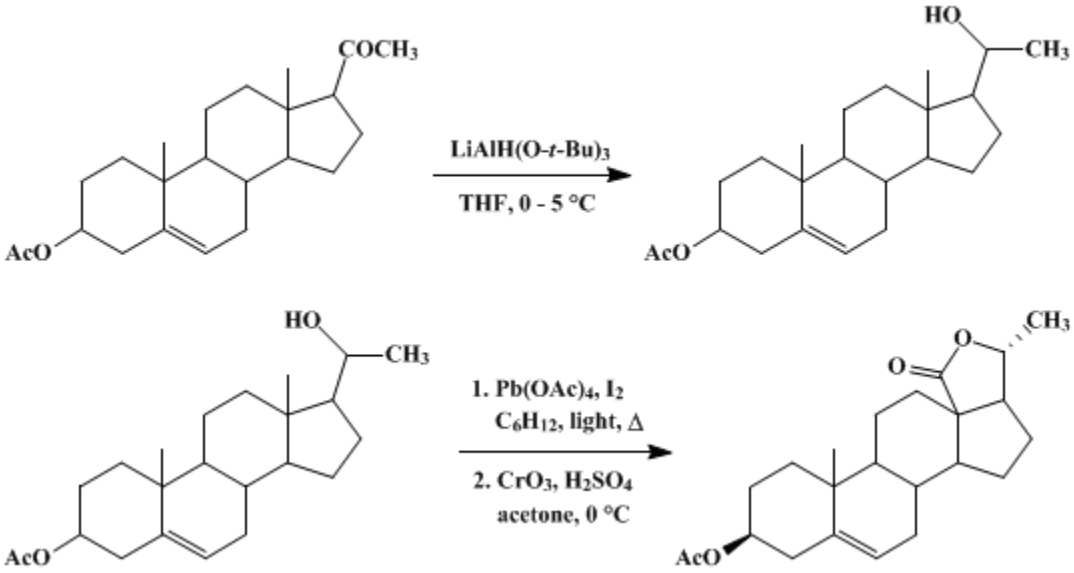
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.045.0057

Organic Syntheses, Coll. Vol. 5, p.692 (1973); Vol. 45, p.57 (1965).

18,20-LACTONE OF 3β-ACETOXY-20β-HYDROXY-5-PREGNENE-18-OIC ACID

[Pregn-5-en-18-oic acid, 3β,20β-dihydroxy, 18,20-lactone, 3-acetate]



Submitted by K. Heusler, P. Wieland, and Ch. Meystre[1].
Checked by E. J. Corey and William E. Russey.

1. Procedure

A. *3β-Acetoxy-20β-hydroxy-5-pregnene*. In a 2-l. five-necked flask fitted with a mechanical stirrer, 250-ml. dropping funnel, thermometer, nitrogen-inlet tube, and reflux condenser with calcium chloride tube is placed 750 ml. of anhydrous tetrahydrofuran (Note 1). The vessel is flushed with nitrogen, and 101.6 g. (0.4 mole) of lithium aluminum tri-*t*-butoxyhydride[2] (Note 2) is added. The suspension is cooled to about 2°, and 71.7 g. (0.2 mole) of pregnenolone acetate (Note 3) is added in one portion while stirring, the particles adhering to the wall of the flask being rinsed into the solution with an additional 50 ml. of tetrahydrofuran. The reaction mixture is stirred at 0–5° for 6 hours. A solution of 100 g. of ammonium sulfate in 150 ml. of water is added, with stirring, over a 15–20 minute period through the dropping funnel, the temperature of the reaction mixture being kept below 10° by efficient cooling with ice. A considerable quantity of hydrogen is evolved. There is added 20 g. of filter aid (Celite® or Hyflo Supercel®), the mixture is stirred for another 30 minutes, and it is finally filtered with suction through a layer of filter aid. The reaction vessel is rinsed and the filter residue thoroughly washed with 1.5 l. of tetrahydrofuran (Note 4). The filtrate is evaporated to dryness under reduced pressure. The crystalline residue is dissolved in 750 ml. of hot acetone, filtered (if necessary), and the solution is concentrated to a volume of about 200 ml. (crystallization may begin during this evaporation). The flask is kept overnight at 0° to −10° and the product isolated by suction filtration. The crystals are washed with 75 ml. of ice-cold acetone and dried at 60°. The yield of the product is 54–57 g. (75–79%), m.p. 161–164°,[3] $[\alpha]^{25}D$ −74° (*c* 1.0, $CHCl_3$) (Note 5).

B. *3β-Acetoxy-18-iodo- and 18-hydroxy-18,20β-oxido-5-pregnene*. In a 5-l. three-necked flask fitted with a mechanical stirrer, a thermometer, and a reflux condenser are placed 3 l. of cyclohexane (Note 6), 180 g. (*ca.* 0.37 mole) of commercial lead tetraacetate containing approximately 10% acetic acid (Note 7), 24 g. (0.095 mole) of iodine and 30 g. (0.083 mole) of 3β-acetoxy-20β-hydroxy-5-pregnene. The reaction mixture is stirred and heated to the boiling point by irradiation with a 1000-watt lamp (Note 8) from underneath. When the iodine color has disappeared (usually after about 60–90 minutes) (Note 9), the reaction mixture is cooled to room temperature, filtered with suction, and the filter residue with 600

ml. of cyclohexane. The filtrate is washed with two 500-ml. portions of 5% sodium thiosulfate solution and then with water. The combined aqueous solutions are extracted once with 500 ml. of ether. To the combined organic layers is added 6 ml. of pyridine, the solution is dried over sodium sulfate, filtered (Note 10), and the solvent evaporated under reduced pressure at a bath temperature of 35–40° (preferably by using a rotary evaporator). About 60 g. of an oily residue (Note 11), which is immediately oxidized (Note 12), is obtained.

C. *Oxidation to the 18,20-lactone of 3β-acetoxy-20β-hydroxy-5-pregnene-18-oic acid*. The above residue is dissolved in 600 ml. of acetone (Note 13), the solution is transferred to a 3-l. three-necked flask with a rigid mechanical stirrer, a dropping funnel, and a thermometer; the evaporation flask is rinsed with an additional 120 ml. of acetone. The solution is cooled to 0° to +5°, and 38.4 ml. of a chromic acid solution[4] (prepared by mixing 13.3 g. of chromium trioxide and 11.5 ml. of concentrated sulfuric acid and carefully diluting the mixture to 50.0 ml. with water while cooling) is slowly added within 10 minutes from the dropping funnel. The mixture is stirred (Note 14) for another 30 minutes at 0° to +5°, and a solution of 270 g. of crystalline sodium acetate in 780 ml. of water is added. The dark green solution is transferred to a separatory funnel, and it is extracted once with 2.4 l. and once with 600 ml. of benzene. Each extract is washed twice with 600 ml. of half-saturated sodium chloride solution, dried over sodium sulfate, and the solvent is evaporated under reduced pressure. The combined semisolid residue (48–50 g.) is triturated with 50 ml. of ether and kept overnight at 0° to −10°. The crude product is filtered, and the filter residue is washed with pentane. The yield of crystalline lactone is 14–16 g. (45–52% based on pure 3β-acetoxy-20β-hydroxy-5-pregnene). For further purification the product is dissolved in 200 ml. of hot acetone, if necessary 250 mg. of charcoal is added, the mixture is brought to the boiling point on a steam bath, filtered through a layer of filter aid, and the filter residue is washed with warm acetone. The solution is concentrated on the steam bath to a volume of about 90 ml. During this operation, crystallization begins. Then 150 ml. of hexane is added. the mixture is again concentrated to a volume of about 50–80 ml. with swirling, and finally kept at 0° overnight. A first crop of 12.0–13.5 g. (39–43%) of pure lactone, m.p. 201–206°, is obtained, $[\alpha]^{25}D$ −44° to −45° (*c* 1.0, $CHCl_3$). Concentration of the mother liquor yields a second crop of 0.3–2.7 g. of less pure lactone.

2. Notes

1. Tetrahydrofuran freshly distilled from lithium aluminum hydride should be used. A commercial product with a peroxide content giving a positive iodine test must be treated with about 0.3% of cuprous chloride (boiling for 30 minutes and distillation) before the addition of the hydride. *[Caution! See p. 976.]*
2. Obtained from Metal Hydrides Inc., Beverly, Massachusetts.
3. A commercial product, m.p. 142.5–148.5°; $[\alpha]^{20}D$ +141.5° (*c* 1.003, $CHCl_3$) was used.
4. Tetrahydrofuran free of peroxide, distilled from cuprous chloride, may be used. *[Caution! See p. 976.]*
5. The first crop of the product contains only a trace of the 20α-epimer.[3] The main portion of this compound is found in the mother liquor. Use of the material of a second crop for the subsequent steps is not recommended. The residue of the mother liquor can, however, be reoxidized to pregnenolone acetate by the method described in step C. By crystallization of the oxidation product of the mother liquor residue from methanol, 13–14 g. of pure pregnenolone acetate can be recovered.
6. Commercial product, redistilled. Small amounts of cyclohexene do not interfere.
7. Obtained from Fluka A. G., Buchs, S. G., Switzerland, and Arapahoe Chemical Co., Boulder, Colorado. Dry lead tetraacetate may also be used.
8. An ordinary 1000-watt lamp was used for heating as well as irradiation. The light reduces the induction period and accelerates the reaction. It is important that the solution be at reflux during the irradiation; an aluminum foil tent may be used to prevent excessive loss of energy from the light/heat source. In smaller runs the intensity of the light should be reduced accordingly (see (Note 9)).
9. The disappearance of the iodine color is not indicative of the end of the reaction, since lead tetraacetate itself reacts with iodine under the reaction conditions giving lead diacetate, carbon dioxide, and methyl iodide. Under intense irradiation the decolorization can take place very quickly. In this case the rate of the decomposition of lead tetraacetate becomes comparable to the rate of the desired hypoiodite reaction, and the intermediate 18-iodo-20-alcohol will accumulate. The latter compound is oxidized by chromic acid to the 18-iodo-20-ketone. If an accumulation of the iodo alcohol is observed, a

weaker light source or a larger excess of lead tetraacetate and iodine should be used to bring the reaction to completion.
10. The filtrate contains labile iodine derivatives which in light and at room temperature give off iodine. If the solution is not concentrated immediately, it should be kept at 0° in the dark; but it should be processed within less than 4 hours because of the instability of the hemiacetal-type intermediate.
11. The oil contains considerable amounts of derivatives formed by reaction with the solvent, *e.g.*, cyclohexanol acetate, bicyclohexyl, and a number of high-boiling, iodine-containing substances. These by-products are removed only after oxidation.
12. It is important to oxidize the product as soon as possible because the crude 18,20-hemiacetal is unstable. In solution, in the presence of traces of acid, bimolecular anhydro products are formed which are stable to chromic acid oxidation and greatly diminish the yield of lactone.
13. Commercial acetone, boiled with 0.05% potassium permanganate for about 2 hours and distilled from potassium carbonate, was used.
14. The chromium sulfate tends to aggregate in large lumps. The stirrer should therefore be rigid and at least an inch away from the bottom of the flask.

3. Discussion

The preparation of the title lactone has been described by a multistep synthesis from holarrhimine.[5,6] The method described in detail above is essentially an application of the "hypoiodite reaction" published by Ch. Meystre and co-workers.[7] These authors also describe the isolation of the intermediate hemiacetal in pure form. Saturated lactones epimeric at C-20 have also been obtained by chromic acid oxidation of 18,20-dihydroxy compounds[8] which were in turn prepared by treatment of 20-hydroxypregnanes with lead tetraacetate, acetolysis of the resulting 18,20β-oxides, and hydrolysis. Saturated lactones of the 20α- and 20β-series were also obtained by photolysis of the corresponding 20-nitrites, hydrolysis, and oxidation.[9]

4. Merits of the Preparation

For the substitution of the angular methyl groups in steroids five methods are known: (a) homolysis of N-chloramines [Löffler-Freytag reaction[10] (only C-18)]; (b) oxidation of alcohols with lead tetraacetate;[11] (c) photolysis of nitrite esters;[12] (d) homolysis of hypochlorites;[13] (e) the "hypoiodite reaction."[14]

Of these methods the hypoiodite cleavage appears to be the simplest and most efficient one. It leads directly to compounds which are oxidized at the angular C-18 substituent to the aldehyde stage. In common with method (b), it has the advantage that an alcohol can be used directly as starting material, which under the reaction conditions is transformed into a derivative which is then homolytically cleaved; but, in contrast to method (b), the hypoiodite method is much less susceptible to steric effects, 20β-alcohols being oxidized almost as efficiently as 20α-alcohols. Methods (a), (c), and (d) require the formation of reactive derivatives in a separate step before homolysis. No special apparatus or special light source is needed for the hypoiodite reaction. Further applications and the scope of the reaction are discussed elsewhere.[15]

The lactone described can be used as starting material for the preparation of a number of 18-oxygenated steroids. Hydrolysis and Oppenauer oxidation[6,7] leads to the 18,20-lactone of 3-oxo-20β-hydroxy-4-pregnene-18-oic acid. This lactone is a suitable starting material for the preparation of 18-hydroxy- and 18-oxoprogesterone.[16] On the other hand, microbiological oxidation leads to the corresponding 11α-hydroxylactone[17] which is a suitable starting material for the preparation of aldosterone.[18]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 529
- Org. Syn. Coll. Vol. 5, 976

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

18,20-LACTONE OF 3β-ACETOXY-20β-HYDROXY-5-PREGNENE-18-OIC ACID

lithium aluminum tri-t-butoxyhydride

3β-Acetoxy-18-iodo- and 18-hydroxy-18,20β-oxido-5-pregnene

18,20-lactone of 3-oxo-20β-hydroxy-4-pregnene-18-oic acid

18-hydroxy- and 18-oxoprogesterone

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

potassium permanganate (7722-64-7)

Cyclohexene (110-83-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

aluminum (7429-90-5)

carbon dioxide (124-38-9)

cyclohexane (110-82-7)

iodine (7553-56-2)

acetone (67-64-1)

pyridine (110-86-1)

lead diacetate

chromic acid (7738-94-5)

cuprous chloride (7758-89-6)

Methyl iodide (74-88-4)

ammonium sulfate (7783-20-2)

Pentane (109-66-0)

chromium sulfate (15244-38-9)

chromium trioxide (1333-82-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

pregnenolone acetate

Pregn-5-en-18-oic acid, 3β,20β-dihydroxy, 18,20-lactone, 3-acetate

3β-Acetoxy-20β-hydroxy-5-pregnene (14553-79-8)

cyclohexanol acetate (622-45-7)

bicyclohexyl (92-51-3)

aldosterone

lead tetraacetate (546-67-8)