Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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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.

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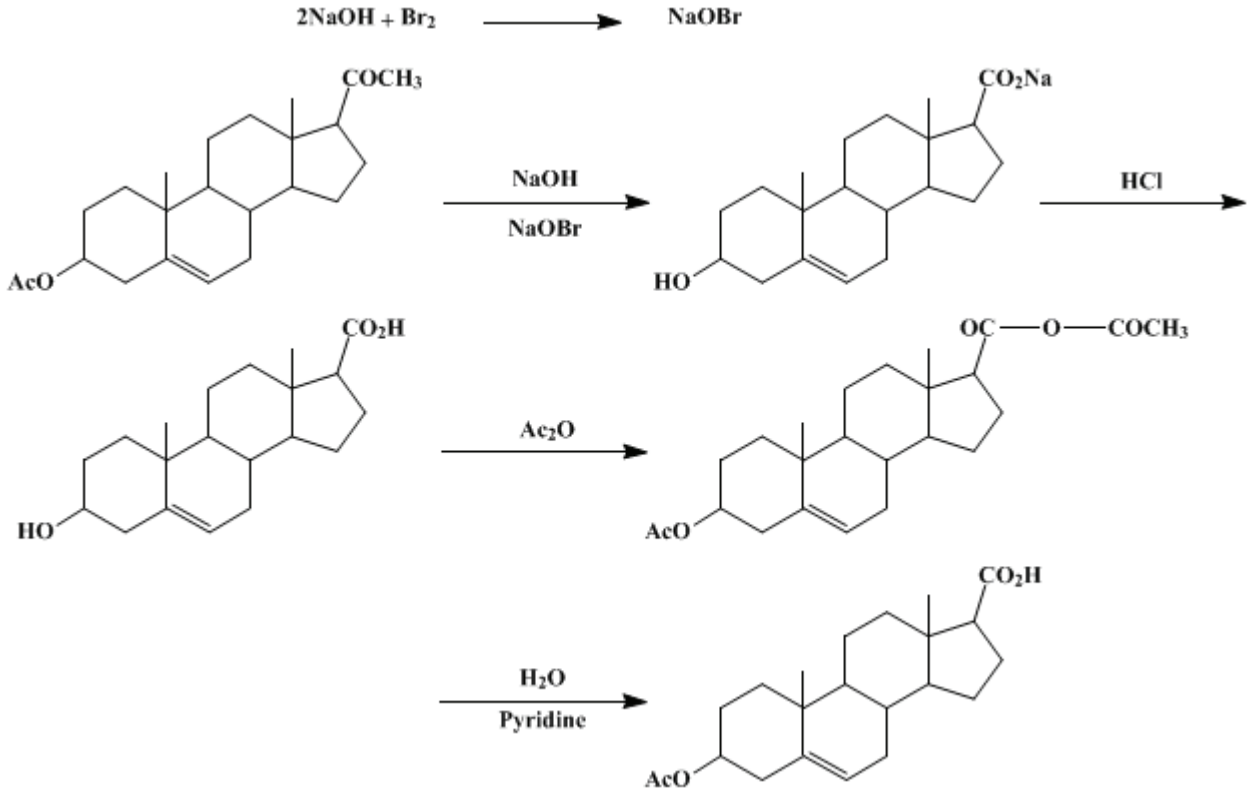
3β-ACETOXYETIENIC ACID

[3β-Acetoxy-5-androstene-17β-carboxylic acid]



Submitted by J. Staunton and E. J. Eisenbraun[1].
Checked by W. G. Dauben and J. H. E. Fenyes..

1. Procedure

A solution of 42 g. (1.05 moles) of sodium hydroxide in 360 ml. of water is placed in a 1-l. three-necked, round-bottomed flask fitted with a mechanical stirrer and a thermometer and is cooled to −5° in an ice-salt bath. The stirrer is started, and 43 g. (0.263 mole) of bromine is added from a separatory funnel at such a rate that the temperature remains below 0° (addition time about 5 minutes). The ice-cold solution is diluted with 240 ml. of dioxane (Note 1) that has previously been cooled to 13–14° (Note 2). This solution is kept at 0° until required.

A solution of 28.8 g. (0.08 mole) of 3β-acetoxy-5-pregnen-20-one (pregnenolone acetate) (Note 3) in 1.1 l. of dioxane (Note 1) is diluted with 320 ml. of water and placed in a 5-l. three-necked, round-bottomed flask fitted with a mechanical stirrer and a thermometer (Note 4). The stirrer is started and the mixture is cooled in ice. When the internal temperature has fallen to 8°, the cold hypobromite solution is added in a steady stream. The temperature of the reaction mixture is maintained below 10° throughout the reaction. A white precipitate begins to form after 10 minutes, and the solution becomes colorless during 1 hour. The mixture is stirred for an additional 2 hours, and then the excess sodium hypobromite is destroyed by the addition of a solution of 10 g. of anhydrous sodium sulfite in 100 l. of water (Note 5).

The stirrer and thermometer are removed and the flask is fitted with a condenser for reflux. The mixture is heated under reflux for 15 minutes, and the solution, while still hot (90°), is acidified by the cautious addition of 50 ml. of concentrated hydrochloric acid (Note 6). The clear yellow solution is kept

at 5° for 24 hours. The crystalline precipitate is collected by suction filtration, washed with water, and dried at 100° at atmospheric pressure. The yield of 3β-hydroxyetienic acid, m.p. 274–276°, is 18–20 g. An additional 3–5 g. of product can be obtained by subjecting the filtrate to steam distillation until a white precipitate is formed. The etienic acid collected from the cooled solution melts at 268–272°. The total yield is 23–24 g. (91–95%).

The 3β-hydroxyetienic acid is placed in a 500-ml. round-bottomed flask fitted with a condenser protected with a drying tube and is dissolved with warming in 150 ml. of dry pyridine. After the solution has cooled to room temperature, 20 ml. of acetic anhydride is added; a white crystalline precipitate starts to form immediately. After the mixture has stood for 18–24 hours, it is treated with 20 ml. of water and boiled until the precipitate has dissolved (Note 7). The clear solution is diluted with 70 ml. of water and allowed to cool. The crystalline product is collected by suction filtration, washed with water, and dried in a vacuum oven at 105°/20 mm. The yield of 3β-acetoxyetienic acid, m.p. 235–238°, is 23–24 g. Recrystallization from glacial acetic acid gives a purer product, m.p. 238–240°. The yield is 16–18 g. (55–63% based on the amount of pregnenolone acetate used).

2. Notes

1. Dioxane as supplied by Matheson-Coleman Bell Co. was used without purification.
2. The temperature of the hypobromite solution is kept below 10° to avoid the formation of sodium bromate.
3. Pregnenolone acetate (3β-acetoxy-5-pregnen-20-one) supplied by Syntex S. A., Apartado Postal 2679, Mexico, D. F., was used.
4. It is advisable to carry out any operation involving dioxane in a fume hood.
5. Although this amount of sodium sulfite is sufficient to destroy the excess sodium hypobromite, the solution may still give a positive test with starch-iodide paper because of the presence of peroxides in the dioxane used. It is not necessary to destroy these peroxides before proceeding.
6. The solution should be swirled gently during the addition of the hydrochloric acid. Since this operation causes the dioxane to boil, it must be carried out in a fume hood.
7. The anhydride of etienic acid is hydrolyzed in this process to give the soluble acid. Prolonged boiling should be avoided to prevent extensive attack on the less readily hydrolyzed acetate group.

3. Discussion

3β-Hydroxy-Δ^5-etiocholenic acid has been prepared from pregnenolone acetate by the action of sodium hypoiodite;[2] by oxidation of the furfurylidene derivative;[3] and by oxidation of the benzylidene derivative of the 5,6-dibromide followed by debromination.[4] The side chain of 3β-hydroxy-Δ^5-bisnorcholenic acid has been systematically degraded to give the etienic acid.[5] Two syntheteic approaches have involved, respectively, the replacement of the halogen in 17-chloro-3-acetoxy-Δ^5-androstene by an alkali metal followed by treatment with carbon dioxide[6] and the conversion of dehydroandrosterone acetate to its cyanohydrin, which then was successively dehydrated, hydrolyzed, and selectively hydrogenated to furnish 3β-hydroxyetienic acid.[7,8].

4. Merits of Preparation

3β-Acetoxyetienic acid has been found to be particularly suitable for the resolution of alcohols. Thus it was employed by Woodward and Katz for the resolution of 1α-hydroxydicyclopentadiene;[9] by Djerassi, Warawa, Wolff, and Eisenbraun for the resolution of *trans*-3-*tert*-butylcyclohexanol;[10] and by Djerassi and Staunton for the resolution of *cis,cis*-1-decalol.[11]

References and Notes

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

3β-Hydroxy-Δ^5-etiocholenic acid

benzylidene derivative of the 5,6-dibromide

3β-hydroxy-Δ^5-bisnorcholenic acid

17-chloro-3-acetoxy-Δ^5-androstene

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

carbon dioxide (124-38-9)

acetate

pyridine (110-86-1)

sodium bromate (7789-38-0)

hypobromite

sodium hypobromite

dioxane (123-91-1)

3β-Acetoxyetienic acid,
3β-Acetoxy-5-androstene-17β-carboxylic acid (7150-18-7)

3β-acetoxy-5-pregnen-20-one

pregnenolone acetate

3β-hydroxyetienic acid

etienic acid

sodium hypoiodite

furfurylidene

1α-hydroxydicyclopentadiene

trans-3-tert-butylcyclohexanol

cis,cis-1-decalol