Organic Syntheses

A Publication
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.

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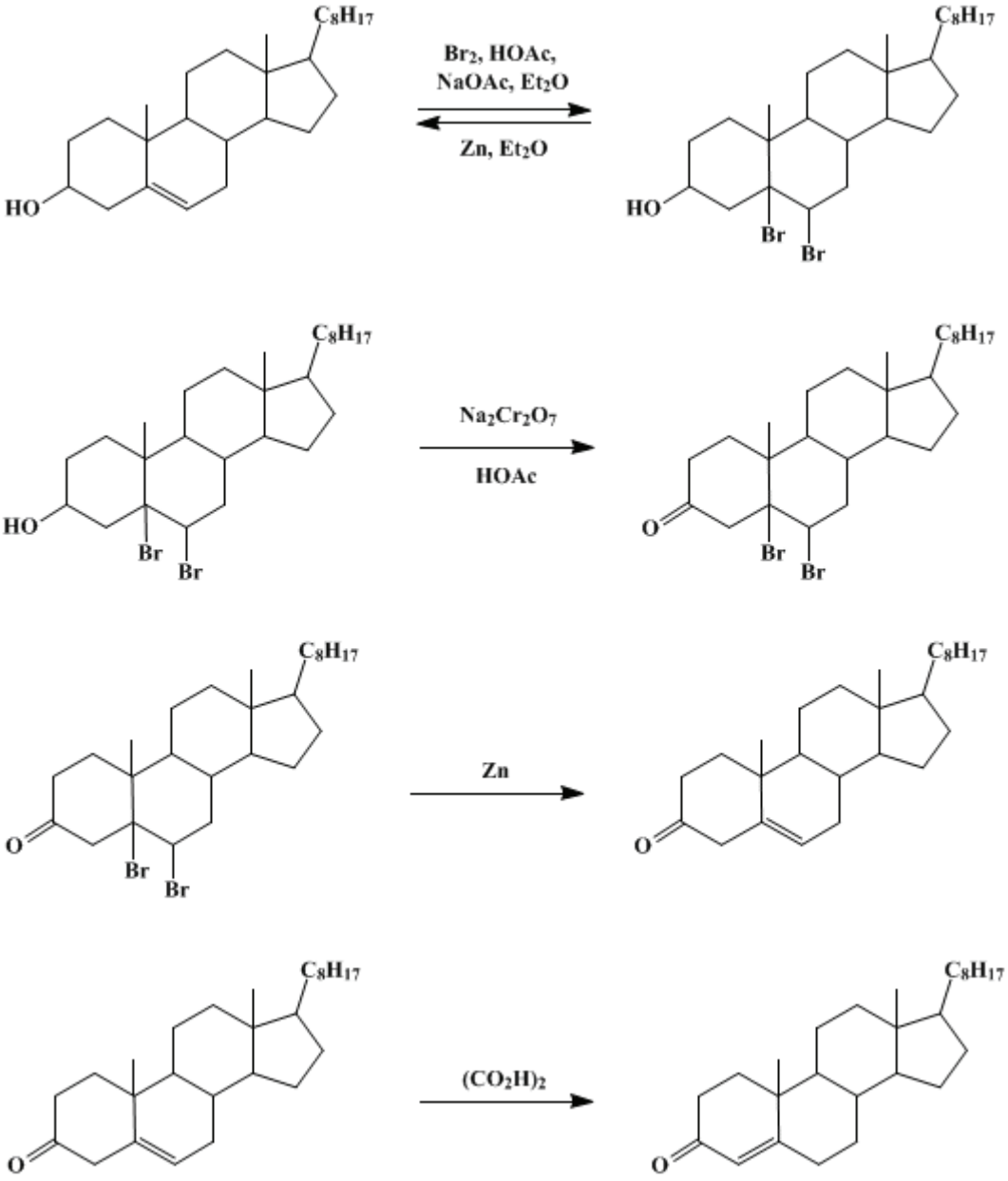
CHOLESTEROL, Δ⁵-CHOLESTEN-3-ONE, AND Δ⁴-CHOLESTEN-3-ONE

[Cholesterol, Cholest-5-en-3-one, and Cholest-4-en-3-one]



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1. Procedure

A. *Cholesterol dibromide*. In a 4-l. beaker 150 g. (0.39 mole) of commercial cholesterol (Note 1) is dissolved in 1 l. of absolute ether by warming on the steam bath and stirring with a stout glass rod; the solution is then cooled to 25°. A second solution is prepared by adding 5 g. of powdered anhydrous sodium acetate (0.06 mole) (Note 2) to 600 ml. of acetic acid, stirring the mixture and breaking up the lumps with a flat stirring rod; 68 g. (0.4 mole) of bromine is then added and the solution is poured with

stirring into the cholesterol solution. The solution turns yellow and promptly sets to a stiff paste of dibromide. The mixture is cooled in an ice bath to 20°, and then the product is collected on a 16-cm. Büchner funnel (Note 3). The cake is pressed down and washed with acetic acid until the filtrate is completely colorless; 500 ml. is usually sufficient. A second crop of satisfactory dibromide is obtained by adding 800 ml. of water to the combined filtrate and washings, collecting the precipitate, and washing it with acetic acid until colorless. Dibromide moist with acetic acid is satisfactory for most transformations; dry dibromide, even when highly purified by repeated crystallization, begins to decompose (darkens) within a few weeks. When material prepared as described is dried to constant weight at room temperature, it is obtained as the 1:1 dibromide/acetic acid complex. Yields obtained in the first and second crops, respectively, are: 171–186 g. and 13–25 g., total yield 197–199 g. (84–85%) (Note 1).

B. *Cholesterol from the dibromide.* The acetic acid-moist filter cake of dibromide from 150 g. of cholesterol is transferred (Note 3) to a 3-l. round-bottomed flask and covered with 1.2 l. of U.S.P. ether, and the suspension is stirred mechanically above a bucket of ice and water that can be raised as required (Note 4), (Note 5). Forty grams (0.61 g. atom) of fresh zinc dust is added in the course of 5 minutes. The first 5- to 10-g. portion is added without cooling; when the reaction has started, as evidenced by solution of part of the dibromide and by ebullition, the cooling bath is raised during the remainder of the addition. At the end, the ice bath is lowered, and the mixture, which soon sets to a paste of white solid (Note 6), is stirred for 15 minutes longer. Then 50 ml. of water is added to dissolve the white solid, and the ethereal solution is decanted into a separatory funnel and washed with 400 ml. of water containing 25 ml. of 36% hydrochloric acid. After three more washings with 400-ml. portions of water, the solution is shaken thoroughly with 300 ml. of water and 150 ml. of 25% sodium hydroxide solution, and the ethereal solution is tested with moist blue litmus paper to make sure that all the acetic acid is removed (Note 7). The solution is then dried over magnesium sulfate and evaporated to a volume of 600 ml., methanol (600 ml.) is added, and the solution is evaporated to the point where crystallization just begins (about 1 l.). After standing at room temperature and then at 0–4°, the main crop of cholesterol is collected and dried at room temperature; yield 108–110 g., m.p. 149.5–150° (Note 8). A second crop of 8.4–10.4 g., m.p. 148–149°, is obtained after evaporation of the mother liquor to a volume of 250 ml. (Note 9); total yield 117–120 g. (78–80% from commercial cholesterol) (Note 10).

C. *5α,6β-Dibromocholestan-3-one*. The moist dibromide from 150 g. of cholesterol (part A) is suspended in 2 l. of acetic acid in a 5-l. round-bottomed flask equipped with a stirrer and mounted over a bucket of ice and water that later can be raised to immerse the flask (Note 5). The suspension is stirred at room temperature (25–30°), and a solution, preheated to 90°, of 80 g. (2 oxygen equivalents) of sodium dichromate dihydrate in 2 l. of acetic acid is poured in through a funnel (Note 3). The mixture reaches a temperature of 55–58° during the oxidation, and all the solid dissolves in 3–5 minutes. After another 2 minutes the ice bucket is raised until the flask is immersed; stirring is then stopped, and the mixture is allowed to stand in the ice bath without disturbance for 10 minutes to allow the dibromoketone to separate in easily filterable crystals. With stirring resumed, the temperature is brought to 25° and then, after addition of 400 ml. of water, to 15°. The product is collected on a 21-cm. Büchner funnel, and the filter cake is drained until the flow of filtrate amounts to no more than 25 drops per minute. The suction is released, the walls of the funnel are washed down with methanol, and 200 ml. of methanol is added. After a few minutes' standing, suction is applied and the crystals are drained thoroughly of solvent before they are washed in the same way with 200 ml. of fresh methanol. The last drops of filtrate should be completely colorless. Dried to constant weight at room temperature in a dark cupboard, the dibromoketone consists of shiny white crystals, m.p. 73–75° (dec.), $[\alpha]_D^{25}$ −47° chloroform (c = 2.11) (Note 11); yield about 171 g. (96% in the oxidation or 81% from cholesterol).

D. Δ^5-*Cholesten-3-one*. (Note 12) The moist 5α,6β-dibromocholestan-3-one from 150 g. of cholesterol is transferred to a 3-l. round-bottomed flask and covered with 2 l. of U.S.P. ether and 25 ml. of acetic acid. The suspension is stirred mechanically, and ice bath is raised into position (Note 5), and the temperature is brought to 15°. The ice bath is then lowered, and 5 g. of fresh zinc dust is added. As soon as the exothermic reaction of debromination sets in, the temperature is controlled to 15–20° by cooling during the addition (in about 5 minutes) of 35 g. more zinc dust. The ice bath is then lowered, and the ethereal solution containing suspended zinc dust is stirred for 10 minutes longer. With continued stirring, 40 ml. of pyridine is added; this precipitates a white zinc salt (Note 13). The mixture is filtered

through a Büchner funnel, and the filter cake is washed well with ether. The colorless filtrate is washed with three 600-ml. portions of water and then shaken thoroughly with 600 ml. of 5% aqueous sodium bicarbonate solution until free from acetic acid as indicated by testing the ethereal solution with moist blue litmus paper. The solution is dried over magnesium sulfate and evaporated to a volume of about 1 l.; 500 ml. of methanol is added, and the evaporation is continued until the volume is approximately 1.2 l. Crystallization is allowed to proceed at room temperature, then at 0–4°, and the large colorless prisms are collected by suction filtration; yield in the first crop 87–94 g., melting point in the range 124–129° (camphorlike odor), $[\alpha]_D^{25}$ −2.5° chloroform (c = 2.03), no selective absorption at 242 mμ. Concentration of the mother liquor gives a second crop of 12–19 g. melting in the range 117–125° and suitable for conversion to Δ^4-cholesten-3-one; total yield 106–108 g. (71–72% from cholesterol).

E. Δ^4-*Cholesten-3-one*. A mixture of 100 g. of Δ^5-cholesten-3-one (0.26 mole), 10 g. (0.11 mole) of anhydrous oxalic acid (Note 14), and 800 ml. of 95% ethanol is heated on the steam bath until all the solid is dissolved (15 minutes) and for 10 minutes longer, and then is allowed to stand at room temperature. If crystallization has not started after a period of several hours, the solution is seeded or scratched. After crystallization has proceeded at room temperature and then at 0–4°, the large, colorless, prismatic needles that separate are collected by suction filtration; yield in the first crop 88–92 g., m.p. 81–82°, $[\alpha]_D^{25}$ 92° chloroform (c = 2.01); $\lambda_{max.}^{ethanol}$ 242 mμ (ε = 17,000). A second crop (5.0–7.5 g., melting in the range 78–82°) is obtained after concentration of the mother liquor to a volume of about 100 ml., and a third crop (3–4 g., low melting) by dilution with water. Recrystallization of these crops from 95% ethanol gives a total of 6.8–8.1 g. of satisfactory material, m.p. 81–82°; total yield 96–98 g. (68–69% over-all yield from cholesterol).

2. Notes

1. Cholesterol of high quality and of recent production was employed. Cholesterol undergoes slow autoxidation in the solid state, and samples that have been in storage for a few years give lower yields of dibromide. The checkers used U.S.P. material, m.p. 149–150°, as supplied by Wilson Company, Chicago, Illinois.
2. The yield of dibromide dropped from 84% to 73% when no buffering sodium acetate was used. No improvement resulted from doubling the quantity of sodium acetate specified. Buffered bromination in a stirred suspension of acetic acid (no ether) at 20° raised the yield to 89%, but this material on debromination afforded sterol of low melting point (145–147°) containing halogen (Beilstein test).
3. The operation should be done in a hood, and the hands should be protected with Neoprene gloves.
4. If dry dibromide is used, 25 ml. of acetic acid is added to the suspension.
5. The ice bucket is conveniently mounted on an automobile jack.
6. The solid appears to be a complex of cholesterol and a zinc salt.
7. If the acetic acid is not removed some cholesteryl acetate may be formed during the evaporation.
8. The melting-point determination should be done in an evacuated capillary tube. In an open tube autoxidation occurs readily enough to lower the melting point when the bath is heated very slowly.
9. The residual mother liquor contains about 4 g. of material containing bromine not removed by repetition of the treatment with zinc dust.
10. Purification of cholesterol through the dibromide completely eliminates cholestanol, 7-dehydrocholesterol, and lathosterol (Δ^7-cholestenol). The first crop of material from methanol-ether is also free from cerebrosterol (24-hydroxycholesterol) and 25-hydroxycholesterol, a product of autoxidation present in cholesterol that has been stored in the crystalline state for a few years with access to air. When material of highest purity is desired, only first-crop dibromide should be employed, since debromination of second-crop material gives sterol melting at 146–147° and giving a positive Beilstein test.
11. Dibromocholestanone sometimes begins to decompose (turns purplish) after standing in the dark for a few hours; it rapidly darkens when dried at 70° or when exposed to bright sunlight. Hence it is advisable to use the material moist with methanol directly after preparation.
12. For success in the preparation of this labile non-conjugated ketone in high yield and purity, the intermediates, cholesterol dibromide and dibromocholestanone, should be processed further in the solvent-moist state as soon as prepared. The three reactions can be completed easily in one day.
13. If the bulk of the ionic zinc is not precipitated at this point it will cause troublesome emulsions when

the solution is washed with water.
14. When isomerization of 100-g. batches of non-conjugated ketone was effected in ethanol under catalysis by either hydrochloric acid or sodium hydroxide (followed by neutralization of the yellow enolate solution with acetic acid), a permanent yellow coloration developed, the first-crop material was yellowish and melted at 78–80°, and the second-crop material was very impure.

3. Discussion

Cholesterol dibromide has been prepared by unbuffered[2] and buffered[3] bromination of cholesterol and oxidized to 5α,6β-dibromocholestan-3-one with acid permanganate,[2] chromic acid,[4,5,6] and sodium dichromate.[3] Regeneration of sterols, or more usually of sterol acetates, from their dibromides has been accomplished by use of zinc dust in boiling acetic acid,[2] sodium iodide,[7] ferrous chloride,[8] and chromous chloride,[9] and by the method[3] here described. Δ^5-Cholesten-3-one has been prepared by debromination of dibromocholestanone with zinc dust in boiling ethanol or methanol[5] and by zinc dust in ether containing a little acetic acid.[3]

The Oppenauer oxidation of cholesterol to Δ^4-cholesten-3-one of m.p. 77–79° in 70–93% yield has been reported in these volumes (p. 192).[10] Isomerization of Δ^5-cholesten-3-one by a mineral acid or a base has been conducted satisfactorily only on a micro scale;[5] the method of isomerization with oxalic acid has been reported.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 293

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

Δ^4-Cholesten-3-one

Δ^5-Cholesten-3-one

7-dehydrocholesterol

lathosterol

Δ^7-cholestenol

cerebrosterol

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

bromine (7726-95-6)

oxygen (7782-44-7)

Oxalic acid (144-62-7)

pyridine (110-86-1)

zinc (7440-66-6)

chromic acid (7738-94-5)

sodium dichromate (7789-12-0)

sodium iodide (7681-82-5)

magnesium sulfate (7487-88-9)

cholestanol (80-97-7)

Cholesterol (57-88-5)

Cholesteryl acetate (604-35-3)

sodium dichromate dihydrate (10588-01-9)

Cholesterol dibromide (1857-80-3)

Cholest-4-en-3-one (601-57-0)

Cholest-5-en-3-one (601-54-7)

5α,6β-dibromocholestan-3-one (2515-09-5)

24-hydroxycholesterol

25-hydroxycholesterol

Dibromocholestanone

ferrous chloride (7758-94-3)

chromous chloride (10049-05-5)