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Further Products from 4α-Acetoxy-Δ^5-cholestene-3-one

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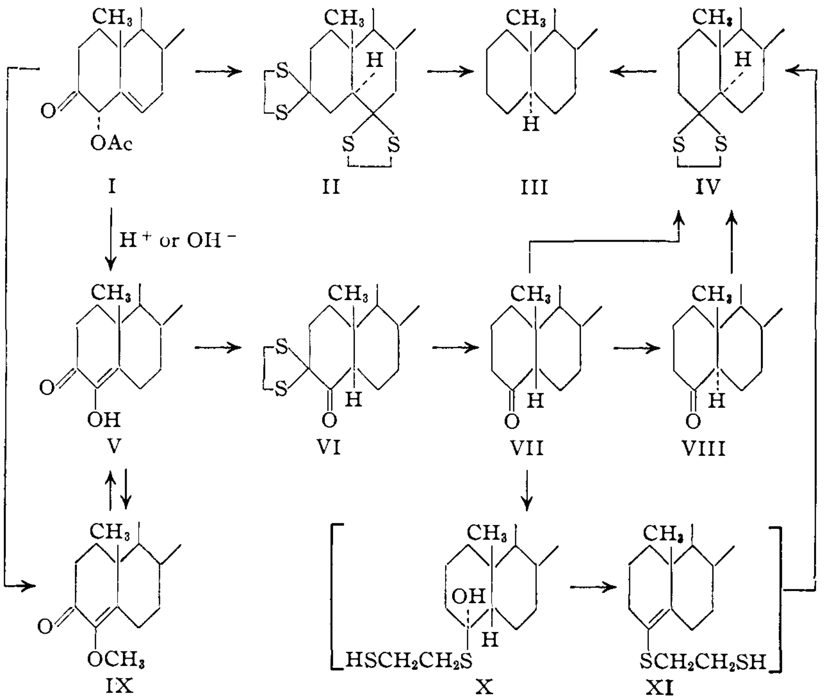
Δ^4-Cholestene-4-ol-3-one (V) reacts with ethanedithiol to give coprostane-3,4-dione-3-ethylenethioketal (VI), which on desulfurization affords coprostane-4-one (VII). Both VII and cholestane-4-one (VIII) yield the thioketal of cholestane-4-one, apparently by different mechanisms. Coprostane-4-one is more hindered to carbonyl reagents than cholestane-4-one, into which it is easily converted by acids or bases. Δ^4-Cholestene-4-ol-3-one methyl ether (IX) is described.

A previous paper[2] reported a number of transformations of 4α-acetoxy-Δ^5-cholestene-3-one (I), a product of lead tetraacetate oxidation of Δ^5-cholestene-3-one, including condensation with ethanedithiol under catalysis by boron fluoride[3] to give cholestane-3,6-dione bis-ethylenethioketal (II). Δ^4-Cholestene-4-ol-3-one (V), which results from acidic or basic hydrolysis of I, has now been found to react differently, for the product obtained with excess ethanedithiol shows carbonyl absorption in the infrared and has the composition of a monoethylenethioketal of a diketone. The structure VI is suggested by the observation that desulfurization of the substance with Raney nickel affords a hitherto undescribed ketone characterized as coprostane-4-one (VII) by its ready isomerization by acid or base to cholestane-4-one (VIII). Coprostane-4-one, however, is stable to boron fluoride in acetic acid or ether solution, that is, under the conditions of formation of the ethylenethioketal precursor. If this derivative (α_D + 125° chf.) does indeed have the structure VI and results from ketal formation at C_3 and ketonization, it would seem that the ketol group renders the *cis* A/B system more stable than the *trans*.[4] The failure of the substance to react with a second mole of reagent can be attributed to hindrance; benzil under the same conditions forms only a monoethylene thioketal.[3]



In the absence of a 3-thioketal group, the 4-carbonyl group shows normal reactivity to ethanedithiol. Thus coprostane-4-one yields an ethylenethioketal, which was found to yield cholestane on desulfurization and to be identical with the derivative obtained from cholestane-4-one. Since coprostane-4-one is stable to the catalyst used (BF_3), the reaction leading to the cholestane derivative IV must involve a mechanism other than isomerization and condensation. A possible route is through the intermediates X and XI, which is similar to the mechanism proposed by Djerassi and Gorman[5] for the formation of ketals. It is assumed that in the addition product X the larger group takes up the more accessible equatorial (β) orientation and hence that the 4α-hydroxyl and the 5β-hydrogen are both axial and disposed to facile elimination. The same mechanism is applicable to the case of cholestane-4-one.

The infrared spectra of cholestane-4-one andc oprostane-4-one are fairly similar for chloroform solutions but markedly different for solutions in carbon bisulfide. Toward carbonyl reagents, the coprostanone is more hindered than the cholestanone, since the latter ketone gave a semicarbazone, a 2,4-dinitrophenylhydrazone and an oxime under conditions in which coprostane-4-one either remained unchanged or gave indefinite products.

One other product derived from 4α-acetoxy-Δ^5-cholestene-3-one (I) and characterized as Δ^4-cholestene-4-ol-3-one methyl ether (IX) was obtained by refluxing a solution of I in methanol containing boron fluoride; at room temperature compound I is converted into the 3-dimethyl ketal acetate.[2] Refluxing gives a mixture of the enol ether IX and the free enol

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[2] L. F. Fieser and R. Stevenson, THIS JOURNAL, **76**, 1728 (1954).

[3] L. F. Fieser, *ibid.*, **76**, 1945 (1954).

[4] It is possible that the enol is converted to the *less* stable ketone by prototropic attack on the less hindered side of the double bond, as observed by H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955), with exocyclic enols, but speculations regarding hindrance effects in a substituted endocyclic system seem premature.

[5] C. Djerassi and M. Gorman, THIS JOURNAL, **75**, 3704 (1953).

V, which crystallize together from methanol as a crystalline and fairly sharp melting complex, which, however, can be resolved by crystallization from petroleum ether, by chromatography, or by acetylation and crystallization. The enol and its ether are interconvertible. The enol ether IX has an absorption maximum at 263 mμ (5,600), whereas the corresponding acetate absorbs at 247 mμ[2] and cholestenone absorbs at 241 mμ (all in ethanol). Thus the bathochromic shifts for 4-methoxyl and 4-acetoxyl substitution are 22 and 6 mμ, respectively. The low intensity of absorption of IX, reminiscent of cisoid systems, is unexpected.

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Experimental

Coprostane-3,4-dione 3-Ethylenethioketal (VI).—A mixture of 300 mg. of pure Δ^4-cholestene-4-ol-3-one[2] (V) and 1 ml. of freshly distilled ethanedithiol was warmed slightly to effect solution. A gel resulted on cooling and was treated with 1 ml. of boron fluoride etherate, which caused separation of a yellow oil, which changed to a pink emulsion on trituration. After 15 min., addition of methanol gave a colorless solution from which a heavy oil separated. Water was added and the mixture extracted with ether; evaporation of the washed and dried solution gave a residual yellow gum, which on trituration with methanol yielded 300 mg. of white solid, m.p. 95–107°. In successive crystallizations of the product some resinous material separated initially and was removed by filtration prior to deposition of crystals. Initial crystallization from methanol gave material melting at 106–110°, α_D +111° Chf. Crystallization from ether–methanol raised the m.p. to 110–112°, and three crystallizations from acetone–methanol gave the m.p.'s 115–117°, 124–125° and 126–128°. The purest material formed soft needles, m.p. 126–128°, α_D +125° Chf. (*c* 1.5).

Anal. Calcd. for $C_{29}H_{48}OS_2$ (476.67): C, 73.07; H, 10.15. Found: C, 73.23; H, 10.21.

Coprostane-4-one (VII). **Preparation** (**a**).—A solution of 480 mg. of V in 50 ml. of acetic acid was treated at 55° with 1.5 ml. of ethanedithiol and 1.5 ml. of boron fluoride etherate, let come to room temperature, and after 45 min. poured into water. Extraction with ether and processing with methanol as above gave 282 mg. of the crude ethylenethioketal VI, m.p. 103–107°. A solution of the material in ether–methanol was filtered from resinous solid, diluted with ethanol, and refluxed with Raney nickel for 6 hr. The filtered solution when concentrated and diluted with water deposited crystalline ketone, m.p. 105–107°. On recrystallization from ethanol the substance was obtained as beautiful needles, m.p. 109–110° (102 mg.), α_D +40.5° Chf. (*c* 1.5), λ^{Chf} 5.89 μ; λ^{CS_2} 5.86, 7.84, 8.50, 8.60 μ.

Anal. Calcd. for $C_{27}H_{46}O$ (386.64): C, 83.87; H, 11.99. Found: C, 83.96; H, 12.02.

(**b**) Δ^4-Cholestene-4-ol-3-one (1.0 g.) was treated with 4 ml. each of ethanedithiol and boron fluoride etherate, and the crude oily product was desulfurized with Raney nickel in ethanol. Evaporation of the filtered solution gave a solid, m.p. 103–107°, and one crystallization from methanol gave needles of coprostanone (500 mg.), m.p. 107.5–109°, α_D + 38° Chf. (*c* 1.5). Concentration of the mother liquor gave 260 mg. of solid, m.p. 80–100°, and the melting range was not improved by recrystallization. A solution of the mixture in ethanol (25 ml.) was treated with concd. hydrochloric acid (1 ml.) and refluxed for 30 min. On concentration, leaflets, m.p. 95–100°, separated. Two recrystallizations from methanol gave 95 mg. of **cholestane-4-one**, as leaflets, m.p. 99–101°, α_D +33° Chf. (*c* 1.8).[6] A mixture with coprostane-4-one melted at 80–85°.

(**c**) **Stability.**—A solution of 42 mg. of coprostane-4-one (VII) in 5 ml. of benzene was adsorbed on a 1 × 8 cm. column of acid-washed alumina. Elution with 50 ml. of benzene gave a solid (39 mg.), which on one crystallization from methanol afforded unchanged coprostane-4-one, m.p. 108–109°. A solution of 29 mg. of VII in 3 ml. of acetic acid was treated at 60° with 3 drops of boron fluoride etherate and let stand for one-half hour. Dropwise addition of water caused separation of a precipitate, which on crystallization from aqueous methanol gave unchanged VII as needles (21 mg.), m.p. 108–109°, α_D +41° Chf. A solution of 50 mg. of VII in 2 ml. of ether was treated with 1 ml. of boron fluoride etherate and let stand at 27° for 2.5 hr.; the recovered product, crystallized from methanol, was unchanged VII, needles (41 mg.), m.p. 108–109°.

(d) **Action of 2,4-Dinitrophenylhydrazine.**—A solution of 50 mg. of coprostane-4-one and 30 mg. of reagent in 2 ml. of acetic acid was refluxed for 5 min., cooled (no precipitate), and the mixture diluted with water, extracted with ether, and the product chromatographed. Crystallization from methanol gave pale yellow needles, m.p. 104–106°, raised to 107.5–108.5° on recrystallization; a mixture with coprostane-4-one melted at 108–109°. The product shows very low-intensity absorption at 368–372 mμ.

Cholestane-4-one (VIII). (a) **From Coprostane-4-one.**—A solution of 48 mg. of coprostane-4-one and 4 drops of concd. hydrochloric acid in 10 ml. of methanol was refluxed for 30 min., concentrated to 5 ml., and a few drops of water added. Two crops of needles were obtained: 32 mg., m.p. 93–94°, and 10 mg., 88–90°. Recrystallization from aqueous methanol gave cholestane-4-one, m.p. and mixed m.p. 99–100°, α_D +31° Chf. (*c* 1.3), $\lambda^{Chf.}$ 5.88 μ, λ^{CS_2} 5.86 μ. A solution of 20 mg. of coprostane-4-one in 3 ml. of methanol was treated with a trace of sodium methoxide and refluxed for 10 min. The product that separated, m.p. 95–96°, on recrystallization gave VII, m.p. 98–99°, λ^{CS_2} 5.85, 7.90, 8.30, 8.69 μ.

(b) **Preparation.**—Conversion of Δ^4-cholestene-4-one to Δ^4-cholestene *via* the dibenzylmercaptal[7] (α_D + 128°) was tried with unpromising results. Condensation with benzylmercaptan in the presence of boron fluoride etherate, perchloric acid[5] or zinc chloride and sodium sulfate[7] gave products of low rotation (+60, +102 and +98°) and showing absorption at 268 mμ indicative of the presence of cholestenone thioenol benzyl ether[8] (α_D −105°). Desulfurization gave crude material (m.p. 59–65°) which could not be purified by crystallization.

Repetition of the procedure reported[3] gave **Δ^4-cholestene-3-one ethylenethioketal**, m.p. 111–113° dec., α_D +112° Chf. (*c* 2.2); the m.p. is between the values previously reported[3,7] and the rotation agrees with the value reported by one of us.[3] Desulfurization, effected by refluxing 9 g. of the derivative and Raney nickel (9 teaspoonfuls) in 1 l. of ethanol for 5.5 hr. gave crude **Δ^4-cholestene** in two crops: 4.2 g., m.p. 73–76°, α_D +63° Chf. (*c* 2.1), and 2.4 g., m.p. 65–70°. Bromination of this material in ether–acetic acid and two crystallizations from ether–methanol gave pure dibromide, m.p. 114.6–116°, α_D +39° Chf. (*c* 2.0), and debromination of 550 mg. with sodium iodide in acetone gave pure Δ^4-cholestene, m.p. 82–83° (310 mg.), α_D +75° Chf. (*c* 1.8).[9] The procedure of low-temperature nitration[10] proved convenient. Thus 15 ml. of fuming nitric acid was added dropwise with stirring during 45 min. to a solution of 2 g. of crude Δ^4-cholestene (m.p. 73–76°, α_D +63°) in 30 ml. of absolute ether with ice cooling. A green solution resulted and a white precipitate settled. The latter dissolved when the mixture was stirred without cooling for 45 min. longer. The ethereal solution was washed with water, bicarbonate solution and water; dried and evaporated at reduced pressure. The residual oily solid (yellowish) was taken up in acetic acid (60 ml.), water (5 ml.) and zinc dust (4 g.) were added, and the mixture stirred for 1 hr. at room temperature and then refluxed for 2 hr., with addition of 4 g. more zinc dust after the first hour. The filtered solution was concentrated in vacuum until zinc acetate started to separate, diluted and extracted with ether. The product, a brown oil, was chromatographed on alumina. Petroleum ether eluted a colorless gum, and then benzene eluted a yellow gum which on crystallization from methanol gave

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[6] (a) L. Ruzicka, Pl. A. Plattner and M. Furrer, *Helv. Chim. Acta*, **27**, 727 (1944), gave m.p. 99–99.5°, α_D +29.5°; (b) A. Butenandt and G. Ruhenstroth-Bauer, *Ber.*, **77**, 397 (1944), reported m.p. 96–98°.

[7] H. Hauptmann, THIS JOURNAL, **69**, 562 (1947).

[8] G. Rosenkranz, St. Kaufmann and J. Romo, *ibid.*, **71**, 3689 (1949).

[9] D. H. R. Barton and W. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

[10] C. E. Anagnostopolous and L. F. Fieser, THIS JOURNAL, **76**, 532 (1954).

colorless **cholestane-4-one**, m.p. 94–97°. Recrystallization gave material of m.p. 98.5–100°, α_D +31° Chf. (*c* 2.0).[11]

Anal. Calcd. for $C_{29}H_{46}O$ (386.64): C, 83.87; H, 11.99. Found: C, 83.58; H, 11.92.

Cholestane-4-one Ethylenethioketal (IV).—A solution of 50 mg. of cholestane-4-one in 0.5 ml. of ethanedithiol was treated with 0.5 ml. of freshly distilled boron fluoride etherate and let stand for 6 hr., when a crystalline solid had separated. On addition of methanol the solid dissolved and then, on further dilution, reprecipitated. One crystallization from chloroform–methanol gave feathery needles, m.p. 117–118°, α_D −5° Chf. (*c* 2.1). The analytical sample was dried in vacuum at 70° for 1 week.

Anal. Calcd. for $C_{29}H_{50}S_2$ (462.69): C, 75.28; H, 10.89. Found: C, 74.88; H, 10.68.

Similar treatment of coprostane-4-one (260 mg.) gave an identical product (240 mg.), m.p. and mixed m.p. 119–120°, α_D −5° Chf. (*c* 1.3).

Desulfurization of IV (415 mg.) by refluxing a solution in absolute ethanol (250 ml.) with Raney nickel for 16 hr. and concentration of the filtered solution to 30 ml. gave 210 mg. of **cholestane**, m.p. 80–81°, undepressed by an authentic sample. Concentration of the mother liquor afforded a second crop (75 mg.), m.p. 79.5–80.5°.

Cholestane-4-one Semicarbazone.—A solution of 100 mg. of semicarbazide hydrochloride and 100 mg. of crystalline sodium acetate in 0.8 ml. of water was added to a hot solution of 55 mg. of the ketone in 5 ml. of absolute ethanol. After 2 minutes a large gelatinous precipitate had formed, and after refluxing for 8 min. the mixture was cooled and a solid collected (70 mg.), m.p. 260° dec. The semicarbazone separated from chloroform–methanol as a gel, which changed on standing for a few hours to a filterable solid, m.p. 269–271°.

Anal. Calcd. for $C_{28}H_{49}ON_3$ (443.70): N, 9.47. Found: N, 9.58.

Coprostane-4-one, treated under identical conditions, or even when the period of refluxing was extended to 1 hr., was recovered unchanged.

Cholestane-4-one 2,4-Dinitrophenylhydrazone.—A solution of the ketone (50 mg.) and the hydrazine (30 mg.) in acetic acid (2 ml.) was boiled for 5 min. and let cool, when a yellow solid separated (m.p. 135–170°). This was eluted from an alumina column with benzene and crystallized twice from chloroform–methanol to give small felted needles, m.p. 186–188°, λ^{CHCl_3} 368–372 mμ (17,500).

Anal. Calcd. for $C_{33}H_{50}O_4N_4$ (566.76): N, 9.89. Found: N, 9.84.

The derivative was also obtained by reaction of the ketone (20 mg.) in methanol (0.5 ml.) with a few drops of Brady reagent. The crude product, m.p. 115–135°, on purification as above gave an identical product, m.p. 186–188°.

Cholestane-4-one Oxime.—A solution of hydroxylamine hydrochloride (100 mg.) and crystalline sodium acetate (100 mg.) in water (0.8 ml.) was added to a solution of the ketone (56.7 mg.) in absolute ethanol (4.5 ml.). Precipitation of solid was almost immediate. The suspension was refluxed for 1 hr., concentrated, cooled, and the product (62 mg., m.p. 211–214°) crystallized from absolute ethanol to give flat prisms, m.p. 216–218°. Melting points of 205°[11] and 205–207°[6b] are reported.

Anal. Calcd. for $C_{27}H_{47}ON$ (401.65): C, 80.73; H, 11.80. Found: C, 80.55; H, 11.58.

Similar treatment of coprostane-4-one gave a crude product, m.p. 75–80°, not improved by crystallization. The material had no infrared carbonyl absorption.

Cholestane-4β-ol.—A solution of cholestane-4-one (50 mg.) in anhydrous ether (10 ml.) was added to a suspension of lithium aluminum hydride (180 mg.) in ether and the mixture was refluxed for 2 hr. The product, recovered in the usual way, crystallized from methanol as small needles (20 mg.), m.p. 132–133°; second crop (11 mg.), m.p. 128–131°. Recrystallization of the combined material from methanol gave needles, m.p. 132–133°, α_D +30° Chf. (*c* 1.4). Both Tschesche and Hagedorn[12] and Barton and Rosenfelder[9] report m.p. 131–132°, α_D +29°.

Δ^4-Cholestene-4-ol-3-one Methyl Ether (IX).—A suspension of 4 g. of 4α-acetoxy-Δ^5-cholestene-3-one in 200 ml. of methanol and 4 ml. of freshly distilled boron fluoride etherate was brought to the boiling point, when the solid dissolved, refluxed for 1 hr., diluted with 15 ml. of water, and let stand overnight at 0°. The solid which separated (2.34 g., m.p. 130–135°) on crystallization from methanol gave a **complex** of properties unchanged by further crystallization from methanol: m.p. 133–136°, α_D +55° Chf. (*c* 2.3), λ^{EtOH} 266–268 mμ (6,200); λ^{Chf} 2.90, 5.91, 6.05, 9.0 μ. However, crystallization from 30–60° petroleum ether afforded soft needles of the enol methyl ether IX, m.p. 143–146°, and two recrystallizations from methanol gave long flat needles, m.p. 150–151°, α_D +49° Chf. (*c* 1.9), λ^{EtOH} 263 mμ (5,600); λ^{Chf} 5.91, 6.06, 9.00 μ; yellow color with tetranitromethane.

Anal. Calcd. for $C_{28}H_{46}O_2$ (398.65): C, 81.10; H, 11.18; OCH_3, 7.48. Found: C, 81.21; H, 10.82; OCH_3, 7.35.

Chromatography of the petroleum ether mother liquor afforded 272 mg. of solid (eluted by benzene) identified after one crystallization from methanol as additional IX, and 37 mg. (eluted by ether) of Δ^4-cholestene-4-ol-3-one (V), which crystallized from methanol as rosettes of needles, m.p. 147–149°, λ^{EtOH} 279 mμ. Chromatography of the original boron fluoride–methanol mother liquor and crystallization of the benzene eluate (190 mg., m.p. 150–160°) afforded cholestane-3,6-dione, m.p. 171–172°, α_D +11° Chf. (*c* 1.7), λ^{Chf} 5.83 μ.

The ether IX was also isolated from the complex (500 mg.) by acetylation in pyridine (18 hr., 25°) and two crystallizations of the product from methanol, which gave long flat needles (240 mg.), m.p. 150–151.5°, α_D +50° Chf. (*c* 2.3), λ^{EtOH} 262.5 mμ (5,600).

The enol ether IX was also obtained from the Δ^4-cholestene-4-ol-3-one (V), which was prepared conveniently by refluxing for 50 min. a mixture of 1 g. of 4α-acetoxy-Δ^5-cholestene-3-one, 15 ml. of dioxane and 2 ml. of concd. hydrochloric acid. Addition of water precipitated an oil which solidified, and crystallization from methanol gave 900 mg. of V, m.p. 145–147°; recrystallized, m.p. 149–150°, α_D +82° Chf. (*c* 1.6), λ^{EtOH} 278 mμ (12,500). A solution of 90 mg. of V and 0.2 ml. of boron fluoride etherate in 10 ml. of methanol was refluxed for 1 hr. The product, recovered as above and crystallized from methanol was the complex, m.p. and mixed m.p. 136–137°. The reverse reaction occurred on refluxing the ether IX (159 mg., m.p. 150–151°) in 10 ml. of 95% ethanol and 0.2 ml. of concd. hydrochloric acid for 2 hr. and dilution to saturation; the enol V separated as fibrous needles (96 mg.) and recrystallization gave material of m.p. and mixed m.p. 148.5–149.5°.

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[11] A. Windaus, *Ber.*, **53**, 488 (1920).

[12] R. Tschesche and A. Hagedorn, *ibid.*, **68**, 2248 (1935).