[CONTRIBUTION FROM THE CHEMICAL LABORATORY, HARVARD UNIVERSITY]

Synthesis of 11-Ketosteroids.[1] I. Dichromate Oxidation of a Bile Acid $\Delta^{7,9(11)}$-Diene

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Oxidation of methyl 3α-acetoxy-$\Delta^{7,9(11)}$-choladienate (I) with sodium dichromate in acetic acid gave the $\Delta^{9(11)}$-7-ketone V (41%) and the Δ^{8}-7,11-diketone II (10–15%). The latter product was transformed by reduction of the double bond and removal of the less hindered 7-keto group into the methyl ester acetate of 11-ketolithocholic acid (IV). The β,γ-unsaturated ketone V is easily isomerized to the conjugated ketone IX, which can be converted back to the diene I and oxidized through the enol acetate X to XI. Performic acid oxidizes methyl $\Delta^{7,9(11)}$-lithocholadienate in good yield to the Δ^{8}-7-ketone (IX, as 3-formate).

The work to be reported in this series was directed toward discovery of methods for introduction of oxygen at C_{11} into sterols offering potentialities as starting materials for cortisone production: ergosterol, diosgenin and stigmasterol. Since we were concerned with the methodology of a single operation rather than with development of a specific practical process, we employed cholesterol as a model for Δ^{5}-sterols in general. The plan of approach was, first, extension of the functional group system from C_5 to C_{11} by methods introduced by Windaus: conversion of a Δ^{5}-stenol to the 5,6:7,8-diene,[4] selective reduction of the 5,6-double bond,[5] and dehydrogenation of the Δ^{7}-stenol to the 7,8:9,11-diene.[6] A model $\Delta^{7,9(11)}$-diene of the bile acid series also became available to us through the work of Rajagopalan, who developed an improved method of preparing methyl cholate 3,7-diacetate[7] and found that the substance can be converted smoothly through the 12-ketone to the $\Delta^{9(11)}$-12-ketones[8]; which on Wolff–Kishner reduction affords $\Delta^{7,9(11)}$-lithocholadienic acid in good yield.[1a,9] This substance appeared attractive as a model for initial exploration because 11-ketolithocholic acid is a known compound[10] available[11] for comparison; the extent to which reactions in the bile acid series might be applicable to sterol dienes would remain for investigation.

Initial reports in May, 1951, on oxidation of steroid $\Delta^{7,9(11)}$-dienes by our group[1a] and by Tishler, Chemerda and co-workers at Merck[12] were soon followed by related reports from Syntex[13] and from the groups at Zurich[14] and Glasgow.[15] In the few instances where our work and that in other laboratories touch common ground the results are in substantial agreement.

The idea of attempting oxidation of methyl $\Delta^{7,9(11)}$-lithocholadienate (I) to the Δ^{8}-7,11-diketone (II) with hexavalent chromium was suggested to us by Windaus' early observation[16] that cholesterylene, essentially the $\Delta^{3,5}$-diene, on chromic acid oxidation is converted in part into Δ^{4}-cholestene-3,6-dione.[17] Use of the milder sodium dichromate dihydrate in anhydrous acetic acid had been found advantageous in a study of the oxidation of cholesterol.[18] Oxidation of the diene I by this method gave a mixture separated by crystallization into a colorless, sparingly soluble component, m.p. 184° (41% yield), and by chromatography into a more soluble, yellow component, m.p. 115° (10–15% yield). These are, respectively, the β,γ-unsaturated 7-ketone V and the unsaturated 7,11-diketone II. The latter substance corresponds in color and roughly in its absorption maximum (271 mμ) to Δ^{4}-cholestene-3,6-dione (λ^{EtOH} 252 mμ), and like this substance[16] it is reducible with zinc and acetic acid and affords the colorless saturated 7,11-diketone III. Wolff–Kishner reduction of III followed by esterification and acetylation gave two products, one of which proved identical with the known 3α-acetoxy-11-ketocholanate (IV). The second product was methyl lithocholate 3-acetate, the formation of which is in accord with a recent finding that the 11-keto group is removable by drastic Wolff–Kishner reduction.[19] A better route is by desulfuration of the easily prepared 7-ethylene thioketal derivative VII.[20]

The high melting oxidation product V, which is transparent to ultraviolet light, was at first[1a] thought to be an unsaturated monoöxide, but the presence of a ketonic function was established by reduction with sodium borohydride to an alcohol reconvertible into V by dichromate oxidation. Also, the infrared spectrum, kindly determined on a Perkin–Elmer 12c single beam spectrometer at the Syntex laboratory through the courtesy of Dr. Carl Djerassi, showed not only a band at 1736 cm.$^{-1}$, corresponding exactly to the ester carbonyl band found for methyl 3α-acetoxy-$\Delta^{7,9(11)}$-cholanate, but also a band at 1720 cm.$^{-1}$ attributable

(1) The main results of our work have been reported in the following communications: (a) L. F. Fieser, J. E. Herz and W.-Y. Huang, THIS JOURNAL, **73**, 2397 (1951); (b) L. F. Fieser, J. C. Babcock, J. E. Herz, W.-Y. Huang and W. P. Schneider, *ibid.*, **73**, 4053 (1951).

(2) National Institutes of Health predoctoral fellow, 1950–1952.

(3) du Pont predoctoral fellow, 1951–1952.

(4) A. Windaus, H. Lettré and Fr. Schenck, *Ann.*, **520**, 98 (1935).

(5) A. Windaus and J. Brunken, *ibid.*, **460**, 225 (1928).

(6) A. Windaus and E. Auhagen, *ibid.*, **472**, 185 (1929).

(7) L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **72**, 5530 (1950).

(8) L. F. Fieser, S. Rajagopalan, E. Wilson and M. Tishler, *ibid.*, **73**, 4133 (1951).

(9) Further details will be reported in a paper on mono- and dienic bile acids.

(10) A. Lardon and T. Reichstein, *Helv. Chim Acta*, **26**, 586 (1943).

(11) H. Heymann and L. F. Fieser, THIS JOURNAL, **73**, 5252 (1951).

(12) E. M. Chamberlain, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, *ibid.*, **73**, 2396 (1951).

(13) (a) G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 3546 (1951); (b) C. Djerassi, O. Mancera, G. Stork and G. Rosenkranz, *ibid.*, **73**, 4496 (1951).

(14) H. Heusser, K. Eichenberger, P. Kurath, H. R. Dällenbach and O. Jeger, *Helv. Chim. Acta*, **34**, 2106 (1951); H. Heusser, K. Heusler, K. Eichenberger, C. G. Honegger and O. Jeger, *ibid.*, **35**, 295 (1952); H. Heusser, R. Anliker, K. Eichenberger and O. Jeger, *ibid.*, **35**, 936 (1952).

(15) R. C. Anderson, R. Budziarek, G. T. Newbold, R. Stevenson and F. S. Spring, *Chemistry and Industry*, 1035 (1951).

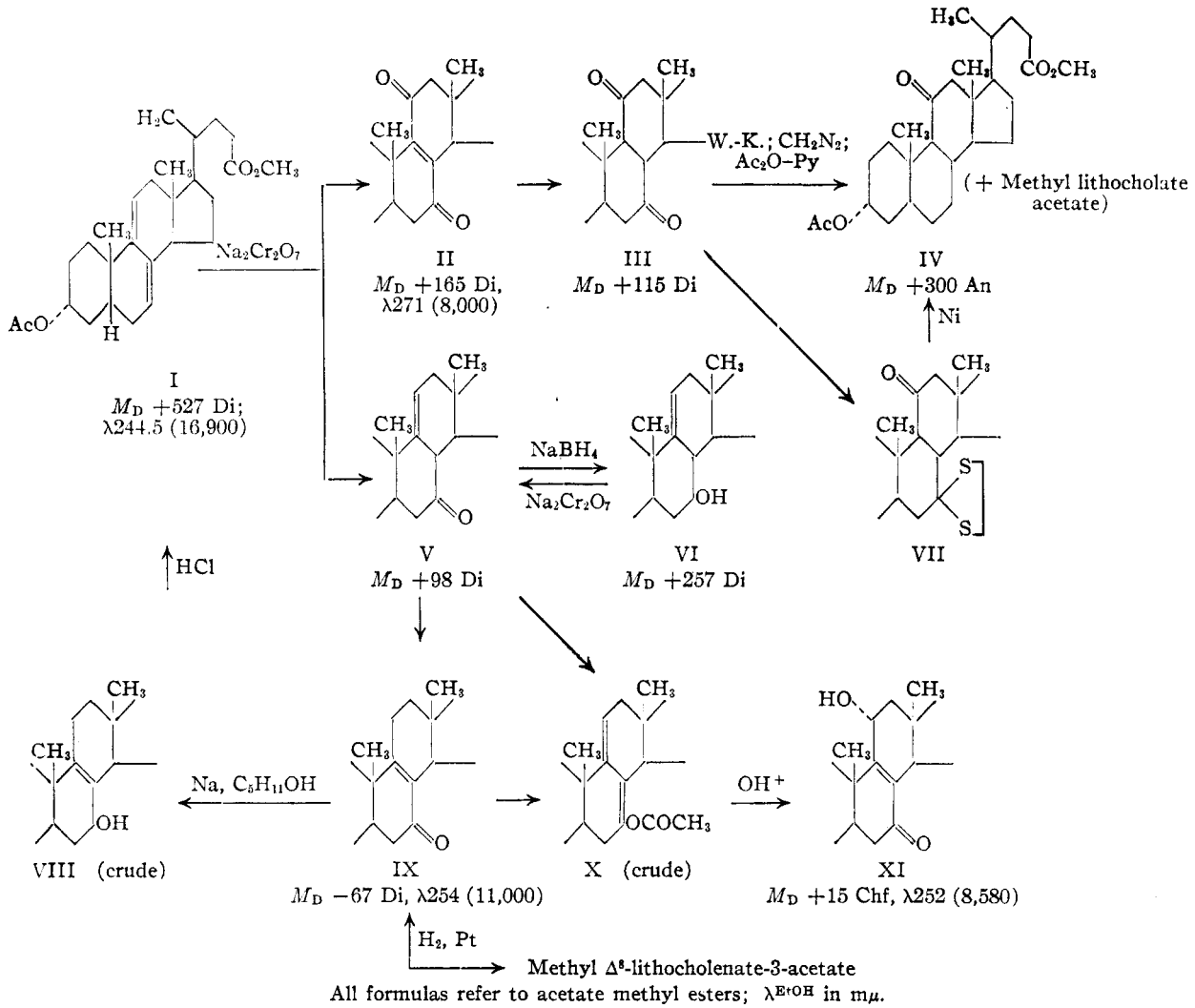
(16) A. Windaus, *Ber.*, **39**, 2249 (1906).

(17) See L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 233.

(18) L. F. Fieser, THIS JOURNAL, **73**, 5007 (1951).

(19) R. B. Moffett and J. H. Hunter, *ibid.*, **73**, 1973 (1951).

(20) *Cf.* A. Ruff and T. Reichstein, *Helv. Chim. Acta*, **34**, 70 (1951).



All formulas refer to acetate methyl esters; λ^{EtOH} in mμ.

to a ketonic function. The non-conjugated ketone is isomerized by zinc–acetic acid or by heating it with aqueous dioxane at 160° to an α,β-unsaturated ketone of λ^{EtOH} 254 mμ (11,000). Since this substance was found to be hydrogenated in acetic acid with platinum catalyst to methyl 3α-acetoxy-Δ^8-cholenate,[9] the ketone group must be at either C_7 or C_{11}, and since the substance is different from the known methyl 3α-acetoxy-11-keto-Δ^8-cholenate[11] it can be assigned the structure of 3α-acetoxy-7-keto-Δ^8-cholenate (IX). The oxidation product is thus the $\Delta^{9(11)}$-7-ketone (V). A procedure for its reconversion to the starting diene (I) is by isomerization to IX, reduction of the carbonyl group with sodium and amyl alcohol and dehydration with mineral acid. Another way of utilizing this chief product of the oxidation is by application of a method first reported by the Syntex group.[13b] The β,γ- and α,β-unsaturated ketones on enol-acetylation give an oily product of the same characteristics that reacts with perphthalic acid to give the 11α-hydroxy-Δ^8-7-ketone XI, identical with a product to be described in paper III of this series.

In view of the formation of an 11-keto-3,9-oxido hemiketal on oxidation of methyl 9,11-oxidolithocholate,[11] we explored the chromic acid oxidation of free methyl $\Delta^{7,9(11)}$-lithocholadienate but obtained merely products analogous to II and V except for the presence at C_3 of a keto group in place of the acetoxy function. An identical Δ^8-3,7,11-triketone was prepared from II by deacetylation and oxidation. The β,γ-unsaturated 7-ketone V could not be deacetylated under mild acidic or alkaline conditions without bond migration, but the 7-hydroxy compound VI could be deacetylated at C_3 and the product oxidized to the $\Delta^{9(11)}$-3,7-diketone formed in the original oxidation. Methyl 3,7-diketo-Δ^8-cholenate was obtained both by isomerization of the $\Delta^{9(11)}$-isomer and from IX.

The action of other oxidizing agents on the bile acid diene was investigated with the following results. Performic acid reacted smoothly with the 3α-hydroxy ester to give methyl 3α-formoxy-7-keto-Δ^8-cholenate in good yield. In view of the transformation of the corresponding 3-acetate through X to XI, this oxidation offers preparative possibilities. Since the Syntex group[13a] have found that performic acid oxidizes sterol $\Delta^{7,9(11)}$-dienes largely to 9,11-oxido-7-ketones, the course of the reaction is evidently dependent upon the nature of the A/B ring junction. Oxidation of methyl 3α-acetoxy-$\Delta^{7,9(11)}$-choladienate with potassium permanganate in acetic acid solution or with 1 mole of perbenzoic acid in chloroform afforded the

$\Delta^{9(11)}$-7-ketone V in yields of 20–30%. On the other hand, oxidation of the acetate ester with 2 moles of perbenzoic acid gave the Δ^{8}-7-ketone IX, the 11α-hydroxy-Δ^{8}-7-ketone XI, and a product provisionally regarded as the 9,11-oxido-7-ketone. Oxidation with hydrogen peroxide–ferrous sulfate according to Clemo, Keller and Weiss[21] gave a very small amount of material that appeared to be a mixture of the $\Delta^{9(11)}$- and Δ^{8}-7-ketones (V and IX).

We are greatly indebted to Dr. Max Tishler and Merck and Co., Inc., for special supplies and general coöperation.

Experimental

Methyl 3α,7α-Diacetoxy-12-keto-$\Delta^{9(11)}$-cholenate (W.-Y. H., J. C. B.).—An improvement in the previous procedure[8] consists in use of a simple and effective technique for removal of selenium from the reaction mixture by precipitation of a complex with sodium dichromate. Thus a solution of 49 g. of methyl 3α,7α-diacetoxy-12-ketocholanate, 480 cc. of acetic acid and 18 g. of selenium dioxide was refluxed for 18 hours, cooled and treated with a solution of 3 g. of sodium dichromate dihydrate in 6 cc. of acetic acid, added dropwise with shaking. The finely divided grayish-brown precipitate that promptly separated was removed by filtration through a 1-in. layer of Nuchar on a büchner funnel. Dilution of the bright yellow filtrate with an equal volume of water gave a colorless crystalline precipitate that was collected and washed with dilute acetic acid (1:1) to give 30.0 g. of the $\Delta^{9(11)}$-12-ketone, m.p. 153–155°, α^{25}_{D} +74 ± 1° Di, λ^{EtOH} 236 mμ (11,100). Dilution of the mother liquor with an equal volume of water gave 13.6 g. of yellowish product, m.p. 147–150°, that on crystallization from aqueous methanol afforded 12 g. of satisfactory product, m.p. 152–153° total yield 42 g. (86%).

Fractional crystallization and chromatography of the remaining mother liquor material from large-batch preparations afforded the following derivatives of 3α,7α-dihydroxy-12-keto-$\Delta^{9(11)}$-cholenic acid; 7-monoacetate, m.p. 256–258°; 3,7-diacetate, m.p. 217–218°; methyl ester 3-monoacetate, m.p. 152–153°; methyl ester 7-monoacetate, m.p. 153–154°.

Dichromate Oxidation of Methyl 3α-Acetoxy-$\Delta^{7,9(11)}$-choladienate (W.-Y. H.). **Methyl 3α-Acetoxy-7-keto-$\Delta^{9(11)}$-cholenate** (V, L. F. F.).—Cooled solutions of 10 g. of methyl 3α-acetoxy-$\Delta^{7,9(11)}$-choladienate[1a,9] (m.p. 148–149°, α^{25}_{D} +130° Chf, λ^{EtOH}_{max} 244 mμ, E 16,900) in 100 cc. of acetic acid and of 20 g. of sodium dichromate dihydrate in 50 cc. of acetic acid were mixed, let stand 24 hr. at 25°, and poured into 2 l. of water. The light yellow precipitate on crystallization from methanol afforded 4.43 g. (41%) of light yellow needles of crude β,γ-unsaturated ketone, m.p. 175–178°. Chromatography and repeated crystallization from methanol gave colorless needles, m.p. 184–184.5°, α^{20}_{D} + 22 ± 1° Di, λ^{Chf}_{max} 5.80, 8.0 μ, λ^{CS_2} (Syntex) 1720, 1736 cm.$^{-1}$, no ultraviolet absorption.

Anal. Calcd. for $C_{27}H_{40}O_5$ (444.59): C, 72.94; H, 9.07. Found: C, 72.84; H, 9.17.

Methyl 3α-Acetoxy-7,11-diketo-Δ^{8}-cholenate (II).—The mother liquor from crystallization of the above crude oxidation product was concentrated to dryness under reduced pressure and the gummy brown residue was dissolved in 20 cc. of 1:1 petroleum ether–benzene and adsorbed on 100 g. of acid-washed alumina. Elution with two 100-cc. portions of 1:1 petroleum ether–benzene and then with four 100-cc. portions of benzene, gave crystalline fractions, each of which was crystallized from methanol; elution with benzene–ether mixtures gave gummy fractions. Fraction 1 formed white crystals (105 mg.), m.p. 124–126°, showing no ultraviolet absorption at 220–280 mμ either before or after refluxing with zinc and acetic acid (see below). Fractions 2 and 3 (yellow; 415 mg., m.p. 129–138°; 350 mg., m.p. 119–123°) consisted of mixtures of the β,γ-unsaturated 7-ketone and the unsaturated diketone, partially separable by rechromatography or by repeated crystallization from methanol, in which the diketone is much more soluble. Fraction 6 afforded two kinds of crystals, m.p. 114–116° and 136–138°. Fractions 4 (185 mg.) and 5 (10 mg.), consisting of yellow crystals, m.p. 113–115°, on recrystallization from methanol formed light yellow plates, m.p. 114–115°, α^{22}_{D} +36 ± 1° Di, λ^{EtOH} 271 mμ (8000), λ^{Chf}_{max} 5.81, 5.95, 8.0 μ.

Anal. Calcd. for $C_{27}H_{38}O_6$ (458.57): C, 70.72; H, 8.35. Found: C, 70.65; H, 8.38.

A small amount of the enedione was recovered by processing the mother liquors from crystallization of the β,γ-unsaturated ketone; the total yield was 10–15%.

Methyl 3α-Acetoxy-7-keto-Δ^{8}-cholenate (IX, L. F. F.).—A mixture of 1.2 g. of the β,γ-unsaturated ketone (V), 2.5 g. of zinc dust and 15 cc. of acetic acid was refluxed for 2 hr., treated with a few drops of water and filtered. Further dilution gave crystalline material, m.p. 174–175°, λ^{EtOH}_{max} 245 mμ (4300). This was refluxed again with 2 g. of zinc acetate dihydrate, 15 cc. of acetic acid and 1.5 cc. of water and gave 402 mg. of product, m.p. 177–178°, E 6800, and 36 mg., m.p. 173–175°, E 7800. Two recrystallizations from methanol gave pure conjugated ketone, m.p. 181–182.5°, α_{D} −15 ± 1° Di, λ^{EtOH} 254 mμ (11000), λ^{Chf} 5.78, 5.95, 6.25, 7.9 μ.

Anal. Calcd. for $C_{27}H_{40}O_5$ (444.59): C, 72.94; H, 9.07. Found: C, 72.88; H, 9.13.

Isomerization was also accomplished by heating 103 mg. of V with 6.5 cc. of dioxane and 1.5 cc. of water in a sealed Pyrex tube at 150–160° for 2 days. Evaporation to dryness and crystallization of the residue from methanol gave colorless needles, m.p. 177–179°, λ^{EtOH}_{max} 253 mμ (7100); no depression in m.p. on admixture with above sample.

Methyl 3α-Acetoxy-7-hydroxy-$\Delta^{9(11)}$-cholenate (J.C.B.).—A solution of 170 mg. each of methyl 3α-acetoxy-7-keto-$\Delta^{9(11)}$-cholenate (V) and sodium borohydride in 15 cc. of methanol was let stand overnight at 26° and diluted with water, when 130 mg. of the reduction product separated in rectangular plates, m.p. 108–109°, α^{25}_{D} +57.5 ± 1° Di, λ^{Chf} 2.91, 5.80 μ.

Anal. Calcd. for $C_{27}H_{42}O_5$ (446.61): C, 72.61; H, 9.48. Found: C, 72.56; H, 9.45.

A 20-mg. sample of the alcohol was oxidized with sodium dichromate in acetic acid at 25°, when the 7-ketone V separated in long needles, m.p. 177–179°. Crystallization from methanol gave 16 mg. of V, m.p. and mixed m.p. 180–181°, α_{D} +22 ± 2° Di, no ultraviolet absorption.

$\Delta^{9(11)}$-Cholene-3α,7,24-triol was obtained by refluxing 455 mg. of methyl 3α-acetoxy-7-keto-$\Delta^{9(11)}$-cholenate (V) with 0.2 g. of lithium aluminum hydride in 10 cc. of tetrahydrofuran for 2 hr. The solution was cooled, treated with a little aqueous sodium sulfate solution and the product extracted with ether. Crystallization from methanol gave 279 mg. of triol, m.p. 155–157°, α^{20}_{D} +46.5 ± 0.5° Di.

Anal. Calcd. for $C_{24}H_{40}O_3$ (376.56): C, 76.55; H, 10.71. Found: C, 76.47; H, 11.01.

Methyl 3α-Acetoxy-Δ^{8}-cholenate from IX.—Methyl 3α-acetoxy-7-keto-Δ^{8}-cholenate (IX) absorbed no hydrogen in ethyl acetate solution in the presence of palladium–charcoal, but a solution of 500 mg. in 60 cc. of acetic acid in the presence of 60 mg. of platinum oxide absorbed 2 moles of hydrogen in about an hour and gave 301 mg. of crystalline product, m.p. 125–128°. Three crystallizations from aqueous methanol gave material melting at 144.5–146°, α^{24}_{D} +61 ± 1° Chf, unsaturated to tetranitromethane, no depression in m.p. of authentic sample.[9]

Anal. Calcd. for $C_{27}H_{42}O_4$ (430.61): C, 75.31; H, 9.83. Found: C, 75.45; H, 9.71.

7-Keto-Δ^{8}-lithocholenic Acid.—Methyl 3α-acetoxy-7-keto-$\Delta^{9(11)}$-cholenate (2 g.) was refluxed for 4 hr. under nitrogen with 2 g. of potassium hydroxide in 50 cc. of methanol and 10 cc. of water. The resulting deep yellow solution was diluted with 400 cc. of water, acidified with dilute hydrochloric acid and the precipitate was washed and dried; m.p. 205–210°, 1.75 g. Crystallization from acetone gave 1.2 g. of pure acid, m.p. 210–212°, α^{24}_{D} −38 ± 1° Di, λ^{EtOH} 254.5 mμ (8900); a second crop (0.33 g.) melted at 206–209°.

Anal. Calcd. for $C_{24}H_{36}O_4$ (388.53): C, 74.19; H, 9.34. Found: C, 74.03; H, 9.32.

The methyl ester was obtained by the action of diazomethane on a suspension of the acid in ether and crystallized

(21) G. R. Clemo, M. Keller and J. Weiss, *J. Chem. Soc.*, 3470 (1950).

from methanol; m.p. 132–133.5°, α^{24}_D −32 ± 1° Di, λ^{EtOH} 254.5 (8900).

Anal. Calcd. for $C_{25}H_{36}O_4$ (402.55): C, 74.59; H, 9.51. Found: C, 74.38; H, 9.31.

The methyl ester 3-acetate was prepared by letting a solution of 100 mg. of the methyl ester in 0.5 cc. of dioxane, 0.2 cc. of pyridine and 0.3 cc. of acetic anhydride stand at 20° for 22 hr. and adding a few drops of methanol and water; 54 mg. of nearly pure acetate separated, m.p. 180–181°, α^{20}_D −15 ± 1° Di, λ^{EtOH} 254 mμ (8900); no depression in m.p. of the ester acetate resulting from zinc–acetic acid isomerization of the β,γ-unsaturated ketone.

Conversion of 7-Keto-Δ^9-lithocholenic Acid to $\Delta^{7,9(11)}$-Lithocholadienic Acid.—A solution of 392 mg. of 7-keto-Δ^8-lithocholenic acid in 20 cc. of *n*-amyl alcohol was heated to boiling under nitrogen, 1.2 g. of sodium was added and the mixture was refluxed gently until all the sodium had reacted. The resulting solution showed no ultraviolet absorption either as such or after neutralization with acetic acid; a strong band at 245 mμ appeared when a test portion was treated with hydrochloric acid. Since attempts to isolate the allylic alcohol were not successful, the reduction mixture was evaporated under reduced pressure and the residue dissolved in water and the solution acidified with hydrochloric acid. The crude acid that precipitated was washed well, dried and crystallized from acetone, which yielded 120 mg. of $\Delta^{7,9(11)}$-lithocholadienic acid, m.p. 192–195° (no depression in mixed m.p.), λ^{EtOH} 244.5 mμ (15,800), α_D +122 ± 1° Di; methyl ester acetate, m.p. and mixed m.p. 147–148°.

Methyl 3α-Acetoxy-7,11-diketocholanate (III).—A mixture of 0.1 g. of zinc dust, 35 mg. methyl 3α-acetoxy-7,11-diketo-Δ^8-cholenate (II), 2.8 cc. of acetic acid, and 0.2 cc. of water was refluxed for 6 hr., diluted with a few drops of water and filtered hot. After dilution to turbidity the product crystallized (m.p. 154–155°); two recrystallizations from methanol gave 15 mg. of colorless product, m.p. 161–162°, α^{19}_D +25 ± 1° Di, λ^{Chf} 5.77, 5.82, 8.0 μ.

Anal. Calcd. for $C_{27}H_{40}O_6$ (460.59): C, 70.40; H, 8.75. Found: C, 70.28; H, 8.94.

3α-Acetoxy-7,11-diketocholanic Acid.—When refluxing of the above zinc–acetic acid reduction mixture was extended for 24 hr. some hydrolysis of the methyl ester group occurred and the crude product was a mixture (m.p. 230–245°) separated by chromatography on acid-washed alumina. Benzene–ether (9:1) eluted some of the above acetate methyl ester, m.p. 160–161°, α^{17}_D +26 ± 1° Di (found: C, 70.43; H, 8.73). Ether–methanol (19:1) eluted crystalline free acid (m.p. 240–250°), which on recrystallization from methanol melted at 250–252°, α^{17}_D +38 ± 1° Di, λ^{Chf} 2.88, 3.0–4.0, 5.78, 5.85, 8.0 μ.

Anal. Calcd. for $C_{26}H_{38}O_6$ (446.56): C, 69.93; H, 8.58. Found: C, 70.31; H, 8.90.

Esterification with diazomethane gave material, m.p. 160–161°, identical with that from the benzene–ether eluate.

7,11-Diketolithocholic acid was obtained by refluxing 40 mg. of the acetate methyl ester with 150 mg. of potassium hydroxide in 3 cc. of methanol for 2 hr., evaporating the solution and acidifying a solution of the residue in water. Crystallization of the precipitate from aqueous acetone gave 30 mg. (86%) of pure acid, m.p. 197–198°, α^{25}_D −5.2 ± 1° Di.

Anal. Calcd. for $C_{24}H_{36}O_5$ (404.53): C, 71.25; H, 8.97. Found: C, 71.41; H, 9.02.

The methyl ester, prepared with diazomethane and crystallized from aqueous methanol, melted at 135–136°, α^{22}_D −4.5 ± 1.5° Di.

Anal. Calcd. for $C_{25}H_{38}O_5$ (418.55): C, 71.74; H, 9.15. Found: C, 71.91; H, 9.23.

Acetylation in pyridine gave the original acetate ester, m.p. 160–161°.

Separation of Methyl 3α-Acetoxy-7,11-diketocholanate (III) from Methyl 3α-Acetoxy-7-keto-Δ^8-cholenate (IX).—Separation of the dichromate oxidation mixture can be conducted advantageously following reduction of the enedione and isomerization of the β,γ-unsaturated ketone, as follows. A 300-mg. portion of oxidation mixture, m.p. 120–150°, $E^{EtOH}_{270} > 4{,}000$, was refluxed for 2 hr. with 1 g. of zinc dust, 10 cc. of acetic acid and 1 cc. of water. The crystalline product (180 mg.), m.p. 148–151°, E^{EtOH}_{254} 1,530 (calcd. as the α,β-unsaturated ketone) was dissolved in 2 cc. of benzene and the solution was diluted with 20 cc. of petroleum ether. On standing at 25° it slowly deposited clusters of prismatic needles. Recrystallization from methanol gave 40 mg. of nearly pure saturated diketo ester acetate, m.p. 158.5–159.5°, E^{EtOH}_{255} 384. Evaporation of the benzene–petroleum ether mother liquor and crystallization from methanol gave 70 mg. of a second crop, m.p. 151–153°, E^{EtOH}_{255} 1,730.

Wolff–Kishner Reduction of Methyl 3α-Acetoxy-7,11-diketocholanate (III).—A mixture of 428 mg. of III, 5 cc. of triethylene glycol and 0.5 cc. of 85% hydrazine hydrate was refluxed for 0.5 hr., cooled slightly, treated with 0.65 g. of potassium hydroxide pellets, added in three portions with vigorous shaking and refluxed for 20 min. more. The solution was evaporated until the temperature of the liquid reached 200° and refluxing was continued at this temperature for 3 hr. The cooled mixture was poured into 50 cc. of water and acidified with hydrochloric acid, which produced a gelatinous precipitate. Supercel was added and the product collected by suction filtration, washed, dried and extracted with acetone in a soxhlet extractor. Concentration of the acetone extract gave light cream-colored crystals, m.p. 198–201°, that could not be purified by crystallization from acetone. Hence the acid was esterified with diazomethane and the ester acetylated in 2 cc. of dioxane with 1.2 cc. of acetic anhydride and 0.8 cc. of pyridine (17 hr. at 22°). On dilution with a few drops of water a crystalline product separated, m.p. 127–128°. This was dissolved in 2 cc. of benzene and adsorbed onto 5 g. of alumina. Petroleum ether–benzene (2:3) eluted material that on crystallization from methanol gave 10 mg. of **methyl 3α-acetoxycholanate** as white needles, m.p. 133–134°, α^{22}_D +44° An, λ^{Chf} 5.80 μ; no depression in m.p. on admixture with authentic sample.

Anal. Calcd. for $C_{27}H_{44}O_4$ (432.62): C, 74.95; H, 10.25. Found: C, 75.33; H, 10.18.

Elution with benzene and crystallization from methanol gave **3α-acetoxy-11-ketocholanate**, m.p. 131°, α^{22}_D +67° An, λ^{Chf} 5.80, 5.87 μ mixed m.p. with authentic sample showed no depression.

Anal. Calcd. for $C_{27}H_{42}O_5$ (446.61): C, 72.61; H, 9.48. Found: C, 72.70; H, 9.69.

Methyl 3α-Acetoxy-7,11-diketocholanate 7-Ethylenethioketal (VII).—A mixture of 178 mg. of methyl 3α-acetoxy-7,11-diketocholanate and 1.5 cc. of ethylene dithiol was saturated with gaseous hydrogen chloride for 35 min. below −15° and then kept at 0° for 3 hr. The mixture was then treated with excess solid sodium bicarbonate and extracted with ether. Evaporation of the washed and dried extract left a crystalline residue that when crystallized from ether gave 92 mg. of thioketal, m.p. 161–163°. A further crystallization from ether raised the m.p. to 162–163.5°, α^{24}_D +27.6 ± 1° Di.

Anal. Calcd. for $C_{29}H_{44}O_5S_2$ (536.76): C, 64.89; H, 8.26; S, 11.96. Found: C, 65.20; H, 8.49; S, 11.86.

Concentration of the mother liquor gave a second crop of 55 mg. of material, m.p. 159–161°, total yield 147 mg. (71%).

Desulfuration was accomplished by refluxing for 9.5 hr. 85 mg. of thioketal in 60 cc. of methanol with nickel freshly prepared from 15 g. of Raney alloy. The solution was filtered and the metal washed with methanol and ether; evaporation under reduced pressure left a solid residue that on crystallization from aqueous methanol gave 46 mg. of **methyl 3α-acetoxy-11-ketocholanate**, m.p. 131–132°, α^{25}_D +70° An; no depression with authentic sample.

Oxidation of Methyl $\Delta^{7,9(11)}$-Lithocholadienate (J. C. B.).—**Methyl 3-Keto-$\Delta^{7,9(11)}$-choladienate** was obtained by refluxing 1.5 g. of methyl $\Delta^{7,9(11)}$-lithocholadienate in 12 cc. of acetone and 22.5 cc. of benzene with 2.2 g. of aluminum *t*-butoxide for 17 hr. The reaction mixture afforded 0.53 g. of crystals from methanol, m.p. 134–136°. Several recrystallizations raised the m.p. to 143.5–144°, λ^{Chf} 5.78, 5.83 μ, λ^{EtOH} 239, 245.5 mμ (13,700, 13,600), α^{21}_D +86 ± 1° Chf.

Anal. Calcd. for $C_{25}H_{36}O_3$ (384.54): C, 78.08; H, 9.44. Found: C, 77.41; H, 9.59.

Methyl 3,7-Diketo-$\Delta^{9(11)}$-cholenate (a) From the Hydroxy Ester.—A solution of 500 mg. of chromic anhydride in

1 cc. of water was added dropwise with cooling to 500 mg. of methyl $\Delta^{7,9(11)}$-lithocholadienate in 5 cc. of acetic acid. After 4 hr. at 5° and then overnight at 25°, dilution afforded 150 mg. of the diketone which after several crystallizations from acetone melted at 169–171°, $\alpha^{21}D$ −16.8 ± 1° Chf, no ultraviolet absorption.

Anal. Calcd. for $C_{25}H_{36}O_4$ (400.54): C, 74.96; H, 9.06. Found: C, 74.75; H, 8.90.

Isolation of the Δ^8-3,7,11-triketone from the mother liquors is described below. A second oxidation, conducted at 34–35° for 22 hr., yielded 155 mg. of twice crystallized diketone, m.p. 164–167°, and 91 mg. of triketone, m.p. 185–186°.

(b) **Comparison Sample.**—Deacetylation of 3α-acetoxy-7-keto-$\Delta^{9(11)}$-cholenate either with methanol and boron fluoride etherate (24 hr. at 26°) or with potassium bicarbonate in aqueous methanol (3 days at 26°, then 8 hr. at 55°) was attended with bond migration, and in each case methyl 3α-hydroxy-7-keto-Δ^8-cholenate, m.p. 131–132°, was formed in quantitative yield. Therefore a solution of 50 mg. of methyl 3α-acetoxy-7-hydroxy-$\Delta^{9(11)}$-cholenate in 1.5 cc. of methanol and 3 drops of boron fluoride etherate was let stand at 27° for 36 hr. and diluted with water, when the 3,7-diol separated in fine needles, m.p. 114–116°. Oxidation of this with excess sodium dichromate in acetic acid and two crystallizations from dilute methanol gave material melting at 165–168°, undepressed on admixture with the above sample (a).

Methyl 3,7,11-Triketo-Δ^8-cholenate.—Chromatography of the mother liquor of the above oxidation (a) afforded 80 mg. more of the diketone followed by 50 mg. of the triketone. After two recrystallizations from methanol the substance was obtained as pale yellow prismatic needles, m.p. 184–185°, $\alpha^{23}D$ +28° Chf, λ^{EtOH} 271 mμ (8,700).

Anal. Calcd. for $C_{25}H_{34}O_5$ (414.52): C, 72.42; H, 8.27. Found: C, 72.16; H, 8.22.

The product did not depress the m.p. of a comparison sample, m.p. 178–180°, prepared by hydrolyzing 70 mg. of methyl 3α-acetoxy-7,11-diketo-Δ^8-cholenate in methanol (5 cc.), water (0.5 cc.) and potassium carbonate (0.5 g., 2 days at 25°), esterifying with diazomethane, and oxidizing with dichromate in acetic acid (15 mg., 159–170°).

Methyl 3,7-diketo-Δ^8-cholenate resulted from isomerization of 25 mg. of the 3,7-diketo-$\Delta^{9(11)}$-ester in 5 cc. of methanol with 0.3 cc. of boron fluoride etherate (18 hr. at 28°). On dilution, 15 mg. of product separated and after recrystallization from methanol it melted at 170–172°. It depressed the m.p. of the starting material but not that of a sample prepared by oxidation of methyl 3α-hydroxy-7-keto-Δ^8-cholenate (102 mg.) with dichromate in acetic acid. After 2 days, addition of water precipitated 80 mg. of diketone, m.p. 163–167°. Two crystallizations raised the m.p. to 170–172°, $\alpha^{20}D$ +30 ± 1° Chf, λ^{EtOH} 253 mμ (9,100).

Anal. Calcd. for $C_{25}H_{36}O_4$ (400.54): C, 74.96; H, 9.06. Found: C, 74.31; H, 9.21.

Action of Other Oxidizing Agents. Performic Acid (J. C. B.).—A suspension of 1.3 g. of methyl $\Delta^{7,9(11)}$-lithocholadienate in 39 cc. of 88% formic acid was warmed to effect solution, cooled rapidly to produce a fine suspension of the 3-formate and treated at 26° with 0.65 cc. of 30% hydrogen peroxide. After 2.5 hr. the resulting yellow-green solution was diluted with water, chilled and the crystalline precipitate collected and washed. The yield of crude **methyl 3α-formoxy-7-keto-Δ^8-cholenate**, m. p. 149–156°, was 0.91 g. (63%). One crystallization from acetone gave 0.63 g. of product of constant m.p. 164–166°, $\alpha^{26}D$ −1.6 ± 1° Di, λ^{EtOH} 255 mμ (8,900).

Anal. Calcd. for $C_{26}H_{38}O_5$ (430.56): C, 72.52; H, 8.90. Found: C, 72.22; H, 9.12.

Reaction with 2,4-dinitrophenylhydrazine in alcohol containing sulfuric acid was attended with deformylation and gave **methyl 3α-hydroxy-7-keto-Δ^8-cholenate 2,4-dinitrophenylhydrazone**, m. p. 203–204°.

Anal. Calcd. for $C_{31}H_{42}O_7N_4$ (582.68): C, 63.89; H, 7.27; N, 9.62. Found: C, 63.84; H, 7.36; N, 9.07.

The formate ester resulting from performic acid oxidation was converted into derivatives that corresponded closely with those described above: hydroxy acid, m.p. 209–210°, $\alpha^{23}D$ −38 ± 1° Di, λ^{EtOH} 254 mμ (8,900); found: C, 74.57; H, 9.33; hydroxy methyl ester, m.p. 135–136°, $\alpha^{23}D$ −32 ± 2° Di; found: C, 74.71; H, 9.66; methyl ester acetate, m.p. 180–181° (no depression with above sample), αD −15 ± 1° Di; found: C, 72.92; H, 9.18.

Wolff–Kishner reduction of methyl 3α-formoxy-7-keto-Δ^8-cholenate gave crude **Δ^8-lithocholenic acid** as flat needles, m.p. 176–180°, $\alpha^{21}D$ +61 ± 2° Di; **the methyl ester acetate** melted at 138–140°, $\alpha^{23}D$ +74 ± 2° Di, no depression of earlier sample.[9]

Anal. Calcd. for $C_{27}H_{42}O_4$ (430.61): C, 75.31; H, 9.83. Found: C, 75.38; H, 9.70.

Potassium Permanganate (J. C. B.).—3α-Acetoxy-$\Delta^{7,9(11)}$-choladienate was recovered unchanged after attempted oxidation with permanganate in acetone. On addition of 0.58 g. of potassium permanganate in 3 cc. of 60% acetic acid to 1 g. of the diene acetate ester in 25 cc. of acetic acid decolorization occurred rapidly. After 0.5 hr. at 25° water and ether were added, together with enough sodium bisulfite to dissolve the manganese dioxide. The washed and dried ether extract was concentrated and the solvent displaced by methanol; 0.32 g. (30%) of **methyl 3α-acetoxy-7-keto-$\Delta^{9(11)}$-cholenate** (V), m.p. 177–180°, separated. Recrystallized from methanol, it melted at 182–183° (undepressed on admixture with authentic material), $\alpha^{22}D$ +20 ± 1° Di. Chromatography of the mother liquor material afforded no other crystalline product.

Perbenzoic Acid (W.-Y. H.). (a) **1 Mole.**—A solution of 1.07 g. of methyl 3α-acetoxy-$\Delta^{7,9(11)}$-choladienate in 1.5 cc. of chloroform was treated with 6.35 cc. of 0.433 *M* perbenzoic acid in chloroform with cooling and the solution was kept in a refrigerator (3°) for 24 hr. The solution, diluted with more chloroform, was washed with aqueous sodium sulfite solution to remove excess peracid, washed thoroughly with water, dried and evaporated at reduced pressure. The yellowish gummy residue was chromatographed and afforded, in fractions eluted by benzene, about 200 mg. of colorless needles. Recrystallization from methanol gave pure **methyl 3α-acetoxy-7-keto-$\Delta^{9(11)}$-cholenate**, m.p. and mixed m.p. 183–184°, $\alpha^{20}D$ +22 ± 1° Di.

(b) **2 Moles.**—A cooled mixture of 6 g. of the diene ester acetate in 20 cc. of chloroform and 70 cc. of 0.91 *M* perbenzoic acid in chloroform was kept at 3° for 12 days and worked up as in (a). The product solidified on removal of the solvent (below 50°) and chromatographed on 150 g. of alumina. Petroleum ether–benzene mixtures (1:1; 1:3) eluted only gums. Elution with 100-cc. portions of benzene and crystallization from methanol then gave the following fractions: 4 (245 mg.), m.p. 140–144°; 5 (215 mg.), m.p. 150–155°; 6 (110 mg.), m.p. 165–170°; 7 (55 mg.), m.p. 165–175°. Benzene–ether mixtures (19:1 to 4:1) eluted small amounts of material melting around 200°; then benzene–ether (1:1) eluted, in fractions 14 and 15, 375 mg. of material m.p. 169–170°.

Fraction 4 showed weak absorption at 228, 235 and 263 mμ, removed by three crystallizations from cold chloroform–methanol. The recrystallized product was nearly colorless, m.p. 152–153.5°, $\alpha^{25}D$ +39.2 ± 0.6° Chf, λ^{Chf} 5.78, 7.9 μ. It is regarded provisionally as **methyl 3α-acetoxy-7-keto-9,-11-oxidocholanate.**

Anal. Calcd. for $C_{27}H_{40}O_6$ (460.59); C, 70.40; H, 8.75. Found: C, 70.81; H, 8.91.

Fractions 5–13 were all yellow and showed strong absorption at 255 mμ. Fractions 6 and 7, combined and crystallized twice from methanol, gave **methyl 3α-acetoxy-7-keto-Δ^8-cholenate**, m.p. and mixed m.p. 180–181°, λ^{EtOH} 254 mμ (8,000), λ^{Chf} 5.78, 5.95, 6.25, 7.9 μ.

Fractions 14 and 15, crystallized from methanol, gave pure **3α-acetoxy-11α-hydroxy-7-keto-Δ^8-cholenate,**[22] m.p. and mixed m.p. 170–171°, λ^{EtOH} 253 mμ (8,400). This same compound was also obtained in the following manner (J. C. B.).[23] By refluxing methyl 3α-acetoxy-7-keto-$\Delta^{9(11)}$-cholenate with acetic anhydride–acetyl chloride under nitrogen for 4–5 hr. and evaporating the solvent in vacuum, an enol acetate was obtained that failed to crystallize but seemed largely homogeneous: λ^{EtOH} 242 mμ (11,450), αD +105 ± 2° Di. The Δ^8-7-ketonic isomer gave similar material, λ^{EtOH} 243 mμ (14,300). Treatment of the oily enol acetate with perphthalic acid in ether (1 week at 25°) and crystallization of the product from methanol afforded

(22) L. F. Fieser, W.-Y. Huang and W. P. Schneider, THIS JOURNAL, **75**, 124 (1953).

(23) *Cf.* C. Djerassi, O. Mancera, M. Velasco, G. Stork and G. Rosenkranz, *ibid.*, **74**, 3321 (1952).

3α-acetoxy-11α-hydroxy-7-keto-Δ⁸-cholenate, m.p. 168–169° (no depression in mixed m.p.), α^{24}_D +3 ± 1° Chf, λ^{EtOH} 252 mμ (8,580).

Hydrogen Peroxide–Ferrous Sulfate (W.-Y. H).—A solution of 1 g. of methyl 3α-acetoxy-Δ$^{7,9(11)}$-choladienate in 200 cc. of acetic acid was stirred mechanically while 25 cc. of 30% hydrogen peroxide and 50 cc. of 5% ferrous sulfate heptahydrate were dropped in simultaneously in the course of 10 min. at 40°. Stirring was continued at 40° for 8 hr. and the brown solution was left overnight at 25°, treated with sodium bisulfite to destroy any oxidizing agent, and evaporated in vacuum to a small volume. This was extracted with ether in a continuous extractor and the residue from evaporation of the ether was treated with excess diazomethane. Chromatography on 25 g. of alumina gave solid material only in the benzene eluate, which afforded about 40 mg. of slightly yellowish material, m.p. 165–170°, which appeared to be a mixture of **methyl 3α-acetoxy-7-keto-Δ$^{9(11)}$- and Δ^{8}-cholenates**. Crystallized from methanol, it had the constants: m.p. 173–174°, λ^{EtOH} 254 mμ (3,450), λ^{Chf} 5.78, 5.83, 5.97, 6.25, 7.94 μ. A 20-mg. portion was refluxed for 2 hr. with potassium hydroxide in aqueous methanol and the material obtained on acidification was crystallized from acetone and gave **7-keto-Δ⁸-lithocholenic acid**, m.p. 210–213° (no depression on admixture), λ^{EtOH} 253.5 mμ (8,600).

Silver Benzoate–Iodine (W.-Y. H.).—In a preliminary experiment 430 mg. of methyl 3α-acetoxy-Δ$^{7,9(11)}$-choladienate treated with excess reagent afforded on chromatography (benzene eluate) 80 mg. of material m.p. 132–137°. Crystallized from methanol, it melted at 142–143°, α_D +31.4 ± 0.5° Chf, λ^{EtOH} 231.5 mμ (44,400), λ^{Chf} 2.75, 2.91, 5.85, 5.87, 6.25, 7.9 μ. The analysis is in fair agreement with that for a product of the addition of two benzoate groups containing a mole of methanol.

Anal. Calcd. for $C_{42}H_{64}O_9$ (702.85): C, 71.77; H, 7.74. Found: C, 72.00, 71.47; H, 7.36, 7.53.

The material was refluxed with methanolic sodium hydroxide for 2 hr. and then treated with dichromate in acetic acid at 25°; the resulting material still showed benzoate absorption at about 230 mμ and no absorption at 270 mμ.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, HARVARD UNIVERSITY]

Synthesis of 11-Ketosteroids. II. 11-Ketocholestanol

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Dichromate oxidation of Δ$^{7,9(11)}$-cholestadienyl benzoate (I) gave, in yields of a few per cent. only, the Δ⁸-7,11-diketone (II) and the Δ$^{9(11)}$-7-ketone III. Reduction of II with zinc and acetic acid followed by Wolff–Kishner reduction afforded 11-ketocholestanol (XI). 7-Keto-Δ⁸-cholestenyl benzoate (VII) was isolated from the mixture resulting from refluxing the total oxidation product with zinc and acetic acid. Oxidation of I with hydrogen peroxide and ferrous sulfate gave the 9α,11α-oxido-7-ketone V, a substance of a type first described by the Syntex group and convertible through IX into X by the methods they have reported.

Schenck, Buchholz and Wiese[2] prepared Δ⁷-cholestenol by reduction of 7-dehydrocholesterol with sodium and ethanol and obtained material, m.p. 122–123°, α_D 0° Chf; acetate, m.p. 118–119°, α_D 0° Chf. By dehydration of 7α-hydroxycholestanyl acetate and purification of the resulting stenyl acetate mixture by chromatography and crystallization, Wintersteiner and Moore[3] obtained stenol of m.p. 122–123°, α_D +6.5° Chf; acetate, m.p. 118–119°, α_D +4.2° Chf.[4] We first tried hydrogenation of 7-dehydrocholesterol, kindly supplied by the du Pont Company, with platinum catalyst in ethyl acetate, but obtained partially isomerized material, possibly due to a trace of acetic acid in the solvent. Following a suggestion of Dr. Max Tishler, we then tried hydrogenation in dioxane in the presence of Raney nickel and regularly obtained very satisfactory material in 80% yield. Our most highly purified sample of Δ⁷-cholestenol[5] had the constants: m.p. 125–126°, α_D +3.9° Chf, +10.0° Di; acetate m.p. 118–119°, α_D +2.4°, Chf, +9.4° Di.

Dehydrogenation of Δ⁷-cholestenol with mercuric acetate[6] in chloroform–acetic acid under nitrogen at 25° and benzoylation gave the starting material, Δ$^{7,9(11)}$-cholestadienyl benzoate (I) in 43.5% overall yield. Oxidation with sodium dichromate in benzene–acetic acid at 25° gave a mixture from which two components were isolated by chromatography. One is characterized as the Δ⁸-7,11-diketone II by its yellow color, low-intensity absorption at 268 mμ and reduction with zinc dust to the saturated 7,11-diketone VI. The other is a monooxygen derivative showing no ultraviolet absorption and isomeric with the conjugated Δ⁸-7-ketone VII, which was isolated along with the saturated 7,11-diketone VI by chromatographing the mixture resulting from zinc–acetic acid reduction of the total oxidation mixture. The conjugated ketone VII could be selectively hydrogenated to a saturated ketone identified, after hydrolysis, as 7-ketocholestanol (VIII), which fixes the position of the carbonyl group. An attempt to prove the position of the double bond in VII by Wolff–Kishner reduction gave a stenyl mixture of α_D +20° Di that was found on selenium dioxide analysis[7] to contain 31.5% Δ⁷-cholestenol. Since the latter substance is almost optically inactive, the main component must be rather strongly dextrorotatory and hence is probably Δ⁸-cholestenol (α_D +50° Chf) rather than Δ$^{8(14)}$-cholestenol (α_D +20° Chf). Our 7-keto-Δ⁸-cholestenyl benzoate differs in M_D from the value + 141° Di calculated[8] for cholestanyl benzoate by the increment − 207 Di; the increment found for the corresponding acetates is −203 Chf.[9]

(1) Abbott Laboratories predoctoral fellow, 1950–1951.

(2) Fr. Schenck, K. Buchholz and O. Wiese, *Ber.*, **69**, 2696 (1936).

(3) O. Wintersteiner and M. Moore, THIS JOURNAL, **65**, 1507 (1943).

(4) W. Buser, *Helv. Chim. Acta*, **30**, 1379 (1947), obtained impure material (α_D −20°) by the method of Schenck, Buchholz and Wiese; by the method of Wintersteiner and Moore he obtained stenyl acetate, m.p. 116–119°, α_D +0.6° chf.

(5) L. F. Fieser, THIS JOURNAL, **73**, 5007 (1951).

(6) A. Windaus and E. Auhagen, *Ann.*, **472**, 185 (1929).

(7) Method of Koji Nakanishi, see ref. 5.

(8) L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero and T. Utne, THIS JOURNAL, **74**, 3309 (1952).

(9) L. F. Fieser, unpublished.