et al.,[10] have shown that the formation of dihydrosapogenin is associated with complete loss of the characteristic sapogenin side chain bands. The dihydrosapogenins produced by $LiAlH_4$ reduction, under acidic conditions, as well as by catalytic reduction using PtO_2, do not give the characteristic side chain peaks at either 10.14, 10.85, 11.1 and 11.75 μ or 10.18, 10.85, 11.1 and 11.55 μ.[8-10]

Experimental[11]

Dihydrodiosgenin (22a,5-Furostene-3β,26-diol) (III). By $LiAlH_4$–HCl Reduction.—Diosgenin (22a,5-spirosten-3β-ol) (1.0 g.), placed in a standard tapered 3-neck flask, equipped with an air-tight stirrer, a condenser with a $CaCl_2$ drying tube and a glass stopper, was dissolved in 500 ml. of anhydrous diethyl ether (over sodium) with stirring. The solution was saturated, at room temperature (25°), with anhydrous hydrogen chloride from a cylinder. Solid $LiAlH_4$, in pea-size amounts, was then added to the reaction mixture, with vigorous stirring, allowing sufficient time for each piece to react before an additional amount was added. After all the $LiAlH_4$ (3.0 g.) had been added, the reaction mixture was refluxed gently for 2 hours. An excess of HCl was maintained throughout the reaction. A few drops of water at a time were added until the excess $LiAlH_4$ was decomposed, then 100 ml. of water was added. A gray suspension appeared in the water layer but dissolved completely on standing overnight. The ether layer was separated from the water layer (acidic) and the water layer washed with additional amounts of ether. The combined ether fraction was washed with water, until neutral, then concentrated to dryness. The yield of product was 0.90 g. (90%). Recrystallized from acetone, the dihydrodiosgenin melted at 158–160°, $[\alpha]^{20}D$ −35° $CHCl_3$. Recrystallization of the dihydrosapogenins did not raise the melting points over 2°, thus indicating a high degree of purity of the crude products.

Acetylation of dihydrodiosgenin with acetic anhydride, with a few drops of pyridine present, at 25° yielded dihydrodiosgenin diacetate (22a,5-furostene-3β,26-diol 3,26-diacetate) (IV), m.p. 115–117° $[\alpha]^{20}D$ −39° $CHCl_3$.

Anal. Calcd. for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found: C, 74.45; H, 9.73.

Dihydrotigogenin (5α,22a-Furostane-3β,26-diol) (V).—Tigogenin (5α,22a-spirostan-3β-ol) (1.0 g.) yielded 0.90 g. (90%) of crude V when reacting with $LiAlH_4$–HCl under the same conditions as in the preparation of III; recrystallized from acetone, m.p. 163–166° (lit. m.p. 167–170°,[7] $[\alpha]^{20}D$ −4° $CHCl_3$.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.41; H, 10.92.

Acetylation of dihydrotigogenin at 25° yielded dihydrotigogenin diacetate (5α,22a-furostane-3β,26-diol 3,26-diacetate) (VI), m.p. 116–117° (lit. m.p. 114–116° (7)), $[\alpha]^{20}D$ −15° $CHCl_3$.

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.03. Found: C, 74.15; H, 10.04.

Dihydrosarsasapogenin (22b-Furostane-3β,26-diol) (VII). (a) **By $LiAlH_4$–HCl Reduction.**—Sarsasapogenin (22b-spirostan-3β-ol) (1.0 g.) yielded 0.88 g. (88%) of crude VII when reacting under the same condition as in the preparation of III; recrystallized from acetone, m.p. 157–160° (lit. m.p. 165° (3)), $[\alpha]^{20}D$ −2° $CHCl_3$.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.45; H, 11.05.

Benzoylation of VII at 95° for one hour yielded a crystalline product, dihydrosarsasapogenin dibenzoate (22b-furostane-3β,26-diol 3,26-dibenzoate) (VIII); recrystallized from acetone, m.p. 95–97°.

Anal. Calcd. for $C_{41}H_{54}O_5$: C, 78.55; H, 8.68. Found: C, 78.37; H, 8.51.

Acetylation of VII with acetic anhydride yielded an oil which could not be crystallized, $[\alpha]^{20}D$ −5° $CHCl_3$.

(b) **By $LiAlH_4$–HBr Reduction.**—Sarsasapogenin (1.0 g.) was treated under the same conditions as in the preparation of III, except that the ether solution was saturated with anhydrous HBr gas, which had been passed through tubes of $CaCl_2$ and copper turnings to remove any trace of moisture and bromine. $LiAlH_4$ (3.0 g.) was added as before but the solution had to be resaturated with the anhydrous HBr before the addition was complete because the acidity decreased greatly as the hydride was added. After refluxing for 3 hours the material was worked up as for III; yield of crude VII 0.75 g. (75%); recrystallized from acetone, m.p. 158-161°; Br, absent.

PHILADELPHIA, PA.

(10) R. N. Jones, E. Katzenellenbogen and K. Dobriner, THIS JOURNAL, **75**, 158 (1953); "Collected Infrared Absorption Spectra of Steroid Sapogenins," National Research Council of Canada and Sloan-Kettering Institute for Cancer Research, N.R.C. No. 2929 (1953).

(11) We are indebted to M. E. Wall, of this Laboratory, for supplying the spirostanols and spirostenol used in this work.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, HARVARD UNIVERSITY]

Synthesis of $\Delta^{9(11)}$- and $\Delta^{20(22)}$-Cholestenol

BY LOUIS F. FIESER AND WEI-YUAN HUANG[1]

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The $\Delta^{9(11)}$-isomer of cholesterol was prepared by a synthesis starting with Δ^7-cholestenol and proceeding through the enol acetate of Δ^8-cholestene-3β-ol-7-one 3-acetate, Δ^8-cholestene-3β,11α-diol-7-one 3-acetate and 11-ketocholestanyl acetate. The $\Delta^{20(22)}$-isomer resulted from dehydration of cholestane-3β,22ξ-diol 3-acetate; the structure was established by ozonization to allopregnane-3β-ol-20-one.

Identification of one of the companions of cholesterol as Δ^7-cholestenol[2,3] prompted the present extension of the list of known double-bond isomers. The starting material for the synthesis of $\Delta^{9(11)}$-cholestenol was 3β-acetoxy-8α,9α-oxidocholestane-7-one, obtained by chromic acid oxidation[3] of Δ^7-cholestenyl acetate in 10.3% yield. Reduction of the oxidoketone with zinc and acetic acid[3,4] gave Δ^8-cholestene-3β-ol-7-one 3-acetate, which on reaction with isopropenyl acetate gave an enol acetate I. Although non-crystalline, this derivative had the expected D-diene type of ultraviolet absorption spectrum. As in analogous cases[5,6] the enol acetate reacted with monoperphthalic acid to give a Δ^8-ene-11-ol-7-one (II) reducible by hydrogenation to a saturated 11-ol-7-one (III); the enol ace-

(1) National Institutes of Health predoctoral fellow at the time this work was done (1951–1952).

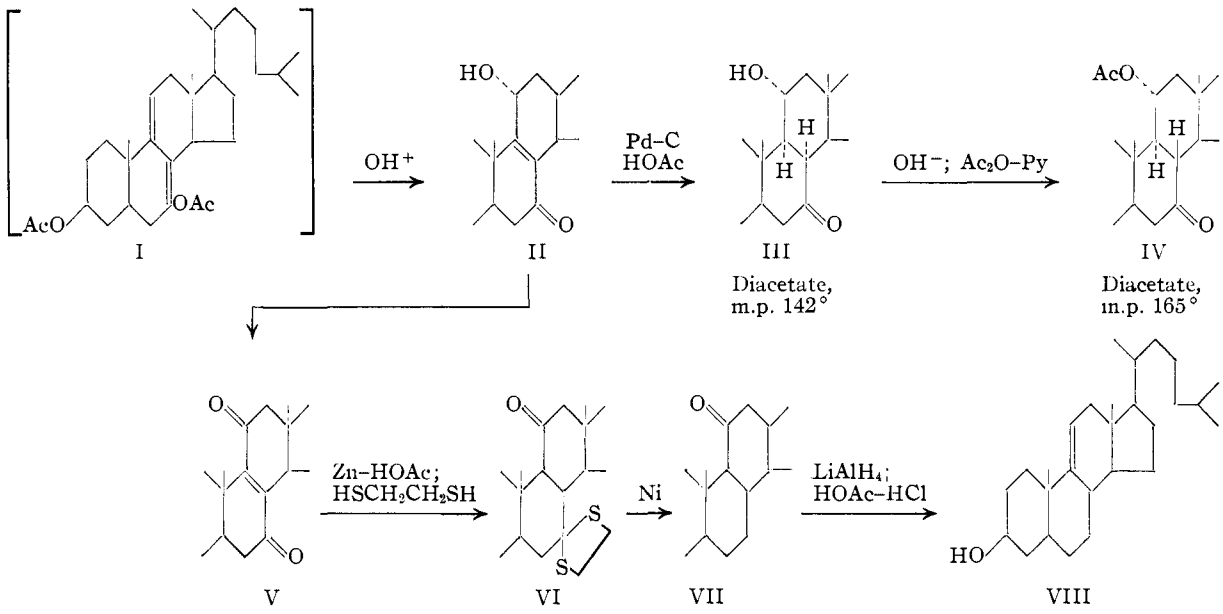
(2) L. F. Fieser, THIS JOURNAL, **73**, 5007 (1951).

(3) L. F. Fieser, *ibid.*, **75**, 4395 (1953).

(4) H. Heusser, G. Saucy, R. Anliker and O. Jeger, *Helv. Chim. Acta*, **35**, 2090 (1952).

(5) G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 3546 (1951); C. Djerassi, O. Mancera, G. Stork and G. Rosenkranz, *ibid.*, **73**, 4496 (1951); C. Djerassi, O. Mancera, M. Velasco, G. Stork and G. Rosenkranz, *ibid.*, **74**, 3321 (1952).

(6) L. F. Fieser, W.-Y. Huang and J. C. Babcock, *ibid.*, **75**, 116 (1953).



tate from $\Delta^{8(14)}$-cholestene-3β-ol-7-one 3-acetate gave a product that appears to be $\Delta^{8(14)}$-cholestene-3β,6ξ-diol-7-one 3-acetate. The free hydroxyl group of the cholestane-3β,11-diol-7-one 3-acetate is acylable, hence the 11-hydroxyl group is α-oriented. Saponification of the saturated derivative III and reacetylation give a diacetate isomeric with the original III-diacetate. The more stable isomer must have the B/C *trans*-ring junction, as in IV, and hence the product of hydrogenation has the unnatural α-orientation at C_8 III and is the product of *cis* addition of hydrogen.

The Δ^8-ene-11α-ol-7-one II was oxidized to 7,11-diketo-Δ^8-cholestene-3β-ol-3-acetate (V), analogous to the known benzoate,[7] and this was converted through the saturated diketone[8] and the monoethylenethioketal VI to cholestane-3β-ol-11-one 3-acetate (VII). Wolff–Kishner reduction of the saturated diketone proved less satisfactory since, as in an analogous case[9] a mixture of the 11-ketone and cholestanol resulted. The synthesis was completed by lithium aluminum hydride reduction of the 11-ketone and dehydration.

22-Ketocholestanyl acetate was prepared from 3β-hydroxy-Δ^5-bisnorcholenic acid, kindly supplied by Dr. Arnold C. Ott of The Upjohn Company, both by conversion to 22-ketocholesteryl acetate according to Cole and Julian[10] and hydrogenation, and by hydrogenation and ketone synthesis. Reduction of the ketone with lithium or sodium borohydride or with lithium aluminum hydride proceeded in a single steric sense, and the cholestane-3β,22ξ-diol 3-acetate resulting from lithium borohydride reduction in tetrahydrofuran at 0° on dehydration with phosphorus oxychloride in pyridine afforded a stenyl acetate identified as the $\Delta^{20(22)}$-isomer by ozonization to allopregnane-3β-ol-20-one 3-acetate.

(7) L. F. Fieser and J. E. Herz, *ibid.*, **75**, 121 (1953).

(8) *Cf.*, J. Heusser, K. Heusler, K. Eichenberger, C. G. Honegger and O. Jeger, *Helv. Chim. Acta*, **35**, 295 (1952).

(9) L. F. Fieser, J. E. Herz and W.-Y. Huang, THIS JOURNAL, **73**, 2397 (1951).

(10) W. Cole and P. L. Julian, *ibid.*, **67**, 1369 (1945).

Table I summarizes the physical constants of the nine cholestenols now known and the *MD* increments for acetylation. The shift in *MD* found for introduction of the 9(11)-double bond is +15 for cholestanol and +36 for the acetate. We have not

TABLE I

PROPERTIES OF THE CHOLESTENOLS

Δ	Stenol M.p., °C.	*MD*, Chf	Acetate M.p., °C.	*MD*, Chf	ΔAc
4[11]	132	(+170[a])	85		
5[12]	150	−154	116	−188	−34
6[13]	115	−359	105	−381	−22
7[14]	126	+6	119	+10	+4
8[15]	129	+193	126	+150	−43
8(14)[16,17]	120	+81	78	+43	−38
9(11)	123	+104	105	+96	−8
14[18]	131	+124	92	+94	−30
20(22)	117	+25	96.5	+6	−19
Cholestanol[12]	141	+89	110	+60	−29

[a] In benzene.

found any strictly comparable cases for comparison.[19] That the value $\Delta^{C=C}$ +95° reported for the case of $\Delta^{9(11)}$-22-isospirostene-3β-ol 3-acetate[20] is notably higher is probably attributable to a vicinal effect of the oxide-bridged side chain. A definite vicinal effect of a 17-keto group is evident from

(11) R. Schoenheimer and E. A. Evans, *J. Biol. Chem.*, **114**, 567 (1936).

(12) *MD* values of D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 783 (1948).

(13) D. H. R. Barton and W. J. Rosenfelder, *ibid.*, 2459 (1949); O. Wintersteiner and M. Moore, THIS JOURNAL, **72**, 1923 (1950).

(14) *MD* values: Fieser.[3]

(15) D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 214 (1949).

(16) A. Windaus, O. Linsert and H. J. Eckhardt, *Ann.*, **534**, 22 (1938).

(17) D. H. R. Barton, *J. Chem. Soc.*, 813 (1945).

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

(19) The $\Delta^{C=C}$ value of +109 cited by D. H. R. Barton and W. Klyne, *Chemistry and Industry*, 755 (1948); see also D. H. R. Barton, *J. Chem. Soc.*, 512 (1946), was based on data for zymosterol, at the time thought to have a 9(11)-double bond.

(20) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951); W. A. Jacobs and E. E. Fleck, *J. Biol. Chem.*, **88**, 545 (1930); R. Tschesche and A. Hagedorn, *Ber.*, **68**, 1412 (1935).

the following Δ-values: $\Delta^{9(11)}$-androstene-3,17-dione,[21,22] +157 (EtOH); $\Delta^{9(11)}$-androstene-3α-ol-17-one,[23] +125 (EtOH); acetate,[23] +160 (EtOH); $\Delta^{9(11)}$-androstene-3β-ol-17-one,[21,22,24] +108 (EtOH).

Experimental

Δ^8-Cholesten-3β,11α-diol-7-one 3-Acetate (II).—For preparation of the starting material, Δ^8-cholestene-3β-ol-7-one acetate, 20 g. of Δ^7-cholestenol was oxidized with chromic acid,[3] 3β-acetoxy-8α,9α-oxidocholestane-7-one was separated by crystallization (yield pure 2.205 g., 10.3%) and 3β-acetoxy-8α,14α-oxidocholestane-7-one was isolated by chromatography of the mother liquor material (yield pure 2.364 g., 11.1%). Reduction of the former isomer with zinc and acetic acid afforded the pure Δ^8-ene-7-one in 71.5% yield.

A mixture of 758 mg. of Δ^8-cholestene-3β-ol-7-one 3-acetate, 77 mg. of *p*-toluenesulfonic acid and 3 cc. of isopropenyl acetate was distilled very slowly in the course of 6 hr., with addition of 0.5 cc. of isopropenyl acetate at 1-hr. intervals. The excess reagent was then removed under reduced pressure and the slightly brownish residue taken up in ether. The ethereal solution was washed with bicarbonate solution, water and saturated sodium chloride solution, dried and evaporated. The residual crude enol acetate I, which could not be induced to crystallize, had an ultraviolet absorption maximum at 241 mμ (EtOH); it was oxidized directly with 8.5 cc. of 0.31 *M* monoperphthalic acid in ether. After 48 hr. at 25° enolone II was isolated by extraction with ether; after concentration of the washed and dried solution, fine needles separated, m.p. 157–159°. Alternately, the ether was removed completely and the residue was crystallized from methanol to give 534 mg. (68%) of prismatic plates, m.p. 157–158°, α_D −2.0° Di (*c* 2.45), λ^{EtOH} 253 mμ (8300), λ^{Chf} 2.75, 2.88, 5.80, 5.98, 6.27, 8.0 μ.

Anal. Calcd. for $C_{29}H_{46}O_4$ (458.66): C, 75.94; H, 10.11. Found: C, 75.79; H, 10.04.

On chromatography of the mother liquor material from a total of 2.5 g. of Δ^8-cholestene-3β-ol-7-one 3-acetate an additional 5% of II was obtained in late fractions eluted by 4:1 benzene–ether. Earlier fractions, eluted by benzene, afforded, after crystallization from methanol, 55 mg. of a product that appears to be an **8,9-oxido derivative** of II, m.p. 174–175°, α_D −32.6° Chf (*c* 2.39), no ultraviolet absorption in the range 220–290 mμ, λ^{Chf} 2.76, 2.9, 5.83, 5.85, 8.0 μ.

Anal. Calcd. for $C_{29}H_{46}O_5$ (474.66): C, 73.38; H, 9.77. Found: C, 73.48; H, 9.89.

Peracid Oxidation of the Enol Acetate of $\Delta^{8(14)}$-Cholestene-3β-ol-7-one 3-Acetate.—The enol acetate, prepared as described above for the isomer from 928 mg. of the $\Delta^{8(14)}$-ene-7-one acetate, showed absorption in ethanol at 246 mμ. Oxidation with 15 cc. of 0.3 *M* perphthalic acid gave a crude product of λ^{EtOH} 255 mμ that was chromatographed on 29 g. of acid-washed alumina. The 1:3 petroleum ether–benzene eluates on recrystallization from methanol gave 85 mg. of pale cream colored stout needles, m.p. 160–162°, α_D −30° Chf (*c* 1.56), λ^{EtOH} 258 mμ (8,400), λ^{Chf} 2.95, 5.83, 6.02, 6.25, 8.0 μ; this is tentatively regarded as **$\Delta^{8(14)}$-cholestene-3β,6ξ-diol-7-one 3-acetate.**

Anal. Calcd. for $C_{29}H_{46}O_4$ (458.66): C, 75.94; H, 10.11. Found: C, 75.73; H, 10.10.

Later eluates afforded after crystallization from methanol 95 mg. of white plates, m.p. 172–173°, α_D −69° Chf (*c* 1.30), λ^{EtOH} 265 mμ, λ^{Chf} 2.9, 5.82, 5.95, 6.23, 8.0 μ; the analysis indicated an oxygen content higher than that of the first product.

8α-Cholestane-3β,11α-diol-7-one 3-Acetate (III).—A mixture of 703 mg. of Δ^8-cholestene-3β,11α-diol-7-one 3-acetate, 249 mg. of 10% palladium–charcoal, and 28 cc. of acetic acid was shaken with hydrogen for 2 hr. and the solution filtered (no absorption at 220–270 mμ). On chromatography of the crude reaction product, 1:3 petroleum ether–benzene and benzene eluted 278 mg. of crystalline material, which after two crystallizations from methanol gave pure saturated diolone acetate, m.p. 177–179°, α_D −86.5° Di (*c* 0.62), λ^{Chf} 2.8–2.9, 5.83–5.85, 8.0 μ.

Anal. Calcd. for $C_{29}H_{48}O_4$ (460.67): C, 75.61; H, 10.50. Found: C, 75.57; H, 10.58.

Late benzene–ether eluates afforded 141 mg. of unidentified crystalline material, m.p. 150–160°; recrystallized from methanol, m.p. 167–169° (depressed by III), saturated to tetranitromethane (found: C, 74.01; H, 9.93).

8α-Cholestane-3β,11α-diol-7-one 3,11-diacetate crystallized from methanol–water, melted at 142–143°, α_D −97.5° Di (*c* 0.82), λ^{Chf} 5.79, 7.95 μ.

Anal. Calcd. for $C_{31}H_{50}O_5$ (502.71): C, 74.06; H, 10.03. Found: C, 74.27; H, 10.09.

Cholestane-3β,11α-diol-7-one 3,11-Diacetate (IV).—The above diacetate (m.p. 142–143°) was saponified and the product reacetylated (in pyridine at 25°). The resulting diacetate had the constants: m.p. 163–165°, α_D −46° Chf (*c* 1.00), λ^{Chf} 5.82, 8.0 μ.

Anal. Calcd. for $C_{31}H_{50}O_5$ (502.71): C, 74.06; H, 10.03. Found: C, 73.71; H, 10.11.

Δ^8-Cholestene-3β-ol-7,11-dione 3-Acetate (V).—Solutions of 534 mg. of Δ^8-cholestene-3β,11α-diol-7-one 3-acetate and 0.3 g. of sodium dichromate dihydrate in 3–5 cc. of acetic acid were mixed at 25°. After 2 hr. the mixture was diluted with water, when 529 mg. of crude crystalline product separated, m.p. 100–105°. One recrystallization from methanol–water yielded 403 mg. (76%) of pure dione as light yellow crystals, m.p. 135–137°, α_D +39° Di (*c* 1.03), λ^{EtOH} 269 mμ (8,500), λ^{Chf} 5.81, 5.94, 8.0 μ.

Anal. Calcd. for $C_{29}H_{44}O_4$ (456.64): C, 76.27; H, 9.71. Found: 76.44; H, 9.78.

Cholestene-3β-ol-7,11-dione 3-Acetate 7-Monoethylenethioketal (VI).—The crude cholestane-3β-ol-7,11-dione 3-acetate (soft needles, m.p. 169–170°[8]) obtained by heating 286 mg. of the Δ^8-derivative with 0.4 g. of zinc dust, 10 cc. of acetic acid and 1 cc. of water for 15 min. on the steam-bath (fine soft needles from aqueous methanol, m.p. 169–170°[8]) was dissolved in 3 cc. of ethanedithiol and the solution saturated with dry hydrogen chloride at −15° for 35 min. After the red mixture had stood at 0° for 3 hr., excess solid sodium bicarbonate was added, excess mercaptan was removed by evaporation in vacuum (25°), and the residue extracted with ether. Evaporation of the washed and dried extract left a solid residue that was purified by crystallization from ether: 182 mg., m.p. 196–197°; recrystallized, m.p. 198–199°, α_D +1.4° Chf (*c* 2.23).

Anal. Calcd. for $C_{31}H_{50}O_3S_2$ (534.83): C, 69.61; H, 9.42; S, 11.99. Found: C, 69.86; H, 9.51; S, 11.84.

The mother liquor on chromatography afforded 51 mg. more product, m.p. 194–195°; total yield from the unsaturated diketone 70%.

Wolff–Kishner reduction of cholestane-3β-ol-7,11-dione 3-acetate (123 mg.) at 200° gave 88 mg. of crude product that on recrystallization from methanol–water gave 60 mg. of a mixture (m.p. 142–144°) that on fractional crystallization gave 15 mg. of a first crop (m.p. 137–139°) showing no carbonyl infrared absorption; recrystallized, this melted at 141–142°, α_D +24° Chf, and was identified as **cholestanol** by mixed m.p. determination. The more soluble portion afforded 20 mg. of **cholestane-3β-ol-11-one**, m.p. 148–151°, λ^{Chf} 2.79–2.92, 5.90 μ, undepressed on admixture with an authentic sample[7] (m.p. 149–151°).

Cholestane-3β-ol-11-one Acetate (VII).—A solution of 147 mg. of the above 7-monoethylenethioketal in 60 cc. of methanol was refluxed for 22 hr. with Raney nickel (3 g.) freshly prepared from alloy (6 g.). The solution was filtered, the metal washed thoroughly with chloroform and the filtrate and washings evaporated to dryness at reduced pressure. Crystallizations from methanol gave 44 mg. of soft, fine needles, m.p. 115–116°, recrystallized, m.p. 118–119°, α_D +41.5° Chf (*c* 1.06), λ^{Chf} 5.85–5.89, 7.95 μ.

Anal. Calcd. for $C_{29}H_{48}O_3$ (444.67): C, 78.33; H, 10.88. Found: C, 79.65; H, 10.30.

The analysis suggests that the sample of acetate was contaminated with a little free 3-ol resulting from saponification by a trace of alkali adsorbed on the nickel.

$\Delta^{9(11)}$-Cholestenyl Acetate.—Crude cholestane-3β-ol-11-one acetate (44 mg., m.p. 115–116°) resulting from the de-

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(22) C. W. Shoppee, *Helv. Chim. Acta*, **23**, 740 (1940).

(23) H. L. Mason and E. J. Kepler, *J. Biol. Chem.*, **161**, 235 (1945); L. Ruzicka, M. W. Goldberg, J. Meyer, H. Brüngger and E. Eichenberger, *Helv. Chim. Acta*, **17**, 1395 (1934).

(24) L. Ruzicka, M. W. Goldberg and H. Brüngger, *ibid.*, **17**, 1389 (1934).

sulfurization reaction was refluxed with 0.1 g. of lithium aluminum hydride in 5 cc. of dry tetrahydrofuran for 6 hr. and the mixture decomposed with dilute acid and extracted with ether. The crude product, which in the infrared showed a very strong hydroxyl band and no carbonyl absorption, was refluxed for 30 min. with 15 cc. of 4:1 acetic acid–36% hydrochloric acid. The solution was then evaporated in vacuum nearly to dryness and a solution of the residue in ether was washed free of acid, dried and evaporated. The residual material was dissolved in 2 cc. of petroleum ether and chromatographed on 5 g. of alumina. The crystalline material from petroleum ether and 1:1 petroleum ether–benzene eluates on recrystallization from methanol gave 18 mg. of soft fine needles, m.p. 105°, α_D +22.5° Chf (*c* 1.20); unsaturated to tetranitromethane.

Anal. Calcd. for $C_{29}H_{48}O_2$ (428.67): C, 81.25; H, 11.29. Found: C, 81.19; H, 11.40.

Terminal elution of the column with ether gave a small amount of $\Delta^{9(11)}$-cholestenol that had escaped acetylation in the course of the dehydration.

$\Delta^{9(11)}$-Cholestenol (VIII).—Saponification of the acetate by refluxing it with aqueous methanolic potassium hydroxide for 2 hr. gave the free alcohol, which when crystallized from methanol–water melted at 117–118° and on recrystallization at 122–123°, α_D +27° Chf (*c* 0.30); unsaturated to tetranitromethane.

Anal. Calcd. for $C_{27}H_{46}O$ (386.64): C, 83.87; H, 11.99. Found: C, 83.48; H, 12.26.

22-Ketocholesteryl Acetate.—This ketone was prepared according to Cole and Julian[10] starting with 3β-hydroxy-Δ^5-bisnorcholenic acid. Acetylation of 10 g. of crude hydroxy acid, m.p. 285° (pyridine and acetic anhydride, 30 hr. at room temperature), and crystallization from aqueous acetic acid gave a first crop of 7.9 g. of acetate, m.p. 234–235° dec., α_D −74.5° Chf (*c* 2.50), λ^{Chf} 2.8–3.2, 5.75–5.78, 7.9 μ; a second crop (1.8 g.), m.p. 224–228°, on recrystallization gave 0.85 g. of acetate, m.p. 230–233° dec. Physical constants reported are: m.p. 235° dec. (stable form), 224–226° dec. (metastable form),[25] α_D −73.5° Chf.[26] Condensation of the acid chloride from 7.8 g. of acetoxy acid with isoamylcadmium chloride and crystallization of the reaction product from ether–methanol gave a first crop (3.0 g.) of 22-ketone, m.p. 154–155.5°, α_D −63.7° Chf (*c* 2.26), λ^{Chf} 5.76–5.80, 7.9 μ, and a second crop (4.0 g., m.p. 145–149°), which when recrystallized gave 1.45 g. of pure ketone, m.p. 152–153°. Cole and Julian report: m.p. 152°, α_D −63° Chf. Chromatography of the material recovered from the mother liquors afforded 3.49 g. of pure product (m.p. 150–152°; eluted by petroleum ether–benzene and crystallized from ether–methanol); total yield 7.94 g. (88%).

22-Ketocholestanyl Acetate. (a) **From 3β-Hydroxy-Δ^5-bisnorcholenic Acid.**—Hydrogenation of 488 mg. of the unsaturated acid suspended in acetic acid (Adams catalyst) was complete in 2.5 hr. (clear solution) and afforded 401 g. of 3β-hydroxybisnorallocholanic acid, m.p. 267–269° (recrystallized from acetic acid, m.p. 269–270°; Fernholz[25] reports m.p. 270°). Acetylation of 624 mg. in pyridine at room temperature for 24 hr. and crystallization from aqueous acetic acid gave 565 mg. of 3β-acetoxy-bisnorallocholanic acid, m.p. 194–195°, α_D −15° Chf (*c* 2.72), λ^{Chf} 2.8–3.25, 5.76–5.81, 7.9 μ (Fernholz,[25] m.p. 194°), and a second crop (82 mg.), m.p. 190–192°. The acid chloride from 3.05 g. of acetoxy acid was condensed with isoamylcadmium chloride and the crude reaction product adsorbed onto 80 g. of alumina from a solution in 1:1 petroleum ether–benzene. Fractions eluted by petroleum ether–benzene (1:1, 1:3) melting in the range 100–110° when combined and crystallized from acetone–water yielded 1.33 g. of material, m.p. 110–112°, 0.94 g., m.p. 108–110°, and 0.34 g., m.p. 106–108°. Two recrystallizations from aqueous acetone gave material of constant m.p. 114–115°, α_D −9.6° Chf (*c* 2.81), λ^{Chf} 5.80, 5.83, 7.95 μ.

Anal. Calcd. for $C_{29}H_{48}O_3$ (444.67): C, 78.33; H, 10.88. Found: C, 78.50; H, 10.63.

(b) **From 22-Ketocholesteryl Acetate.**—A solution of 644 mg. of 22-ketocholesteryl acetate in 25 cc. of acetic acid absorbed 1 equivalent of hydrogen in about one-half hour in the presence of 72 mg. of platinum oxide; in 15 hr. more only one-quarter equivalent more gas was consumed. On chromatography of the crude product (m.p. 130–150°) petroleum ether–benzene mixture eluted 250 mg. of 22-ketocholestanyl acetate, m.p. 110–112°, identical with that of (a), and 9:1 benzene–ether eluates afforded 27 mg. of cholestane-3β,22ξ-diol 3-acetate, m.p. 190–191°, identical with the material described below.

In a larger run (4.9 g.) additional quantities of catalyst were added in an attempt to effect better conversion to the saturated diol, but the yield of diol obtainable by crystallization was low (0.68 g.) and chromatography afforded 0.8 g. more diol along with starting material (1 g.).

22-Ketocholestanol, obtained by refluxing the acetate with aqueous methanolic potassium bicarbonate for 8 hr. and crystallized from aqueous methanol, melted at 125–127°, α_D −1.6° Chf (*c* 3.07), λ^{Chf} 2.9, 5.84 μ.

Anal. Calcd. for $C_{27}H_{46}O_2$ (402.64): C, 80.54; H, 11.52. Found: C, 80.64; H, 11.70.

Cholestane-3β,22ξ-diol 3-Acetate.—A solution of 1.05 g. of 22-ketocholestanyl acetate in 20 cc. of dry tetrahydrofuran was let stand with 130 mg. of lithium borohydride at 0° for 24 hr. and decomposed with ice-cold dilute acetic acid. The reaction product (m.p. 120–135°) when chromatographed gave 111 mg. of crude diol 3-acetate, m.p. 185° (9:1 benzene–ether), which on two crystallizations from methanol afforded pure material, m.p. 192–192.5°, α_D −1.8° Chf (*c* 2.82), λ^{Chf} 2.9, 5.80, 7.95 μ.

Anal. Calcd. for $C_{29}H_{50}O_3$ (446.69): C, 77.97; H, 11.28. Found: C, 77.95; H, 11.36.

Earlier chromatogram fractions (m.p. about 100°) seemed to contain starting ketone and afforded, on further reduction and chromatography, 333 mg. more of pure diol 3-acetate, m.p. 190–191°. Late fractions (1:1 benzene–ether) afforded material, m.p. 175–180°, that appeared to be free 3β,22ξ-diol.

Cholestane-3β,22ξ-diol.—Hydrolysis of the 3-acetate (31 mg.) with sodium carbonate (10 mg.) in 9:1 methanol–water (10 cc., refluxed 16 hr.) and crystallization from acetone gave the free diol, m.p. 180–182°, α_D +8.0° Chf (*c* 0.75), λ^{Chf} 2.75, 2.9μ.

Anal. Calcd. for $C_{27}H_{48}O_2$ (404.65): C, 80.14; H, 11.96. Found: C, 79.95; H, 12.04.

The free diol also resulted on reduction of 22-ketocholestanyl acetate with sodium borohydride in methanol at room temperature or with lithium aluminum hydride.

The diacetate, crystallized from aqueous methanol, melted at 125–127°, α_D −9.5° Chf (*c* 1.59).

Anal. Calcd. for $C_{31}H_{52}O_4$ (488.73): C, 76.18; H, 10.73. Found: C, 75.92; H, 10.65.

The same diacetate resulted from refluxing cholestane-3β,22ξ-diol 3-acetate with 4:1 acetic acid–hydrochloric acid for one-half hour.

$\Delta^{20(22)}$-Cholestenyl Acetate.—Phosphorus oxychloride (3 cc.) was added dropwise to an ice-cold solution of 680 mg. of cholestane-3β,22ξ-diol 3-acetate in 10 cc. of pyridine, and the mixture was let stand at 25° for 48 hr. and then poured dropwise onto crushed ice. Extraction with ether and crystallization from acetone–methanol afforded a first crop of 194 mg. of product, m.p. 95–96.5°, α_D +1.3° Chf (3.08), λ^{Chf} 5.80, 6.2, 7.95 μ, positive tetranitromethane test; second crop, 88 mg., m.p. 72–77°, recrystallized, m.p. 78–82°.

Anal. Calcd. for $C_{29}H_{48}O_2$ (428.67): C, 81.25; H, 11.29. Found: C, 80.98; H, 11.21.

A fine stream of 5% ozone was bubbled through a solution of 115 mg. of the acetate in 15 cc. of chloroform for 1 hr., a little water was added and the mixture heated on the steam-bath for 0.5 hr. The cooled mixture was then extracted with ether and the ethereal solution washed with bicarbonate solution; no insoluble sodium salt or water-insoluble acid was observed. The dried solution on evaporation left a residue having an infrared spectrum similar to that of **allopregnane-3β-ol-20-one 3-acetate**, and on chromatography on 2 g. of alumina 1:1 petroleum ether–benzene and benzene eluted the pure ketone m.p. 142–144°; semicarbazone m.p. 265° dec., λ^{Chf} 2.82, 2.92, 5.79, 5.89, 6.34, 7.95 μ; the ketone and its derivative did not depress the m.p. of authentic samples.

$\Delta^{20(22)}$-Cholestenol.—The acetate (60 mg.) was refluxed with 150 mg. of potassium hydroxide in 5 cc. of aqueous methanol for 2 hr. and the product crystallized from ace-

(25) E. Fernholz, *Ann.*, **507**, 128 (1933).

(26) A. Butenandt and G. Fleischer, *Ber.*, **70**, 96 (1937).

tone–methanol: m.p. 115–117°, α_D +6.5° Chf (*c* 1.07), λ^{Chf} 2.9 μ. A solution of the stenol in chloroform gives a bright yellow color with tetranitromethane; the Liebermann–Burchard test is deep brown.

Anal. Calcd. for $C_{27}H_{46}O$ (386.64): C, 83.87; H, 11.99. Found: C, 83.90; H, 11.81.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

A Superior Method for Reducing Phenol Ethers to Dihydro Derivatives and Unsaturated Ketones

BY A. L. WILDS AND NORMAN A. NELSON[1]

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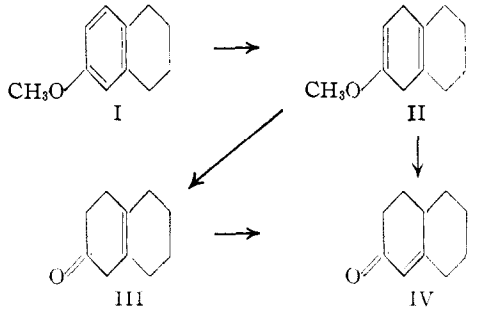
A new procedure has been developed for reduction of phenolic ethers to dihydro enol ethers, suitable for cleavage to β,γ- or α,β-unsaturated ketones. This method, using lithium in liquid ammonia and a cosolvent (ether or 1,2-dimethoxyethane) and adding alcohol last, is a more powerful reduction method than that of Birch; it has given markedly superior yields with 4-cyclohexylanisole, 4-cyclohexylphenoxyethanol, 1-methoxy-5,6,7,8-tetrahydronaphthalene, estradiol-3-methyl ether and hexahydrohexestrol monomethyl ether. It is at least as good as the Birch sodium procedure with the easily reducible compounds anisole and 2-methoxy-5,6,7,8-tetrahydronaphthalene. With the difficultly reducible 1-methoxytetrahydronaphthalene it is shown that the concentration of lithium metal and rate of addition of alcohol are critical factors. These and other observations are discussed in relation to the possible mechanism for the reduction.

The reduction of a phenolic ether to its dihydro derivative, by the action of sodium and alcohol in liquid ammonia, was first described by Wooster for anisole.[2] During the past nine years this reaction has been clarified, improved and utilized extensively by Birch and his associates.[3] In most favorable examples Birch's procedure gives excellent yields of the dihydro compound which, being an enol ether, can be hydrolyzed easily to a β,γ-unsaturated ketone. The latter frequently can be isomerized to the corresponding α,β-unsaturated ketone. Thus, 2-methoxytetrahydronaphthalene (I) was reduced to the enol ether II which was hydrolyzed to $\Delta^{9\text{-}10}$-2-octalone (III) or $\Delta^{1\text{-}9}$-2-octalone (IV), isolated as the 2,4-dinitrophenylhydrazones in yields as high as 82% based on I.[4] In certain other examples, however, the method has failed or given low yields.



We became interested in further perfecting and applying the method to certain rather insoluble and unreactive phenolic ethers, in order to convert them to unsaturated ketones, as intermediates for synthesis and as part of a program of preparing analogs of the non-aromatic steroidal hormones, under investigation in this Laboratory over the past twelve years.[5] 4-Cyclohexylanisole (V) has served as a useful example of a moderately difficult type suitable for studying this reduction, and its use has led to a simple but much more potent method than that of Birch.

The application of Birch's conditions to 4-cyclohexylanisole (V), *viz.*, addition of sodium metal to a mixture of liquid ammonia, alcohol and phenolic ether, gave little or no reduction, 95% of the starting ether being recovered. Moreover, the use of ether as a cosolvent, beneficial in other cases of compounds insoluble in ammonia at −33°,[6] and replacement of ethanol by methanol or the slower reacting isopropyl alcohol failed to give reduction. Indeed the latter modification applied to 4-methoxybiphenyl gave some reduction of the *non-oxygenated* ring affording 4-cyclohexylanisole in small yield.

Birch has found it necessary with hexestrol and estradiol to prepare derivatives more soluble in ammonia than the methyl ethers, such as the monoethers of ethylene glycol or glycerol, in order to obtain reduction in moderate yields.[7] In the present work the use of the β-hydroxyethyl ether of 4-hydroxybiphenyl resulted in a mixture which contained cyclohexylbenzene, the hydroxyethoxy group having been eliminated during reduction.[8] Evidently the remainder of the product did not contain the desired enol ether since no dinitrophenylhydrazone could be prepared from it. On the other hand, the hydroxyethyl ether of 4-cyclohexylphenol did give some reduction to the enol ether since a crude dinitrophenylhydrazone could be isolated in 19% yield. The limited extent of reduction, however, served to underline the inadequacy of the Birch method in this case.

(1) Wisconsin Alumni Research Foundation Research Assistant, 1949–1950; Syntex Fellow, 1950–1951; Homer Adkins Fellow, 1951–1952.

(2) C. B. Wooster, U. S. Patent 2,182,242 (Dec. 5, 1939); see also C. B. Wooster and K. L. Godfrey, THIS JOURNAL, **59**, 596 (1937).

(3) (a) A recent reference: A. J. Birch, J. A. K. Quartey and H. Smith, *J. Chem. Soc.*, 1768 (1952); (b) reviewed by A. J. Birch, *Quart. Rev.*, **4**, 69 (1950), and (c) G. W. Watt, *Chem. Revs.*, **46**, 317 (1950).

(4) A. J. Birch, *J. Chem. Soc.*, 430 (1944); 593 (1946); and Experimental of present paper.

(5) See, for example, A. L. Wilds and C. H. Shunk, THIS JOURNAL, **72**, 2388 (1950); also M. A. Spielman and P. G. Carpenter, unpublished work; see P. G. Carpenter, Ph.D. Thesis, University of Wisconsin, 1941.

(6) See J. C. Sheehan and G. D. Laubach, THIS JOURNAL, **72**, 2478 (1950).

(7) A. J. Birch and S. M. Mukherji, *J. Chem. Soc.*, 2531 (1949).

(8) Birch has also observed cases of elimination of the oxygen-containing group, *J. Chem. Soc.*, **102**, 1642 (1947).