The Conversion of Cholesterol into 10α-Cholesterol

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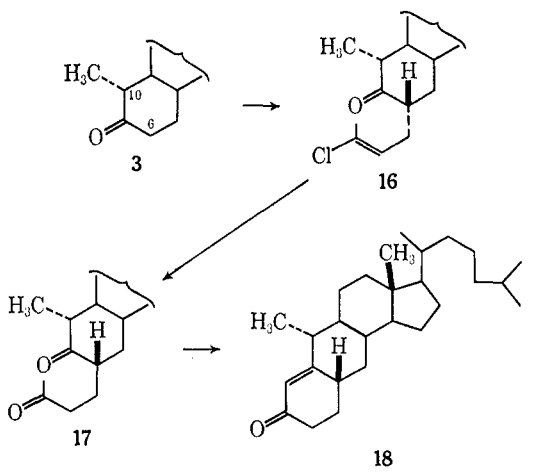
Cholesterol was degraded by a sequence of five reactions to the known BCD intermediate de-A-cholest-9-en-5-one (**5**). Ring A was then restored by methyl vinyl ketone annelation to give 10α-cholest-9(11)-en-5α-ol-3-one (**8**). Hydrogenation of the 9(11) double bond and elimination of the 5α-hydroxyl group generated a mixture of 10α-cholest-4-en-3-one (**12**) and 10α-cholest-5-en-3-one (**13**), which were both converted into the same enol acetate **14**. Reduction with sodium borohydride yielded 10α-cholesterol.

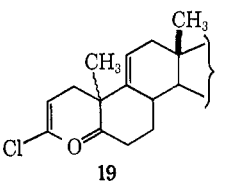
The discovery of the interesting clinical effects of some of the 9β,10α- ("retro") steroids[1] has stimulated interest in steroids of unnatural configuration, and several papers[2-11] have recently described the conversion of steroids into 10α-steroids. We now report the conversion of cholesterol (**1**) into 10α-cholesterol (**15**) by the 11-step sequence shown in Scheme I in a overall yield of 6.4%. While our work was in progress, Uskoković, *et al.*,[6] reported in a preliminary note a synthesis of 10α-progesterone by a route closely similar to ours. This similarity is pointed out at relevant points in our discussion below.

The first objective, the removal of ring A, was accomplished by conversion of cholesterol (**1**) into cholest-4-en-3-one[12] and thence into Windaus' keto acid (**2**)[13] and Inhoffen's ketone (**3**).[14-16] We then attempted to re-form ring A by a preferential condensation at the 10 position without blocking the 6 position. Unfortunately, our results parallelled those of Pinder and Robinson,[17] who had previously found that **3** was alkylated only at C-6. When **3** was treated with 1,3-dichlorobut-2-ene[18,19] in the presence of sodium *t*-amylate,[20] an oily product was obtained in 43% yield which was shown by its nmr spectrum (doublet for the C-10 methyl group) to be the 6-substituted ketone **16**, and not the desired 10-substituted ketone. The configuration of the chlorobutenyl group was assumed to be the more stable α, since alkylation took place under equilibrating conditions. The chloro ketone **16** was converted by treatment with cold, concentrated sulfuric acid[19] into the diketone **17**, and the latter was cyclized in acetic acid–hydrochloric acid[19] to the anthra steroid **18**. This represents a novel route to the anthra steroids.[21,22]



We next decided to try to direct the condensation to the 10 position by introducing a double bond to give the unsaturated ketone **5**, since a rather similar ketone had been found by Barkley, *et al.*,[23] to condense preferentially at C-10. (A further example came from the synthesis of 10α-progesterone by Uskoković, *et al.*,[6] while our work was in progress.)

The unsaturated ketone **5**[16] was prepared by brominating **3** with N-bromosuccinimide to give **4** (a more convenient method than that of Hartshorn and Jones[16]) and dehydrobrominating the latter by lithium chloride in dimethylformamide. The 1,3-dichlorobut-2-ene method of ring formation[18-20] failed completely when applied to **5**, since the initial adduct (or mixture of adducts) **19** could not be further transformed into the desired intermediates.



(1) For a brief review see D. Taub and T. B. Windolz in "Encyclopedia of Chemical Technology," Vol. 18, R. E. Kirk and D. F. Othmer, Ed., John Wiley & Sons, Inc., New York, N. Y., 1969, pp 880–883; E. H. Reerink, H. F. L. Schöler, P. Westerhof, A. Querido, A. A. H. Kessenaar, E. Diczfalusy, and K. C. Tillinger, *Nature*, **186**, 168 (1960); A. M. Krubiner, G. Saucy, and E. P. Oliveto, *J. Org. Chem.*, **33**, 3548 (1968).

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(14) H. H. Inhoffen and Huang-Minlon, *Chem. Ber.*, **72**, 1686 (1939).

(15) S. A. Julia, A. Eschenmoser, H. Heusler, and N. Tarkoy, *Helv. Chim. Acta*, **36**, 1885 (1953).

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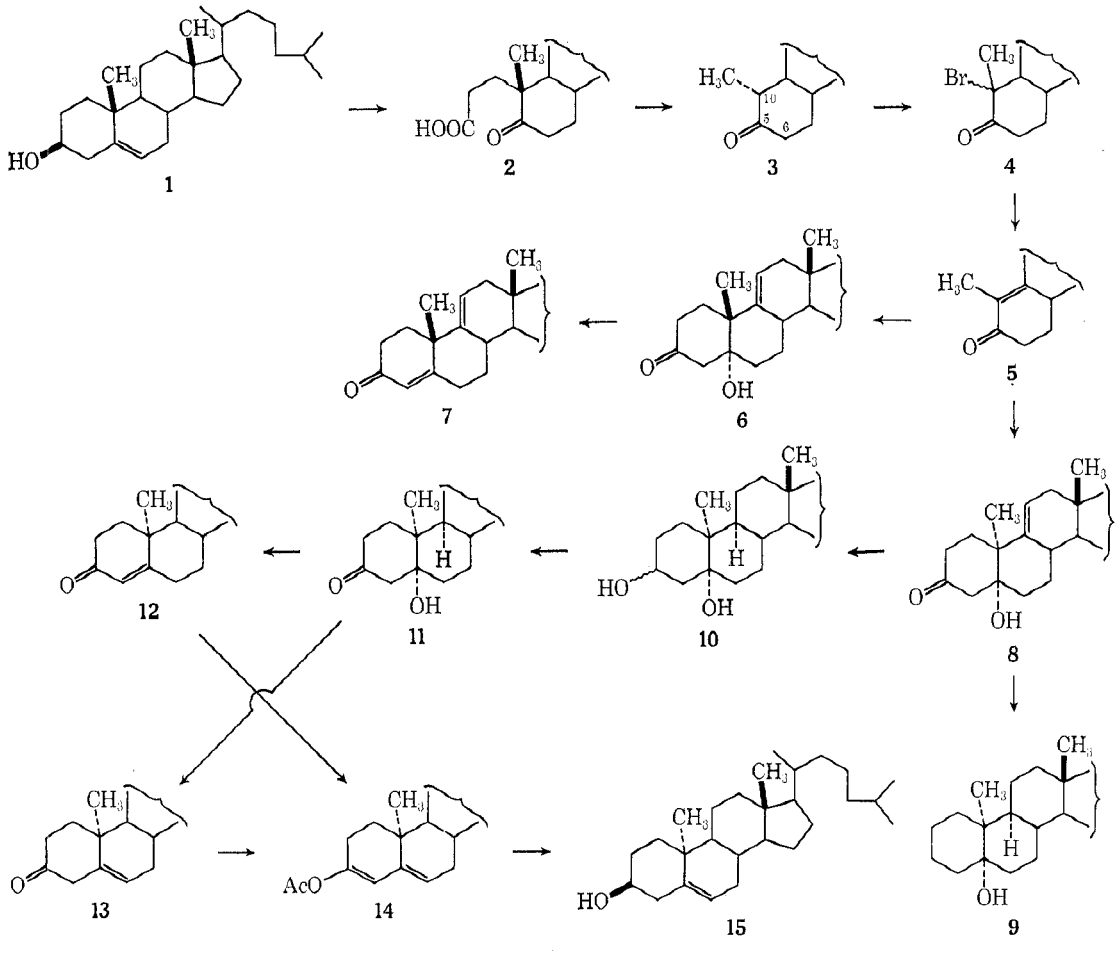
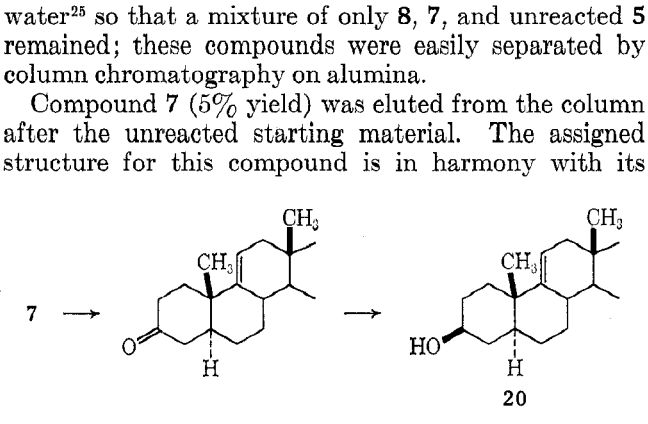
SCHEME I



However, the unsaturated ketone **5** did react with methyl vinyl ketone in the presence of sodium ethoxide to give two compounds in the ratio of *ca.* 5:1 (by tlc), which were probably the 10α epimer **8** and the 10β epimer **6**, respectively.[24] It was also found that when the reaction mixture was left for several days at 5°, the 10β isomer **6** suffered base-catalyzed elimination of water[25] so that a mixture of only **8**, **7**, and unreacted **5** remained; these compounds were easily separated by column chromatography on alumina.

Compound **7** (5% yield) was eluted from the column after the unreacted starting material. The assigned structure for this compound is in harmony with its



combustion analysis and infrared, ultraviolet, and nmr spectra. The latter was almost identical with that of cholest-4-en-3-one with the addition of a broad peak at 5.45 ppm owing to the vinyl proton at C-11. Further proof for the structure **7** was provided by converting it into the known 5α-cholest-9(11)-en-3β-ol (**20**)[26] by hydrogenation and reduction. Two products were obtained. Both appeared from their infrared spectra to be unsaturated alcohols, but only the major product could be crystallized. The melting point (134–135°) differed from that reported for **20** (123°), although the optical rotations were almost the same; it is possible that it had a different crystalline form, because the acetate was shown to be identical by melting point and mixture melting point with a sample of 5α-cholest-9(11)-en-3β-ol acetate[26] generously provided by Professor L. F. Fieser.

Compound **8** (37% yield) was next eluted from the column. Its structure was supported by its combustion analysis, infrared spectrum, and nmr spectrum (a singlet at 0.82 ppm for the C-19 protons, a singlet at 1.98 ppm for the OH, removed by D_2O, and a broad peak at 5.63 ppm for the C-11 vinyl proton). The tertiary character of the alcohol was indicated by the nmr spectrum (no peak at 3.4–4.5 ppm[27]) and by the resistance to oxidation with Jones reagent.[28] Hydrogenation of **8** over platinum in acetic acid gave a saturated alcohol **9** (20% yield) and a diol **10** (80% yield). The alcohol was believed to have the tertiary structure **9** because it was not oxidized by Jones

(24) The major product was expected to be the 10α isomer from consideration of the "principle of perpendicular attack" discussed by L. Velluz, J. Valls, and G. Nominé, *Angew. Chem. Intern. Ed. Engl.*, **4**, 181 (1965). See also ref 23.

(25) It is shown later that cholest-4-en-3-one of the 10α series is more strained than that of the 10β series; it is possible that this greater strain is reflected in the transition states leading to them, so that β elimination takes place less readily from **8** than from **6**.

(26) L. F. Fieser and W.-Y. Huang, *J. Amer. Chem. Soc.*, **75**, 5356 (1953).

(27) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p 55.

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reagent.[28] Several other catalysts and solvents were investigated in an attempt to minimize the hydrogenolysis leading to **9**, but they were not effective in reducing the 9(11) double bond.

The oily diol was not purified but was immediately oxidized by Jones reagent[28] to 10α-cholestan-5α-ol-3-one (**11**) in 74% overall yield from **8**. The infrared spectrum of the ketol **11** was essentially the same as that of **8**, except that the bands of the double bond had disappeared. Hydrogenation of the double bond of **8** would be expected to take place from the less hindered underside of the molecule to give the 9α configuration shown for **10** and thence **11**. The 5α and 10α configurations of **11** are in accord with its negative Cotton effect according to the octant rule,[29] assuming a chair conformation for ring A.

Subjected to refluxing benzene containing a trace of *p*-toluenesulfonic acid, ketol **11** lost water, and the two unsaturated ketones **12** and **13** were separated from the product mixture by chromatography. The major product, 10α-cholest-4-en-3-one (**12**), was an oil whose infrared and ultraviolet spectra showed it to be an α,β-unsaturated ketone. The crystalline 2,4-dinitrophenylhydrazone had an ultraviolet spectrum closely similar to that of the same derivative of natural cholest-4-en-3-one.[30]

The minor product was obtained as a crystalline solid, for which the β,γ-unsaturated structure **13** was indicated by its infrared spectrum. Both **12** and **13** were converted by treatment with perchloric acid–acetic anhydride[31] into the same enol acetate **14**, having an ultraviolet spectrum (uv max 236 mμ) very similar to that of the 10β epimer (uv max 236 mμ), which was prepared in a similar manner from cholest-4-en-3-one.

Alkaline hydrolysis of **14** gave a mixture of **12** and **13** in the ratio (presumably thermodynamically controlled) of 2:1. Ginsig and Cross[3] found that equilibration of 10α-testosterone with potassium *t*-butoxide gave the α,β- and β,γ-unsaturated ketones in the ratio of 1:2. In both cases the proportion of unconjugated ketone in the equilibrium mixture is vastly greater than in the equilibrium mixture of the corresponding 10β compounds.[32] Molecular models show that in **12** ring B is forced to exist in a skew-boat conformation, whereas in **13** it can exist in a more stable half-chair conformation; this effect will destabilize the otherwise more stable conjugated ketone and cause **12** and **13** to be more equally stable.

Reduction of the enol acetate **14** with sodium borohydride in aqueous methanol (a modification of the procedure of Belleau and Gallagher[33]) gave 10α-cholesterol (**15**). Oxidation of this compound under mild conditions[28] gave **13**, thus proving the position of the double bond. The β configuration of the C-3 hydroxyl group was deduced from the nmr spectrum. This showed a fairly broad peak at 3.35 ppm which was due to both the hydroxyl and C-3 protons; after treatment with deuterium oxide the peak became smaller by removal of the hydroxyl proton and much sharper ($W_{1/2}$ = 2.5 Hz). This is characteristic of an equatorial proton α to a hydroxyl group.[34] By comparison, the natural 10β-cholesterol showed a very broad peak at *ca.* 3.4 ppm which was due to the axial α-carbinol proton. The formation of the axial alcohol **15** is probably a case of "steric approach control" in the reduction of the intermediate **13** (from the hydrolysis of **14** during the process) by the bulky solvated borohydride ion,[35] the "convex" α face of **13** being more accessible than the "concave" β face.[36]

The overall nmr spectra of natural and 10α-cholesterol were very similar (except for the hydroxyl and α-carbinol peaks). Surprisingly, the C-19 protons group showed the same chemical shift (0.817 ppm) for both compounds; it might be expected to be at lower field for the 10α isomer, since it does not seem to be able to "see" as much of the steroid ring system.[37]

10α-Cholesterol at a concentration of 10^{-4} *M* failed to prevent the *in vitro* formation of natural cholesterol from 2[^{14}C]-acetate in albino rat liver homogenate.[38]

Experimental Section[39]

10α-De-A-cholestan-5-one (3).—The following procedure is elaborated from that of Hartshorn and Jones,[16] who gave few experimental details.

A 6.7-g portion of sodium methoxide was added to a solution of 23.5 g of **2** in 300 ml of MeOH, and neutralization was completed by adding 0.25 *N* sodium methoxide in MeOH to a phenolphthalein end point. The solution was evaporated to dryness under reduced pressure, and the sodium salt was dried further at 100° for 2 hr. Sodium phenylacetate was similarly prepared from phenylacetic acid. A 25-g portion of the sodium salt of **2**, 100 g of sodium phenylacetate, and 3 g of asbestos fiber were ground together in a mortar, and then pyrolyzed in a 250-ml, round-bottom flask connected by a 90° elbow to a side-arm receiving flask evacuated to 0.05 Torr by a diffusion pump. The flask was heated from 250 to 310° by a bath of molten solder, and kept at the latter temperature for 2 hr. The elbow was heated to 250° by a heating tape, and the receiving flask was cooled with tap water. A pale yellow oil, wt 19.3 g, collected in the receiving flask and was taken up in hexane and chromatographed in two lots on 300-g columns of alumina. The oily solid eluted from the column with hexane was crystallized from petroleum ether (bp 30–60°), giving 6.7 g of **3**, mp 61–62° (lit.[16] mp 62–63°). A further 6.5 g was obtained by chromatography of the mother liquors; total yield 69%. The 2,4-dinitrophenylhydrazone had a melting point of 173–174° (lit.[16] mp 177–178°).

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(33) B. Belleau and T. F. Gallagher, *J. Amer. Chem. Soc.*, **78**, 4458 (1951).

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(37) Reference 34a, p 16.

(38) We are grateful to R. D. Dvornik of Ayerst, McKenna, and Harrison, Ltd., Montreal, Canada, for this test.

(39) Infrared spectra were obtained on Perkin-Elmer 337 or 521 grating spectrophotometers using CCl_4 as solvent; nmr spectra were taken on a Varian A-60 spectrometer using CCl_4 or $CDCl_3$ as solvents and tetramethylsilane as an internal standard; ultraviolet spectra were obtained with a Unicam SP-800 spectrophotometer using 95% EtOH as solvent. Melting points are corrected. Optical rotations were taken on a Carl Zeiss 0.005° photoelectric polarimeter using $CHCl_3$ solutions in a 1-dm tube, and the ORD curve was obtained on a JASCO spectropolarimeter. Column chromatography was carried out on Woelm neutral alumina, grade III. All solutions were dried over anhydrous magnesium sulfate before evaporation. Elemental analyses were performed by Dr. C. Daessle, Montreal, Canada, and by Alfred Bernhardt, Mulheim (Ruhr), West Germany.

6α-(3'-Chlorobut-2'-enyl)-10α-de-A-cholestan-5-one (16).—A solution of 3.8 *N* sodium *t*-amylate[39] in 1.25 ml of dry benzene was added at 5° under nitrogen to a stirred solution of 1.50 g of **3** and 0.71 g of freshly distilled 1,3-dichlorobut-2-ene in 10 ml of dry benzene. The mixture was stirred for 1 hr while warming to room temperature, and was then refluxed for 2 hr. It was diluted with ether, washed with water and saturated, aqueous NaCl solution, dried, and evaporated, The oily residue was chromatographed on 80 g of alumina. Elution with hexane–5% ether yielded 0.82 g (43%) of **16** as a clear oil: ir 3040 and 1675 (HC=C) and 1725 cm^{-1} (C=O); nmr 0.71 (s, C-18 protons), 0.80 (d, J = 4.5 Hz, C-19 protons), 2.2 (s, vinyl methyl), and 5.47 ppm (m, vinyl proton). Analysis by vpc using a glass column (10 ft × 4 mm) packed with 3% SE-30 on Chromosorb W at 250° with a N_2 flow of 90 ml/min demonstrated the product purity, t_R 13.5 min.

6α-(3'-Oxobutyl)-10α-de-A-cholestan-5-one (17).—A solution of 0.80 g of **16** in 5 ml of glacial HOAc was added under N_2 to 12 ml of ice-cold, concentrated H_2SO_4. The dark solution was stirred at 0° for 5 min, and then poured over 50 g of crushed ice. The resulting mixture was extracted with ether, and the organic solution was washed with water and with saturated, aqueous $NaHCO_3$, dried, and evaporated. The oily residue, wt 0.677 g, was chromatographed on 20 g of alumina. Elution with benzene yielded 0.283 g (37%) of **17** as a clear oil, ir 1720 cm^{-1} (C=O).

10α,6β-Anthracholest-4-en-3-one (18).[40]—A solution of 0.283 g of **17** in 5 ml of glacial HOAc and 0.5 ml of concentrated HCl was left overnight at room temperature. It was then diluted with water and extracted with ether. The organic extract was washed with water and with saturated, aqueous $NaHCO_3$, dried, and evaporated. The oily residue was chromatographed on 20 g of alumina. Hexane–benzene (1:1) eluted 0.122 g (43%) of the anthra steroid **18**, which was crystallized twice from MeOH: mp 122.5–123.5°; uv max 244 mμ (log ε 4.10); ir 3030 and 1625 (HC=C) and 1680 cm^{-1} (C=O); nmr 0.70 (s, C-18 protons), 0.85 (d, J = 3.5 Hz, C-19 protons), and 5.65 ppm (s, C-4 vinyl proton).

Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.47; H, 11.33.

The unsaturated ketone formed a red 2,4-dinitrophenylhydrazone, mp 166.5–167.5°.

Anal. Calcd for $C_{33}H_{48}O_4N_4$: C, 70.18; H, 8.57. Found: C, 70.21; H, 8.56.

De-A-cholest-9-en-5-one (5).—A stirred suspension of 6.94 g of **3** and 3.92 g of N-bromosuccinimide in 100 ml of pentane and 350 ml of CCl_4 was illuminated for 45 min by a 500-W photoflood lamp. The flask was cooled by an air stream to prevent overviolent refluxing. The mixture was cooled, filtered, and evaporated at room temperature to yield a oily, brown residue containing the bromide **4**. This was dissolved with 3.4 g of anhydrous LiCl in 35 ml of dimethylformamide, and the mixture was heated on the steam bath for 4 hr with occasional swirling. It was then cooled, diluted with ether, washed with water and saturated, aqueous NaCl, dried, and concentrated under reduced pressure to give 6.85 g of a dark brown oil which was chromatographed on 210 g of alumina. Hexane and hexane–benzene mixtures eluted 2.95 g of **3**, which was recycled, 0.88 g of a mixture, and 2.46 g of **5**, a pale yellow oil: overall yield 55%; ir 3050 and 1610 (HC=C) and 1675 cm^{-1} (C=O); uv max 249 mμ (log ε 4.16) [lit.[16] uv max 248.5 mμ (log ε 4.21)]; nmr 0.80 (s, C-18 protons) and 1.69 ppm (s, C-19 protons) and no olefinic protons.

A dark red 2,4-dinitrophenylhydrazone was formed by **5**, mp 179.0–179.5° (lit.[16] mp 179–181°).

10α-Cholest-9(11)-en-5α-ol-3-one (8).—To 8.30 g of **5** in 60 ml of anhydrous dioxane, a solution of 0.58 g of sodium in 190 ml of absolute EtOH was added. This was cooled to −15° under N_2 and 6.5 ml of freshly distilled methyl vinyl ketone in 50 ml of anhydrous dioxane was dripped in over 9.5 hr with stirring. The reaction was left at 0° under N_2 for 2 days, whereupon an additional 2 ml of methyl vinyl ketone in 2 ml of dioxane was added, and the solution left as before for an additional 2 days. Glacial HOAc (10 ml) was then added, and the solvent was removed at room temperature under reduced pressure. After dilution with water, the mixture was extracted twice with ether, and the organic layer was washed with water and saturated, aqueous $NaHCO_3$, dried, concentrated, and chromatographed on 285 g of alumina to yield 3.73 g (37%) of **8**, eluted by benzene–10% ether. This was recrystallized from petroleum ether: mp 148.5–149.5°; $[\alpha]^{25}D$ +61° (c 0.55); ir 3600 (OH), 3050 and 1675 (HC=C) and 1720 cm^{-1} (C=O); nmr 0.59 (s, C-18 protons), 0.82 (s, C-19 protons), 1.98 (s, hydroxyl proton, removed by D_2O), 1.5–3.0 (m, protons α to carbonyl), and 5.63 ppm (broad s, C-11 vinyl proton).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 81.26; H, 10.96.

Cholesta-4,9(11)-dien-3-one (7).—During the previous chromatography, a brown oil was obtained from the earlier fractions, which was shown by tlc to be mostly unreacted ketone **5** (18% yield) plus a slightly more polar compound. This was obtained crystalline after standing for several weeks, and was recrystallized from petroleum ether and MeOH to give 0.465 g (5%) of **7**: mp 116–116.5°; $[\alpha]^{25}D$ +81° (c 1.84); ir 3040 and 1610 (HC=C) and 1680 cm^{-1} (C=O); uv max 241 mμ (log ε 4.18); nmr 0.65 (s, C-18 protons), 0.82 (s, C-19 protons), 5.45 (broad s, C-11 vinyl proton), and 5.73 ppm (s, C-4 vinyl proton).

Anal. Calcd for $C_{27}H_{42}O$: C, 84.75; H, 11.07. Found: C, 84.55; H, 11.05.

5a-Cholest-9(11)-en-3β-ol (20).—An 84-mg sample of cholesta-4,9(11)-dien-3-one (**7**) was hydrogenated over 61 mg of prereduced Adams catalyst in 15 ml of HOAc containing 1 drop of concentrated HCl until rapid uptake of H_2 ceased (30 min). After filtration the solution was diluted with ether, washed with water and saturated, aqueous $NaHCO_3$, dried, and concentrated. The residue was dissolved in 50 ml of acetone and oxidized to the ketone(s) with Jones reagent.[28] Excess oxidant was destroyed with 5 ml of MeOH, and the solution was diluted with ether and washed with water and saturated, aqueous $NaHCO_3$. The solvent was evaporated and the residue was dissolved in 10 ml of anhydrous diglyme to which 200 mg of lithium tri-*t*-butoxyaluminum hydride was then added. After the solution had been stirred overnight at 25°, water was added to destroy the excess hydride followed by 10 ml of glacial HOAc. The solution was extracted with ether, and the organic layer was washed with water and saturated, aqueous $NaHCO_3$, dried, concentrated, and chromatographed on 10 g of alumina. Hexane–10% benzene eluted an oil which did not crystallize, and benzene eluted 20 mg of 5α-cholest-9(11)-en-3β-ol (**20**), which was recrystallized from MeOH: mp 134–135°; $[\alpha]^{25}D$ +25° (c 0.13) (lit.[26] mp 123°, $[\alpha]D$ +27°); ir 3625 and 3300 (OH) and 3040 and 1675 cm^{-1} (HC=C).

The acetate was prepared by the method of Edwards and Rao:[31] mp 105–108°; $[\alpha]^{25}D$ +24° (c 0.17) (lit.[26] mp 105°, $[\alpha]D$ +22.5°).

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.21; H, 11.20.

The acetate was shown to be identical by melting point and mixture melting point with a genuine sample of 5α-cholest-9(11)-en-3β-ol acetate.

10α-Cholestan-5α-ol-3-one (11).—A solution of 266 mg of **8** in 20 ml of glacial HOAc was hydrogenated at 1 atm over 196 mg of prereduced Adams catalyst. After 2 equiv of hydrogen was absorbed (4 hr), ether was added and the catalyst was filtered off. The filtrate was washed with water and saturated, aqueous $NaHCO_3$ solution, dried, and concentrated under reduced pressure to give a mixture of the saturated diol **10** and the alcohol **9**, ir 3620 and 3400 cm^{-1} (OH). The crude mixture in 50 ml of acetone was oxidized by Jones reagent,[28] excess oxidant being destroyed by the addition of 5 ml of MeOH. The solution was diluted with ether, washed with water and saturated, aqueous $NaHCO_3$ solution, dried, and concentrated to give a solid which was crystallized from petroleum ether to yield 197 mg of **11** (74% from **8**): mp 170.5–171°; $[\alpha]^{25}D$ +49° (c 0.24); ir 3610 and 3400 (OH) and 1710 cm^{-1} (C=O); ORD (c 0.10, $CHCl_3$) $[\phi]_{400}$ +30°, $[\phi]_{350}$ +30°, $[\phi]_{327}$ 0°, $[\phi]_{312}$ −80° (max), $[\phi]_{300}$ −35° (inflection), $[\phi]_{302}$ 0°, $[\phi]_{300}$ +45°, $[\phi]_{290}$ +190°, $[\phi]_{280}$ +250°, and $[\phi]_{275}$ +310°.

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.69; H, 11.22.

Palladium or platinum in EtOH or EtOAc, with or without a trace of perchloric acid, and tris(triphenylphosphine)rhodium chloride[41] in benzene with hydrogen pressures of 1–4 atm were all tried in vain attempts to improve the yield of **11**.

10α-Cholestan-5α-ol (9).—The combined mother liquors from the crystallization of **11** were chromatographed on alumina. Hexane–10% benzene eluted **9** (20% yield from **8**), which was

(40) Numbering system suggested in ref 22.

(41) A. J. Birch and K. A. M. Walker, *J. Chem. Soc.*, 1894 (1966).

crystallized from MeOH: mp 79.5–80°; $[\alpha]^{25}D$ +53° (*c* 0.18); ir 3640 and 3350 cm^{-1} (OH).

Anal. Calcd for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.72; H, 12.25.

A solution of 50 mg of **9** in acetone was treated with Jones reagent,[28] but only starting material was isolated.

10α-Cholest-4-en-3-one (12) and 10α-Cholest-5-en-3-one (13).—In 10 ml of dry benzene, 123 mg of **11** was refluxed for 2 hr with a trace of *p*-toluenesulfonic acid. Dilution with ether, washing with saturated, aqueous $NaHCO_3$, drying, and evaporation of the solvent gave a clear oil which was chromatographed on 12 g of alumina. Hexane–25% benzene eluted 27 mg (22%) of of a white solid, which was crystallized from MeOH–H_2O to give **13**: mp 112–112.5°; $[\alpha]^{25}D$ −104° (*c* 0.68); ir 3030 and 1680 (HC=C) and 1720 cm^{-1} (C=O).

Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.14; H, 11.56.

Hexane–50% benzene eluted 90 mg (73%) of a clear oil which could not be crystallized and was assigned structure **12**: ir 3030 and 1630 (HC=C) and 1680 cm^{-1} (conjugated C=O); uv max 243 mμ (log ε 4.15).

The oil formed a red, crystalline 2,4-dinitrophenylhydrazone: mp 185–185.5°; uv max 260 mμ (log ε 4.23), 293 (4.02), and 392 (4.44). The uv of the analogous 10β compound[30] was 256 mμ (log ε 4.33), 281 (4.20), 292 (4.06), and 393 (4.47).

Anal. Calcd for $C_{33}H_{48}O_4N_4$: C, 70.18; H, 8.57. Found: C, 70.08; H 8.73.

10α-Cholesta-3,5-dien-3-ol Acetate (14).—Both **12** and **13** were convertible into the same enol acetate (**14**) by the method of Edwards and Rao.[31] In later experiments the crude mixture of **12** and **13** derived from 825 mg of the ketol **11** was treated with the following reagent: 10 ml of a solution of 0.05 ml of 72% perchloric acid in 50 ml of absolute EtOAc was poured into a 50-ml volumetric flask containing 30 ml of absolute EtOAc and 4.8 ml of acetic anhydride and the flask was made up to 50 ml with EtOAc. After standing for 10 min the reaction product was diluted with ether and saturated aqueous $NaHCO_3$ was added. The ether phase was washed well with the $NaHCO_3$ solution, dried, and concentrated.

To the residue was added 5 ml of MeOH containing a trace of pyridine, and the whole was evaporated to dryness, and crystallized from MeOH to give 733 mg of the enol acetate **14** (84% overall yield from **11**): mp 93–94°; $[\alpha]^{25}D$ +32° (*c* 0.36); ir 3030 and 1660 (HC=C) and 1755 cm^{-1} (C=O); uv max 236 mμ (log ε 4.18).

Anal. Calcd for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.75; H, 10.93.

Alkaline Hydrolysis of 10α-Cholesta-3,5-dien-3-ol Acetate (14).—In 2 ml of MeOH, 5 mg of **14** was dissolved and 0.25 ml of 5% aqueous NaOH was added. The solution was refluxed for several minutes, cooled, diluted with ether, washed with water and saturated, aqueous NaCl, and dried, and the solvent was evaporated. The ir spectrum of the product showed two strong carbonyl peaks: 1720 (unconjugated ketone **13**) and 1680 cm^{-1} (conjugated ketone **12**). Their absorption intensities were in the ratio 1:2, respectively.

10β-Cholesta-3,5-dien-3-ol Acetate.—This compound was made for uv comparison purposes by the same method as the 10α analog: mp 83–84° (clears at 110°) [lit.[42] mp 80° (clears at 105–110°)]; uv max 236 mμ (log ε 4.26).

10α-Cholesterol (15).—A 3-g sample of sodium borohydride in 30 ml of 85% aqueous MeOH was added to a solution of 615 mg of the enol acetate **14** in 400 ml of MeOH at 5°, and the resulting solution was stirred and allowed to warm up to 25°. After 2.5 hr a further 0.5 g of borohydride was added and the solution was stirred overnight. The MeOH was removed under reduced pressure, ether was added, and enough 2 *N* HCl was added to make the aqueous layer slightly acidic, this phase being extracted well with ether. The combined ether extracts were washed with water and saturated, aqueous $NaHCO_3$, dried, concentrated, and chromatographed on 30 g of alumina. Hexane–50% benzene eluted a solid which was crystallized from MeOH to give 468 mg (84%) of **15** as white needles: mp 118.5–119°; $[\alpha]^{25}D$ −46° (*c* 1.14); ir 3620, 3350, 1390, 1375, and 1050 (COH), and 3040 and 1675 cm^{-1} (HC=C); nmr 0.69 (s, C-18 protons), 0.817 (s, C-19 protons), 3.45 (broad s, α-carbinol proton and hydroxyl proton, the latter disappears on D_2O exchange to give a sharp s, $W_{1/2}$ = 2.5 Hz), and 5.44 ppm (d, J = 6 Hz, C-6 vinyl proton).

Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.76; H, 11.79.

10α-Cholesterol Acetate.—This compound was prepared by acetylation of 10α-cholesterol by the method of Edwards and Rao:[31] mp 124–124.5°; $[\alpha]^{25}D$ −47° (*c* 1.48); ir 3040 and 1675 (HC=C) and 1740, 1375 (d), 1250, and 1040 cm^{-1} (COAc).

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.14; H, 11.40.

Oxidation of 10α-Cholesterol (15).—To 20.5 mg of **15** in 5 ml of acetone, Jones reagent[28] was added in slight excess; 2 ml of MeOH was then added, followed by ether and saturated, aqueous $NaHCO_3$. The ether layer was dried and concentrated, and the white solid was crystallized from MeOH to give **13**, identified by melting point and mixture melting point.

Registry No.—**1**, 57-88-5; **3**, 23820-60-2; **5**, 23820-61-3; **7**, 23820-62-4; **8**, 23820-63-5; **9**, 23820-64-6; **11**, 23820-65-7; **12**, 23820-66-8; **12** 2,4-dinitrophenylhydrazone, 23820-67-9; **13**, 23820-68-0; **14**, 23820-69-1; **15**, 23820-70-4; **15** acetate, 23820-71-5; **16**, 23820-72-6; **17**, 23820-73-7; **18**, 23820-74-8; **18** 2,4-dinitrophenylhydrazone, 23820-75-9; **20**, 23820-76-0.

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(42) H. Reich and A. Lardon, *Helv. Chim. Acta*, **29**, 671 (1946).