Steroid Oxetanones. 3. Synthesis of 5,7α-Epoxy-5α-cholestan-6-ones[1,2]

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Received July 12, 1976

Bromination of 5α-hydroxy-6-oxo cholestanes with pyridinium hydrobromide perbromide in hot acetic acid gave the corresponding 7α-bromo derivatives accompanied by significant amounts of by-products. Epimerization at C-7 by lithium bromide in dimethylformamide produced the 7β-bromo isomers which, upon treatment with methanolic potassium hydroxide in dimethyl sulfoxide, gave 5,7α-epoxy-5α-cholestan-6-ones and 5-hydroxy-7α-methoxy-5α-cholestan-6-ones. Spectroscopic data verify the structural assignments for the bromo ketones, oxetanones, and methoxy ketones. Among the few literature reports concerning the preparation of steroid oxetanones, this is the first to describe the production of α-methoxy ketones as competing products.

Since our report[3] on the synthesis of 5,7β-epoxy-5β-cholestan-6-one (**1**) and its ring A derivatives, few additional examples of this class of compounds have appeared in the literature. "As yet, there is no convenient general synthesis of oxetan-3-ones" is a statement[4] that accurately represents the situation regarding the preparation of this interesting class of compounds. The success of the method involving the bromination of steroidal α-ketols, followed by ring closure to the oxetanone upon treatment of the trans bromohydrin with base,[3] is often stymied in simplier acyclic compounds by cleavage of the α-ketol during the bromination reaction.[4] The bromination of 5-hydroxy-5β-cholestan-6-ones with pyridinium hydrobromide perbromide (PHP) produced no such complications.[3] We now report that similar treatment of the 5-hydroxy-5α-cholestan-6-ones invariably gives side products that decrease the yield of the desired 7α-bromo derivatives. However, the bromohydrins produced are readily converted to the corresponding oxetanones after epimerization to the 7β-bromo compounds.

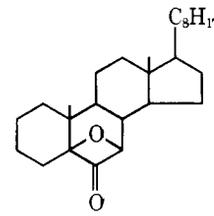
Bromination of 5-hydroxy-5α-cholestan-6-one (**2a**) with 1 equiv of PHP in hot acetic acid gave the 7α-bromo derivative (**2b**) in 39% yield along with unidentified material(s) that contained no hydroxy group. While brominations in the 5β-hydroxy series lead directly to 7α-bromo compounds that possess the trans relationship of bromine and hydroxyl necessary for oxetanone formation,[3] conversion of **2b** to the 7β-bromo epimer **2c** was essential. Attempted epimerization by hydrogen bromide in acetic acid[5] failed but treatment of **2b** with excess lithium bromide in dimethylformamide (DMF)[6] for an extended period at room temperature resulted in the production of **2c** in high yield. This procedure, although involving a long reaction period, did not produce an α,β-unsaturated ketone as occurred in the reported epimerization of 7α-bromo-6-oxo steroids utilizing a hot lithium carbonate–DMF mixture.[6] Treatment of **2c** with methanolic potassium hydroxide solution in dimethyl sulfoxide (Me_2SO)[3,6a] gave 5,7α-epoxy-5α-cholestan-6-one (**3a**) in moderate yield plus a small amount of 5-hydroxy-7α-methoxy-5α-cholestan-6-one (**4d**). The latter compound presumably arose by displacement with inversion of the 7β-bromine by methoxide ion formed from the equilibrium

$$KOH + MeOH \rightleftharpoons KOMe + H_2O$$

There was no indication of α-methoxy ketone formation in the reaction with base of 7α-bromo steroids in the 5β-hydroxy series,[3] probably owing to the typical inhibition to attack from the top side of the molecule.

That a trans relationship of the hydroxy and bromo substituents is needed for oxetanone formation is indicated by the fact that reaction of the 7α-bromo compound **2b** with methanolic potassium hydroxide–Me_2SO gave 5,7β-dihydroxy-5α-cholestan-6-one (**4b**) as the sole product. It appears likely that the conversion of **2b** to **4b** proceeded through an intermediate epoxy alcohol or ether (a pathway known to be taken by some α-bromo ketones[7]) since the crude reaction product before acidification contained little carbonyl absorption in its IR spectrum. The 7β-hydroxy compound **4b** was converted to the 7β-tosyloxy derivative (**4c**). Upon treatment with base, **4c** gave a low yield of oxetanone **3a** and unreacted **4c**. Thus, no advantage was found in using the tosyloxy substituent as a leaving group.

When the 7β-bromo steroid **2c** was treated with sodium bicarbonate in hot Me_2SO, the major product was 5,7α-dihydroxy-5α-cholestan-6-one (**4a**), accompanied by a trace of



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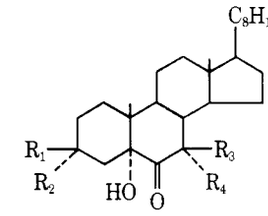
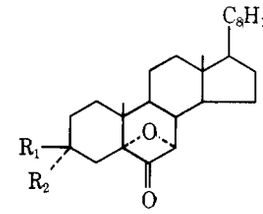
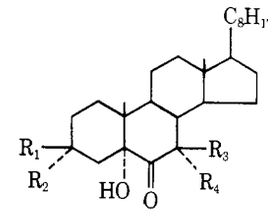


2a, $R_1 = R_2 = R_3 = R_4 = H$
b, $R_1 = R_2 = R_3 = H$; $R_4 = Br$
c, $R_1 = R_2 = R_4 = H$; $R_3 = Br$
d, $R_1 = OAc$; $R_2 = R_3 = R_4 = H$
e, $R_1 = OAc$; $R_2 = R_3 = H$; $R_4 = Br$
f, $R_1 = OAc$; $R_2 = R_4 = H$; $R_3 = Br$
g, $R_1 = R_3 = R_4 = H$; $R_2 = OAc$
h, $R_1 = R_3 = H$; $R_2 = OAc$; $R_4 = Br$
i, $R_1 = R_4 = H$; $R_2 = OAc$; $R_3 = Br$



3a, $R_1 = R_2 = H$
b, $R_1 = OH$; $R_2 = H$
c, $R_1 = OAc$; $R_2 = H$
d, $R_1 = H$; $R_2 = OH$
e, $R_1 = H$; $R_2 = OAc$



4a, $R_1 = R_2 = R_3 = H$; $R_4 = OH$
b, $R_1 = R_2 = R_4 = H$; $R_3 = OH$
c, $R_1 = R_2 = R_4 = H$; $R_3 = OTs$
d, $R_1 = R_2 = R_3 = H$; $R_4 = OCH_3$
e, $R_1 = OH$; $R_2 = R_3 = H$; $R_4 = OCH_3$

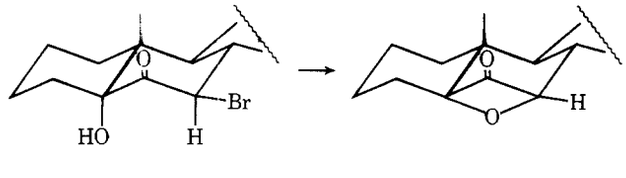
oxetanone **3a**. Displacement of bromine by hydroxyl with inversion of configuration at C-7 was a minor side reaction in the 7α-bromo-5β-hydroxy series[3] and the course of the reaction with **2c** illustrates the preference for displacement vs. oxetanone formation when a weak base is used and the bromine-bearing carbon is open to attack.

Hanna has reported[6a] that the reaction of 3β-acetoxy-5-hydroxy-7α-bromo-5α-cholestan-6-one (**2e**) with lithium carbonate–DMF gave the 7β-bromo epimer (**2f**) in 33% yield accompanied by a trace of 3β-acetoxy-5,7α-epoxy-5α-cholestan-6-one (**3c**) and significant amounts of conjugated ketones. Alternately, the hydroxy oxetanone **3b** was obtained in 50% yield by treatment of **2f** with methanolic potassium hydroxide in Me_2SO. It was assumed in the former reaction that the oxetanone **3c** arose from the bromo ketones **2f** produced by epimerization of **2e**. We reinvestigated this sequence in order to optimize the yield of oxetanone **3c** and and to determine if an α-methoxy ketone is also formed in the reaction of **2f** with base. Attempts at the bromination of 3β-acetoxy-5-hydroxy-5α-cholestan-6-one (**2d**) by the only recorded procedure[5,6a,8] were unsuccessful in our hands. However, PHP treatment of **2d** in hot acetic acid gave **2e** in good yield, accompanied by unidentified side products. Epimerization of **2e** with *hot* lithium bromide–DMF gave a complex mixture from which the desired 7β-bromo compound **2f** was readily separated by column chromatography. Treatment of **2f** with methanolic potassium hydroxide in Me_2SO resulted in the isolation of the oxetanone **3b** and a second compound not previously detected,[6a] 3β,5-dihydroxy-7α-methoxy-5α-cholestan-6-one (**4e**). These results were consistent with those observed for the reaction of **2c** with base.

The physical constants (melting point, $[\alpha]_D$) we found for **3b** were quite different from those reported by Hanna.[6a] Spectroscopic and analytical data verify our structural assignment (see Experimental Section). Acetylation of **3b** gave **3c**.

Bromination of 3α-acetoxy-5-hydroxy-5α-cholestan-6-one (**2g**) with PHP gave the 7α-bromo derivative **2h** in moderate yield along with the usual unidentified by-products. Attempts at isomerization of **2h** to **2i** with lithium bromide–DMF at room temperature for 91 h produced little reaction but epimerization did occur at elevated temperatures within 18 h. The crystallized product, 3α-acetoxy-5-hydroxy-7β-bromo-5α-cholestan-6-one (**2i**), was contaminated by a small amount of an impurity that was removed by column chromatography. Treatment of **2i** with methanolic potassium hydroxide–Me_2SO gave much 3α-hydroxy-5,7α-epoxy-5α-cholestan-6-one (**3d**) according to the IR spectrum of the crude product but separation of **3d** from other products by column or thick layer chromatography was only mildly successful. The oxetanone **3d** was finally obtained by fractional crystallization of column fractions rich in **3d**. Acetylation of a portion of the crude product resulted in an acetate mixture that stubbornly refused separation as well, but a small amount of the acetate (**3e**) of **3d** was obtained. Although no α-methoxy ketone was obtained in a pure state from this reaction, its presence in some chromatographic fractions was indicated by the characteristic absorption in the NMR spectrum at ca. 206 Hz (cf. spectral data for **4d** and **4e** in Experimental Section).

The conversion of 5-hydroxy-7β-bromo-5α-cholestan-6-ones to the corresponding oxetanones does not involve a major conformational change such as that necessitated in the production of the isomeric oxetanones from the 5β-hydroxy compounds.[3] Whereas in the latter cases the change in the environment of a C-3 hydrogen is readily observed by NMR analysis,[3] no significant change in the half-band width of the C-3 hydrogen is noted in the 5α-hydroxy compounds. The ultraviolet data show the usual bathochromic shifts and hyperchromic effects due to the bromine substituents in the 7α-bromo compounds and the IR and NMR data are in complete accord with all assignments.[3]



Rearrangements of simple oxetanones by Grignard reagents[9] and by acid[10] have been reported. We intend to investigate the behavior of steroid oxetanols (derived from the ketones reported here) under similar conditions.

Experimental Section

Melting points were taken in open capillaries in a Mel-Temp apparatus and are uncorrected. Optical rotations were determined in ca. 1% $CHCl_3$ solutions and are accurate to ±2°. Infrared spectra were taken on a Perkin-Elmer Model 735 spectrometer in CCl_4 solutions unless otherwise indicated. Ultraviolet spectra were obtained on a Bausch and Lomb Spectronic 505 spectrometer in absolute ethanol solutions. NMR spectra were determined on a Varian T-60 spectrometer in $CDCl_3$ solutions containing Me_4Si as an internal standard; chemical shifts are in hertz relative to Me_4Si. Microanalyses were conducted by Micro-Analysis, Inc., Wilmington, Del. Preliminary examinations of crude products and column fractions were carried out by TLC on Baker-flex silica gel 1B sheets and spectroscopically. Solutions were dried with anhydrous Na_2SO_4. Dimethyl sulfoxide (Me_2SO) and dimethylformamide (DMF) were Baker reagent grade and used as purchased. Alumina refers to Merck acid-washed grade and silica gel to Baker Analyzed reagent.

Preparation of 7α-Bromo Ketones. General Procedure. The given volume of glacial acetic acid was heated to the indicated temperature. Pyridinium hydrobromide perbromide (PHP) and the steroid were then added immediately and the solution was swirled vigorously with no further heating. After 4–11 min, the light yellow solution was diluted with water and the product was collected, washed with much water, and recrystallized as noted.

A. 5-Hydroxy-7α-bromo-5α-cholestan-6-one (2b). Reaction of 16.169 g (40.22 mmol) of **2a**[11] with 12.947 g (40.47 mmol) of PHP in 400 ml of HOAc at 70 °C gave, after successive recrystallizations from aqueous acetone and acetone–methanol, 5.855 g of **2b** as white needles: mp 148.5–150.5 °C, dec 177 °C; $[\alpha]_D$ +7°; IR ($CHCl_3$) 3571, 1709 cm^{-1}; UV 336 nm (ε 98); NMR 40 (s, 3, 18-H), 47.5 (s, 3, 19-H), 136 (s, 1, OH), 252 Hz (d, J = 3 Hz, 1, C-7 H). Column chromatography (silica gel) of the mother liquor residue yielded an additional 1.674 g of **2b** from ether–methanol, mp 151.5–152.5 °C (total yield, 39%).

Anal. Calcd for $C_{27}H_{45}BrO_2$ (481.55): C, 67.34; H, 9.42; Br, 16.60. Found: C, 67.37; H, 9.23; Br, 16.76.

B. 3β-Acetoxy-5-hydroxy-7α-bromo-5α-cholestan-6-one (2e). Treatment of 50.73 g (110.1 mmol) of **2d**[8] with 35.60 g (111.3 mmol) of PHP in 1550 ml of HOAc at 90 °C gave a crude product that was recrystallized from acetone–methanol to yield 36.67 g (62%) of **2e** as fluffy, white needles with double mp 151–153 °C, 167.5–168 °C, dec 197 °C. Recrystallization of a sample from petroleum ether gave mp 171–172.5 °C; $[\alpha]_D$ +8°; IR ($CHCl_3$) 3575, 3430, 1720, 1710 cm^{-1}; UV 334 nm (ε 97); NMR 42 (s, 3, 18-H), 49.5 (s, 3, 19-H), 120.5 (s, 3, AcO), 195 (s, 1, OH), 252 (d, J = 3 Hz, 1, C-7 H), 307 Hz (m, $W_{1/2}$ = 22 Hz, 1, C-3 H) [lit. mp 170–171 °C; $[\alpha]_D$ +7.5° (dioxane);[8] $[\alpha]_D$ +7° ($CHCl_3$); UV 333.5 nm (ε 109)[5]].

C. 3α-Acetoxy-5-hydroxy-7α-bromo-5α-cholestan-6-one (2h). Reaction of 11.716 g (25.432 mmol) of **2g**[12] with 8.267 g (25.84 mmol) of PHP in 300 ml of HOAc at 95 °C yielded, from petroleum ether, 5.858 g (43%) of **2h** as small, white needles, mp 142–143 °C, dec 195 °C. Recrystallization of a sample from ether–petroleum ether gave mp 144–144.5 °C; $[\alpha]_D$ +15°; IR 3571, 1751, 1721 cm^{-1}; UV 334.5 nm (ε 101); NMR 42 (s, 3, 18-H), 48.5 (s, 3, 19-H), 125 (s, 3, AcO), 211 (s, 1, OH), 253 (d, J = 3 Hz, 1, C-7 H), 318 Hz (m, $W_{1/2}$ = 9 Hz, 1, C-3 H).

Anal. Calcd for $C_{29}H_{47}BrO_4$ (539.60): C, 64.55; H, 8.78; Br, 14.81. Found: C, 64.55; H, 8.76; Br, 14.62.

5-Hydroxy-7β-bromo-5α-cholestan-6-one (2c). A solution of 7.111 g (14.77 mmol) of **2b** and 7.74 g (89.4 mmol) of anhydrous LiBr[6a] in 200 ml of DMF was stirred magnetically at room temperature for 166.5 h.[13] The colorless solution was treated with 9 ml of glacial HOAc and diluted with 250 ml of water. The mixture was extracted twice with ether and the combined extracts were washed twice with water, once (rapidly) with 0.1 N aqueous KOH, and again with water, and dried. The white solid obtained by removal of the solvent was chro-

matographed on 125 g of silica gel. Elution with benzene gave 738 mg of unchanged **2b** which was recrystallized from methanol to yield 570 mg as white needles with mp 151–152.5 °C. Further elution with benzene gave 6.166 g (87%) of **2c** as a white solid. Recrystallization of a 190-mg sample from aqueous methanol and then methanol gave 106 mg of **2c** as small, white plates: mp 143.5–144 °C dec; $[\alpha]_D$ +35°; IR ($CHCl_3$) 3600, 3450, 1730 cm^{-1}; UV 299.5 nm (ε 56); NMR 41.5 (s, 3, 18-H), 46 (s, 3, 19-H), 121 (s, 1, OH), 312 Hz (d, J = 9 Hz, 1, C-7 H).

Anal. Calcd for $C_{27}H_{45}BrO_2$ (481.55): C, 67.34; H, 9.42; Br, 16.60. Found: C, 67.37; H, 9.43; Br, 16.33.

3β-Acetoxy-5-hydroxy-7β-bromo-5α-cholestan-6-one (2f). A mixture of 27.68 g (51.30 mmol) of **2e** and 54.53 (629.7 mmol) of LiBr in 1 l. of DMF was maintained at 75 ± 2 °C for 24 h. The burgundy colored solution was cooled, then poured into a mixture of crushed ice and 120 ml of glacial HOAc. The orange solid was collected, washed with water, dried, and chromatographed on 454 g of alumina. The material eluted with 10% ether–benzene was recrystallized from CCl_4–methanol, giving 10.20 g of **2f** as off-white needles: mp 172.5–174 °C dec; $[\alpha]_D$ +4°; IR ($CHCl_3$) 3585, 3460, 1725, 1720 cm^{-1}; UV 300.5 nm (ε 50); NMR 42 (s, 3, 18-H), 48 (s, 3, 19-H), 120 (s, 3, AcO), 236 (s, 1, OH), ~302 (m, $W_{1/2}$ = 22 Hz, 1, C-3 H), 312 Hz (d, J = 8 Hz, 1, C-7 H) [lit.[6a] mp 176–177 °C; $[\alpha]_D$ 0°; IR 3580, 3460, 1728 cm^{-1}; UV 300 nm (ε 54); NMR 309 Hz (C-7 H)]. Concentration of mother liquor produced 1.623 g of **2f**, mp 170–173 °C dec.

A fraction (6.332 g) eluted with 25% ether–benzene was crystallized from CCl_4–methanol and recrystallized from methanol to give an additional 2.478 g of **2f** as white needles, mp 171–173 °C, dec 175.5 °C (total yield of **2f**, 52%).

3α-Acetoxy-5-hydroxy-7β-bromo-5α-cholestan-6-one (2i). A mixture of 4.619 g (8.560 mmol) of **2h** and 9.44 g (109 mmol) of LiBr in 140 ml of DMF was heated at 81 ± 3 °C for 18 h. The product was isolated in the manner employed for **2f**. Two recrystallizations from aqueous ethanol gave 3.534 g (77%) of **2i**, mp 159.5–161.5 °C, dec 205 °C. The product (UV, ε ~132) contained a small amount of some impurity which was removed by chromatography of a 327-mg sample on 20 g of alumina. Elution with benzene, combination of identical fractions, and recrystallization from 95% ethanol gave 184 mg of pure **2i** as white plates: mp 156–157 °C, dec 224 °C; $[\alpha]_D$ +24; IR 3560, 1750, 1740 cm^{-1}; UV 298.5 nm (ε 51); NMR 41.5 (s, 3, 18-H), 45 (s, 3, 19-H), 126 (s, 3, AcO), 192 (s, 1, OH), 309 (d, J = 9 Hz, 1, C-7 H), 321 Hz (m, $W_{1/2}$ = 9 Hz, 1, C-3 H).

Anal. Calcd for $C_{29}H_{47}BrO_4$ (539.60): C, 64.55; H, 8.78; Br, 14.81. Found: C, 64.64; H, 8.83; Br, 14.71.

5,7α-Dihydroxy-5α-cholestan-6-one (4a). A mechanically stirred solution of 910 mg (1.89 mmol) of **2c** and 1.00 g of $NaHCO_3$ in 35 ml of Me_2SO was heated at 98–99 °C for 4.75 h. Crushed ice was added to the hot solution and the resulting precipitate was collected, dried, and recrystallized from chloroform–petroleum ether to yield 485 mg of **4a**: mp 177–178 °C; $[\alpha]_D$ −49°; IR ($CHCl_3$) 3590, 3370, 1718 cm^{-1}; UV 325.5 nm (ε 71); NMR 38.5 (s, 3, 18-H), 46 (s, 3, 19-H), 234 (s, 2, OH), 234 Hz (d, J ~ 2 Hz, 1, C-7 H).

Anal. Calcd for $C_{27}H_{46}O_3$ (418.64): C, 77.46; H, 11.07. Found: C, 77.34; H, 11.02.

The solid obtained from the mother liquor was chromatographed on 25 g of silica gel. Elution with benzene yielded 62 mg of a white solid that was recrystallized from ether–methanol to give 35 mg (4.6%) of the oxetanone **3a** as white needles with mp 96–97 °C. Elution with ether produced an additional 104 mg of **4a** (74%).

5,7β-Dihydroxy-5α-cholestan-6-one (4b). A suspension of 2.434 g (5.054 mmol) of **2b** in 60 ml of Me_2SO was magnetically stirred as 15 ml of 1.03 N methanolic potassium hydroxide solution was added in one portion. The steroid dissolved within 2 min and after a total reaction time of 17 min, the yellow solution was poured into a mixture of crushed ice and salt. The product was extracted twice with ether and the combined extracts were washed twice with water and dried. The colorless oil (very weak C=O in IR) obtained by removal of the solvent was dissolved in 65 ml of acetone and 5 ml of water, then treated with 7 ml of 10% H_2SO_4. After 30 min, water was added and the precipitate was collected by filtration. Recrystallization from ether–petroleum ether gave 1.208 g of **4b** with mp 180–182 °C; $[\alpha]_D$ +4°; IR 3605, 3495, 3425, 1715 cm^{-1}; UV 294 nm (ε 55); NMR 39.5 (s, 3, 18-H), 44.5 (s, 3, 19-H), 179 (s, 2, OH), 276 Hz (d, J = 7 Hz, 1, C-7 H). One further recrystallization from the same solvents gave mp 183–184.5 °C. A further 519 mg of **4b** with mp 174–178 °C was obtained by recrystallization of the solid deposited from the first mother liquor (total yield, 82%).

Anal. Calcd for $C_{27}H_{46}O_3$ (418.64): C, 77.46; H, 11.07. Found: C, 77.52; H, 11.12.

5-Hydroxy-7β-tosyloxy-5α-cholestan-6-one (4c). A solution of 929 mg (2.22 mmol) of **4b** and 1.958 g (10.27 mmol) of *p*-toluenesulfonyl chloride in 5 ml of pyridine was allowed to remain at room temperature for 19 h. The gum that separated upon the addition of crushed ice and 5 ml of concentrated HCl was worked with a rod until it solidified. The product was filtered, washed with water, dried, and crystallized from petroleum ether yielding 1.235 g (97%) of **4c** with mp 157–161.5 °C, dec ~200 °C. Recrystallization from ether–cold methanol gave mp 167.5–169 °C, dec 215 °C; $[\alpha]_D$ +4°; IR 3605, 3510, 1744, 1600, 1185, 1175 cm^{-1}; NMR 37 (s, 3, 18-H), 42 (s, 3, 19-H), 144 (s, 3, ArMe), 164 (s, 1, OH), 350 (d, J = 8 Hz, 1, C-7 H), 438 (d, J = 8 Hz, 2, ArH), and 473 Hz (d, J = 8 Hz, 2, ArH).

Anal. Calcd for $C_{34}H_{52}O_5S$ (572.86): C, 71.29; H, 9.15; S, 5.60. Found: C, 71.01; H, 9.33; S, 5.42.

Reaction of 7β-Bromo and 7β-Tosyloxy Ketones with Methanolic Potassium Hydroxide. General Procedure. To a magnetically stirred suspension of the steroid in Me_2SO was added a volume of standardized methanolic potassium hydroxide solution ("base").[3,6a] After a time at room temperature, the pale yellow solution was poured into an ice–salt–water mixture. The mixture was extracted twice with ether and the combined extracts were washed twice with salt water, dried, and evaporated. The products were isolated as indicated.

A. Bromo Ketone 2c. Treatment of 3.338 g (6.932 mmol) of **2c** with 4.60 ml of 1.21 N base in 115 ml of Me_2SO for 21 min gave a yellow oil that was chromatographed on 45 g of silica gel. Elution with 63% benzene–petroleum ether gave a white solid that was recrystallized from ether–methanol, yielding 1.475 g of 5,7α-epoxy-5α-cholestan-6-one (**3a**) as long, white needles: mp 96.5–97.5 °C; $[\alpha]_D$ −34°; IR 1810, 880, 855 cm^{-1}; UV 289.5 nm (ε 47); NMR 39 (s, 3, 18-H), 51 (s, 3, 19-H), 290 Hz (s, 1, C-7H).

Anal. Calcd for $C_{27}H_{44}O_2$ (400.62): C, 80.94; H, 11.07. Found: C, 80.78; H, 11.09.

Elution with 85% benzene–petroleum ether gave 169 mg of 5-hydroxy-7α-methoxy-5α-cholestan-6-one (**4d**) as an oil containing a trace of the oxetanone **3a**.

The solid eluted with benzene was recrystallized from methanol, yielding 304 mg of unreacted starting material **2c**, mp 141–142.5 °C, dec 145 °C.

Fractions containing mixtures were combined and rechromatographed on 40 g of silica gel. Recovered were an additional 86 mg of oxetanone **3a**, mp 96.5–97.5 °C; 208 mg of bromo ketone **2c**, mp 142–143 °C, dec 143.5 °C; and 133 mg of the pure methoxy ketone **4d** as an oil that resisted crystallization but which gave the correct analysis: $[\alpha]_D$ −48°; IR 3495, 1720, 1075, 1060 cm^{-1}; UV 330.5 nm (ε 85); NMR 38 (s, 3, 18-H), 46 (s, 3, 19-H), 205 (s, 3, MeO), ~208 (d, J ~ 2 Hz, 1, C-7 H), 296 Hz (s, 1, OH).

Anal. Calcd for $C_{28}H_{48}O_3$ (432.66): C, 77.72; H, 11.18. Found: C, 77.81; H, 11.20.

Based upon recovered **2c**, total yields were 66% for **3a** and ~12% for **4d**.

B. Bromo Ketone 2f. Reaction of 9.172 g (17.00 mmol) of **2f** with 28.60 ml of 1.19 N base in 300 ml of Me_2SO for 7 min gave an oil that was chromatographed on 300 g of alumina. Elution with 25% ether–benzene gave semicrystalline material that crystallized from methanol, giving 3.753 g of 3β-hydroxy-5,7α-epoxy-5α-cholestan-6-one (**3b**) as white needles with double mp 70–75, 108–110 °C. Recrystallization from petroleum ether gave white prisms of **3b**: mp 108–110 °C; $[\alpha]_D$ −29°; IR 3630, 3440, 1812, 910, 885 cm^{-1}; UV 288.5 nm (ε 44); NMR 40.5 (s, 3, 18-H), 54 (s, 3, 19-H), 141 (s, 1, OH), 228 (m, $W_{1/2}$ = 24 Hz, 1, C-3 H), 297 Hz (s, 1, C-7 H) [lit.[6a] mp 174–177 °C; $[\alpha]_D$ 0°; IR 3612, 3430, 1815 cm^{-1}].

Further elution with 25% ether–benzene gave 1.275 g of solid that was recrystallized from petroleum ether, yielding 817 mg of 3β,5-dihydroxy-7α-methoxy-5α-cholestan-6-one (**4e**): mp 147–148 °C; $[\alpha]_D$ −48°; IR 3630, 3485, 1712, 1080, 1060 cm^{-1}; UV 331 nm (ε 84); NMR 39 (s, 3, 18-H), 48 (s, 3, 19-H), 206 (s, 3, MeO), ~208 (d, J ~ 2 Hz, 1, C-7 H), 244 (m, $W_{1/2}$ = 26 Hz, 1, C-3 H), ~244, 296 Hz (s, 2, OH).

Anal. Calcd for $C_{28}H_{48}O_4$ (448.66): C, 74.95; H, 10.78. Found: C, 74.72; H, 10.77.

The residues from all mother liquors were combined and rechromatographed on 50 g of alumina. Recovered were 523 mg of oxetanone **3b**, mp 111.5–113 °C, and 215 mg of the methoxy ketone **4e**, mp 145–147 °C.

Total yields: **3b**, 60%; **4e**, 14%.

C. Bromo Ketone 2i. The reaction of 2.699 g (5.002 mmol) of **2i** with 6.20 ml of 1.21 N base in 90 ml of Me_2SO for 7 min gave a colorless oil that was chromatographed on 40 g of silica gel. All fractions contained mixtures of oxetanone **3d** and other products. The fraction (259 mg) containing oxetanone of highest purity was recrystallized twice from 95% ethanol, giving 126 mg of pure 3α-hydroxy-5,7α-epoxy-

5α-cholestan-6-one (**3d**) as small, white needles: mp 112.5–114 °C; [α]D −37°; IR 3610, 3480, 1810, 910, 885 cm^{-1}; UV 286.5 nm (ε 57); NMR 40.5 (s, 3, 18-H), 52 (s, 3, 19-H), 129 (s, 1, OH), 246 (m, $W_{1/2}$ = 8 Hz, 1, C-3 H), 299.5 Hz (s, 1, C-7 H).

Anal. Calcd for $C_{27}H_{44}O_3$ (416.62): C, 77.83; H, 10.65. Found: C, 78.00; H, 10.63.

Evaporation of the first mother liquor gave an additional 69 mg of **3d**, mp 110.5–112.5 °C. Other fractions (686 mg) rich in **3d** were combined and recrystallized twice from 95% ethanol, giving 48 mg of **3d**, mp 110.5–111.5 °C.

The remaining fractions and mother liquor residues were combined and acetylated in the usual manner.[7] The resulting mixture of acetates could not be resolved by thick layer chromatography on silica gel, hence was chromatographed on 120 g of alumina. Elution with benzene gave six homogeneous fractions which were combined and recrystallized from methanol, yielding 239 mg of 3α-acetoxy-5,7α-epoxy-5α-cholestan-6-one (**3e**) as soft, white needles, mp 93–95 °C. Recrystallization from aqueous methanol gave mp 94–95.5 °C; [α]D −37°; IR 1810, 1738, 918, 885 cm^{-1}; UV 289.5 nm (ε 61); NMR 40.5 (s, 3, 18-H), 53 (s, 3, 19-H), 125 (s, 3, AcO), 296 (s, 1, C-7 H), 304 Hz (m, $W_{1/2}$ = 10 Hz, 1, C-3 H).

Anal. Calcd for $C_{29}H_{46}O_4$ (458.66): C, 75.94; H, 10.11. Found: C, 75.82; H, 10.18.

Total yield of oxetanone (**3d** + **3e**) 22%. All other fractions contained inseparable mixtures.

D. Tosyloxy Ketone 4c. A suspension of 346 mg (0.604 mmol) of **4c** in 16 ml of Me_2SO was treated with 0.50 ml of 1.179 N base for 10 min. The resulting oil was chromatographed on 14 g of silica gel. Elution with 80% benzene–petroleum ether produced 71 mg of a solid that was recrystallized from ether–methanol to give 50 mg (21%) of oxetanone **3a**, mp 95–96 °C. Further fractions contained mixtures of starting material and unidentified products.

3β-Acetoxy-5,7α-epoxy-5α-cholestan-6-one (3c). A sample (138 mg, 0.331 mmol) of oxetanone **3b** was acetylated in the usual manner.[6a] Recrystallization of the product from methanol gave 107 mg (70%) of **3c**: mp 110–110.5 °C; [α]D −36°; IR 1810, 1740, 910, 885 cm^{-1}; UV 287.5 nm (ε 44); NMR 40.5 (s, 3, 18-H), 54 (s, 3, 19-H), 121.5 (s, 3, AcO), 290 (m, $W_{1/2}$ = 24 Hz, 1, C-3 H), 295 Hz (s, 1, C-7 H) [lit.[6a] mp 108–111 °C; [α]D −23.3°; IR 1815, 1730 cm^{-1}]. Recrystallization from aqueous ethanol did not alter the melting point.

Registry No.—**2a,** 19043-54-0; **2b,** 60009-78-1; **2c,** 60803-76-1; **2d,** 1258-38-4; **2e,** 50630-98-3; **2f,** 50631-05-5; **2g,** 60803-77-2; **2h,** 60803-78-3; **2i,** 60803-79-4; **3a,** 60803-80-7; **3b,** 50631-08-8; **3c,** 50801-48-4; **3d,** 60803-81-8; **3e,** 60803-82-9; **4a,** 60803-83-0; **4b,** 60803-84-1; **4c,** 60803-85-2; **4d,** 60803-86-3; **4e,** 60803-87-4; PHP, 39416-48-3.

References and Notes

(1) This work was supported, in part, by grants from the Merck Co. Foundation and the Committee on Educational Aid of E. I. du Pont de Nemours and Co. The competent technical assistance of Thomas P. Demuth, Jr., Robert B. Nachbar, Jr., and Scott R. Wilson is gratefully acknowledged.
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(13) In comparison to the relative facility with which **2b** was isomerized to **2c**, the C-5 epimer[3] of bromo ketone **2e** was recovered unchanged after 186 h at room temperature when treated with an equal mass of LiBr in DMF. Further treatment of the same sample with a 2.4-fold excess of LiBr in DMF at room temperature for 92 h gave no reaction. The difficulty encountered in the epimerization in the 5β-hydroxy series may be ascribed to the unfavorable interactions of the C_5–OH, C=O, and C_7–Br dipoles in the resulting 7β-bromo compound.

Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. 47. Cannabinoid Compounds[1]

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Received July 19, 1976

The ^{13}C NMR spectra of (−)-Δ^9-THC, (−)-Δ^8-THC, (±)-Δ^8-*abn*-THC, (±)-*cis*-Δ^9-THC, and four related ketones were recorded and their carbon shifts assigned. A ^{13}C NMR spectral diagnosis of the position of the double bond, location of the aromatic hydroxy and *n*-pentyl groups, and stereochemistry of the bridgeheads in THC derivatives is portrayed. A pyridine-induced shift procedure for the determination of phenol substitution patterns is introduced.

Several years have passed since the appearance of a ^{13}C NMR analysis of Δ^8- and Δ^9-tetrahydrocannabinol (THC) and some of their derivatives.[2,3] The carbon shift assignment had been based preponderantly on the correlation of the δ values among a small group of related compounds. In the light of present, better understanding of the chemical shift parameter as a function of bonding configuration, several shift correlations in the previous study are suspect. As a consequence a reinvestigation of Δ^8- and Δ^9-THC, with the use of additional ^{13}C NMR structure probes, was instituted, the goal of which being not only the proper shift assignment of the tetrahydrocannabinols but also the ^{13}C NMR differentiation of the natural products from their positional and stereochemical isomers. In the course of this work a technique for the recognition of the substitution pattern of phenols also came under study.

The analysis of eight substances—ketones **1a**,[5] **1b**, **1c**, and **2**,[5] (−)-Δ^9-THC (**3**),[6,7] (−)-Δ^8-THC (**4a**),[6,7] (±)-Δ^8-*abn*-THC (**4b**), (±)-*cis*-Δ^9-THC (**5**)[5]—was undertaken. The positional isomer **4b** of Δ^8-THC and its ketone precursor **1c** were prepared in the following fashion. Treatment of the chromanone **6a**, prepared by the acid-induced condensation of olivetol and β-methylcrotonic acid,[5] with benzyl bromide and base and subsequent formylation of the resultant benzyl ether **6b**