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# The True Course of the Solvolysis of 3β-Tosyloxy-5β-hydroxycholestan-6-one, or the $S_N2$ Inversion Rule Upheld

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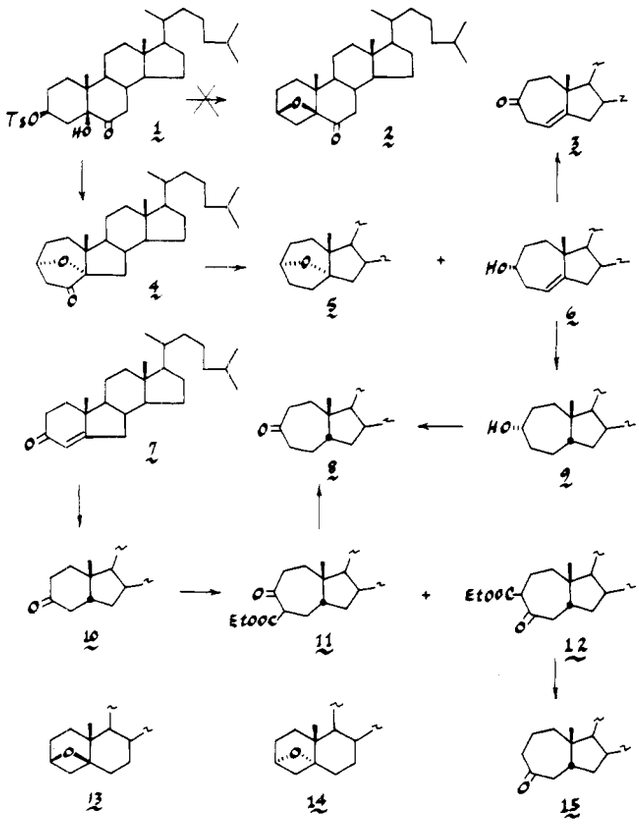
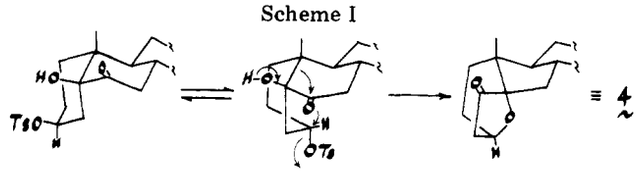
The product of solvolysis of 3β-tosyloxy-5β-hydroxycholestan-6-one (**1**) has been shown to be the *A*-homo-*B*-norketo oxide **4** by $^1H$ NMR spectroscopy and transformation into ketone **8**, which was synthesized by A-ring expansion of *cis*-*B*-norcholestan-3-one (**10**). The formation of **4** follows the rearrangement sequence in Scheme I with inversion at C-3. The rearrangement occurs in both the forward and reverse directions under a variety of conditions.

The requirement of inversion in the $S_N2$ reaction at carbon is one of the basic tenets of organic reaction mechanisms.[1] While theoretical calculations have predicted certain circumstances under which retention in an $S_N2$ reaction might be observed, the search for an actual example has so far met with failure.[1] In this regard, the report[2] some time ago of the solvolysis of 3β-tosyloxy-5β-hydroxycholestan-6-one (**1**) was



of more than passing interest. The product obtained from a variety of solvents was assigned the oxetanone structure **2**, and it was suggested that the reaction proceeded via a transition state involving "partial bonding from the oxygen [at C-5] to C-3 before significant carbonium ion character at C-3 is developed."[2a] Although the reaction caused raised eyebrows,[3,4]

Scheme I



it has not been challenged.[5,6] Our attention was attracted because such a transition state amounts to an unprecedented retention of configuration during an $S_N2$ substitution.[7] Also, if the reaction were really the simple displacement suggested, it is difficult to understand why the C-3 epimer of **1** with the correct stereochemistry for a normal $S_N2$ reaction with inversion was inert under the same conditions.[2a] When it is further considered that the carbonyl IR absorption (1757 $cm^{-1}$ in $CCl_4$) of the solvolysis product is not appropriate for an α-alkoxycyclohexanone (expected[8] 1713–1724 $cm^{-1}$ in $CCl_4$), it was clear that a more plausible rationalization of the reaction was required.

An alternative course for the solvolysis which would not require violation of the $S_N2$ inversion rule involves participation of the 6-carbonyl oxygen of **1** in a displacement at C-3 with concomitant stereoelectronically favorable A/B ring rearrangement as shown in Scheme I.[9] This reaction leads by inversion at C-3 to a different keto oxide **4** whose 3-oxotetrahydrofuranyl carbonyl group would absorb at about 1757 $cm^{-1}$.[10] Moreover, the mechanism of Scheme I accounts for the failure of the C-3 epimer of **1** to react since it could not do so with inversion.[11]

Structures **2** and **4** are readily distinguishable by $^1H$ NMR spectroscopy in conjunction with deuterium exchange experiments. While each structure has an H–C–O group with the hydrogen coupled to two adjacent methylene groups and each has a carbonyl α-methylene group, only **4** has the exchangeable α-methylene adjacent to the H–C–O group. In the preparation of the solvolysis product for these experiments, the use of anhydrous isopropyl alcohol gave the best yield in our hands. The compound incorporated two, and only two, deuterium atoms on exchange in NaOD–$D_2O$–dioxane with the disappearance of two protons from the δ 2–3 region of its $^1H$ NMR spectrum (Figure 1).[12] The pattern of the H–C–O signal in the $d_2$ solvolysis product was now much simplified (Figure 1), proving that the exchanged hydrogens had been

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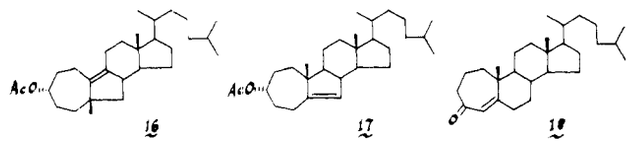
coupled to this proton. In confirmation, when the two sets of peaks in the δ 2–3 region of the spectrum of the nondeuterated solvolysis product were irradiated, the same simplification of the H–C–O signal at δ 4.68 resulted. Therefore, structure **2** was excluded as a possibility for the solvolysis product, and structure **4** was strongly favored. Chemical proof for structure **4** was obtained as follows.

Wolff–Kishner reduction of the solvolysis product yielded mostly the normal reduced oxide **5** together with about 10% of the homoallylic alcohol **6** from the characteristic reductive elimination of α-alkoxy ketones. The physical constants of the oxide, mp 43 °C and $[\alpha]_D$ −10°, were not identical with those of either cholestane 3α,5α-oxide (**14**) (mp 86 °C, $[\alpha]_D$ +59°)[13] or cholestane 3β,5β-oxide (**13**) (mp 55 °C, $[\alpha]_D$ +45°).[14] The small proportion of the homoallylic alcohol **6** encouraged attempts to obtain more by cleavage of the ether bridge of the major product **5**. With $BF_3$·$Et_2O$–$Ac_2O$ at room temperature the only product was a monoacetate of rearranged structure, probably **16**.[15,16] However, when the reaction temperature was




**16** **17** **18**

lowered to 0–5 °C, two other products could be intercepted, one of which was probably **17**, and the other was the acetate of the desired **6** which was saponified. The $^1H$ NMR spectrum of the alcohol contained one olefinic H at δ 5.30 coupled to an adjacent $CH_2$ in agreement with **6**. Note that this alcohol was not identical with cholesterol, the expected reductive elimination product from **2**; nor was the unsaturated ketone obtained by Corey oxidation of the alcohol identical with $\Delta^5$- or $\Delta^4$-cholesten-3-one. This ketone, **3**, mp 103.5 °C, was unconjugated and still contained a trisubstituted double bond whose olefinic proton signal at δ 5.40 was coupled to the ketone α-methylene at δ 2.9–3.6 (double irradiation). The β,γ position of the double bond in **3** was more stable than the α,β-conjugated arrangement since deuterium exchange under equilibrating conditions in NaOD–$D_2O$–dioxane gave **3**-$d_4$ as the product.[17] In the ketone-$d_4$, the O=$CCH_2$C=C proton signals at δ 2.9–3.6 were absent and the olefinic H was a broadened singlet ($w_{1/2}$ = 6 Hz) as expected for **3**-*2,2,4,4*-$d_4$.

Final confirmation of the *A*-homo-*B*-nor carbon skeleton of the solvolysis product **4** came from correlation with a compound of unambiguous carbon skeleton synthesized from the known *B*-nor-$\Delta^4$-cholesten-3-one (**7**).[18,19] Attempts to expand the A ring of **7** directly to **3** with diazomethane–$BF_3$·$Et_2O$ according to the conditions successfully used on $\Delta^4$-cholesten-3-one[17a] gave only polyhomologation and no detectable **3**. Diazoacetic ester–$Et_3O^+BF_4^-$ ring expansion of $\Delta^4$-cholesten-3-one as a model for **7** gave, after hydrolysis and decarboxylation, only the undesired conjugated ketone **18** in low yield. Attempted A-ring expansion of $\Delta^4$-cholesten-3-one (as a model for **7**) by ring opening of the two cyclopropyl ketones obtained from the Simmons–Smith reaction did not lead to *A*-homo ketones.

After these unsuccessful approaches to prepare **3**, a different tack was tried. Hydrogenation of **7** with Pd/C in methanol gave the saturated ketone **10** whose cis A/B ring junction has previously been proved by ORD comparison of both the cis and trans ketones[20] and is now corroborated by its $^{13}C$ NMR spectrum.[21] A-Ring expansion of **10** by diazoacetic ester–$Et_3O^+BF_4^-$ produced an approximately 1:1 mixture of the two β-keto esters **11** and **12** which was hydrolyzed and decarboxylated to a mixture of **8** and **15**.[22] After thick-layer separation, structures could be assigned unambiguously on the basis of established reversal in Cotton effect of the ORD curves of such cis *A*-homo-3- and -4-keto steroids[23] because the shapes of the

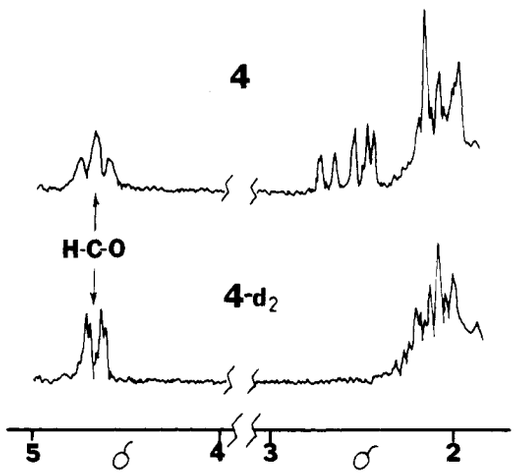



**Figure 1.** Pertinent parts of the 100 MHz $^1H$ NMR spectra of the keto oxide from solvolysis of **1** and the deuterated keto oxide.

cis *A*-homo-*B*-nor ketones in their various conformations are very nearly those of the cis *A*-homo/chair B-ring ketones. The less polar of the two ketones, mp 79 °C, with the negative Cotton effect is the 4-ketone **15**, while the more polar ketone, mp 106 °C, with the small positive Cotton effect is the 3-ketone **8**. The latter was found to be identical (melting point, mixture melting point, $[\alpha]_D$, and $^{13}C$ NMR) with the ketone **8** obtained from Wolff–Kishner alcohol **6** as follows. Hydrogenation of **6** with Pd/C in methanol gave the saturated alcohol **9**, whose A/B cis ring fusion was certain from its $^{13}C$ NMR spectrum,[21] and oxidation of this alcohol gave the pure A/B cis ketone **8**.

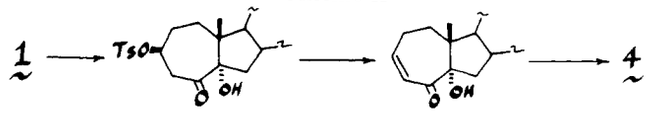
The only feature of **4** for which evidence has not yet been presented is the orientation of the oxide ring which must be the same as the orientation of the hydroxyl group in the homoallylic alcohol **6**. The fused cycloheptene ring of **6** will adopt the more stable chair conformation,[24] whose lack of flexibility and absence of pseudorotation allow the use of band half-widths for stereochemical assignment. The $w_{1/2}$ of 9 Hz for the H–C–O signal of **6** at δ 4.01 is only consistent with the equatorial β configuration for this hydrogen.[25] Similarly, the $w_{1/2}$ of the H–C–O peak in the somewhat more flexible dihydro compound **9** was 11 Hz. Therefore, the hydroxyl group must have the axial α configuration in conformation **19**, in agreement with the α-oxide stereochemistry in **4** as required by Scheme I.

There is an alternative sequence (see Scheme II) which could be envisioned for the formation of the now proven structure **4** of the solvolysis product. However, the 5-endo-trig conjugate addition would not be expected to occur since the reverse elimination does not.[12] Also, if this path were followed, the 3α-tosylate epimer of **1** should give **4** contrary to observation.

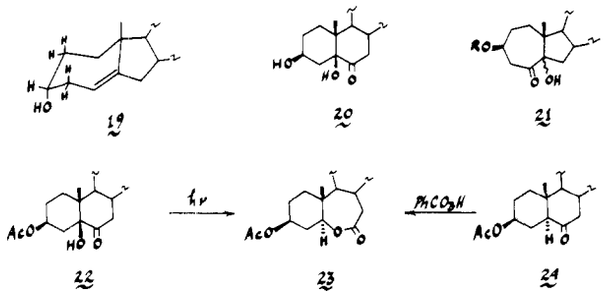
The revised formula **4** readily accommodates the many facts recorded[2b] about the chemistry of the solvolysis product. For example, the 0.5 ppm upfield shift of the C-3 H–C–O proton on the reduction of the ketone[2b] is expected for **4** but not for **2**; the resistance of the oxide ring of the alcohol corresponding to **4** to $BF_3$ at room temperature is not surprising, whereas it would be for the oxide ring of the alcohol from **2**.[15]

At this point, the question must be raised of whether the

Scheme II



tosylate 1 and its parent diolone **20** really have six-membered A and B rings or whether they are perhaps already rearranged

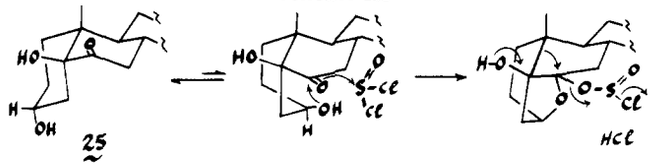


to **21** (R = H or Ts) since ketol rearrangements can occur readily under both basic and acidic conditions. Although the starting diolone **20** has been oxidized to the hydroxy diketone, which has been dehydrated to the conjugated enedione both in acid and base,[26] these are conditions which could conceivably allow rearrangement of the skeleton of **20.** The most convincing evidence that the diolone and its acetate, **20** and **22,** do have the six-ring structure is that of Cookson et al., who have cleaved photochemically the acetate **22** under neutral conditions and obtained the lactone acetate **23,** identical with one of the Baeyer–Villiger cleavage products of 3β-acetoxycholestan-6-one (**24**).[27] The tosylate is prepared from **20** under conditions not expected to promote ketol rearrangements, and its $^{13}C$ NMR spectrum (see Experimental Section) is almost identical with that of the diolone acetate **22.** Therefore, it is correctly assigned structure **1.**

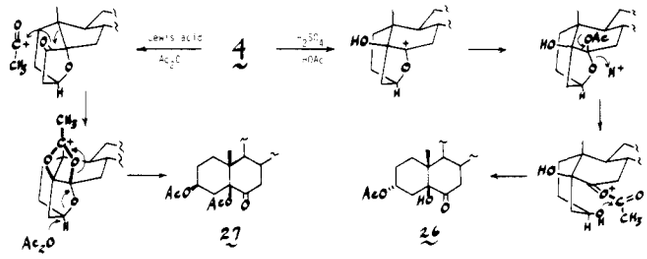
Finally some reactions requiring comment illustrate how generally this A/B rearrangement occurs in both directions. One of the reactions, which shows that even the 3α-OH configuration is permissible if the rearrangement is initiated at the other end, is the rearrangement of **25** to **4** on treatment with $SOCl_2$;[2b] this observation is readily accounted for by Scheme III. Two other reactions show that the retro-rearrangement of **4** can lead to either the 3α- or 3β-OH configuration. As reported earlier[2b] and confirmed by us, **4** reacts with $H_2SO_4$–HOAc to yield the 3α-OAc epimer **26** of the original 3β,5β-diolone **20.** However, when $BF_3$·$Et_2O$–$Ac_2O$ or $SnCl_4$–$Ac_2O$ reacts with **4,** the product is cleanly the 3β,5β-diOAc **27.** One of the ways in which this difference in reaction course can be rationalized is depicted in Scheme IV.

The keto oxide **4** is also rearranged to the 3α,5β-diolone structure with aqueous $HClO_4$ in THF and under thioketalization conditions. Conversely, the 3α,5β-diolone **25** is rearranged thermally to **4** at 200 °C, whereas the 3β,5β-epimer **20** is inert under these conditions.

Scheme III



Scheme IV



## Experimental Section

**General.** Melting points were determined on a Reichert-Kofler microscope hotstage and are corrected. UV spectra were recorded with MeOH solutions on a Cary Model 118 spectrophotometer. IR spectra were recorded on a Beckman Acculab 4 instrument with $CHCl_3$ solutions. The $^1H$ NMR spectra were recorded on Varian T-60 and XL-100 spectrometers with $CDCl_3$ solutions containing $Me_4Si$; reported peaks are from 100 MHz spectra. The $^{13}C$ NMR spectra were run in with $CDCl_3$ solutions on a Varian XL-100 instrument.[21] Abbreviations in proton spectrum descriptions are the following: b = broad, s = singlet, d = doublet, t = triplet, m = multiplet, and $w_{1/2}$ = band half-width. Optical rotations were measured with $CHCl_3$ solutions in a 1-dm tube on a Rudolph Model 80 polarimeter. ORD curves were measured on a Jasco UV/ORD-5 instrument. Exact masses and deuterium analyses were determined on a MAT 311A mass spectrometer.

Camag DF-5 silica gel was used for thick- and thin-layer chromatography. TLC plates were sprayed with a 4:1 $H_2SO_4$–$HNO_3$ mixture. Unless otherwise specified, preparative plates were 20 × 20 cm and contained 20 g of silica gel. A UV lamp or $I_2$ vapor was used to visualize bands.

Reactions were worked up by partitioning between water and ether or $CHCl_3$. Organic solutions were washed to neutrality and dried with saturated NaCl solution and anhydrous $MgSO_4$ before being evaporated at aspirator vacuum on a rotating evaporator.

Microanalyses were done in the Analytische Laboratorien, Engelskirchen, West Germany.

P.E. refers to petroleum ether, bp 65–68 °C, and p.e. refers to petroleum ether, bp 30–60 °C.

**3β,5β-Dihydroxycholestan-6-one (20).** 3β,5α-Dihydroxycholestan-6-one was prepared by oxidation of cholestane-3β,5α,6β-triol with NBS–water–dioxane according to the procedure of Fieser and Rajagopalan[28] and used without further purification (TLC showed less than 5% triol contaminant). A mixture of 1.40 g of this ketone was refluxed with 50 mL of 10% methanolic KOH for 12 h according to published procedures.[9,27,29] Workup gave an oily solid mixture which was separated by preparative TLC (benzene–ether, 75:25). The band at $R_f$ 0.50 gave 620 mg (44%) of a colorless oil which crystallized on trituration with p.e. Two recrystallizations from ether–p.e. gave 290 mg of granules of pure **20:** mp 100–101.5 °C; $[\alpha]^{20}_D$ − 5.8° (*c* 2.00, $CHCl_3$) (lit.[27] mp 62 °C, $[\alpha]_D$ −6°; lit.[29] noncrystalline, $[\alpha]_D$ −5.5°; lit.[26] noncrystalline, $[\alpha]_D$ −5°); IR 3460 (OH) and 1700 (C=O) $cm^{-1}$; $^1H$ NMR δ 0.66, 0.74, 0.82, and 0.96 (4 peaks from Me), 4.05 (b d , 1 H, *J* = 9 Hz, H-C-O), 4.34 (d, 1 H, *J* = 9 Hz, OH), and 4.42 (s, 1 H, OH). Molecular ion calcd for $C_{27}H_{46}O_3$, 418.3447; found, 418.3443.

A sample prepared by the method of Rowland[26] and purified by preparative TLC was identical (melting point, mixture melting point, TLC, IR, and $^1H$ NMR) with the above material.

**3β-Tosyloxy-5β-hydroxycholestan-6-one (1).** The 3β-*p*-toluenesulfonate **1** was prepared by allowing 1.80 g of diolone **20** and 3.60 g of *p*-TsCl in 18 mL of dry pyridine to stand at room temperature for 8 days according to the procedure of Rowland and Sands.[30] Workup and two recrystallizations from $CHCl_3$–P.E. gave 850 mg (34%) of tosylate **1:** mp 140.5–141 °C dec; $[\alpha]^{19.5}_D$ −9.7° (*c* 1.00, $CHCl_3$) [lit.[30] mp 144–145 °C dec, $[\alpha]_D$ −11° (*c* 1.35)]; IR 3740 (OH) and 1705 (C=O) $cm^{-1}$; $^1H$ NMR δ 0.63, 0.73, 0.83, 0.90, and 0.94 (5 peaks from Me), 2.40 (s, 3 H, $ArCH_3$), 3.83 (b s, 1 H, OH), 4.90 (m, 1 H, H-C-O), and 7.46 ($A_2B_2$, 4 H, ArH).

The $^{13}C$ NMR spectra of the diolone **20,** the diolone 3β-acetate **22,**[26] and the diolone 3β-tosylate **1** were identical within experimental error except for C-2, C-3, C-4, and C-5. The differences in the chemical shifts listed below (in this order) for these carbon atoms are those expected to result from the change of OH to OAc to OTs on the same structure: **20,** δ 28.0, 65.5, 37.2, and 81.9; **22,** δ 25.6, 67.4, 34.9, and 80.0; **1,** δ 25.4, 75.7, 35.8, and 79.5.

**3α,5α-Oxido-*A*-homo-*B*-norcholestan-4a-one (4).** A solution of 200 mg of **1** in 5 mL of dry *i*-PrOH[31] was refluxed for 6 h. Most of the *i*-PrOH was removed by distillation, and the residual granular solid was chromatographed directly on a preparative plate developed in benzene–ether (95:5). Extraction of the band at $R_f$ 0.5 gave 80 mg (57%) of colorless **4,** mp 112–113 °C. Two recrystallizations from acetone–MeOH raised the melting point to 114–115 °C: $[\alpha]^{19}_D$ +16° (*c* 1.43, $CHCl_3$) (lit.[2b] mp 115–116.5 °C, $[\alpha]_D$ +14°); IR 1747 $cm^{-1}$ in $CHCl_3$ and 1752 $cm^{-1}$ in $CCl_4$ (five-ring C=O); $^1H$ NMR δ 0.64, 0.74, 0.83, and 0.90 (4 peaks from Me) and 4.68 (b t, 1 H, H-C-O). Molecular ion calcd for $C_{27}H_{44}O_2$, 400.3341; found, 400.3339.

**Wolff–Kishner Reduction of 4.** A solution of 300 mg of oxido ketone **4,** 900 mg of NaOH, and 3 mL of 85% $H_2NNH_2$·$H_2O$ in 5 mL of diethylene glycol was stirred (magnetic bar) and heated at 180 °C

under $N_2$ for 3 h. After distillation of water and excess $H_2NNH_2$, heating was continued at 210 °C for 3 h more. Workup gave an amber oil which was chromatographed on a preparative plate developed in benzene–ether (90:10). Extraction of the band at $R_f$ 0.73 gave 160 mg (55%) of oily solid **3α,5α-oxido-*A*-homo-*B*-norcholestane.** Two recrystallizations from acetone at −70 °C gave colorless needles of **5**: mp 41.5–43 °C; $[\alpha]^{19}_D$ −10.1° (*c* 2.05, $CHCl_3$); IR, no OH or C=O absorption; $^1H$ NMR δ 0.65, 0.73, 0.83, and 0.89 (4 peaks from Me) and 4.28 (m, 1 H, H-C-O). Molecular ion calcd for $C_{27}H_{46}O$, 386.3548; found, 386.3545.

Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.72; H, 12.08.

Extraction of the band at $R_f$ 0.42 yielded 30 mg (10%) of **3α-hydroxy-*A*-homo-*B*-nor-4a-cholestene (6)** as a colorless foam (later obtained crystalline): IR 3440 $cm^{-1}$ (OH); $^1H$ NMR δ 0.66, 0.82, 0.89, and 0.93 (4 peaks from Me), 4.01 (m, $w_{1/2}$ = 9 Hz, 1 H, H-C-O), and 5.30 (m, 1 H, HC=C). Additional constants are reported below for the crystalline sample obtained from **5**.

On the same TLC plate developed in benzene–ether (50:50), **6** had $R_f$ 0.55 and cholesterol had $R_f$ 0.42. For comparison, 3-*epi*-cholesterol has mp 142–143 °C and $[\alpha]_D$ −42° ($CHCl_3$).[32]

***A*-Homo-*B*-nor-4a-cholesten-3-one (3).** A mixture of 98 mg of **6**, 250 mg of pyridinium chlorochromate, and 3 mL of $CH_2Cl_2$ was stirred (magnetic bar) at room temperature for 1.5 h. The soluble part of the reaction mixture was chromatographed directly on a preparative plate developed in benzene–ether (95:5). Extraction of the band at $R_f$ 0.69 gave 78 mg (80%) of colorless solid **3** which after two recrystallizations from ether–methanol afforded 45 mg of flat plates of **3**: mp 102–103.5 °C; $[\alpha]^{20}_D$ +159° (*c* 1.53, $CHCl_3$); IR 1700 $cm^{-1}$ (C=O); UV $\lambda_{max}$ 290 (ε 214) and rising end absorption with $\epsilon_{210}$ 7200; $^1H$ NMR δ 0.71, 0.85, 0.92, and 1.06 (4 peaks from Me) and 5.40 (m, $w_{1/2}$ = 16 Hz, 1 H, HC=C). Molecular ion calcd for $C_{27}H_{44}O$, 384.3392; found, 384.3387.

Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.22; H, 11.44.

For comparison, $\Delta^5$-cholesten-3-one has mp 127 °C and $[\alpha]_D$ −4.2° ($CHCl_3$).[33]

**Deuterium Exchanges. (a)** A solution of 15 mg of keto oxide **4** in 0.8 mL of stock deuteration solution (25 mg of Na + 1 mL of $D_2O$ + 1 mL of dioxane) was heated in a sealed tube at 85 °C for 51 h. The contents were taken in ether, washed with $D_2O$, dried, and concentrated to leave 13 mg of colorless solid **4**-$d_2$ which gave a single TLC spot: $^1H$ NMR δ 4.68 (d of closely spaced d, 1 H, H-C-O) (see Figure 1). Deuterium analysis by mass spectroscopy at 20 eV gave 1.4% $d_0$, 9.7% $d_1$, and 88.9% $d_2$.

**(b)** A solution of 13 mg of unsaturated ketone **3** in 0.5 mL of stock deuteration solution [see (a) above] was heated in a sealed tube at 85 °C for 2 h. Workup as above gave 12 mg of colorless solid **3**-$d_4$ which gave a single TLC spot. $^1H$MR absorption in the δ 2.6–3.6 region was missing, and the olefinic H at δ 5.40 was now a broadened singlet with $w_{1/2}$ = 6 Hz. Deuterium analysis by mass spectroscopy at 20 eV gave 0.3% $d_1$, 1.7% $d_2$, 16.4% $d_3$, and 81.5% $d_4$.

***A*-Homo-*B*-norcholest-4a-ene (30).** A solution of 78 mg of ketone **3**, 2 NaOH pellets, and 1 mL of 85% $H_2NNH_2 \cdot H_2O$ in 1 mL of diethylene glycol was treated as for the reduction of **4**. The crude reaction product was chromatographed on a preparative plate developed in P.E.–benzene (75:25). Extraction of the band at $R_f$ 0.88 gave 42 mg (56%) of colorless solid. Two recrystallizations from ether–MeOH gave 22 mg of plates: mp 94–96 °C (lit.[18] mp 84–86 °C); UV $\epsilon_{210}$ 8090; IR, no OH or C=O absorption; $^1H$ NMR δ 5.50 (m, 1 H, =CH–); $^{13}C$ NMR δ 121.1 (=CHR) and 153.7 (=$CR_2$). Impurity peaks were at δ 115.8 (=CHR), 123.5 (=CHR), 130.1 (=CHR), and 130.9 (=CHR). Molecular ion calcd for $C_{27}H_{46}$, 370.3599; found, 370.3593.

***A*-Homo-*B*-nor-5β-cholestan-3α-ol (9).** A solution of 108 mg of homoallylic alcohol **6** in 6 mL of MeOH was hydrogenated for 7.5 h at room temperature and atmospheric pressure in the presence of 25 mg of 10% Pd/C catalyst. The filtered solution was concentrated and chromatographed on two preparative plates with four developments in benzene–ether (90:10). The band at $R_f$ 0.69 yielded 67 mg of colorless solid which after two recrystallizations from MeOH gave 34 mg of colorless granules of the A/B cis alcohol **9**: mp 105–107 °C; $[\alpha]^{20}_D$ +14.6° (*c* 1.30, $CHCl_3$); IR 3610 and 3470 $cm^{-1}$ (OH); $^1H$ NMR δ 0.63, 0.82, 0.88, and 0.93 (4 peaks from Me) and 4.00 (m, $w_{1/2}$ = 11 Hz, 1 H, H-C-O). Molecular ion calcd for $C_{27}H_{48}O$, 388.3705; found, 388.3705. The A/B cis ring fusion was clear from the $^{13}C$ chemical shift of C-19 at δ 25.5 relative to δ 12.3 for C-18.[21]

The preparative layer band at $R_f$ 0.75 yielded 16 mg of colorless oily solid which was mostly unreduced **6** ($^{13}C$ NMR spectrum).

***A*-Homo-*B*-nor-5β-cholestan-3-one (8).** A mixture of 35 mg of saturated alcohol **9** and 35 mg of pyridinium chlorochromate in 2 mL of $CH_2Cl_2$ was stirred (magnetic bar) at room temperature for 1 h. The filtered and concentrated solution was chromatographed on a 10-g preparative layer plate developed in benzene–ether (95:5). The band at $R_f$ 0.39 gave 25 mg of colorless solid, mp 104–106 °C. Two recrystallizations from MeOH gave colorless plates of the ketone **8**: mp 105–106 °C; $[\alpha]^{21}_D$ +19.6° (*c* 1.30, $CHCl_3$); IR 1695 $cm^{-1}$ (C=O); $^1H$ NMR δ 0.67, 0.84, 0.90, and 0.95 (4 peaks from Me). Molecular ion calcd for $C_{27}H_{46}O$, 386.3548; found, 386.3549.

Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 84.03; H, 11.93.

The A/B cis ring fusion was confirmed by the $^{13}C$ chemical shift of C-19 at δ 24.3 relative to δ 12.3 for C-18.[21]

**Reaction of Oxide 5 with $BF_3$. (a)** To a solution of 55 mg of **5** in 0.3 mL of $Ac_2O$ was added 3 drops of redistilled $BF_3$ etherate. After 0.5 h at room temperature, the brown reaction mixture was distilled to dryness under aspirator vacuum. The residual viscous oil was refluxed for 1 h in 1 mL of MeOH containing two KOH pellets. After evaporation of MeOH, the residue was chromatographed on a preparative plate (10 g of silica gel) developed in benzene–ether (95:5). Extraction of the band at $R_f$ 0.54 gave 24 mg of colorless solid. Two recrystallizations from ether–p.e. gave colorless needles of rearranged alcohol, probably **16** (OH for OAc): mp 124.5–125.5 °C; $[\alpha]^{20}_D$ +48.7° (*c* 1.35, $CHCl_3$); IR 3600 $cm^{-1}$ (OH); $^1H$ NMR δ 0.72, 0.83, and 0.90 (3 peaks from Me) and 3.58 (m, $w_{1/2}$ = ~20 Hz, 1 H, H-C-O). Molecular ion calcd for $C_{27}H_{46}O$, 386.3548; found, 386.3545.

Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.76; H, 11.48.

**(b)** A solution of 90 mg of oxide **5**, 0.5 mL of $Ac_2O$, and 90 mg of $BF_3 \cdot Et_2O$ in 1 mL of ether was stirred (magnetic bar) at 0–5 °C for 0.5 h. The reaction was quenched with 5% aqueous $NaHCO_3$ and extracted with ether. The residue from evaporation of the ether was refluxed with 1 mL of MeOH and 4 KOH pellets for 1 h. The product was isolated by partitioning between ether and water to yield 67 mg of amber oil which was chromatographed on a preparative plate developed thrice in benzene–ether (90:10). The band at the solvent front afforded 6 mg of recovered **5**.

The band at $R_f$ 0.62 yielded 25 mg of colorless solid **6**. A cumulative yield of 135 mg of material from several such reactions was recrystallized twice from MeOH to give 105 mg of colorless granules of homoallylic alcohol **6**: mp 97–99 °C; $[\alpha]^{18}_D$ +40.3° (*c* 1.32, $CHCl_3$). Molecular ion calcd for $C_{27}H_{46}O$, 386.3548; found, 386.3545. The compound was identical with the homoallylic alcohol from Wolff–Kishner reduction of **4**.

Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.90; H, 11.72.

The band at $R_f$ 0.59 gave 12 mg of colorless solid. From several reactions 26 mg of this material was recrystallized twice from MeOH to give 6 mg of colorless needles of rearranged alcohol, mp 124–125.5 °C, probably **16** (OH for OAc), identical in all respects with the product from (a) above.

The band at $R_f$ 0.48 gave 10 mg of colorless solid. From several reactions 48 mg of the material was recrystallized twice from MeOH to yield 15 mg of colorless granules of what was probably **3α-hydroxy-*A*-homo-*B*-nor-5-cholestene, (17;** OH for OAc): mp 85–88 °C; $[\alpha]^{20}_D$ −50° (*c* 0.93, $CHCl_3$); IR 3600 and 3460 $cm^{-1}$ (OH); $^1H$ NMR δ 0.68, 0.77, 0.83, 0.90, and 0.96 (5 peaks from Me), 3.56 (m, $w_{1/2}$ = 11 Hz, 1 H, H-C-O), and 5.40 (b s, 1 H, C=CH). Molecular ion calcd for $C_{27}H_{46}O$, 386.3548; found, 386.3545.

**Ketone from Rearranged Alcohol.** A mixture of 68 mg of the unsaturated alcohol, probably **16** (OH for OAc), from the room temperature $BF_3$ reaction above, 140 mg of pyridinium chlorochromate, and 3.5 mL of $CH_2Cl_2$ was stirred (magnetic bar) at room temperature for 2 h. The soluble part of the reaction mixture was chromatographed directly on a preparative plate developed in benzene. Extraction of the band at $R_f$ 0.38 gave 55 mg (80%) of colorless solid which after two recrystallizations from MeOH gave plates of the unsaturated ketone **16** (C=O for CHOAc): mp 78–80 °C; $[\alpha]^{20}_D$ +99 ° (*c* 1.29, $CHCl_3$); IR 1695 $cm^{-1}$ (C=O); UV, rising end absorption with $\epsilon_{215}$ 6370; $^1H$ NMR δ 0.74, 0.84, 0.90, and 1.00 (4 peaks from Me) and no olefinic H. Molecular ion calcd for $C_{27}H_{44}O$, 384.3392; found, 384.3387.

***B*-Nor-4-cholesten-3-one (7).** This ketone was prepared by the procedure of ref 19b and 19c and had mp 60–62 °C (lit.[19b] mp 62–64 °C): IR 1660 $cm^{-1}$ (conjugated C=O); $^1H$ NMR δ 5.86 (b s, 1 H, C=CH). Molecular ion calcd for $C_{26}H_{42}O$, 370.3235; found, 370.3233.

***B*-Nor-5β-cholestan-3-one (10).** A solution of 50 mg of conjugated ketone **7** in 2.5 mL of MeOH was hydrogenated at room temperature and atmospheric pressure in the presence of 10 mg of 10% Pd/C for 6 h. The residue from concentration of the filtered solution was chromatographed on a 10-g layer developed twice in benzene–ether (95:5). The band at $R_f$ 0.49 afforded 30 mg (60%) of colorless solid, mp 65–67 °C. Two recrystallizations from MeOH gave 20 mg of colorless

plates of **10**: mp 67.5–69 °C; $[\alpha]^{20}_D$ +19.3° (*c* 1.45, $CHCl_3$) (lit.[20a] mp 68–70 °C, $[\alpha]_D$ +18.5°); IR 1705 $cm^{-1}$ (C=O); $^1H$ NMR δ 0.67, 0.83, 0.90, and 0.94 (4 peaks from Me). Molecular ion calcd for $C_{26}H_{44}O$, 372.3392; found, 372.3390.

The A/B cis ring fusion was confirmed by the $^{13}C$ chemical shift of C-19 at δ 24.9 relative to δ 12.3 for C-18.[21]

***A*-Homo-*B*-nor-5β-cholestan-3-one (8) and *A*-Homo-*B*-nor-5β-cholestan-4-one (15).** To a stirred (magnetic bar) solution of 50 mg (0.13 mmol) of **10** in 0.5 mL of dry $CH_2Cl_2$ at 0 °C was added a solution of 49 mg (0.26 mmol) of freshly prepared $Et_3O^+BF_4^-$ in 0.2 mL of dry $CH_2Cl_2$ followed by a solution of 27 mg (0.24 mmol) of ethyl diazoacetate in 0.2 mL of dry $CH_2Cl_2$. The bath was allowed to warm to room temperature for 3 h. The reaction mixture was recooled to 0 °C, $Et_3O^+BF_4^-$ and ethyl diazoacetate were again added in the same quantities, and the bath was allowed to warm to room temperature for 3 h. After a third repetition of this treatment, TLC showed the complete absence of **10**. Excess 5% $NaHCO_3$ solution was added, and the mixture was extracted with ether to give an amber oil.

The crude keto esters **11** and **12** were decarbethoxylated by heating with 1 mL of water in a sealed tube at 230 °C for 3 h.[34] Partitioning between ether and water gave 43 mg of crude product which was chromatographed on a 10-g preparative layer developed in benzene–ether (95:5). The band at $R_f$ 0.52 yielded 21 mg of a mixture of ketones **8** and **15** in a ratio of 42:58 from its $^{13}C$ NMR spectrum.

Since TLC of the ketone mixture gave two slightly overlapping spots, the total product (~140–150 mg) from several such reactions was rechromatographed several times in P.E.–EtOAc (95:5, five developments). From the less polar band at $R_f$ 0.50 was obtained 20 mg of solid which after recrystallization from MeOH gave 13 mg of colorless granules of pure 4-ketone **15**: mp 77–79 °C; $[\alpha]^{21}_D$ −9.4° (*c* 0.75, $CHCl_3$) [lit.[18] mp 78–80 °C, $[\alpha]_D$ +21° (?)]; IR 1700 $cm^{-1}$ (C=O); $^1H$ NMR δ 0.65, 0.83, 0.85, 0.90, and 0.95 (5 peaks from Me); ORD (*c* 0.012 M, dioxane) $[\Phi]_{700}$ ~0°, $[\Phi]_{400}$ −157°, $[\Phi]_{320}$ −2835°, $[\Phi]_{313}$ −2678°, $[\Phi]_{310}$ −2757, $[\Phi]_{297}$ 0°, and $[\Phi]_{274}$ +4332°. Molecular ion calcd for $C_{27}H_{46}O$, 386.3548; found, 386.3543.

From the more polar band at $R_f$ 0.40 from several reactions was obtained 40 mg of colorless solid. Four recrystallizations from MeOH gave 15 mg of colorless plates of the pure 3-ketone **8**: mp 103–105 °C; $[\alpha]^{20}_D$ +16.5° (*c* 1.04, $CHCl_3$); IR 1695 $cm^{-1}$ (C=O); $^1H$ NMR δ 0.65, 0.82, 0.89, and 0.94 (4 peaks from Me); ORD (*c* 0.011 M, dioxane) $[\Phi]_{700}$ +87°, $[\Phi]_{589}$ +87°, $[\Phi]_{400}$ +200°, $[\Phi]_{325}$ +300°, $[\Phi]_{310}$ +160°, and $[\Phi]_{270}$ +877°. Molecular ion calcd for $C_{27}H_{46}O$, 386.3548; found, 386.3549. The mixture melting point of this compound was undepressed on admixture with the ketone obtained from the Wolff–Kishner homoallylic alcohol **6** → **9** → **8**. The properties of the two samples were identical within experimental error; in particular, the chemical shifts of all 27 carbon signals in their $^{13}C$ NMR spectra were the same.[21]

That the chromatographic separation of the two isomeric ketones was complete could easily be verified by their $^{13}C$ NMR spectra. The signal from C-5 appeared at δ 50.0 for **8** and at δ 45.3 for **15** in a 10-ppm region free of other signals except for C-4a of **15**.

**Reaction of *B*-Nor-4-cholesten-3-one (7) with $CH_2N_2$.** To a stirred (magnetic bar) solution of 85 mg (0.23 mmol) of **7** in 2 mL of $CH_2Cl_2$ containing 2 drops of freshly distilled $BF_3$·$Et_2O$ was added at room temperature an ethereal solution of $CH_2N_2$ (6 mL; prepared from 250 mg (2.42 mmol) of *N*-methyl-*N*-nitrosourea) in 2-mL aliquots every 15 min. The organic solution was then washed with 5% aqueous $NaHCO_3$ and water, dried, concentrated, and chromatographed on a 10-g preparative layer developed with benzene–ether (94:6). The band at $R_f$ 0.31 gave 40 mg of recovered **7**. The band at $R_f$ 0.58 yielded 28 mg of viscous oil. From several such reactions a total of 97 mg of this material was chromatographed again on a preparative plate developed four times in benzene. The upper portion of the main band gave 34 mg of colorless oil whose mass spectrum indicated it to be a mixture of di- and trihomologation products. The lower portion of the main band yielded 28 mg of oily solid which was crystallized twice from ether–MeOH to give 19 mg of colorless crystals: mp 75–79 °C; IR 1690 $cm^{-1}$ (C=O). The mass spectrum showed it to be mostly dihomologation product.

**Reaction of 4-Cholesten-3-one with Ethyl Diazoacetate.** To a stirred (magnetic bar) solution of 50 mg (0.13 mmol) of 4-cholesten-3-one and 55 mg (0.40 mmol) of $BF_3$·$Et_2O$ in 1.0 mL of $CH_2Cl_2$ at 0–5 °C was added a solution of 45 mg (0.40 mmol) of ethyl diazoacetate in 0.3 mL of $CH_2Cl_2$. The reaction mixture was allowed to warm to room temperature and was stirred for 8 h. The dark brown solution was quenched with 5% aqueous $NaHCO_3$ and worked up. The crude product was decarbethoxylated by refluxing for 8 h with 56 mg of diazabicyclooctane in 7 mL of xylene.[35] Workup gave 25 mg of amber oil whose mass spectrum indicated that about 10% of ring expansion had occurred. TLC comparison with authentic *A*-homo-4a-cholesten-3-one[17a] (less polar) in benzene–ether (95:5) showed this to be absent, and therefore the ring-expanded product is presumably *A*-homo-4a-cholesten-4-one (**18**).

**Reaction of Keto Oxide 4 with $Ac_2O$–$SnCl_4$.** To a stirred (magnetic bar) suspension of 25 mg of keto oxide **4** and 0.5 mL of $Ac_2O$ was added 0.2 mL of $SnCl_4$. The clear solution which resulted soon became yellow and then darkened. After 1 h, water was added and the product extracted with ether. Workup gave 24 mg of yellow oily solid which was chromatographed on a 5-g preparative layer developed in benzene–ether (90:10). The band at $R_f$ 0.63 gave 4 mg of recovered **4**. The band at $R_f$ 0.31 gave 16 mg of off-white solid. One recrystallization from $CHCl_3$–P.E. gave 13.5 mg of colorless needles of **3β,5β-diacetoxycholestan-6-one (27)**: mp 191–192.5 °C; $[\alpha]^{21}_D$ −28° (*c* 1.20, $CHCl_3$) (lit.[36] mp 192–193.5 °C, $[\alpha]_D$ −26°); IR 1740 (ester C=O) and 1720 (ketone C=O) $cm^{-1}$; $^1H$ NMR δ 0.66, 0.84, and 0.90 (3 peaks from Me), 2.00 (s, 3 H, $CH_3C$=O), 2.14 (s, 3 H, $CH_3C$=O), 3.30 (b d, 1 H, $J$ = 16 Hz, C-4H?), and 5.20 (b s, $w_{1/2}$ = 8 Hz, 1 H, H–C–OAc). Molecular ion calcd for $C_{31}H_{50}O_5$, 502.3658; found, 502.3659; calcd for base peak $C_{27}H_{44}O_2$, 400.3341; found, 400.3340.[37]

**Reaction of Keto Oxide 4 with $Ac_2O$–$BF_3$·$Et_2O$.** With 23 mg of **4**, 0.7 mL of $Ac_2O$, and 0.2 mL of $BF_3$·$Et_2O$, the reaction was carried out as with $SnCl_4$ above. Chromatography and recrystallization gave 13 mg of colorless needles of 3β,5β-diacetoxy ketone **27**, identical with the product of the $SnCl_4$ reaction.

**Reaction of Keto Oxide 4 with HOAc–$H_2SO_4$.** The reaction was carried out as reported by Rowland[2b] on 75 mg of keto oxide **4**. The crude product was chromatographed on a preparative plate developed in benzene–ether (95:5). The band at $R_f$ 0.24 gave 53 mg of colorless solid, mp 123–125 °C. One recrystallization from ether–MeOH gave colorless needles of pure **3α-acetoxy-5β-hydroxycholestan-6-one (26)**: mp 124.5–126 °C; $[\alpha]^{20}_D$ −6.0° (*c* 2.00, $CHCl_3$) (lit.[30] mp 126–128 °C, $[\alpha]_D$ −5°); IR 3480 (OH), 1730–1740 (ester C=O), and 1705 (ketone C=O) $cm^{-1}$; $^1H$ NMR δ 0.65, 0.70, 0.83, 0.90, and 0.94 (5 peaks from Me), 2.02 (s, 3 H, $CH_3C$=O), and 5.09 (m, $w_{1/2}$ = ~20 Hz, 1 H, H–C–OAc). Molecular ion calcd for $C_{29}H_{48}O_4$, 460.3552; found, 460.3550.

**Reaction of Keto Oxide 4 with $HClO_4$.** A solution of 25 mg of **4** and 0.2 mL of 70% $HClO_4$ in 1 mL of THF was refluxed for 2 h. Workup gave 23.5 mg of oily solid which was chromatographed on a 5-g preparative layer developed in benzene–ether (50:50). The band at $R_f$ 0.42 yielded a 14.5 mg of colorless solid. One recrystallization from ether–p.e. gave colorless granules of **3α,5β-dihydroxycholestan-6-one (25)**: mp 121–123.5 °C; IR 3460 (OH) and 1705 (C=O) $cm^{-1}$; $^1H$ NMR δ 0.65, 0.70, 0.83, 0.90, and 0.93 (5 peaks from Me) and 3.70 (b m, $w_{1/2}$ = ~20 Hz, 1 H, axial H–C–O). Molecular ion calcd for $C_{27}H_{46}O_3$, 418.3447; found, 418.3443. The compound was identical (melting point, mixture melting point, TLC, IR, and $^1H$ NMR) with a sample prepared by solvolysis of **1** in wet ethanol according to ref 30.

**Reaction of Keto Oxide 4 with Ethanedithiol–$BF_3$·$Et_2O$.** A solution of 25 mg of keto oxide **4**, 0.5 mL of ethanedithiol, and 3 drops of $BF_3$·$Et_2O$ was stirred (magnetic bar) at room temperature for 45 min. After evaporation of excess thiol in a stream of nitrogen, the residual solid was chromatographed on a 5-g preparative layer developed in benzene–ether (80:20). The band at $R_f$ 0.15 afforded 25 mg of colorless solid. Two recrystallizations from $CHCl_3$–P.E. gave 23 mg of colorless granules of the **ethylene thioketal of 3α,5β-dihydroxycholestan-6-one**: mp 188–190 °C; $[\alpha]^{21}_D$ −8.0° (*c* 1.00, $CHCl_3$); IR 3600 and 3480 $cm^{-1}$ (OH), $^1H$ NMR δ 0.67, 0.83, 0.89, and 0.97 (4 peaks from Me), 1.58 (b s, 1 H, OH), 2.90 (b s, 1 H, OH), 3.20 (m, 4 H, S–$CH_2CH_2$–S), and 4.01 (b m, $w_{1/2}$ = ~20 Hz, 1 H, H–C–O). Molecular ion calcd for $C_{29}H_{50}O_2S_2$, 494.3252; found, 494.3251.

This product was identical (melting point, mixture melting point, TLC, IR, and $^1H$ NMR) with an authentic specimen prepared from **25** and ethanedithiol by the above procedure.

**Thermal Rearrangement of 3α,5β-Dihydroxycholestan-6-one (25) into Keto Oxide 4.** A 25-mg sample of **25** sealed in a glass tube was heated at 200 °C for 40 min. The solid product was chromatographed on a 5-g preparative layer developed in benzene–ether (90:10). The band at $R_f$ 0.71 yielded 18 mg of colorless solid, mp 108–112 °C. One recrystallization from acetone–MeOH gave 15 mg of glistening plates of keto oxide **4**, mp 112–113.5 °C, which was identical (melting point, mixture melting point, TLC, IR, and $^1H$ NMR) with **4** from solvolysis of **1**.

No **4** was formed when 3β,5β-dihydroxycholestan-6-one was treated under the same conditions.

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**Registry No.**—**1**, 6770-44-1; **3**, 67542-23-8; **4**, 67542-24-9; **5**, 67542-25-0; **6**, 67576-98-1; **7**, 2552-26-3; **8**, 19667-10-8; **9**, 67542-26-1; **10**, 2449-95-8; **11**, 67542-27-2; **12**, 67542-28-3; **15**, 33346-98-4; **16** hydroxy derivative, 67542-29-4; **16** ketone derivative, 67542-30-7; **17** hydroxy derivative, 67542-31-8; **18**, 67542-32-9; **20**, 16526-63-9; **22**, 14956-13-9; **25**, 6580-08-1; **26**, 6580-09-2; **27**, 6579-84-6; **30**, 19548-92-6; *p*-TsCl, 98-59-9; 3β,5α-dihydroxycholestan-6-one, 13027-33-3; 4-cholesten-3-one, 601-57-0; ethyl diazoacetate, 623-73-4; ethylene thioketal of 3α,5β-dihydroxycholestan-6-one, 67542-33-0.

## References and Notes


(1) As the most recent evidence of how assiduously this cornerstone is guarded, witness the recent postulation of retention in an $S_N2$ reaction with *cis*-3-ethoxycyclobutyl brosylate [T. Elgomati, D. Lenoir, and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, **14**, 59 (1975)] and the quick refutation [C. A. Maryanoff, F. Ogura, and K. Mislow, *Tetrahedron Lett.*, 4095 (1975); T. Vergnani, M. Karpf, L. Hoesch, and A. S. Dreiding, *Helv. Chim. Acta*, **58**, 2524 (1975)] and recantation of this heresy [T. Elgomati, J. Gasteiger, D. Lenoir, and I. Ugi, *Chem. Ber.*, **109**, 826 (1976)]. See also a recent example of true retention in a substitution reaction on a cyclopropane ring under $S_N2$ conditions, which reaction probably proceeds through an elimination–addition sequence: R. W. Gray, C. B. Chapleo, T. Vergnani, A. S. Dreiding, M. Liesner, and D. Seebach, *Helv. Chim. Acta*, **59**, 1547 (1976).

(2) (a) A. T. Rowland, A. F. Kriner, and K. P. Long, *J. Org. Chem.*, **34**, 2768 (1969); (b) A. T. Rowland, *Steroids*, **7**, 527 (1966); (c) A. T. Rowland, P. J. Bennett, and T. S. Shoupe, *J. Org. Chem.*, **33**, 2426 (1968).

(3) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms", Elsevier, Amsterdam, 1968, p 275.

(4) D. N. Kirk, *Terpenoids Steroids*, **1**, 287 (1971).

(5) C. J. W. Brooks in "Rodd's Chemistry of Carbon Compounds", Vol. II D, 2nd ed., Elsevier, Amsterdam, 1970, p 45.

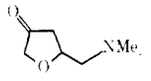
(6) (a) W. F. Johns, Ed., *Terpenoids and Steroids*, **2–7** (1972–1977); (b) *MTP Int. Rev. Sci.: Steroids*, **8** (1973 and 1976).

(7) That this is intended is clear from the orbital picture in ref 2a.

(8) H. O. House and H. W. Thompson, *J. Org. Chem.*, **28**, 166 (1963).

(9) The migration of C-10 from C-5 to C-6 is well known; see, for example, Y. Mazur and M. Nussim, *Tetrahedron Lett.*, 817 (1961); D. Baldwin, J. R. Hanson, and A. M. Holton, *J. Chem. Soc., Perkin Trans. 1*, 2687 (1973). Cf. also compound IV in ref 17a. The possibility of A/B rearrangement by migration of C-4 from C-5 to C-6, although precedented [D. J. Collins, J. J. Hobbs, and R. J. Rawson, *Chem. Commun.*, 135 (1967)], does not lead to a structure consistent with the data.

(10) A value of 1764 $cm^{-1}$ is given for the carbonyl absorption of **28** in $CCl_4$: G. Zwicky, P. G. Waser, and C. H. Eugster, *Helv. Chim. Acta*, **42**, 1177 (1959). Note also the carbonyl absorption at 1750 $cm^{-1}$ ($CH_2Cl_2$) for compound V in ref 17a.

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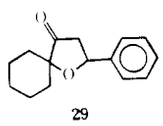
(11) An alternative way in which **4** might have been formed is excluded later in the discussion.

(12) Note that although **4** is a β-alkoxy ketone, the base treatment did not cause elimination to conjugated ketone either reversibly or irreversibly since only two deuterium atoms were incorporated into **4**, and no other product was formed. Compound **4** thus constitutes another example of the high energy barrier to a 5-endo-trig addition–elimination transition state analogous to the case of **29** pointed out by Baldwin: J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Silberman, *J. Org. Chem.*, **42**, 3846 (1977).

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(13) R. B. Clayton, H. B. Henbest, and M. Smith, *J. Chem. Soc.*, 1982 (1957).

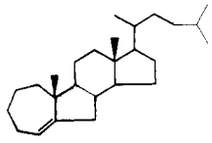
(14) (a) Y. Kondo, J. A. Waters, B. Witkop, D. Guénard, and R. Beugelmans, *Tetrahedron*, **28**, 797 (1972); (b) D. Guénard and R. Beugelmans, *ibid.*, **32**, 781 (1976).

(15) The oxide was unchanged by $BF_3$-$Et_2O$ in benzene at room temperature, which conditions readily open the cholestane 3,5-oxides.[13,14]

(16) The alcohol from saponification of this acetate did not contain olefinic H, and its oxidation gave a nonconjugated ketone different from **3**. $^{13}$C NMR evidence in favor of structure **16** will be presented elsewhere.[21]

(17) Ring-fused cycloheptenones are more stable as the β,γ-unsaturated isomer than in the conjugated form: (a) W. S. Johnson, M. Neeman, S. P. Birkeland, and N. A. Fedoruk, *J. Am. Chem. Soc.*, **84**, 989 (1962); (b) H. Velgová and V. Černý, *Collect. Czech. Chem. Commun.*, **39**, 2476 (1974). See also N. Heap and G. H. Whitham, *J. Chem. Soc. B*, 164 (1966).

(18) An initial attempt at correlation involved the Wolff–Kishner reduction of the unsaturated ketone **3** to the $\Delta^{4a}$ olefin **30**, whose melting point (94–96 °C) was higher than that reported (84–86 °C) for the same compound from solvolysis of *A*-homo-*B*-nor-4a-cholestanyl tosylate: Y. Mazur and M. Nussim, *Tetrahedron*, **24**, 5337 (1968). While our constant-melting sample is about 80% pure **30**, its $^{13}$C NMR spectrum reveals it to be contaminated by ~10% of each of two alkenes containing the –HC=CH– group, probably $\Delta^4$ and/or $\Delta^3$ isomers from double-bond migration during the reduction. A direct comparison of the two samples through the kindness of Professor Mazur was inconclusive because his sample also contained other isomers.



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(19) (a) W. G. Dauben and G. J. Fonken, *J. Am. Chem. Soc.*, **78**, 4736 (1956); (b) K. Tanabe, R. Hayashi, and R. Takasaki, *Chem. Pharm. Bull.*, **9**, 12 (1961); (c) K. Tanabe and Y. Morisawa, *ibid.*, **11**, 536 (1963).

(20) (a) G. H. R. Summers, *J. Chem. Soc.*, 2908 (1959); (b) J. Joska, J. Fajkoš, and F. Šorm, *Collect. Czech. Chem. Commun.*, **25**, 2341 (1960).

(21) J. L. Gough, J. P. Guthrie, and J. B. Stothers, *J. Chem. Soc., Chem. Commun.*, 979 (1972). A discussion of $^{13}$C NMR spectra of these ring expanded and contracted steroids will be submitted elsewhere (J. B. Stothers and V. Dave).

(22) It has been asserted elsewhere that these two ketones have been prepared from **10** by the Demjanow reaction, but no details or physical constants whatsoever were given: M. Ephritikhine and J. Levisalles, *Bull. Soc. Chim. Fr.*, 4332 (1971). A ketone prepared by M. Nussim and Y. Mazur (ref 18) by $CH_2N_2$ expansion of **10** was assigned on unspecified grounds the structure **15** (incorrectly drawn as **8**); the reported mp 78–80 °C agrees with that found for **15** in this work, but the reported $[\alpha]_D$ +21° ($CHCl_3$) does not agree with that ($[\alpha]_D$ −9.4°) found for **15** in this work for a sample known to be pure from its $^{13}$C NMR spectrum.

(23) (a) G. Snatzke, B. Zeeh, and E. Müller, *Tetrahedron Lett.*, 1425 (1963); (b) J. B. Jones and P. Price, *Can. J. Chem.*, **44**, 999 (1966); (c) J. B. Jones and J. M. Zander, *ibid.*, **47**, 3501 (1969).

(24) N. L. Allinger and W. Szkrybalo, *J. Org. Chem.*, **27**, 722 (1962); J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 4537 (1961).

(25) The values found for cyclohexyl hydrogens should apply to fixed cycloheptyl rings: Expected $w_{1/2}$ for equatorial H, 5–10 Hz; for axial H, 15–30 Hz [A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964)].

(26) A. T. Rowland, *J. Org. Chem.*, **27**, 1135 (1962).

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(28) L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **71**, 3938 (1949).

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(31) The *i*-PrOH was dried over 3A molecular sieves and distilled from Mg into a flame-dried flask containing 3A molecular sieves. Karl Fisher titration gave a water content of less than 5 μg/mL.

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(36) A. T. Rowland, *J. Org. Chem.*, **29**, 222 (1964).

(37) This peak is by far the most intense one in the spectrum and corresponds exactly in composition to **4**!