10,13-*trans*-prostadienoic acid (**28**), was obtained as white crystals, mp 86–92 °C, after recrystallization from ether–petroleum ether: IR (KBr) 5.78, 6.03, and 10.23 μm; ^{1}H NMR ($CDCl_3$) δ 6.86. (1, m, 11-**H**), 5.97 (1, d, 10-**H**), 5.58 (2, m, 13-**H**), and 4.08 (1, m, C**HO**); UV (MeOH) λ_{max} 223 nm (7700).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.76; H, 9.93.

The more polar component (0.10 g), 9-oxo-11α,15-dihydroxy-11a-homo-13-*trans*-prostenoic acid (**30**), was obtained as white crystals, mp 77–81 °C, after recrystallization from ethyl acetate–petroleum ether; ^{1}H NMR (acetone-d_6) δ 5.50 (2, m, 13-**H** and 14-**H**), 4.37 (1, m, 11β-**H**), and 4.06 (1, m, 15-**H**).

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.45; H, 9.85. Found: C, 68.85; H, 9.94.

9-Oxo-15-*epi*-hydroxy-11a-homo-10,13-*trans*-prostadienoic Acid (29) and 9-Oxo-11α,15-*epi*-dihydroxy-11a-homo-13-*trans*-prostenoic Acid (31). From 0.83 g of **27** was obtained 523 mg of **29** and 84 mg of **31** after hydrolysis and chromatography as above. The following are the R_f values for the system 100:1 EtOAc–HOAc on silica gel TLC: **28**, 0.60; **29**, 0.63; **30**, 0.29; and **31**, 0.35.

Acknowledgments. The authors wish to express their gratitude to Mr. J. Nocera and Dr. P. Kohlbrenner for the preparation of some of the intermediates, to Messrs. W. Fulmor and G. Morton and staff for spectral data and interpretation, and to Mr. L. Brancone and staff for microanalytical data.

Registry No.—**1,** 29823-18-5; **2** methyl ester, 68184-84-9; **2** ethyl ester, 68184-85-0; **3,** 68184-86-1; **4,** 68184-87-2; **5,** 41432-44-4; **6,** 41301-80-8; **7,** 68184-88-3; **8,** 40964-30-5; **9,** 57756-57-7; **10,** 68224-66-8; **11,** 68224-67-9; **12,** 68184-89-4; **13,** 64122-53-8; **14** halide derivative, 68184-90-7; **15** isomer 1, 68184-91-8; **15** isomer 2, 68224-68-0; **16** isomer 1, 68295-61-4; **16** isomer 2, 68184-92-9; **17,** 55529-87-8; **18** isomer 1, 68224-69-1; **18** isomer 2, 68224-70-4; **19** isomer 1, 61557-46-8; **19** isomer 2, 61557-45-7; **20,** 61557-47-9; **21,** 61557-48-0; **22** isomer 1, 68224-71-5; **22** isomer 2, 68224-72-6; **23** isomer 1, 68224-73-7; **23** isomer 2, 68224-74-8; **24** isomer 1, 68224-75-9; **24** isomer 2, 68224-76-0; **25** isomer 1, 68224-77-1; **25** isomer 2, 68224-78-2; **26,** 61507-63-9; **27,** 61557-49-1; **28,** 61507-64-0; **29,** 61557-50-4; **30,** 61507-65-1; **31,** 61557-51-5; diisobutyl-*trans*-1-octenylalane, 40098-43-9; diisobutyl-*trans*-1-pentenylalane, 57716-76-4; 1-iodo-3-trityloxy-*trans*-1-octene, 52418-91-4; 1-lithio-3-trityloxy-*trans*-1-octene, 60950-73-4; trimethylaluminum, 75-24-1; benzenesulfenyl chloride, 931-59-9; methyl 2-cyclohexanonecarboxylate, 41302-34-5; ethyl 2-cyclohexanonecarboxylate, 1655-07-8.

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Stereochemistry of 14,22-Ethers Formed by Cyclization of Δ^7-22-Hydroxy Steroids[1]

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Received July 12, 1978

The 14,22-ether **2c** produced by mild acid treatment of 3β-benzoyloxy-23,24-bisnor-5α-chol-7-en-22-ol (**1a**) is shown by X-ray crystallography to have the 8β(H),14β configuration.

In 1971, we reported the conversion of the Δ^7-22-hydroxy steroids **1a** or **1b** by very mild acid treatment into the corresponding 14β,22-ethers **2a** or **2b**, respectively.[2] Spectroscopic and chemical evidence fully supported structure **2**. The formation of **2** from **1** was postulated to proceed by an initial acid-catalyzed isomerization of the Δ^7 double bond to the $\Delta^{8(14)}$ position. This $\Delta^{8(14)}$ intermediate was then thought to undergo protonation at C-8 with capture of the resultant C-14 carbonium ion by the C-22 oxygen atom. The configuration at C-8 will naturally be determined by the stereochemistry of proton addition at this position. Although not specifically stated in our communication,[2] it had been assumed that the products had an 8β(H) configuration. Should the products have an 8α(H) configuration, ring B would have to assume a boat conformation. However, the formation of an 8β(H) product requires that the protonation at C-8 and capture of the C-14 carbonium ion occur on the same face of the double bond. Hence, by necessity the cyclization could not be a concerted process. An additional interpretive complication arose by recent observations on the backbone rearrangement of 17α(H)-$\Delta^{8(14)}$-sterols to 17β(H)-Δ^{14} products upon treatment with hydrogen chloride in chloroform.[3] The generality of the 17α(H) → 17β(H) rearrangement was confirmed with the use of 5α-ergosta-8(14),22-dien-3β-ol benzoate (**3**),[4] which, on

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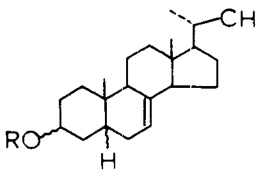
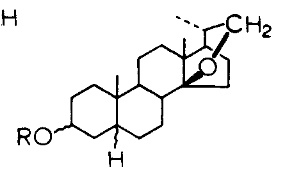
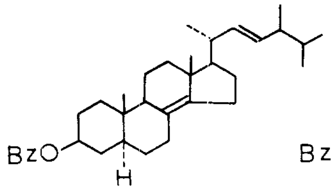


1 a 3β-OBz, 5α-H
b 3α-OAc, 5β-H



2 a 3β-OBz, 5α-H
b 3α-OAc, 5β-H
c 3β-OH, 5α-H



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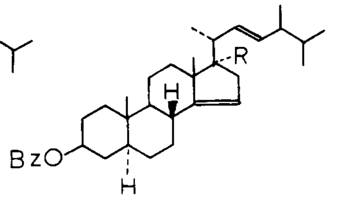
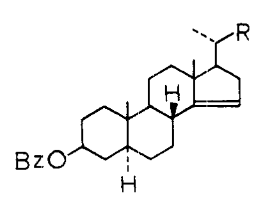
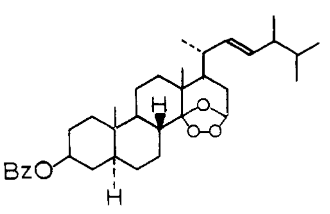


4 a R = 17β(H)
b R = 17α(H)



5 R = CH$_2$OH
6 R = CHO



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treatment with HCl in chloroform at −78 °C, gave the rearranged 5α,17β(H)-ergosta-14,22-dien-3β-ol benzoate (**4a**). In support of structure **4a,** there appeared in its NMR spectrum a signal for the C-18 methyl group at 1.08 ppm. The downfield shift of this signal from its position at 0.90 ppm in the 17α(H) isomer **4b** is characteristic of the isomerized side chain as observed in the C_{27} series.[3] When a chloroform solution of **3** was treated with HCl at −30 °C, the 17α(H) product **4a** was obtained as expected.[4]

Although the conditions used in these backbone rearrangements were substantially different from those used in the 14,22-oxide formation, still the possibility of side chain isomerization during the elaboration of the ether could not be excluded, a priori. Hence, the cyclization products could have the 17β(H)-14α,22-ether structures. In view of the above considerations and the possible utility of compounds such as **2** in the synthesis of cardenolides, we undertook a reexamination of the structures of **2.** We now report the results of chemical and X-ray crystallographic studies which confirm the formulation of **2** as 8β(H),14β,22-ethers.

Results

We first attempted to confirm the 8β(H) configuration of **2a** by synthesizing it in an alternative manner, namely, by cyclization of the Δ^{14}-22-alcohol **5** having a known 8β(H) configuration. Thus, our first objective was the synthesis of **5.** A mixture of 5α-ergosta-8(14),22-dien-3β-ol benzoate (**3**) and 5α-ergosta-14,22-dien-3β-ol benzoate (**4b**) was prepared by HCl/$CHCl_3$ isomerization of 5α-ergosta-7,22-dien-3β-ol benzoate as previously described.[4] The major product (**4b**) was isolated by preparative TLC on silver nitrate impregnated silica gel. Ozonolysis of **4b,** followed by addition of dimethyl sulfide,[5] gave ozonide **7** rather than the desired aldehyde **6.**[6] The ozonide structure **7** was supported by its mass spectrum, which indicated the acquisition by the starting material (**4b**) of an additional 48 mass units. The NMR spectrum showed the absence of aldehydic absorption, the disappearance of the C-15 vinyl hydrogen (at 5.17 ppm in **4b**), and the retention of unchanged peaks for the C-22,23 vinyl hydrogens at 5.23 ppm. A new signal assigned to the C-15 ozonide terminus appeared at 5.74 ppm. Treatment of **7** with zinc and acetic acid at room temperature gave an oily ketoaldehyde having an NMR spectrum consistent with structure **8.**[6] The reactivity of the Δ^{14} double bond in **4b** contrasts with that of corresponding $\Delta^{8(14)}$ or Δ^7 double bonds[2] in which the attack of ozone occurred predominately on the side chain double bond. Because of the high reactivity of the Δ^{14} double bond, the route through the synthesis of **5** was not further explored. We, therefore, concentrated on the use of X-ray crystallography for confirmation of the structure of **2a.**

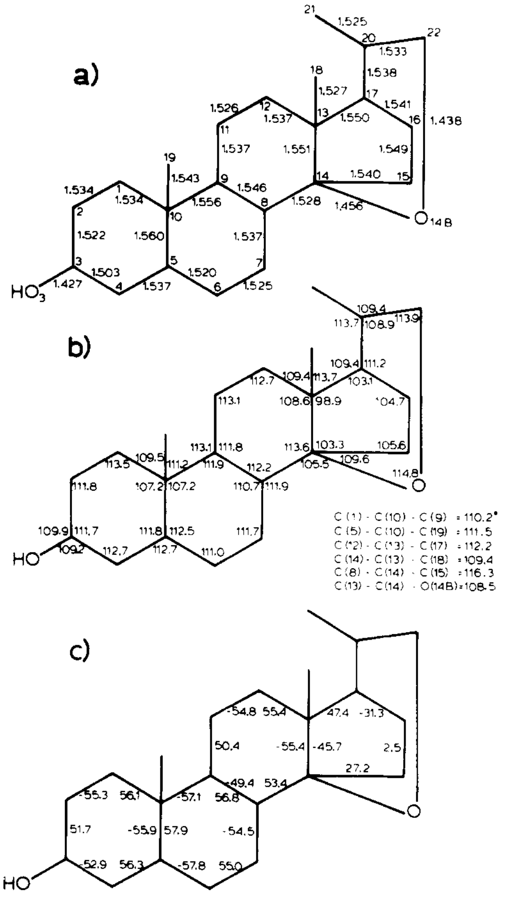

Figure 1. Intramolecular geometry of 14β,22-epoxy-23,24-bisnor-5α-cholan-3β-ol, including (a) bond lengths, (b) valency angles, and (c) endocyclic torsion angles. A torsion angle α-β-γ-δ is positive if, when viewed down the β-γ bond, the α-β bond will eclipse the γ-δ bond when rotated less than 180° in a clockwise direction.

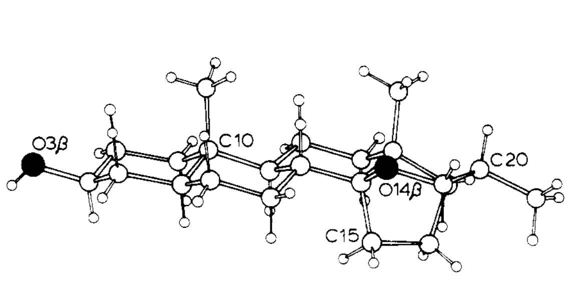

Figure 2. A perspective drawing of the 14β,22-epoxy-23,24-bisnor-5α-cholan-3β-ol molecule.

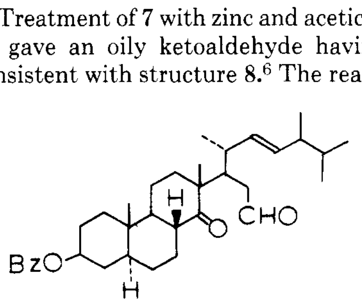

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Table I. Fractional Atomic Coordinates and Estimated Standard Deviations

atom	x/A	y/B	z/C
C(1)	0.8778 (2)	0.3139 (2)	0.7764 (3)
C(2)	1.0136 (2)	0.2972 (2)	0.8678 (3)
C(3)	1.1186 (2)	0.2627 (2)	0.7438 (3)
C(4)	1.1224 (2)	0.3392 (2)	0.5926 (3)
C(5)	0.9857 (2)	0.3544 (2)	0.5018 (3)
C(6)	0.9913 (2)	0.4251 (3)	0.3413 (3)
C(7)	0.8565 (2)	0.4292 (2)	0.2464 (3)
C(8)	0.7470 (2)	0.4685	0.3634 (2)
C(9)	0.7440 (2)	0.3967 (2)	0.5269 (2)
C(10)	0.8802 (2)	0.3963 (2)	0.6274 (2)
C(11)	0.6279 (2)	0.4279 (2)	0.6391 (3)
C(12)	0.4951 (2)	0.4327 (2)	0.5391 (3)
C(13)	0.4977 (2)	0.5102 (2)	0.3833 (3)
C(14)	0.6118 (2)	0.4736 (2)	0.2685 (2)
C(15)	0.5602 (2)	0.3647 (2)	0.1890 (3)
C(16)	0.4070 (2)	0.3737 (2)	0.1850 (3)
C(17)	0.3790 (2)	0.4899 (2)	0.2552 (3)
C(18)	0.5097 (2)	0.6295 (2)	0.4450 (3)
C(19)	0.9153 (2)	0.5122 (2)	0.6974 (3)
C(20)	0.3803 (2)	0.5771 (2)	0.1120 (3)
C(21)	0.2647 (2)	0.5668 (3)	−0.0187 (3)
C(22)	0.5114 (2)	0.5683 (2)	0.0201 (3)
O(3B)	1.2460 (2)	0.2611 (2)	0.8299 (3)
O(14B)	0.6258 (1)	0.5556 (1)	0.1340 (2)

The crystal form of **2a** itself was unsuitable for crystallographic studies. However, alcohol **2c** gave well-formed prisms from ethyl acetate which were subjected to single-crystal X-ray analysis. The X-ray analysis established that the 14,22-ether **2c** has the 14β,22-epoxy-23,24-bisnor-5α-cholan-3β-ol structure.

Experimental Section

Melting points were taken on a hot stage apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 237 spectrophotometer in $CHCl_3$ solutions. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ on a Varian HA-100A spectrometer. Chemical shifts are quoted in parts per million downfield from internal tetramethylsilane (s = singlet, d = doublet, dd = doublet of doublets, and m = multiplet). Mass spectra were recorded on a Nuclide 12-90-G mass spectrometer equipped with a Nuclide DA/CSI.2 data acquisition system, using an ionization voltage of 70 eV.

3β-Benzoyloxy-5α,17β(H)-ergosta-14,22-diene (4a). 3β-Benzoyloxy-5α-ergosta-8(14),22-diene (3,[4] 250 mg) in $CHCl_3$ (2 mL) at −78 °C was treated with dry HCl (passed through H_2SO_4 and $CaCl_2$) at a rate of 10–20 mL/min for 3 h. The solution was then stirred with saturated $NaHCO_3$ (25 mL) for 10 h. The mixture was extracted with $CHCl_3$, and the extract was dried (Na_2SO_4) and evaporated. The residue was separated by preparative TLC on 10% $AgNO_3$–silica gel (solvent: 10% ether–hexane), giving **4b**[4] (35 mg) and **4a** (90 mg) crystallized from $CHCl_3$–MeOH as prisms: mp 136–138 °C; NMR δ 0.91 (s, 3, 19-Me), 1.08 (s, 3, 18-Me), 4.94 (br m, 1, $W_{1/2}$ = 10 Hz, 3α-H), 5.09 (br s, 1, $W_{1/2}$ = 3 Hz, 15-H), 5.24 (m, 2, C-22,23 H), 7.4 (m, 3), 8.03 (m, 2); mass spectrum, m/e (relative intensity) 504 (1.7), 503 (3.9), 502 (M^+, 8.2), 501 (1.3), 487 (8), 403 (11), 378 (42), 377 (100), 255 (34), 254 (26), 241 (13), 161 (17), 149 (10), 147 (30), 133 (11), 125 (11), 107 (17), 105 (23), 95 (11), 93 (14).

3β-Benzoyloxy-14,15-seco-5α-ergost-22-ene 14,15-Ozonide (7). 5α-Ergosta-14,22-dien-3β-ol benzoate[4] (**4b**; 200 mg, 0.398 mmol) in dichloromethane (50 mL) and pyridine (0.2 mL) at −78 °C was treated with ca. 1 equiv of ozone, followed by the addition of dimethyl sulfide (0.5 mL) and methanol (0.5 mL). After evaporation of the solvent, the product mixture was separated by preparative TLC (10% ethyl acetate–hexane), giving recovered **5** (100 mg) and **7** (R_f 0.8, 70 mg) as small needles from $CHCl_3$–MeOH: mp 129–131 °C; IR ν_{max} 1705 cm^{-1}; NMR δ 0.86 (18-Me), 0.98 (19-Me), 5.00 (br m, 1, $W_{1/2}$ = 20 Hz, 3α-H), 5.23 (m, 2, 22,23-H), 5.74 (dd, 1, J_1 = 4 Hz, J_2 = 2 Hz, 15-H), 7.4 (m, 3), 8.05 (m, 2); mass spectrum, m/e (relative intensity) 551 (12), 550 (M^+, 19), 532 (28), 508 (21), 507 (28), 506 (41), 489 (20), 427 (41), 426 (100), 409 (36), 408 (26), 369 (53), 286 (22), 285 (20).

A portion (50 mg) of the ozonide **7** was stirred with zinc dust (100 mg) and acetic acid (0.5 mL) in dichloromethane (25 mL) at room temperature for 2 h. The mixture was diluted with water and extracted with ether. The extract was washed with water, $NaHCO_3$ solution, and saturated NaCl, dried (Na_2SO_4), and evaporated. The product (30 mg) was isolated by preparative TLC (20% ethyl acetate-hexane), giving the ketoaldehyde **8** as an oil: IR ν_{max} 2720, 1730, 1705, 1455, 1280, 1205, 1130 cm^{-1}; NMR δ 0.7–1.0 (complex m), 0.94 (s, 3, 19-Me), 1.12 (s, 3, 18-Me), 2.2–2.7 (m, 3), 4.91 (br m, 1, 3α-H), 5.24 (m, 2, 22,23-H), 7.4 (m, 3), 8.0 (m, 2), 9.77 (dd, 1, $J_1 = J_2$ = 2 Hz).

14β,22-Epoxy-23,24-bisnor-5α-cholan-3β-ol (2c). 14β,22-Epoxy-23,24-bisnor-5α-cholan-3β-ol benzoate[1] (**2a;** 130 mg, 0.30 mmol) was treated with potassium hydroxide in methanol (0.1 M, 10 mL) and ether (10 mL) at room temperature for 20 h. Additional ether was added, and the solution was washed with water and saturated NaCl, dried (Na_2SO_4), and evaporated. The product was purified by preparative TLC (10% ethyl acetate–hexane), giving **2c** (91 mg) as prisms from ethyl acetate: mp 203–206 °C; IR ν_{max} 3600 (sharp), 3400 (br), 1445, 1080 cm^{-1}; NMR δ 0.66 (d, 3, J = 6 Hz, 21-Me), 0.80 (s, 3, 18-Me), 1.02 (s, 3, 19-Me), 2.4 (br m, 1), 3.14 (dd, 1, $J_1 = J_2$ = 12 Hz), 3.65 (dd, 1, J_1 = 12 Hz, J_2 = 6 Hz), 3.7 (br m, 1, $W_{1/2}$ = 10 Hz, 3α-H); mass spectrum, m/e (relative intensity) 334 (3.8), 333 (26), 332 (M^+, 94), 319 (28), 318 (100), 304 (14), 250 (16), 249 (10), 167 (16), 137 (10), 111 (18), 83 (14).

A single crystal grown from ethyl acetate and having dimensions of 0.2 × 0.4 × 0.4 mm was used for the X-ray measurements of the lattice parameters and intensities. The systematic absences in the diffraction pattern indicated the space group to be $P2_1$. The unit cell constants were determined from least-squares analysis of the θ values for 25 reflections to be a = 10.093 (1) Å, b = 12.114 (4) Å, c = 7.806 (2) Å, and β = 92.24 (1)°, resulting in a unit cell volume of 953.7 $Å^3$. The density was calculated to be 1.16 g cm^{-3} based on the presence of two molecules (Z = 2) in the cell. Integrated intensities for 2054 independent reflections having $\theta < 75°$ were measured on an Enraf-Nonius CAD-4 diffractometer using Cu Kα radiation. After the Lorentz and polarization corrections $[(1 + \cos^2 2\theta)/2 \sin 2\theta]$ had been applied to the intensity data, normalized structure factor amplitudes were computed, and the structure was solved by a straightforward application of direct method techniques and found to be 14β,22-epoxy-23,24-bisnor-5α-cholan-3β-ol ($C_{22}H_{36}O_2$, M_r 332.5).

The positional and anisotropic thermal parameters of all nonhydrogen atoms were refined by full-matrix least squares using the 1886 reflections for which the observed intensity was greater than twice the corresponding standard deviation. These reflections were regarded as having intensities significantly greater than the background. The weights used during refinement were the quantities $1/\sigma_F^2$. All hydrogen atoms were located on two successive Fourier difference maps, and the positional and isotropic thermal parameters for these atoms were refined in the final least-squares cycles. The final reliability index, R (defined as $\Sigma\||F_o| - |F_c\||/\Sigma|F_o|$), was 4.2% for the 1886 reflections used in the refinement and 4.7% for all data.

Registry No.—2a, 32308-37-5; **2c,** 68151-28-0; **3**, 68151-29-1; **4a,** 68151-30-4; **4b,** 68199-17-7; **5**, 54048-87-2; **7**, 68151-31-5; **8**, 68151-32-6.

Supplementary Material Available: Tables of the anisotropic thermal parameters of the nonhydrogen atoms and positional and isotropic thermal parameters of the hydrogens (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) The work at The Worcester Foundation for Experimental Biology was supported by Grant No. RR05528 from the National Institutes of Health and by Institutional Funds. The work at the Medical Foundation of Buffalo was supported by NIH Grant CA 10906.

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