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A NOVEL REDUCTIVE REARRANGEMENT OF AN α,β-UNSATURATED STEROIDAL EPOXIDE. A NEW SYNTHESIS OF 5α-CHOLEST-8(14)-EN-3β,15α-DIOL

E. J. Parish and G. J. Schroepfer, Jr.*

(Departments of Biochemistry and Chemistry,
Rice University, Houston, Texas 77005)

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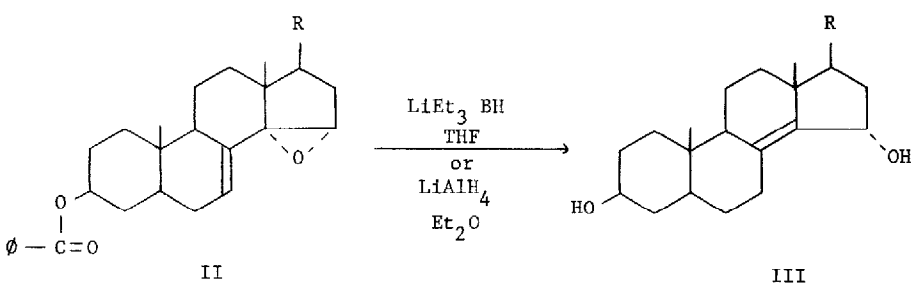
Reduction of 3β-benzoyloxy-5α-cholest-8(14)-en-15-one (I) with lithium aluminum hydride yields two epimers (at C-15) of 5α-cholest-8(14)-en-3β,15-diol which are readily separable by chromatography[1,2]. The less polar diol was designated as diol A and the more polar compound was designated as diol B[1,2]. Unambiguous establishment of the structure of diol B as 5α-cholest-8(14)-en-3β,15β-diol was effected by x-ray crystallographic analysis of the 3β-p-bromobenzoate ester of diol B[3,4]. Our continued interest in the two diols derives from their demonstrated convertibility to cholesterol upon incubation with rat liver homogenate preparations[1,2,5] and their potent inhibitory action on sterol biosynthesis in L-cells and mouse liver cells in culture[6].

The purpose of the present paper is to report that hydride reduction of 3β-benzoyloxy-14α,15α-epoxy-5α-cholest-7-ene (II) with lithium triethylborohydride or lithium aluminum hydride gives, in high yields, 5α-cholest-8(14)-en-3β,15α-diol (III). The overall process constitutes a novel reductive rearrangement of an α,β-unsaturated steroidal epoxide.

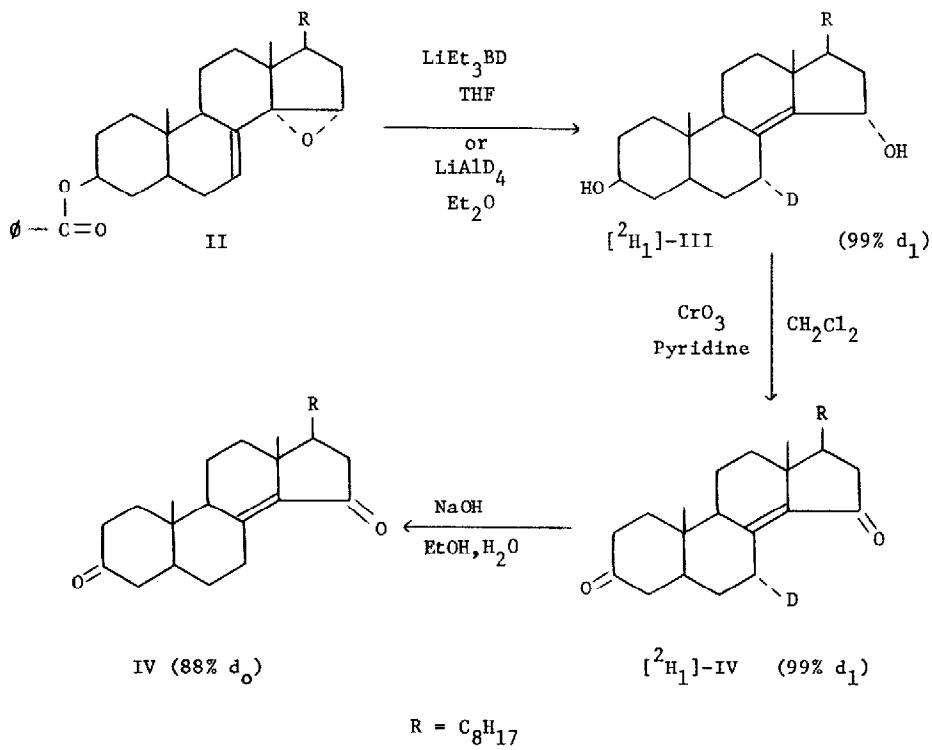


II III

R = C_8H_{17}

Reduction of 3β-benzoyloxy-14α,15α-epoxy-5α-cholest-7-ene (II; 1.0 g), prepared as described elsewhere[7], with a 1M solution of lithium triethylborohydride in tetrahydrofuran (10 ml) for 3 hours at 25° gave, after crystallization from acetone-water, 5α-cholest-8(14)-en-3β,15α-diol (III; 0.73 g; 91% yield) melting at 181-182°; i.r., ν_{max}^{KBr} 3390 and 1052 cm^{-1}; m.s., 402 (M; 24%), 387 (M-CH_3; 20%), 384 (M-H_2O; 100%), 369 (M-CH_3-H_2O; 15%), 289 (M-side chain; 6%); 271 (M-H_2O-side chain; 42%); high resol. m.s., 402.3516 (calc. for $C_{27}H_{46}O_2$: 402.3496); n.m.r., 1.30 (m, methylene envelope), 3.64 (m, 1H, C-3-H), 4.71 (m, 1H, C-15-H); $[\alpha]_D$ + 17.6°. The compound showed a single component on t.l.c. on silica gel G plates (two solvent systems) and had the same spectral and chromatographic properties as III prepared by reduction of I with lithium aluminum hydride[1,3]. Reduction of II (200 mg) with lithium aluminum hydride (75.3 mg) in ether (70 ml), with gentle refluxing for 24 hours, gave, after purification by preparative t.l.c. and crystallization from acetone-water, III (134 mg; 84% yield) melting at 181-182°. The spectral properties and chromatographic behavior were identical with those for authentic III and the sample prepared above.

Reduction of II with lithium triethylborodeuteride or lithium aluminum deuteride, under the respective conditions described above, gave $[^2H_1]$-III.



II

$[^2H_1]$-III (99% d_1)

IV (88% d_o)

$[^2H_1]$-IV (99% d_1)

R = C_8H_{17}

Chromium trioxide-pyridine oxidation of III in methylene chloride gave, in 84% yield, a 5α-cholest-8(14)-en-3,15-dione (IV), m.p. 145.5-146.0°; i.r., ν_{max}^{KBr} 1720,1708 and 1628 cm^{-1}; u.v., λ_{max}^{EtOH} 259 nm (ε=16,600); m.s., 398 (M; 100%); high resolution m.s., 398.3180 (calc. for $C_{27}H_{42}O_2$: 398.3184); n.m.r., 1.40 (m, methylene envelope), 4.21 (m, 1H, C-7 -H); single component on t.l.c. and g.l.c. Chromium trioxide-pyridine oxidation of [$^2H_1$]-III (99% d_1) gave [$^2H_1$]-IV (99% d_1), m.p. 147.5-148.5°; i.r., ν_{max}^{KBr} 2120 (C-D), 1720, and 1626 cm^{-1}; u.v., λ_{max}^{EtOH} 259 nm (ε=16,700); n.m.r., 1.40 (m, methylene envelope), 4.21 (m, 1H, C-7β-H). [$^2H_1$]-IV was heated under reflux with a 10% NaOH solution in 80% ethanol for 45 minutes. Mass spectral analysis of IV reisolated after this treatment indicated the following isotopic composition, 88.2% d_0 and 11.8% d_1.

Reduction of II with either lithium triethylborohydride or lithium aluminum hydride under the conditions described above gave III in high yields. This approach represents a considerable improvement over the previously described synthesis[1,2] by hydride reduction of I, a reaction which gives only modest yields of III which must be separated from its 15β-hydroxy epimer by chromatography.

The observed hydride reduction of II can be envisioned as proceeding by an S_N2' ring opening of the 14α,15α-epoxide function via a mechanism analogous to that described for carbohydrate substrates in which axial hydroxyl and etheral groups are expelled in an S_N2' reductive rearrangement by hydride ions[8]. The process has been postulated to involve formation of an oxygen-alane complex which is syn-related such that the entering hydride is introduced cis to the departing oxygen function[8]. In the case under consideration such a process would involve introduction of hydride at C-7 in the α-configuration. Confirmation of this point was made by reduction of II with either lithium triethylborodeuteride or lithium aluminum deuteride to give [$^2H_1$]-III. Sarett oxidation of [$^2H_1$]-III gave [$^2H_1$]-IV whose n.m.r. spectrum showed the deshielded C-7β-H at 4.22 p.p.m. (δ). Examination of Drieding models indicated that the C-7α-H is not deshielded and is not distinguishable in the n.m.r. spectrum of IV. The deshielding of the C-7β-H by a ketone function at C-15 has also been observed in the case of 5α-androstan-15-one[9]. The n.m.r. spectra of IV and I also showed the multiplet at 4.22 (δ) due to the C-7β-H. In addition, treatment of [$^2H_1$]-IV with aqueous ethanolic NaOH (reflux 45 minutes) resulted in an 88% loss of the isotopic hydrogen. The combined findings indicate localization of the deuterium in [$^2H_1$]-IV and therefore also in [$^2H_1$]-III in the 7α-position.

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