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SYNTHESIS AND STRUCTURE OF 15-OXYGENATED 5α,14β-CHOLEST-7-EN-3β-OL DERIVATIVES

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A number of 15-oxygenated sterols have recently been shown to be potent inhibitors of sterol biosynthesis[1,2]. Moreover, 15-hydroxy derivatives of sterols have been suggested as potential intermediates in the biosynthesis of cholesterol[3-9] and several 15-hydroxy sterols have been shown to be convertible to cholesterol upon incubation with rat liver homogenate preparations[5-7,10].

A classic chemical approach for the introduction of a 15-oxygen function into a sterol was introduced by Barton and associates[11,12]. Barton and Laws[12] reported the formation of 3β-acetoxy-ergosta-7,22-15-one (configuration at C-14 not specified) upon boron trifluoride treatment of the reaction mixture obtained by the action of perphthalic acid upon 3β-acetoxy-ergosta-7,14,22-triene. Our recent success[13] in the isolation and characterization of the product of the action of m-chloro-perbenzoic acid on 3β-benzoyloxy-5α-cholesta-7,14-diene as 3β-benzoyloxy-14α,15α-epoxy-5α-cholest-7-ene(I) has permitted investigation of the action of boron trifluoride on the Δ^7-14α,15α-epoxy steryl ester. The results of the present study indicate that the reaction proceeds with the formation of the corresponding Δ^7-15-ketone with the "unnatural" cis-C-D ring juncture (II). Reduction of the latter compound with lithium aluminum hydride yielded 5α,14β-cholest-7-en-3β,15β-diol (III) and the corresponding 15α-ol epimer (IV). The latter two compounds are potent inhibitors of sterol synthesis[1].

Treatment of I in tetrahydrofuran-ether with boron trifluoride-etherate at 0° for 30 minutes gave, after purification by silica gel column chromatography and crystallization from acetone-water,

3β-benzoyloxy-5α,14β-cholest-7-en-15-one[14] (II; m.p. 113.5-114.0°; i.r., ν_{max}^{KBr} 1750, 1725, 1609, 1285 cm^{-1}; u.v., λ_{max} 230 nm (ε = 28,000); n.m.r., 1.20 (m, methylene envelope), 4.95 (m, 1H, C-3-H), 5.44 (m, 1H, C-7-H), 7.8 (m, 5H, aromatic); m.s., 504 (M; 100%); high resol. m.s., 504.3613 (calc. for $C_{38}H_{48}O_3$: 504.3606); single component on t.l.c.) in 43% yield. Reduction of II with lithium aluminum hydride gave two diols which were purified by preparative t.l.c. and crystallization from acetone-water to give 5α,14β-cholest-7-en-3β,15β-diol[14] (III; 81% yield; m.p. 164.5-165.5° i.r., ν_{max}^{KBr} 3320, 1660, 1150 cm^{-1}; n.m.r., 1.20 (m, methylene envelope), 3.75 (m, 2H, C-3-H and C-15-H), 5.49 (m, 1H, C-7-H); $[\alpha]_D$-10.4°; m.s., 402 (M; 100%); high resol. m.s., 402.3498 (calc. for $C_{27}H_{42}O_2$: 402.3496); single component on t.l.c.) and 5α,14β-cholest-7-en-3β,15α-diol[14] (IV; 9% yield; m.p. 73.5-75.0°; i.r., ν_{max}^{KBr} 3400, 1660, 1045 cm^{-1}; n.m.r., 1.20 (m, methylene envelope), 3.75 (m, 2H, C-3-H and C-15-H), 5.5 (m, 1H, C-7-H); $[\alpha]_D$ + 20.6°; m.s., 402 (M; 59%); high resol. m.s., 402.3498 (calc. for $C_{27}H_{42}O_2$: 402.3496); single component on t.l.c.).

Treatment of III with p-bromobenzoyl chloride in pyridine gave (after standard processing of the reaction mixture, silica gel column chromatography, and crystallization from acetone-water) 3β,15β-bis-p-bromobenzoyloxy-5α,14β-cholest-7-ene (V; m.p. 175-176°; i.r., ν_{max}^{KBr} 1793, 1725, 1593, and 1281 cm^{-1}; n.m.r., 1.20 (m, methylene envelope), 4.95 (m, 2H, C-3-H and C-15-H), 5.40 (m, 1H, C-7-H), 7.85 (m, 8H, aromatic); single component on t.l.c.) in 88% yield. Recrystallization from methylene chloride-ethanol (1:1) yielded crystals suitable for x-ray analysis[15]. Crystal data: $C_{41}H_{54}O_4Br_2$, M = 768.7, monoclinic, space group $P2_1$, a = 14.12 (2), b = 7.46 (1), c = 18.53 (4) Å, α = 90.00 (1)°, β = 97.08 (6)°, γ = 90.00 (1)°, V = 1927 (6) $Å^3$, D_c = 1.32 g cm^{-1}, D_m = 1.31 g cm^{-3}, F(0,0,0)=0.415 e $Å^{-3}$. The structural analysis established the configuration of the oxygen function at carbon atom 15 and established the cis-C-D ring juncture.

The results presented herein outline an important new synthetic route for the preparation of Δ^7-sterols with the "unnatural" cis-C-D ring juncture and constitute the first syntheses of 15-oxygenated Δ^7-sterols with the β-configuration at C-14. Alternative routes for the preparation of Δ^7-steroidal derivatives with the 14β-configuration have been described by Midgley and Djerassi[16] and by Anastasia et al.[17]. Described herein also is the first x-ray analysis of a 14β-Δ^7-sterol derivative.

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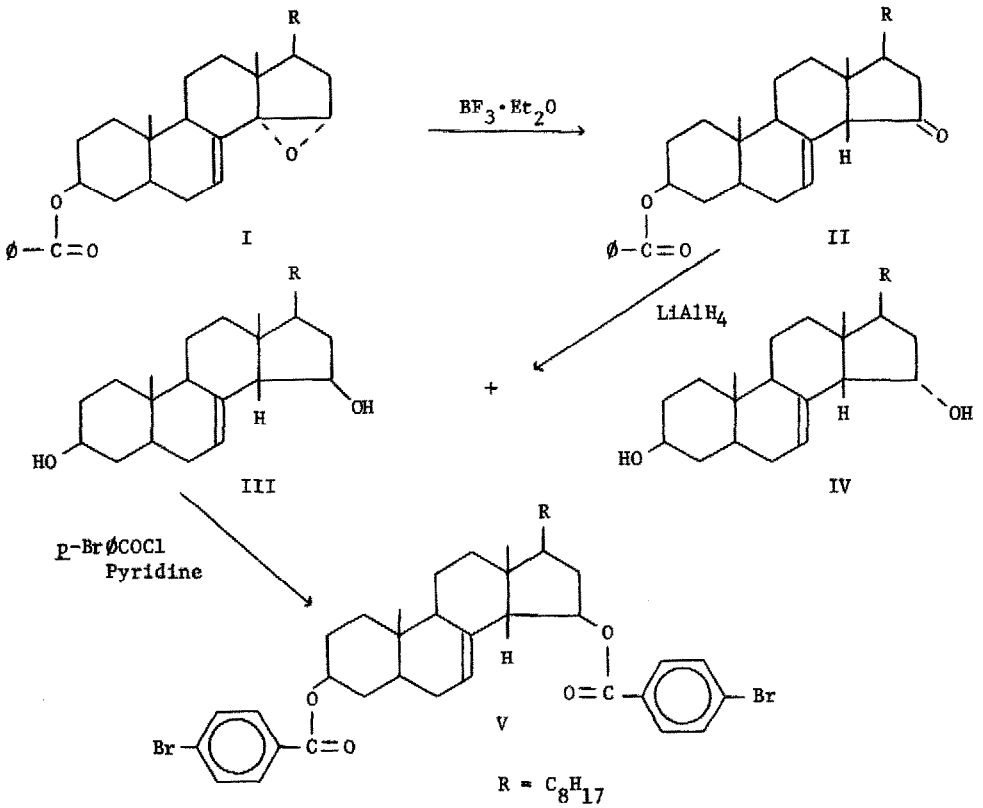

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14. The assignments absolute configurations at carbon atoms 14 and 15 were established by x-ray structural analysis of the bis-p-bromobenzoyloxy-derivative of III.

15. A Syntex $P2_1$ diffractometer with nickel filtered CuKα radiation was used in the 2θ:θ scan mode (scan range 2 to 15 degrees $minute^{-1}$) to collect diffraction data. Data collection was terminated if the intensity of one of the five monitor reflections decreased by 6% of its initial value. A total of 5799 symmetry-related reflections with $\sin\theta/\lambda < 0.6$ (d_{min} = 1Å) was collected using three crystals. Of these reflections 431 were rejected because of unequal background and 49 had zero weight. An additional 275 reflections were collected as overlaps to correlate the three crystal data sets by a linearized least squares method (A.D. Rae, Acta Cryst., 19, 683 (1965)). This method gave a final correlation R of 0.04. The total number of unique reflections was 2215. Corrections for Lorentz and polarization and a semi-empirical absorption correction (A.C.T. North, D.C. Phillips, and F.S. Matthews, Acta Cryst., A24, 351 (1968)) were made. A Patterson map (A. L. Patterson, Z. Krist., A90, 517 (1935)) was used to locate the two bromine atoms. The positions of the bromine atoms were used to approximate the phases in a Fourier synthesis. From this and subsequent Fourier syntheses all non-hydrogen atoms were located. The structure was refined by a least squares method using diagonal, block and full matrices and Hughes (E. W. Hughes, J. Amer. Chem. Soc., 63, 1737 (1941)) weighting scheme. Bromine atoms were given anisotropic temperature factors. The final unweighted R factor was 11% and the weighted R was 5%. The full structural analysis will be presented elsewhere.

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