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Crystal and molecular structure of the product from solvolysis of DHEA tosylate in benzyl alcohol

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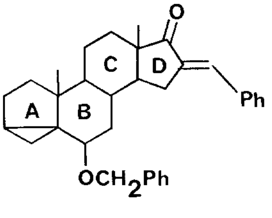
The crystal and molecular structure of the product from the solvolysis of dehydroepiandrosterone (DHEA) tosylate has been determined by X-ray analysis, ^{1}H-NMR, IR, UV, and mass spectrometry. The compound was obtained from DHEA via the 3β-tosyl derivative by refluxing in benzyl alcohol (containing dried potassium acetate) for 12 hr. X-ray analysis shows a planar cyclopropane ring at C(3), C(4), C(5), a β-orientated benzylozy group attached to C(6) and a benzylidene group attached to C(16). Spectroscopic evidence for the presence of these features in the steroid nucleus are presented and details of the synthesis and possible mechanisms of formation are also discussed.

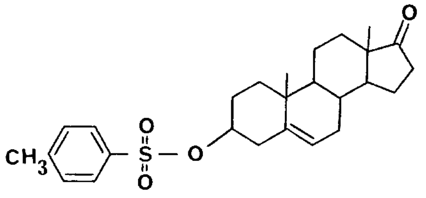
Introduction

The protection of the 5-en-3-ol system in sterols by cyclosteroid formation is a well-known operation in synthetic work. The present study, carried out as part of a search for new protected forms of the cyclosteroid ring system, involved an investigation of the reaction of benzyl alcohol with DHEA tosylate under standard solvolysis conditions.



I

Scheme 1

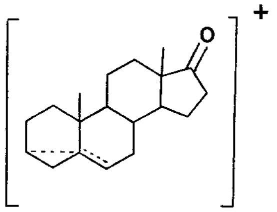


II

Scheme 2

Synthesis

A solution of DHEA tosylate (1.0 g) in benzyl alcohol (25 ml) containing dried potassium acetate (1.2 g) was heated under reflux for 12 hr. Evaporation of the solvent under reduced pressure, followed by crystallization of the crude product from ethanol gave the adduct [(I), 0.3 g], m.p. 185–190° raised to 197–199° after two further recrystallizations from ethanol.



III

Scheme 3

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Experimental

X-Ray analysis

$C_{33}H_{38}O_2$, $M_r = 466.6$, monoclinic, $P2_1$ (No. 4), $a = 10.509(6)$, $b = 9.100(9)$, $c = 14.056(16)$ Å, $\beta = 93.56(7)°$, $V = 1342(2)$ Å^3, $Z = 2$, $D_x = 1.15(2)$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0.71069$ Å, $\mu = 0.37$ cm^{-1}, $F(000) = 504$, $T = 293$ K, $R = 0.071$ for 1654 unique reflexions. A colorless crystal, 0.5 × 0.9 × 0.3 mm, obtained by recrystallization from ethanol was used in the analysis. The reflexion intensities were measured on a Nicolet $P3$ automated diffractometer with graphite monochromated Mo $K\alpha$ radiation. Cell dimensions were obtained from the setting angles of 12 independent reflexions with $2\theta \approx 20°$. The data were corrected for Lorentz and polarization effects, absorption was ignored. A total of 3294 unique intensities were measured with $2\theta \leq 50°$ as $\omega - 2\theta$ scans; 1654 had $F \geq 5\sigma F$. Range of hkl:—$13 \leq h \leq 13, 0 \leq k \leq 11, 0 \leq l \leq 18$. Two reference reflexions monitored periodically showed no significant variation in intensity. The structure was determined with SHELX86 (Sheldrick, 1986) and all H atoms observed in difference maps with SHELX76 (Sheldrick, 1976). Full-matrix least-squares calculations on F with anisotropic thermal parameters for C and O atoms and a common isotropic thermal parameter for the H atoms converged at R 0.071, $w = 1.0$. The positional parameters of the cyclopropane H atom, H(3), were freely refined, the remaining H atoms were allowed

Table 1. Fractional coordinates with esd's and equivalent values of the anisotropic temperature factor coefficients

	$U_{eq} = \frac{1}{3}\Sigma_i\Sigma_j U_{ij} a_i * a_j * a_i \cdot a_j.$			
	x	y	z	U_{eq}(Å^2)
O(1)	0.3949(5)	0.4592	0.2459(4)	0.068
O(2)	−0.2961(5)	0.6775(11)	0.3140(4)	0.072
C(1)	0.2278(9)	0.7171(14)	−0.0147(6)	0.067
C(2)	0.2970(9)	0.8570(15)	0.0171(7)	0.077
C(3)	0.3961(8)	0.8078(15)	0.0930(7)	0.068
C(4)	0.4734(8)	0.6760(15)	0.0693(6)	0.074
C(5)	0.3575(7)	0.6557(13)	0.1277(5)	0.050
C(6)	0.3793(7)	0.6159(13)	0.2313(5)	0.052
C(7)	0.2649(6)	0.6584(14)	0.2864(5)	0.049
C(8)	0.1417(6)	0.5967(12)	0.2402(5)	0.042
C(9)	0.1208(6)	0.6534(13)	0.1370(5)	0.045
C(10)	0.2312(7)	0.6153(13)	0.0728(5)	0.052
C(11)	−0.0123(6)	0.6128(13)	0.0922(5)	0.055
C(12)	−0.1218(6)	0.6552(14)	0.1521(5)	0.053
C(13)	−0.0989(7)	0.5885(12)	0.2521(5)	0.045
C(14)	0.0310(6)	0.6421(13)	0.2955(4)	0.041
C(15)	0.0267(7)	0.6036(13)	0.4022(5)	0.052
C(16)	−0.1132(7)	0.6277(13)	0.4206(6)	0.056
C(17)	−0.1869(7)	0.6389(13)	0.3271(6)	0.055
C(18)	−0.1097(8)	0.4194(12)	0.2506(7)	0.061
C(19)	0.2298(9)	0.4504(13)	0.0425(6)	0.069
C(20)	−0.1738(8)	0.6317(13)	0.5012(6)	0.061
C(21)	−0.1266(8)	0.6115(13)	0.6023(6)	0.059
C(22)	−0.0005(9)	0.5693(13)	0.6301(6)	0.063
C(23)	0.0354(10)	0.5519(14)	0.7254(7)	0.076
C(24)	−0.0566(12)	0.5756(14)	0.7931(7)	0.086
C(25)	−0.1786(13)	0.6152(16)	0.7646(7)	0.095
C(26)	−0.2125(10)	0.6350(17)	0.6719(7)	0.089
C(27)	0.5111(9)	0.3998(15)	0.2203(7)	0.081
C(28)	0.5454(8)	0.2773(15)	0.2910(8)	0.069
C(29)	0.5645(10)	0.1347(19)	0.2608(9)	0.090
C(30)	0.6005(13)	0.0284(21)	0.3228(14)	0.129
C(31)	0.6164(16)	0.0614(26)	0.4158(16)	0.154
C(32)	0.5951(17)	0.2006(28)	0.4444(11)	0.163
C(33)	0.5624(13)	0.3088(19)	0.3821(10)	0.119

Table 2. Bond lengths (Å) and valency angles (°) with esd's

O(1)—C(6)	1.449(12)	O(1)—C(27)	1.403(12)
O(2)—C(17)	1.204(11)	C(1)—C(2)	1.52(2)
C(1)—C(10)	1.538(14)	C(2)—C(3)	1.51(2)
C(3)—C(4)	1.50(2)	C(3)—C(5)	1.53(2)
C(4)—C(5)	1.521(12)	C(5)—C(6)	1.504(12)
C(5)—C(10)	1.538(12)	C(6)—C(7)	1.520(11)
C(7)—C(8)	1.519(11)	C(8)—C(9)	1.543(11)
C(8)—C(14)	1.497(10)	C(9)—C(10)	1.552(11)
C(9)—C(11)	1.543(10)	C(10)—C(19)	1.56(2)
C(11)—C(12)	1.519(11)	C(12)—C(13)	1.537(12)
C(13)—C(14)	1.539(11)	C(13)—C(17)	1.515(12)
C(13)—C(18)	1.54(2)	C(14)—C(15)	1.544(10)
C(15)—C(16)	1.524(11)	C(16)—C(17)	1.487(12)
C(16)—C(20)	1.334(12)	C(20)—C(21)	1.488(12)
C(21)—C(22)	1.411(13)	C(21)—C(26)	1.388(14)
C(22)—C(23)	1.378(13)	C(23)—C(24)	1.41(2)
C(24)—C(25)	1.37(2)	C(25)—C(26)	1.34(2)
C(27)—C(28)	1.52(2)	C(28)—C(29)	1.38(3)
C(28)—C(33)	1.31(2)	C(29)—C(30)	1.34(3)
C(30)—C(31)	1.34(4)	C(31)—C(32)	1.35(4)
C(32)—C(33)	1.35(3)		
C(6)—O(1)—C(27)	115.8(7)	C(2)—C(1)—C(10)	106.4(8)
C(1)—C(2)—C(3)	104.8(10)	C(2)—C(3)—C(4)	116.1(9)
C(2)—C(3)—C(5)	108.0(9)	C(4)—C(3)—C(5)	60.3(8)
C(3)—C(4)—C(5)	60.9(7)	C(3)—C(5)—C(4)	58.8(8)
C(3)—C(5)—C(6)	119.9(9)	C(3)—C(5)—C(10)	107.1(8)
C(4)—C(5)—C(6)	118.2(7)	C(4)—C(5)—C(10)	117.0(7)
C(6)—C(5)—C(10)	120.2(8)	O(1)—C(6)—C(5)	112.5(8)
O(1)—C(6)—C(7)	105.3(8)	C(5)—C(6)—C(7)	110.8(7)
C(6)—C(7)—C(8)	111.6(8)	C(7)—C(8)—C(9)	110.2(7)
C(7)—C(8)—C(14)	110.2(7)	C(9)—C(8)—C(14)	109.0(7)
C(8)—C(9)—C(10)	113.8(7)	C(8)—C(9)—C(11)	112.1(7)
C(10)—C(9)—C(11)	113.6(7)	C(1)—C(10)—C(5)	103.5(8)
C(1)—C(10)—C(9)	110.5(9)	C(1)—C(10)—C(19)	111.2(8)
C(5)—C(10)—C(9)	108.0(7)	C(5)—C(10)—C(19)	111.1(9)
C(9)—C(10)—C(19)	112.3(9)	C(9)—C(11)—C(12)	114.3(7)
C(11)—C(12)—C(13)	109.0(7)	C(12)—C(13)—C(14)	108.8(7)
C(12)—C(13)—C(17)	116.7(8)	C(12)—C(13)—C(18)	112.0(8)
C(14)—C(13)—C(17)	101.1(7)	C(14)—C(13)—C(18)	112.6(8)
C(17)—C(13)—C(18)	105.3(8)	C(8)—C(14)—C(13)	114.0(7)
C(8)—C(14)—C(15)	120.8(7)	C(13)—C(14)—C(15)	103.5(7)
C(14)—C(15)—C(16)	102.7(6)	C(15)—C(16)—C(17)	108.3(7)
C(15)—C(16)—C(20)	131.6(8)	C(17)—C(16)—C(20)	119.9(7)
O(2)—C(17)—C(13)	126.8(8)	O(2)—C(17)—C(16)	126.4(8)
C(13)—C(17)—C(16)	106.7(7)	C(16)—C(20)—C(21)	131.3(8)
C(20)—C(21)—C(22)	123.3(8)	C(20)—C(21)—C(26)	117.5(8)
C(22)—C(21)—C(26)	119.2(8)	C(21)—C(22)—C(23)	119.7(9)
C(22)—C(23)—C(24)	118.6(10)	C(23)—C(24)—C(25)	120.7(10)
C(24)—C(25)—C(26)	120.5(11)	C(21)—C(26)—C(25)	121.2(11)
O(1)—C(27)—C(28)	106.8(8)	C(27)—C(28)—C(29)	121.3(11)
C(27)—C(28)—C(33)	119.3(13)	C(29)—C(28)—C(33)	119.4(13)
C(28)—C(29)—C(30)	121.1(14)	C(29)—C(30)—C(31)	119.0(19)
C(30)—C(31)—C(32)	119.1(21)	C(31)—C(32)—C(33)	122.1(17)
C(28)—C(33)—C(32)	119.2(17)		

to ride on their attached C atoms. Atomic scattering factors from SHELX76. Final $\Delta/\sigma < 0.07$, final $\Delta\rho\text{max} = 0.13\ \text{e}\,\text{Å}^{-3}$, $\Delta\rho\text{min} = -0.09\ \text{e}\,\text{Å}^{-3}$. Molecular geometries were generated by the GX package (Mallinson and Muir, 1985).

Spectroscopic analysis

Infrared spectra were recorded on a Philips PU9000 FTIR spectrophotometer as KBr discs and an EI mass fragmentation pattern was obtained from an AEI MS30 mass spectrometer operating at 70 eV.

Proton NMR spectra were determined with a Perkin-Elmer R34 spectrometer operating at 220 MHz. The solvent used was $CDCl_3$ with TMS as internal standard. The sample concentration was 0.06 mol dm^{-3} and precision ground tubes, 5-mm-o.d., were used.

A Perkin-Elmer LAMBDA 15 uv-visible spectrophotometer was used to record absorption spectra.

Discussion

X-ray analysis

Atomic coordinates are listed in Table 1, bond lengths and valency angles in Table 2, and ring torsion angles in Table 3. The atomic arrangement is shown in Fig. 1.

The planar cyclopropane ring has valency angles 60.3(8), 60.9(7), and 58.8(8)° and lies predominantly on the α face of the molecule. The benzyloxy group attached to C(6) is axial and β orientated. Here C(4)—C(5)—C(10)—C(19) is 76.1(10)° and C(4)—C(5)—C(6)—O(1) is −84.9(10)°. The benzylidene group is attached to C(16) such that C(17)—C(16)—C(20)—C(21) is 174.6(17)° and C(15)—C(16)—C(20)—C(21) is −1.2(10)°. Angular strain is shown by the valency angles involving the sp^2 carbon atoms C(16) and C(17) as these atoms are constrained in a 5-membered ring. As expected the atoms of the benzene rings are associated with higher thermal motion (Fig. 1) than those atoms in the steroid nucleus.

The conformation of the A ring which is linked at C(3), C(5) is shown by the torsion angles in Table 3. It may also be described as a distorted boat with C(1) and C(4) displaced by 0.48(1) and 1.21(1) Å, respectively, from the same side of the C(2), C(3), C(5), C(10) plane. Rings B and C adopt chair conformations and ring D has a half-chair conformation.

Other cyclopropane steroids examined by X-ray crystallography include 3,5-cycloandrostane-6,17-dione (Hanson *et al.*, 1988) and 3,5-cycloandrostan-6β-ol-17-one (Cox *et al.*, 1990).

Table 3. Torsion angles

Ring *A*	
C(10)—C(1)—C(2)—C(3)	31.1(9)°
C(2)—C(1)—C(10)—C(5)	−31.6(9)
C(1)—C(2)—C(3)—C(4)	46.9(10)
C(2)—C(3)—C(4)—C(5)	−96.3(11)
C(3)—C(4)—C(5)—C(10)	95.2(10)
C(4)—C(5)—C(10)—C(1)	−43.6(9)
Ring *B*	
C(10)—C(5)—C(6)—C(7)	−47.4(9)
C(6)—C(5)—C(10)—C(9)	44.5(9)
C(5)—C(6)—C(7)—C(8)	52.7(9)
C(6)—C(7)—C(8)—C(9)	−60.0(9)
C(7)—C(8)—C(9)—C(10)	59.2(9)
C(8)—C(9)—C(10)—C(5)	−48.7(9)
Ring *C*	
C(14)—C(8)—C(9)—C(11)	−51.5(8)
C(9)—C(8)—C(14)—C(13)	58.2(8)
C(8)—C(9)—C(11)—C(12)	52.2(9)
C(9)—C(11)—C(12)—C(13)	−54.1(9)
C(11)—C(12)—C(13)—C(14)	56.4(9)
C(12)—C(13)—C(14)—C(8)	−61.7(9)
Ring *D*	
C(17)—C(13)—C(14)—C(15)	42.3(8)
C(14)—C(13)—C(17)—C(16)	−33.9(8)
C(13)—C(14)—C(15)—C(16)	−34.6(8)
C(14)—C(15)—C(16)—C(17)	13.7(8)
C(15)—C(16)—C(17)—C(13)	12.7(8)

Table 4. Mean plane

In plane atoms: C(2) 0.00(1), C(3) −0.01(1), C(5) 0.00(1), C(10) −0.01(1) Å

Out of plane atoms: C(1) 0.48(1), C(4) 1.21(1) Å

Mechanism of formation

The product is formed by the usual solvolytic process via the carbocation (III) following loss of the tosyl group from dehydroisoandrosterone tosylate (II). The cation (III) is trapped by the solvent (benzyl alcohol) which attacks at C(6) to give the 6β-benzyloxycyclosteroid. The origin of the benzylidene group in ring D is less clear. Possible mechanisms may involve formation of benzaldehyde from benzyl alcohol and subsequent condensation at C(16), or reaction of benzyl alcohol itself at C(16) to give a 16-benzyl-17-ketone, followed by dehydrogenation to give the conjugated ketone.

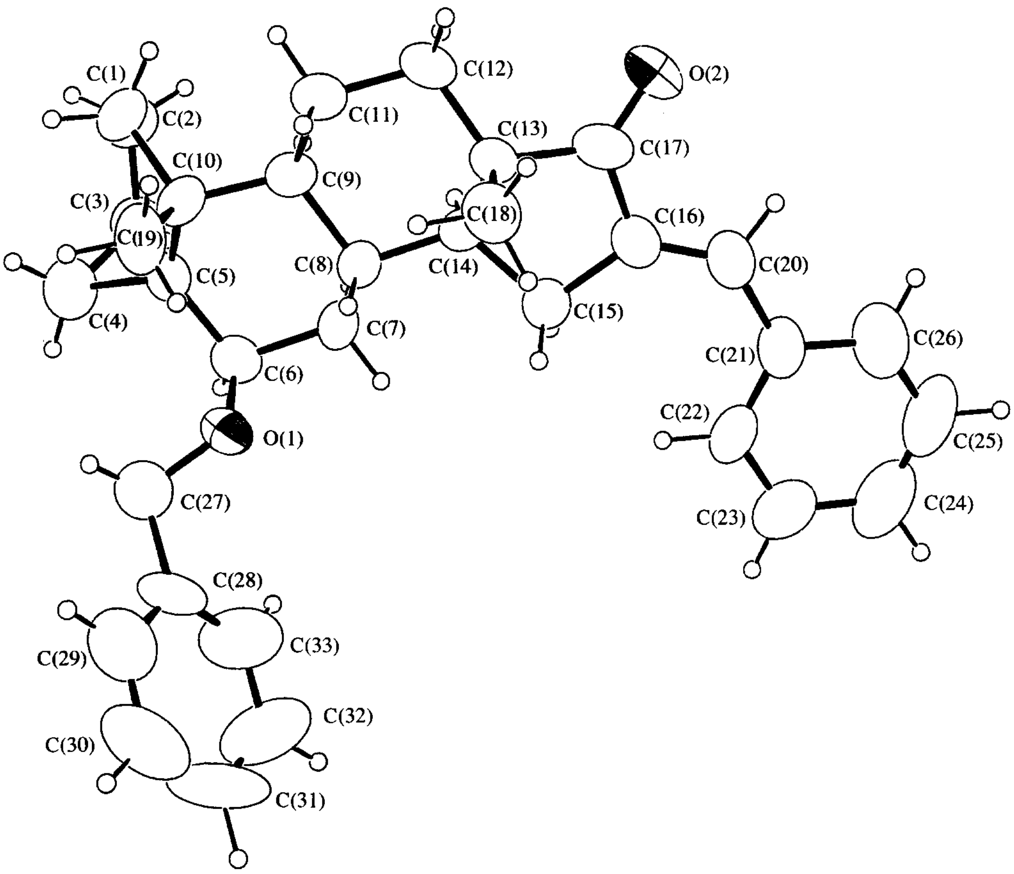

Fig. 1. The atomic arrangement in the molecule.

Spectroscopic results

Characteristic features of a steroid molecule were observed in all spectra and only those of particular interest are mentioned here.

The IR spectrum shows absorption bands at 1715 cm^{-1} characteristic of a conjugated 5-ring ketone, 1082 cm^{-1} characteristic of a C—O ether, 1010 cm^{-1} characteristic of a cyclopropane ring and at 752 and 700 cm^{-1} characteristic of monosubstituted aromatic groups.

The ^{1}H NMR spectrum shows signals for the angular methyl groups at δ 0.92(s) and 1.02(s) ppm, a benzyloxy methylene group at δ 4.53(s) ppm, an olefinic proton at δ 5.37(br s) and aromatic protons at 7.2–7.6(m) ppm.

The EI mass fragmentation pattern shows no parent ion. The highest observed fragment ion at m/z 375 corresponds to loss of a benzyl group (466–91). The loss of a methyl group m/z 360 (15%) is observed and the only other prominent ions are at m/z 185 (17%), 116 (20%), and 91 (100%).

The benzylidene-ketone chromophore gave a λ max in the UV spectrum at 293 nm ($\epsilon \approx 7000$).

References

Cox, P. J., MacManus, S. M., Gibb, B. C., Nowell, I. W., Turner, A.B. and Howie, R. A., (1990) *J. Cryst. Spect. Res.* in press.

Hanson, J. R., Hitchcock, P. B., Reese, P. B., and Truneh, A. (1988) *J. Chem. Soc. Perkin Trans. I*, 1465.

Mallinson, P. R., and Muir, K. W. (1985) *J. Appl. Crystallogr.* **18**, 51.

Sheldrick, G. M. (1976) SHELX76. Program for crystal structure determination (University of Cambridge, England).

Sheldrick, G. M. (1986) SHELX86. Program for the solution of crystal structures from diffraction data. PC version.

Thermal parameters, H atom positions and structure factors have been deposited with the British Lending Library, Boston Spa, Wetherby, West Yorkshire, UK as supplementary publication No. 63128 (17 pages).