

Structure of 5,8 α -Epidioxy-5 α -cholest-6-en-3 β -yl Acetate

BY K. TAKAHASHI, Y. YAMAGUCHI AND A. HAYASHI

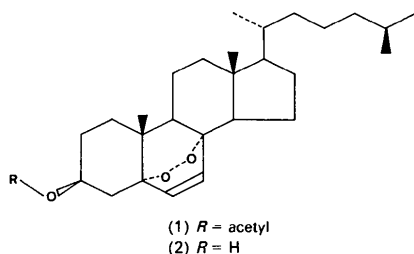
Department of Chemistry, Faculty of Science and Technology, Kinki University, Higashi-Osaka, Osaka 577, Japan

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Abstract. C₂₉H₄₆O₄, $M_r = 458.68$, orthorhombic, $P2_12_12_1$, $a = 7.020$ (2), $b = 10.478$ (4), $c = 36.154$ (9) Å, $V = 2659$ (2) Å³, $Z = 4$, $D_x = 1.15$ Mg m⁻³, $\lambda(\text{Mo } K\alpha) = 0.7107$ Å, $\mu = 0.0692$ mm⁻¹, $F(000) = 1008$, $T = 298$ K, $R = 0.073$ for 1692 observed reflections. The molecular structure of an acetylated sterol derivative obtained from a sea hare egg was determined. The ring conformations are common to those of cholesterol derivatives with the exception of an epidioxy bicyclic ring.

Introduction. Three sterols have been separated from the egg of the sea hare, *Aplysia juliana*, which belongs to the phylum Mollusca (Yamaguchi, Hashiguchi & Hayashi, 1991). The molecular weight of one of the sterols was found to be $M/Z = 416$ by EI/MASS measurements. An acetylated derivative ($M/Z = 458$) of the $m/Z = 416$ sterol gave a single crystal and X-ray crystal analysis was performed for identification and structure determination of the $M/Z = 416$ sterol.

X-ray crystal analysis of the acetylated derivative (1) showed that it had an epidioxy bicyclic ring and the natural $M/Z = 416$ sterol (2) was identified as 5,8 α -epidioxy-5 α -cholest-6-en-3 β -ol.



The epidioxy bicyclic compound (2) has been reported as a product of photochemical oxidation which has shown antitumor activity (Matsueda & Katsukura, 1985).

Experimental. The title compound was obtained as described elsewhere (Yamaguchi, Hashiguchi & Hayashi, 1991). Colorless crystal, $0.5 \times 0.5 \times 0.5$ mm, Rigaku AFC-6 diffractometer, graphite-

monochromated Mo $K\alpha$ radiation. Cell parameters by least squares on setting angles for 20 reflections ($15 < 2\theta < 20^\circ$), 2099 unique reflections ($R_{\text{int}} = 0.064$), of which 1692 were treated as observed in the refinement based on $I > 3\sigma(I)$, $2\theta_{\text{max}} = 55^\circ$ ($0 \leq h \leq 7$, $0 \leq k \leq 11$, $0 \leq l \leq 39$), $\omega/2\theta$ scan mode, scan speed 4° min^{-1} , scan width $(1.123 + 0.35 \tan \theta)^\circ$, background measured for 5 s on each side of the peaks. Three standard reflections monitored every 200 reflections, no significant variation in intensity, no absorption correction. Structure solved by MULTAN87 (Debaerdemaeker, Germain, Main, Tate & Woolfson, 1987) on an INMOS T800 processor. In the final cycles of block-matrix least-squares refinement, all non-H atoms anisotropic, H atoms included using a riding model (C—H 0.96 Å) and an overall isotropic temperatures factor of $U_{\text{eq}} = 0.0319$ Å². 299 parameters refined, $\sum w\Delta F^2$ minimized with $w = 1/[\sigma^2(F_o) + 0.00957F_o^2]$. $R = 0.073$, $wR = 0.096$, $S = 1.145$, $(\Delta/\sigma)_{\text{max}} = 0.05$, $\Delta\rho_{\text{max}} = 0.16$, $\Delta\rho_{\text{min}} = -0.18$ e Å⁻³, scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV).

The coordinates and equivalent isotropic thermal parameters are given in Table 1. Selected bond lengths, bond angles and torsion angles around the bicyclic ring are shown in Table 2. An ORTEP (Johnson, 1976) drawing of the title compound is given in Fig. 1.*

Discussion. The 1692 reflections were not enough to get refined H-atom positions. The R factor is high because the crystal was slightly large and had a flexible side chain.

A MNDO molecular orbital calculation (Dewar & Thiel, 1977) was performed to see the correspondence between the X-ray structure and the MNDO energy-minimized molecular structure (Fletcher &

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates, bond lengths, bond angles, and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54242 (15 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic temperature factors ($\times 10^3$) with e.s.d.'s in parentheses

$$U_{eq} = (U_{11} + U_{22} + U_{33})/3.$$

	x	y	z	$U_{eq}(\text{\AA}^2)$
O(1)	5180 (5)	2242 (4)	3008 (1)	52 (1)
O(2)	4806 (5)	2472 (4)	2610 (1)	50 (1)
O(3)	4705 (7)	2781 (5)	1459 (1)	68 (2)
O(4)	2361 (13)	1405 (6)	1388 (2)	136 (3)
C(5)	3003 (17)	2975 (8)	919 (2)	92 (4)
C(6)	3244 (12)	2291 (8)	1287 (2)	71 (3)
C(7)	5198 (9)	2303 (6)	1819 (2)	54 (2)
C(8)	6898 (12)	1438 (6)	1785 (2)	58 (2)
C(9)	7589 (10)	1066 (6)	2181 (2)	57 (2)
C(10)	8089 (8)	2201 (5)	2428 (2)	40 (2)
C(11)	9870 (8)	2870 (6)	2266 (2)	52 (2)
C(12)	6413 (8)	3122 (5)	2431 (2)	44 (2)
C(13)	5621 (10)	3479 (6)	2056 (2)	54 (2)
C(14)	8390 (8)	1752 (5)	2833 (2)	47 (2)
C(15)	7169 (7)	2585 (6)	3099 (2)	42 (2)
C(16)	7337 (9)	4007 (5)	3015 (2)	47 (2)
C(17)	6879 (8)	4262 (5)	2680 (2)	50 (2)
C(18)	10430 (9)	1614 (6)	2962 (2)	57 (2)
C(19)	10567 (10)	1197 (6)	3374 (2)	53 (2)
C(20)	9513 (10)	2102 (6)	3619 (2)	50 (2)
C(21)	10522 (11)	3407 (6)	3610 (2)	69 (3)
C(22)	7431 (8)	2178 (6)	3491 (2)	48 (2)
C(23)	9165 (10)	1708 (6)	4031 (2)	59 (2)
C(24)	7492 (12)	2547 (9)	4154 (2)	76 (3)
C(25)	6382 (10)	2918 (8)	3802 (2)	71 (3)
C(26)	10855 (12)	1639 (8)	4299 (2)	72 (3)
C(27)	12336 (13)	679 (12)	4208 (2)	99 (4)
C(28)	10192 (13)	1481 (8)	4708 (2)	77 (3)
C(29)	9136 (16)	294 (9)	4794 (2)	91 (3)
C(30)	8693 (15)	155 (10)	5217 (3)	102 (4)
C(31)	7515 (20)	-922 (8)	5316 (3)	107 (4)
C(32)	5707 (31)	-1012 (19)	5171 (3)	208 (9)
C(33)	7352 (22)	-1037 (13)	5722 (3)	144 (6)

Table 2. Selected bond lengths (\AA), bond angles ($^\circ$) and torsion angles ($^\circ$)

O(1)—O(2)	1.482 (6)	O(1)—C(15)	1.479 (8)
O(2)—C(12)	1.468 (8)	O(4)—C(6)	1.174 (12)
C(10)—C(12)	1.522 (10)	C(10)—C(14)	1.552 (10)
C(12)—C(17)	1.531 (10)	C(14)—C(15)	1.556 (10)
C(15)—C(16)	1.525 (10)	C(16)—C(17)	1.281 (10)
C(23)—C(26)	1.533 (11)	C(26)—C(27)	1.484 (15)
C(26)—C(28)	1.559 (12)	C(28)—C(29)	1.481 (14)
C(29)—C(30)	1.567 (16)	C(30)—C(31)	1.444 (18)
C(31)—C(32)	1.376 (26)	C(31)—C(33)	1.477 (21)
O(2)—O(1)—C(15)	110.1 (4)	O(1)—O(2)—C(12)	111.5 (4)
O(2)—C(12)—C(13)	103.1 (5)	C(10)—C(12)—C(13)	115.8 (6)
C(13)—C(12)—C(17)	114.4 (6)	O(1)—C(15)—C(22)	105.0 (5)
C(14)—C(15)—C(22)	111.0 (6)	C(16)—C(15)—C(22)	117.3 (6)
C(15)—O(1)—O(2)—C(12)	-7.3 (6)	O(2)—O(1)—C(15)—C(22)	-173.8 (5)
O(1)—O(2)—C(12)—C(13)	-170.0 (5)	C(14)—C(10)—C(12)—C(13)	-168.4 (6)
C(12)—C(10)—C(14)—C(15)	-10.9 (8)	C(13)—C(12)—C(17)—C(16)	171.9 (7)
C(10)—C(14)—C(15)—C(22)	-179.9 (6)	C(22)—C(15)—C(16)—C(17)	172.7 (7)
C(15)—C(16)—C(17)—C(12)	-4.2 (9)		

Powell, 1963; Davidon, 1968; Pulay, 1980) The conformations of both MNDO and X-ray structures were essentially the same.

The conformation of the rings of the title compound are common to those of cholesterol derivatives except for the bicyclic ring.

The side-chain conformation of the title compound is *gauche* at C(23)—C(26)—C(28)—C(29). A *gauche* conformation of the chain is not common in crystal structures of cholesterol derivatives. Two exceptions are 26-hydroxycholesterol (Uomori, Seo, Sato, Yoshimura & Takeda, 1987) and 298 K cholesterol (Shieh, Hoard & Nordman, 1977). The chole-

sterol undergoes phase transition at 304.6 K and two *gauche* conformations out of eight cholesterol molecules in an asymmetric unit change to *trans* conformation (Hsu & Nordman, 1983). It suggests that the structural energies of *gauche* and *trans* conformations of a flexible chol chain are almost the same. The MNDO calculations gave a small energy difference between *gauche* and *trans* conformations of 0.56 kcal mol⁻¹ (2.34 kJ mol⁻¹).

Compound (2) (epidioxycholestenol) is a sterol which has a peroxide in the form of a bicyclic ring, and had not been found in living systems previously. Matsueda & Katsukura (1985) have reported this compound as a product of photochemical oxidation of provitamin D₃ (cholesta-5,7-dien-3 β -ol or 3 β ,7-dehydrocholesterol). Another example of epidioxide formation is in the catalytic oxygenation of ergosteryl acetate (Barton, Leclerc, Magnus & Menzies, 1972). The cholestadienol (provitamin D₃) was not found in the egg of the sea hare (Yamaguchi, Hashiguchi & Hayashi, 1991) though it is common in mollusks. The 1,4-addition of the photosensitized singlet oxygen molecule to the diene is a common reaction. It is suggested that cholestadienol is easily photo-oxidized to the epidioxy cholestenol (2) with or without a photosensitizer in the egg of sea hare.

The possibility of photo-oxidation of cholestadienol by the excited oxygen molecule was examined. The structure of the cholestadienol was derived from the epidioxycholestenol by removing epidioxy O atoms. The structure energy was minimized first by molecular mechanics (MMP2; Allinger & Yuh, 1980) and then by MNDO. HOMO and LUMO were $\psi_{\text{HOMO}} = 0.504\varphi_1 + 0.364\varphi_2 - 0.396\varphi_3 - 0.528\varphi_4$ and $\psi_{\text{LUMO}} = -0.545\varphi_1 + 0.390\varphi_2 + 0.401\varphi_3 - 0.542\varphi_4$, where $\varphi_1, \varphi_2, \varphi_3, \varphi_4$ are 2p atomic orbitals of the diene. The MO energy eigenvalues of HOMO and LUMO were $E_{\text{HOMO}} = -8.59$ and $E_{\text{LUMO}} = -0.14$ eV. The $^1\Delta_g$ excited state of the oxygen molecule has two antibonding SOMOs of $E_{\text{SOMO}} = -11.094$ eV (Herzberg, 1950). HOMO of cholestadienol has opposite coefficients at φ_1 and φ_4 . Both orbital energies and symmetries suggest 1,4-cycloaddition between the diene of cholestadienol and the $^1\Delta_g$ oxygen molecule.

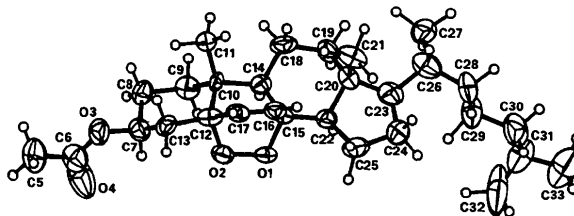


Fig. 1. ORTEP (Johnson, 1976) drawing of (1) with thermal ellipsoids at the 30% probability level. H atoms are shown as spheres of arbitrary radius.

The epidioxycholestenol (2) is reported to show a cytotoxicity against mouse lymphopenia and anti-tumor activity against KB cells derived from human epidermoid carcinoma in mice (Matsueda & Katsukura, 1985). The MNDO calculation of the epidioxycholestenol shows that HOMO has bonding π orbitals and LUMO has antibonding π orbitals at the carbon-carbon double bond. Rather small coefficients were found at epidioxy O atoms. It is suggested that the double bond is more reactive both as an electrophile and as a nucleophile than the peroxide for 5,8 α -epidioxy-5 α -cholest-6-en-3 β -ol.

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Structure and Conformation of a Hetero-Substituted Cyclooctane

BY CONCEPCION FOCES-FOCES AND FELIX HERNANDEZ CANO

UEI de Cristalografía, Instituto de Química-Física 'Rocasolano', CSIC, Serrano 119, 28006 Madrid, Spain

AND PILAR CABILDO, ROSA MARIA CLARAMUNT AND JOSE ELGUERO

Departamento de Química Orgánica, Instituto de Química Médica, UNED y CSIC, Ciudad Universitaria, 28040 Madrid, Spain

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Abstract. 5,6,12,13-Tetrahydrobispyrazolo[1,2-*a*:1',2'-*e*][1,2,5,6]tetrazocinium dibromide, $C_{10}H_{14}N_4^{2+} \cdot 2Br^-$, $M_r = 350.06$, monoclinic, $C2/c$, $a = 12.7119$ (5), $b = 6.9016$ (2), $c = 14.6312$ (5) Å, $\beta = 105.755$ (3)°, $V = 1235.41$ (8) Å³, $Z = 4$, $D_x = 1.882$ g cm⁻³, $\lambda(Cu K\alpha) = 1.5418$ Å, $\mu = 82.48$ cm⁻¹, $F(000) = 688$, $T = 298$ K, $R(wR) = 0.038$ (0.048) for 999 observed reflections with $I > 3\sigma(I)$. The title compound contains a central eight-membered ring with an internal crystallographic center of symmetry and is in a chair conformation. The lateral pyrazole rings support the cationic charge and the bromide anions present short contacts with some hydrogen atoms.

Introduction. One of the cornerstones of conformational analysis is that concerning medium-sized rings (Hendrickson, 1967; Dunitz, 1979). Among these, one of the most fascinating compounds is dibenzo-1,5-cyclooctadiene (5,6,11,12-tetrahydrodibenzo[*a,e*]-

cyclooctene) (I) (Ollis, Stoddart & Sutherland, 1974), since the two aromatic rings simplify the conformational problem (two dihedral angles equal to 0°). Most heterocyclic analogs of (I) have the heteroatoms in place of the saturated carbons (positions 5, 6, 7 or 12) (Moore & Anet, 1984). Among the rare heterocycles with heteroatoms on the fused benzene rings, 6,7,13,14-tetrahydrodipyrido[1,2-*a*:1',2'-*e*]diazocinium salts (II) (crystal structure unknown) (Glover, Pointer, Wilford & Elder, 1981) and 6,7,14,15-tetrahydrobisbenzimidazo[1,2-*a*:1',2'-*e*]diazocine (III) (structure reported) (Elguero, Katritzky, El-Osta, Harlow & Simonsen, 1976) have been described. The structure and conformation of 5,6,12,13-tetrahydrobispyrazolo[1,2-*a*:1',2'-*e*][1,2,5,6]-tetrazocinium dibromide (IV) is presented here.

