ORGANIC COMPOUNDS

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3α,7α,12α-Trihydroxy-5β-cholan-24-oic Acid Methyl Ester Ethanolate (Methyl Cholate Ethanolate)

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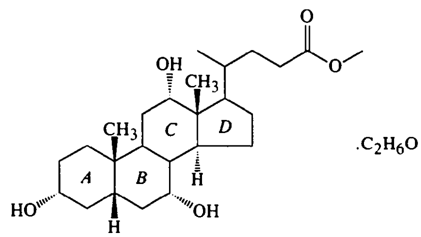
Abstract

The crystal structure of methyl cholate ethanolate, $C_{25}H_{42}O_5.C_2H_6O$, has been determined and found to be isostructural with two other alcohol-solvated methyl cholate structures, methyl cholate methanolate and methyl cholate 2-propanolate.

Comment

Our examination of solid-state pseudopolymorphs led us to the bile acid, cholic acid (3α,7α,12α-trihydroxy-5β-cholan-24-oic acid), and its sodium salt, sodium cholate (sodium 3α,7α,12α-trihydroxy-5β-cholan-24-oate). Isostructural forms of cholic acid have been reported when solvated with methanol, ethanol, and 1-propanol (Johnson & Schaefer, 1972; Jones & Nassimbeni, 1990). Likewise, sodium cholate also produced isostructural forms when solvated with methanol and ethanol (Wahle, Stowell & Byrn, 1995; Wahle & Byrn, 1996). The methyl ester derivative of cholic acid, methyl cholate [3α,7α,12α-trihydroxy-5β-cholan-24-oic acid methyl ester] displays a similar trend to the isostructural forms of methyl cholate methanolate and methyl cholate 2-propanolate (Miyata *et al.*, 1987; Miki *et al.*, 1992). Methyl cholate ethanolate has been reported previously (Norton & Haner, 1965) but no coordinates were included. Here we continue our examination of cholic acid derivatives by reporting the structure of methyl cholate ethanolate (I).



(I)

The *ORTEP*II (Johnson, 1976) diagram of the title structure is presented in Fig. 1. The rings have a geometry similar to the other cholic acid structures reported to date, with a *cis* ring junction for the *A* and *B* rings and *trans* ring junctions for the *B* and *C* and *C* and *D* rings. When the methanol-solvated and ethanol-solvated structures are overlaid using a least-squares fit, the steroid rings and side chains are

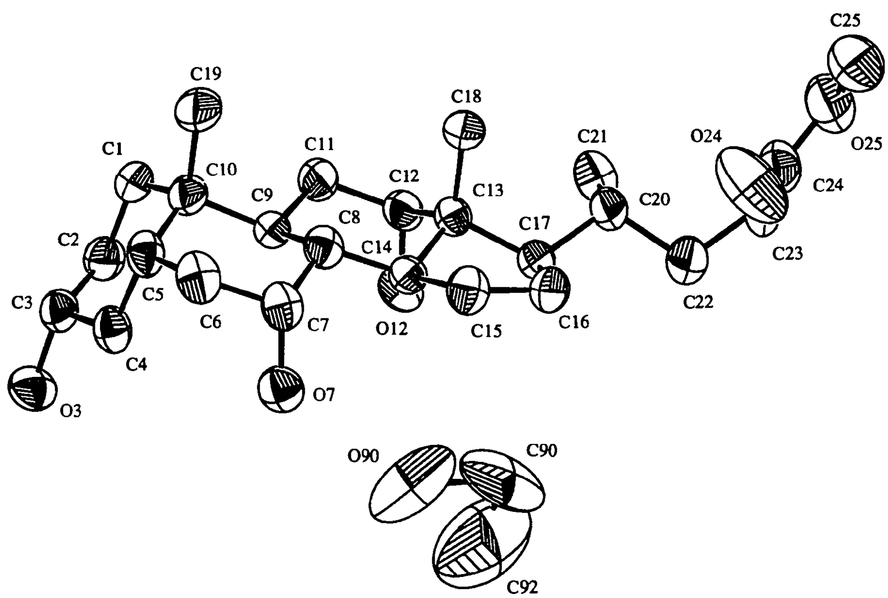


Fig. 1. *ORTEP*II (Johnson, 1976) diagram showing 50% probability displacement ellipsoids for non-H atoms. The ethanol molecule is also included.

quite similar. All three alcohol-solvated methyl cholate structures pack in a layer pattern. Fig. 2 shows the three packing diagrams drawn using *QUANTA*4.0 (Molecular Simulations Incorporated, 1994).

We found that the methylene C atom of the ethanol molecule was disordered over two positions, C90 and C91. The solvent molecules in the cholic acid alcohol-solvates are also disordered (Jones & Nassimbeni, 1990). Hydrogen bonding between the ethanol molecule and the O7 and O12 hydroxyl O atoms holds the ethanol in a cavity; additional hydrogen bonding occurs between the hydroxyl O3 and the hydroxyl O7 and O12 atoms (Fig. 3; Table 2). All the O···O distances fall within the normally accepted range for hydrogen bonds.

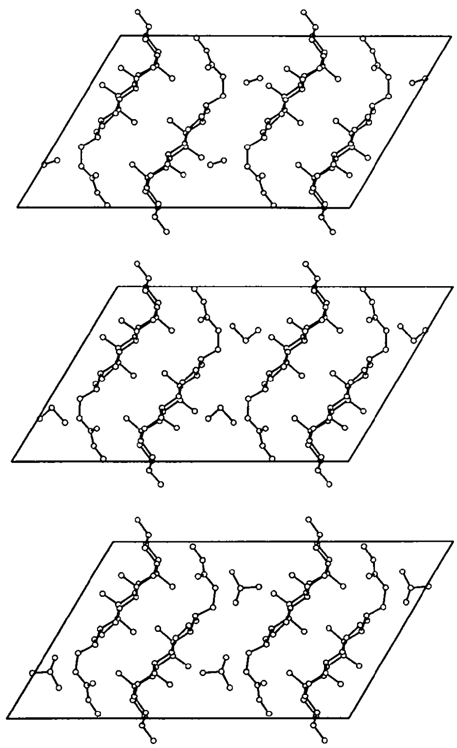


Fig. 2. Packing diagrams for methyl cholate methanolate (top), methyl cholate ethanolate (middle) and methyl cholate 2-propanolate (bottom) viewed down the *b* axis.

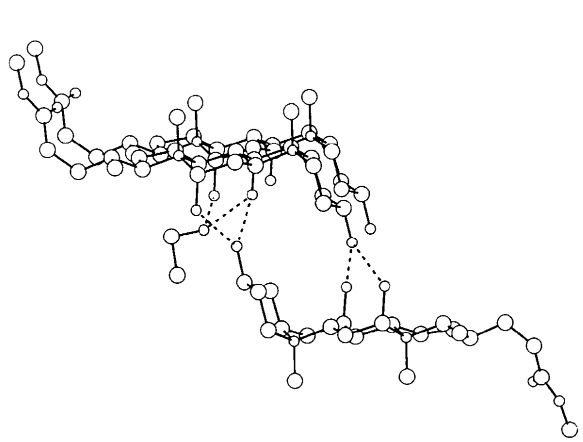


Fig. 3. Hydrogen-bonding network for methyl cholate ethanolate, H atoms are omitted for clarity. Dashed lines represent the hydrogen bonds.

Experimental

The title compound was prepared by recrystallization of methyl cholate (Sigma Chemical Co., St. Louis, Missouri) by slow evaporation from absolute ethanol (Midwest Grain Products Co., Weston, Missouri).

Crystal data

$C_{25}H_{42}O_5.C_2H_6O$	Cu $K\alpha$ radiation
$M_r = 468.68$	$\lambda = 1.54184$ Å
Monoclinic	Cell parameters from 25 reflections
$C2$	$\theta = 40$–$53°$
$a = 25.483$ (4) Å	$\mu = 0.609$ mm^{-1}
$b = 8.0133$ (19) Å	$T = 297$ K
$c = 15.339$ (4) Å	Chunk
$\beta = 121.581$ (14)°	$0.25 \times 0.25 \times 0.22$ mm
$V = 2668$ (2) Å^3	Colorless
$Z = 4$	
$D_x = 1.17$ Mg m^{-3}	
D_m not measured	

Data collection

Enraf–Nonius CAD-4 diffractometer	$R_{int} = 0.035$
$\theta/2\theta$ scans	$\theta_{max} = 74.33°$
Absorption correction: none	$h = -31 \rightarrow 26$
3015 measured reflections	$k = -9 \rightarrow 0$
2905 independent reflections	$l = 0 \rightarrow 19$
2266 observed reflections $[I > 2\sigma(I)]$	3 standard reflections frequency: 83 min intensity decay: 3.5%

Refinement

Refinement on F^2	$\Delta\rho_{max} = 0.47$ e Å^{-3}
$R[F^2 > 2\sigma(F^2)] = 0.062$	$\Delta\rho_{min} = -0.45$ e Å^{-3}
$wR(F^2) = 0.190$	Extinction correction: *SHELXL*93 (Sheldrick, 1993)
$S = 1.101$	
2905 reflections	
315 parameters	Extinction coefficient: 0.0022 (5)
H atoms riding	
$w = 1/[\sigma^2(F_o^2) + (0.1347P)^2 + 1.0921P]$ where $P = (F_o^2 + 2F_c^2)/3$	Atomic scattering factors from *International Tables* Vol *C* Tables 4.2.6.8 and 6.1.1.4
$(\Delta/\sigma)_{max} = 0.002$	

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
O3	0.98556 (14)	0.8019 (5)	0.6339 (2)	0.0601 (14)
O7	0.9294 (2)	1.0753 (4)	0.3067 (3)	0.0564 (15)
O12	0.95376 (14)	0.5688 (4)	0.2101 (2)	0.0531 (13)
O24	0.8089 (3)	0.8353 (9)	−0.3091 (4)	0.129 (3)
O25	0.7861 (2)	0.6167 (7)	−0.4097 (3)	0.0890 (19)

O90	1.0015 (2)	0.2621 (6)	0.2655 (4)	0.142 (5)
C1	0.8498 (2)	0.6018 (7)	0.4037 (3)	0.0545 (16)
C2	0.9147 (2)	0.6124 (7)	0.4956 (3)	0.0528 (16)
C3	0.9240 (2)	0.7777 (7)	0.5494 (3)	0.0495 (16)
C4	0.9104 (2)	0.9190 (6)	0.4753 (3)	0.0500 (18)
C5	0.8460 (2)	0.9119 (7)	0.3803 (3)	0.0513 (16)
C6	0.8347 (2)	1.0624 (7)	0.3093 (4)	0.0588 (19)
C7	0.8641 (2)	1.0456 (6)	0.2461 (3)	0.0520 (19)
C8	0.8485 (2)	0.8788 (6)	0.1903 (3)	0.0469 (16)
C9	0.8651 (2)	0.7308 (6)	0.2649 (3)	0.0426 (15)
C10	0.8310 (2)	0.7436 (7)	0.3246 (3)	0.0502 (16)
C11	0.8585 (2)	0.5613 (7)	0.2128 (3)	0.0532 (19)
C12	0.8878 (2)	0.5542 (6)	0.1472 (3)	0.0468 (15)
C13	0.8631 (2)	0.6946 (6)	0.0672 (3)	0.0422 (15)
C14	0.8777 (2)	0.8607 (6)	0.1258 (3)	0.0432 (16)
C15	0.8632 (2)	0.9924 (7)	0.0445 (4)	0.0549 (19)
C16	0.8813 (2)	0.9091 (7)	−0.0256 (4)	0.0574 (19)
C17	0.8951 (2)	0.7233 (6)	0.0057 (3)	0.0454 (16)
C18	0.7933 (2)	0.6704 (8)	−0.0079 (3)	0.0572 (18)
C19	0.7603 (2)	0.7289 (10)	0.2488 (4)	0.072 (2)
C20	0.8776 (2)	0.6064 (7)	−0.0861 (3)	0.0516 (16)
C21	0.8893 (3)	0.4244 (8)	−0.0570 (4)	0.068 (3)
C22	0.9113 (2)	0.6604 (9)	−0.1415 (4)	0.064 (2)
C23	0.8775 (3)	0.6007 (10)	−0.2528 (4)	0.076 (3)
C24	0.8227 (3)	0.6994 (9)	−0.3234 (4)	0.070 (3)
C25	0.7295 (3)	0.7184 (10)	−0.4917 (4)	0.104 (4)
C90	1.0219 (2)	0.1597 (7)	0.1897 (4)	0.164 (11)
C91	1.0436 (2)	0.1809 (6)	0.2710 (4)	0.158 (18)
C92	1.0833 (2)	0.1209 (6)	0.2686 (4)	0.242 (15)

Table 2. *Contact distances (Å)*

O12···O90	2.676 (6)	O12···O3[ii]	2.780 (3)
O7···O90[i]	2.689 (8)	O7···O3[ii]	2.874 (4)

Symmetry codes: (i) $x, 1+y, z$; (ii) $2-x, y, 1-z$.

The methylene C atom in the ethanol solvent molecule had a site-occupation factor of 0.5 (not refined). No further investigation into this disorder was attempted. Positions of ethanolic H atoms were not calculated. The positions of the remaining H atoms were calculated initially. Torsion angles were refined for the four methyl and three hydroxyl groups. Bond lengths were found to be in normal ranges except for O25—C25 [1.558 (7) Å]. E.s.d.'s on C—C bonds within the steroid ranged from 0.005 to 0.009 Å.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1977). Cell refinement: *CAD-4 Software*. Data reduction: *PROCESS MolEN* (Fair, 1990). Program(s) used to solve structure: Direct methods (*SHELXS86*; Sheldrick, 1985). Program(s) used to refine structure: *SHELX93* (Sheldrick, 1993). Molecular graphics: *ORTEPII* (Johnson, 1976). Software used to prepare material for publication: *CIF VAX MolEN* (Fair, 1990).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BK1233). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Enraf–Nonius (1977). *CAD-4 Operations Manual*. Enraf–Nonius, Delft, The Netherlands.
Fair, C. K. (1990). *MolEN. An Interactive Intelligent System for Crystal Structure Analysis*. Enraf–Nonius, Delft, The Netherlands.
Johnson, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
Johnson, P. L. & Schaefer, J. P. (1972). *Acta Cryst.* **B28**, 3083–3088.
Jones, E. L. & Nassimbeni, L. R. (1990). *Acta Cryst.* **B46**, 399–405.
Miki, K., Masui, A., Kasai, N., Goonewardena, W., Shibakami, M., Takemoto, K. & Miyata, M. (1992). *Acta Cryst.* **C48**, 503–507.
Miyata, M., Goonewardena, W., Shibakami, M., Takemoto, K., Masui, A., Miki, K. & Kasai, N. (1987). *J. Chem. Soc. Chem. Commun.* pp. 1140–1141.
Molecular Simulations Incorporated (1994). *QUANTA4.0*. Molecular Simulations Inc., Burlington, USA.
Norton, D. A. & Haner, B. (1965). *Acta Cryst.* **19**, 477–478.
Sheldrick, G. M. (1985). *SHELXS86. Program for the Solution of Crystal Structures*. University of Göttingen, Germany.
Sheldrick, G. M. (1993). *SHELXL93. Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.
Wahle, M. C. & Byrn, S. R. (1996). *Acta Cryst.* **C52**, 2495–2499.
Wahle, M. C., Stowell, J. G. & Byrn, S. R. (1995). *Acta Cryst.* **C52**, 325–328.

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$2\alpha,3\alpha:7\beta,8\beta$-Diépoxy-*trans*-himachalane

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Abstract

The stereochemistry of the major isomer, $C_{15}H_{24}O_2$, resulting from the epoxidation of γ-*trans*-himachalene has been established and hence the configurations of the resulting derivatives have been deduced. The seven-membered ring is chair shaped while the six-membered ring adopts a 1,2-diplanar conformation.

Commentaire

La synthèse des γ-*trans*-himachalènes et de ses isomères, l'α-, l'α'-, l'α''- et le γ'-*trans*-himachalènes, a été publiée (Benharref, Bernardini, Fkih-Tetouani, Jacquier & Viallefont, 1981). L'obtention de ces hydrocarbures sesquiterpéniques à partir de leurs isomères (les *cis*-himachalènes), constituants principaux de l'huile essentielle du cèdre de l'Atlas (*Cedrus Atlantica*), a été étudiée par plusieurs auteurs (Joseph & Dev, 1968*a*,*b*; Nambudiry, Rao & Krishna, 1974; Benharref, Bernardini, Fkih-Tetouani, Jacquier & Viallefont, 1981).

Nous avons réalisé l'époxydation du γ-*trans*-himachalène (1) et obtenu des composés dont la