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A steroidal phenyldihydro-1,3-oxazine derivative

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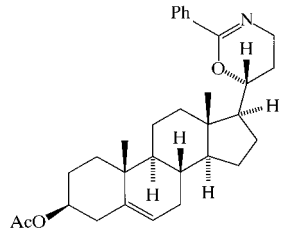
The structure of methyl (6*R*)-6-(3′β-acetoxy-5′-androsten-17′β-yl)-2-phenyl-5,6-dihydro-4*H*-[1,3]oxazine, $C_{31}H_{41}NO_3$, synthesized from an azidopregnene derivative, is reported. The dihydro-1,3-oxazine ring is connected in the β position to the sterane skeleton at C-17′. An *R* configuration was found at C-6.

Comment

Over the last few decades, increasing attention has been paid to the synthesis of cardenolide and bufadienolide analogues which are expected to have better therapeutic indices (Megges *et al.*, 1978) than the natural glycosteroids. Extensive investigations have shown that for cardiotonic activity, the presence of the 17β side chain containing C═N double-bond moieties is more important than the presence of the unsaturated lactone ring (Thomas *et al.*, 1974; Shiao, 1982; Wicha & Masnyk, 1985). Paryzek & Błaszczyk (1999) recently published a novel approach to the synthesis of the butenolide ring of cardenolides.

3β-Acetoxy-5-pregnen-20-one with methyl formate in the presence of sodium methylate gave 3β-hydroxy-21-hydroxymethylene-5-pregnen-20-one. The reduction of this product with sodium borohydride yielded a trihydroxy compound. This was acetylated, and after selective deacetylation on alumina, we obtained the 21-hydroxymethyl derivative. The selective functionalization of the side chain produced the 21-azidomethyl-20-hydroxy compound. This steroid was treated under Schmidt reaction conditions (Bach & Wolber, 1982) with benzaldehyde in the presence of boron trifluoride diethyl etherate yielding the title compound, (I). The reaction sequence will be published elsewhere (Wölfling *et al.*, 2000).

The crystal structure of (I) shows that the C atom attached to C-17′ (C-6) has an *R* configuration, *i.e.* the reduction of the C-20 carbonyl of the basic steroid – according to earlier observations (Hirsch & Fujimoto, 1970; Fieser & Fieser, 1959) – ran stereoselectively. The *B*/*C* and the *C*/*D* ring fusions are *trans*. Rings *A* and *C* adopt chair conformations, while ring *B*



(I)

shows a distorted half-chair conformation. Ring *D* and the 1,3-oxazine ring display slightly distorted half-chair conformations. The sterane skeleton is an equatorial substituent of the 1,3-oxazine ring. The phenyl ring lies nearly in the plane, determined by atoms O20, C70 and N. The total puckering amplitudes (Cremer & Pople, 1975) of the *A*, *B*, *C*, *D*, 1,3-oxazine and phenyl rings are Q = 0.552, 0.467, 0.573, 0.469, 0.462 and 0.002 Å, respectively.

Crystal structures of some other androstene derivatives have been reported: androst-8-ene (Drouin *et al.*, 1991), androst-9(10)-ene (Ginderow *et al.*, 1993) and androst-4-ene (Anthony *et al.*, 1999). Compounds with the androst-5-ene skeleton were studied, among others, by Cox *et al.* (1990), Stankovic *et al.* (1994) and Lazar *et al.* (1998).

Experimental

The starting material of our reaction sequence (3β-hydroxy-5-pregnen-20-one) was obtained from the Sigma Chemical Co. (St Louis, Missouri, USA).

Crystal data

$C_{31}H_{41}NO_3$
M_r = 475.65
Monoclinic, $P2_1$
a = 9.438 (2) Å
b = 8.529 (2) Å
c = 16.503 (3) Å
β = 98.38 (3)°
V = 1314.3 (5) Å^3
Z = 2
D_x = 1.202 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 8192 reflections
θ = 2.35–25.00°
μ = 0.076 mm^{-1}
T = 133 (2) K
Block, colourless
0.48 × 0.48 × 0.25 mm

Data collection

Stoe–Siemens–Huber four-circle diffractometer
φ and ω scans
Absorption correction: semi-empirical (*SADABS*; Sheldrick, 1999)
T_{min} = 0.964, T_{max} = 0.981
14 574 measured reflections
2416 independent reflections
2177 reflections with $I > 2\sigma(I)$
R_{int} = 0.0486
θ_{max} = 25°
$h = -11 \rightarrow 10$
$k = 0 \rightarrow 10$
$l = 0 \rightarrow 19$
Intensity decay: none

Refinement

Refinement on F^2
$R(F)$ = 0.035
$wR(F^2)$ = 0.083
S = 1.076
2416 reflections
316 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0458P)^2 + 0.2578P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.015 (2)

All starting positions of the H atoms were generated with idealized coordinates using *SHELXL*97 (Sheldrick, 1997). The CH_3 groups were generated with idealized tetrahedral angles and after a structure-factor calculation, the torsion angle of the CH_3 group was adjusted to maximize the sum of the electron density at the three calculated H-atom positions. All non-H atoms were refined anisotropically. The H atoms were refined using a riding model and their isotropic displacement parameters were constrained to be 1.2 times (1.5 times for CH_3 groups) the equivalent displacement parameters of their parent atom. CH_3 groups were also allowed to rotate around the C—*X* bond. Floating-origin restraints were generated automatically by *SHELXL*97, according to the method of Flack & Schwarzenbach (1988). The refinement was carried out against data with Friedel pairs merged.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1998); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); software used to prepare material for publication: *SHELXTL*.

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References

Anthony, A., Jaskólski, M. & Nangia, A. (1999). *Acta Cryst.* C**55**, 787–789.
Bach, R. D. & Wolber, G. J. (1982). *J. Org. Chem.* **47**, 239–245.
Bruker (1998). *SMART*, *SAINT* and *SHELXTL* (Version 5.10). Bruker AXS Inc., Madison, Wisconsin, USA.
Cox, P. J., MacManus, S. M., Gibb, B. C., Nowell, I. W. & Howie, R. A. (1990). *Acta Cryst.* C**46**, 334–336.
Cremer D. & Pople J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Drouin, M., Ruel, R. & Michel, A. G. (1991). *Acta Cryst.* C**47**, 1689–1693.
Fieser, L. F. & Fieser, M. (1959). *Steroids*, p. 568. New York: Reinhold Publishing Corporation.
Flack, H. D. & Schwarzenbach, D. (1988). *Acta Cryst.* A**44**, 499–506.
Ginderow, D., Teutsch, G. & Mornon, P.-P. (1993). *Acta Cryst.* C**49**, 486–489.
Hirsch, A. F. & Fujimoto, G. I. (1970). *J. Org. Chem.* **35**, 495–498.
Lazar, D., Stankovic, S., Sakac, M., Penov-Gasic, K., Kovacevic, R., Medic Mijacevic, L. & Pilati, T. (1998). *Acta Cryst.* C**54**, 1965–1968.
Megges, R., Portius, H. J. & Repke, K. R. H. (1978). 11*th IUPAC Int. Symp. Chem. Nat. Prod., Symp. Pap.*, Vol. 2, edited by N. Marekov, I. Ognyanov & A. Orahovats, pp. 164–166. Sofia: BAN.
Paryzek, Z. & Błaszczyk, K. (1999). *Tetrahedron Lett.* **40**, 5913–5914.
Sheldrick, G. M. (1999). *SADABS*. University of Göttingen, Germany.
Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. University of Göttingen, Germany.
Shiao, M.-J. (1982). *J. Org. Chem.* **47**, 5189–5191.
Stankovic, S., Miljkovic, D., Medic Mijacevic, L., Gasi, K. & Courseille, C. (1994). *Acta Cryst.* C**50**, 312–314.
Thomas, R., Boutagy, J. & Gelbert, A. (1974). *J. Pharm. Sci.* **63**, 1649–1683.
Wicha, J. & Masnyk, M. (1985). *Bull. Pol. Acad. Sci. Chem.* **33**, 19–27, 29–37.
Wölfling, J., Hajnal, A., Szemerédi, Zs. & Schneider, Gy. (2000). In preparation.