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# Non-Natural 14-Hydroxy Steroids. III. (+)-Methyl 17$\beta$-Benzoyloxy-14$\beta$-hydroxy-3$\beta$-isopropenyl-1,7-dioxo-5$\beta$-androstan-19-oate

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## Abstract

This non-natural steroid compound bears an isopropenyl substituent at C3, a methoxycarbonyl group at C10 and a benzoyloxy group at C17. The relative stereochemistry is *cis* for the *A*/*B* ring junction, *anti* between $MeO_2C$—C10 and H—C9, *trans* for the *B*/*C* ring junction, *syn* between H—C8 and HO—C14 and *cis* for the *C*/*D* ring junction, and a chair-boat-chair conformation is adopted.

## Comment

We have reported previously the crystallographic analyses of non-natural 14$\beta$-hydroxy steroid compounds (1) (Michel, Ruel & Michel-Dewez, 1989) and (2) (Drouin, Ruel & Michel, 1991). Relative to non-natural 14$\beta$-hydroxy steroids, racemic compound (1) has an opposite ($\beta$) H—C9 stereochemistry and a C8=C9 double bond characterizes the racemic compound (2). Compound (3) has all of the eight asymmetric carbon centers with the stereochemistry normally found in natural cardiotonic steroids (Lociuro, Tsai & Wiesner, 1988). Furthermore, the C3 and C17 substituents mimic the natural alkoxy and pyrone groups and will potentially allow the synthesis of many more steroid derivatives. This new steroid compound (3) was synthesized from the caesium carbonate-catalyzed aldol reaction on a triketone (4) in 32% yield (Ruel & Deslongchamps, 1992) and, importantly, is enantiomerically pure {$[\alpha]_D$ +61.5° (*c* 1, $CHCl_3$)}. The present crystallographic analysis was undertaken to confirm the structure of this new steroid (3) (Fig. 1).

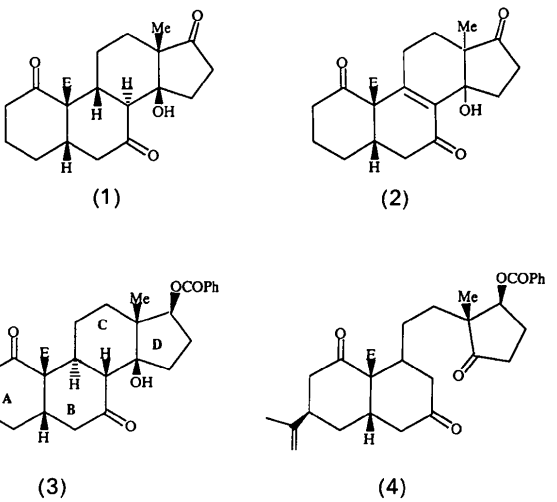


Fig. 1. Molecular formulae ($E$ = $COOCH_3$).

The crystal structure shows that ring *A* has a chair conformation with the C3-isopropenyl substituent equatorial, while ring *B* adopts a boat conformation. Ring *C* has a chair conformation and ring *D* forms an $\alpha$-envelope. The *A*/*B* and *C*/*D* ring junctions are *cis*, the *B*/*C* junction is *trans*, the H9 proton being *anti* to the methoxycarbonyl substituent at C10. According to stereoelectronic control (Deslongchamps, 1983), the aldolic condensation must proceed through a conformation where ring *B* in compound (4) adopts a boat conformation (Lavallée & Deslongchamps, 1988). Consequently, the product (3) obtained under such conditions was expected to adopt the conformation confirmed by the crystal structure: ring *B* adopts the boat conformation (Fig. 2). This molecular arrangement allows the C3-isopropenyl substituent to be equatorial, avoiding the unfavorable 1,3-diaxial interaction with H—C5. The overall conformation is very similar to the previously reported non-natural steroid (1). The *A* ring is oriented such as to give a global conformation more extended than the usual globular shape of cardenolides (Kálmán, Argay, Scharfenberg-Pfeiffer, Höhne & Ribár, 1991, and references therein), where *A*/*B* and *C*/*D* ring junctions are also *cis*. The benzoate fragment is relatively planar; the torsion angle O5—C24—C25—C26 is −7.8 (6)° and the average aromatic bond distance is 1.388 (16) Å. Best-plane calculations on ring *D* show that C14 is 0.54 (1) Å outside the plane defined by C13, C15,

C16 and C17. This deviation corresponds to a slightly deformed $\alpha$-envelope configuration, following the conventional analysis (Brutcher & Leopold, 1966). In the crystal, the molecules are oriented side by side along the *b* axis and almost head-to-head along **a**. The methoxycarbonyl and isopropenyl groups are located near the $2_1$ screw axis. No intermolecular distances corresponding to hydrogen-bonding donor-acceptor criteria were found. No abnormally short contacts were observed.

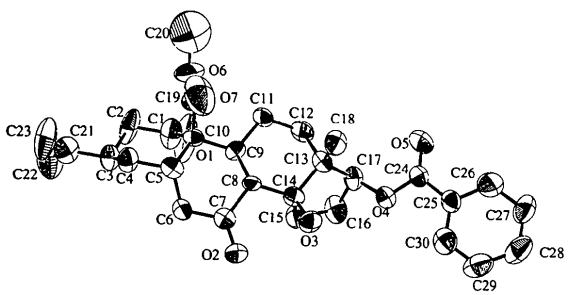


Fig. 2. *ORTEP*II perspective view (Johnson, 1976) of (3) with crystallographic numbering. Thermal ellipsoids are shown at 50% probability levels; H atoms are omitted for clarity.

## Experimental

*Crystal data*

$C_{30}H_{36}O_7$
$M_r$ = 508.61
Orthorhombic
$P2_12_12_1$
$a$ = 6.4939 (3) Å
$b$ = 11.8032 (3) Å
$c$ = 35.0205 (15) Å
$V$ = 2684.28 (18) Å$^3$
$Z$ = 4
$D_x$ = 1.258 Mg m$^{-3}$

Mo $K\alpha$ radiation
$\lambda$ = 0.70930 Å
Cell parameters from 41 reflections
$\theta$ = 30.00-36.00°
$\mu$ = 0.83 mm$^{-1}$
$T$ = 293 K
Irregular prism-like
0.20 × 0.20 × 0.32 mm
Colorless

*Data collection*

Nonius diffractometer
$\omega$-$2\theta$ scans
Absorption correction: none
3441 measured reflections
2054 independent reflections
1456 observed reflections [$I > 2.0\sigma(I)$]

$R_{int}$ = 0.021
$\theta_{max}$ = 44.8°
$h = 0 \rightarrow 6$
$k = 0 \rightarrow 12$
$l = 0 \rightarrow 37$
2 standard reflections
frequency: 60 min
intensity variation: 1.8%

*Refinement*

Refinement on $F$
Final $R$ = 0.072
$wR$ = 0.064
$S$ = 2.59
1456 reflections
330 parameters
H-atom parameters not refined

Weighting scheme based on counting statistics
$(\Delta/\sigma)_{max}$ = 0.077
$\Delta\rho_{max}$ = 0.410 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.220 e Å$^{-3}$
Extinction correction: Zachariasen (1963) and Larson (1967)
Extinction coefficient: 0.6 (1)

The structure was solved by the application of direct methods and refinement by full-matrix least squares on $F$. Anisotropic thermal parameters were refined for all non-H atoms except for C20, which was considered as isotropic, its thermal motion being very large. All H-atom positional parameters were calculated and not refined; the hydroxyl H atom was geometrically placed based on the donor-acceptor distance. Atomic scattering factors as stored in the *NRCVAX* (Gabe, Le Page, Charland, Lee & White, 1989) program are those of Cromer & Waber (1974). Data collection: *NRCCAD DATCOL* (Le Page, White & Gabe, 1986). Cell refinement: *NRCCAD TRUANG*. Data reduction: *NRCVAX DATRD2*. Program(s) used to solve structure: *NRCVAX SOLVER*. Program(s) used to refine structure: *NRCVAX LSTSQ*. Molecular graphics: *ORTEP* (Johnson,1976); *PLUTO* (Motherwell & Clegg, 1978). Software used to prepare material for publication: *PLATON*92 (Spek, 1990).

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

$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

| | $x$ | $y$ | $z$ | $U_{eq}$ |
|---|---|---|---|---|
| O1 | 0.3885 (12) | 0.4803 (7) | 0.1109 (3) | 0.157 (5) |
| O2 | 1.0971 (15) | 0.4714 (5) | 0.18471 (18) | 0.101 (3) |
| O3 | 1.1901 (10) | 0.2441 (5) | 0.17298 (16) | 0.063 (2) |
| O4 | 1.0758 (12) | 0.0042 (5) | 0.19093 (15) | 0.061 (3) |
| O5 | 1.0087 (12) | −0.1510 (5) | 0.1558 (2) | 0.088 (3) |
| O6 | 0.582 (2) | 0.4041 (7) | 0.0300 (2) | 0.173 (7) |
| O7 | 0.928 (2) | 0.4092 (10) | 0.0308 (3) | 0.161 (7) |
| C1 | 0.5194 (19) | 0.5186 (9) | 0.0895 (4) | 0.090 (5) |
| C2 | 0.4849 (16) | 0.6283 (10) | 0.0682 (4) | 0.101 (6) |
| C3 | 0.6401 (16) | 0.7157 (8) | 0.0795 (3) | 0.059 (4) |
| C4 | 0.8504 (14) | 0.6651 (8) | 0.0720 (3) | 0.062 (4) |
| C5 | 0.8875 (14) | 0.5545 (8) | 0.0939 (3) | 0.049 (3) |
| C6 | 0.9120 (19) | 0.5713 (7) | 0.1373 (3) | 0.071 (4) |
| C7 | 0.9983 (18) | 0.4661 (8) | 0.1551 (3) | 0.067 (4) |
| C8 | 0.9571 (14) | 0.3554 (7) | 0.1347 (2) | 0.041 (3) |
| C9 | 0.7451 (13) | 0.3599 (7) | 0.1141 (2) | 0.045 (3) |
| C10 | 0.7266 (15) | 0.4633 (7) | 0.0859 (2) | 0.046 (3) |
| C11 | 0.6959 (15) | 0.2470 (7) | 0.0957 (2) | 0.062 (3) |
| C12 | 0.7055 (15) | 0.1499 (8) | 0.1252 (3) | 0.063 (4) |
| C13 | 0.9230 (16) | 0.1376 (7) | 0.1442 (2) | 0.048 (3) |
| C14 | 0.9794 (14) | 0.2531 (8) | 0.1625 (2) | 0.047 (3) |
| C15 | 0.8407 (17) | 0.2584 (7) | 0.1980 (2) | 0.068 (4) |
| C16 | 0.8153 (17) | 0.1355 (8) | 0.2103 (2) | 0.078 (4) |
| C17 | 0.8849 (17) | 0.0609 (7) | 0.1778 (3) | 0.056 (3) |
| C18 | 1.0807 (16) | 0.0968 (7) | 0.1158 (2) | 0.064 (4) |
| C19 | 0.764 (3) | 0.4227 (13) | 0.0460 (4) | 0.100 (7) |
| C20 | 0.598 (3) | 0.3608 (13) | −0.0096 (5) | 0.211 (7) |
| C21 | 0.6031 (19) | 0.8270 (9) | 0.0579 (3) | 0.076 (5) |
| C22 | 0.428 (3) | 0.8897 (11) | 0.0718 (4) | 0.149 (7) |
| C23 | 0.713 (2) | 0.8657 (10) | 0.0302 (3) | 0.121 (6) |
| C24 | 1.1116 (19) | −0.1028 (8) | 0.1792 (3) | 0.062 (4) |
| C25 | 1.2974 (16) | −0.1490 (8) | 0.1973 (2) | 0.051 (3) |
| C26 | 1.3526 (19) | −0.2631 (9) | 0.1905 (3) | 0.078 (5) |
| C27 | 1.524 (2) | −0.3108 (8) | 0.2085 (3) | 0.076 (5) |
| C28 | 1.6447 (19) | −0.2463 (11) | 0.2318 (3) | 0.083 (5) |
| C29 | 1.590 (2) | −0.1342 (11) | 0.2384 (3) | 0.083 (5) |
| C30 | 1.418 (2) | −0.0858 (8) | 0.2214 (3) | 0.067 (4) |

Table 2. *Geometric parameters* (Å, °)

| | | | |
|---|---|---|---|
| O1—C1 | 1.220 (16) | C9—C10 | 1.575 (11) |
| O2—C7 | 1.221 (13) | C9—C11 | 1.514 (11) |
| O3—C14 | 1.421 (11) | C10—C19 | 1.497 (16) |
| O4—C17 | 1.482 (13) | C11—C12 | 1.544 (13) |
| O4—C24 | 1.348 (11) | C12—C13 | 1.568 (14) |
| O5—C24 | 1.201 (13) | C13—C14 | 1.550 (12) |
| O6—C19 | 1.33 (2) | C13—C17 | 1.505 (12) |

| | | | |
|---|---|---|---|
| O6—C20 | 1.482 (19) | C13—C18 | 1.507 (13) |
| O7—C19 | 1.20 (2) | C14—C15 | 1.536 (12) |
| C1—C2 | 1.511 (17) | C15—C16 | 1.522 (12) |
| C1—C10 | 1.501 (15) | C16—C17 | 1.508 (13) |
| C2—C3 | 1.496 (15) | C21—C22 | 1.44 (2) |
| C3—C4 | 1.514 (14) | C21—C23 | 1.288 (16) |
| C3—C21 | 1.535 (14) | C24—C25 | 1.468 (15) |
| C4—C5 | 1.533 (14) | C25—C26 | 1.414 (14) |
| C5—C6 | 1.541 (15) | C25—C30 | 1.372 (14) |
| C5—C10 | 1.526 (13) | C26—C27 | 1.398 (17) |
| C6—C7 | 1.498 (14) | C27—C28 | 1.364 (16) |
| C7—C8 | 1.513 (13) | C28—C29 | 1.389 (18) |
| C8—C9 | 1.555 (12) | C29—C30 | 1.389 (17) |
| C8—C14 | 1.558 (12) | | |
| C17—O4—C24 | 118.2 (8) | C12—C13—C18 | 111.2 (7) |
| C19—O6—C20 | 113.0 (13) | C14—C13—C17 | 104.2 (6) |
| O1—C1—C2 | 121.2 (10) | C14—C13—C18 | 113.2 (8) |
| O1—C1—C10 | 121.0 (10) | C17—C13—C18 | 115.8 (7) |
| C2—C1—C10 | 117.7 (10) | O3—C14—C8 | 108.0 (7) |
| C1—C2—C3 | 111.1 (10) | O3—C14—C13 | 105.6 (7) |
| C2—C3—C4 | 106.9 (8) | O3—C14—C15 | 111.0 (6) |
| C2—C3—C21 | 110.8 (9) | C8—C14—C13 | 113.7 (6) |
| C4—C3—C21 | 113.2 (9) | C8—C14—C15 | 114.8 (7) |
| C3—C4—C5 | 113.0 (8) | C13—C14—C15 | 103.4 (7) |
| C4—C5—C6 | 113.6 (8) | C14—C15—C16 | 104.7 (7) |
| C4—C5—C10 | 113.7 (8) | C15—C16—C17 | 108.1 (7) |
| C6—C5—C10 | 110.0 (8) | O4—C17—C13 | 112.1 (8) |
| C5—C6—C7 | 110.0 (8) | O4—C17—C16 | 106.3 (8) |
| O2—C7—C6 | 120.5 (9) | C13—C17—C16 | 106.7 (7) |
| O2—C7—C8 | 122.6 (8) | O6—C19—O7 | 125.5 (13) |
| C6—C7—C8 | 116.9 (9) | O6—C19—C10 | 107.6 (13) |
| C7—C8—C9 | 110.2 (7) | O7—C19—C10 | 126.9 (15) |
| C7—C8—C14 | 111.0 (7) | C3—C21—C22 | 113.4 (10) |
| C9—C8—C14 | 113.5 (7) | C3—C21—C23 | 126.0 (11) |
| C8—C9—C10 | 112.6 (7) | C22—C21—C23 | 120.6 (11) |
| C8—C9—C11 | 110.7 (7) | O4—C24—O5 | 123.8 (10) |
| C10—C9—C11 | 113.5 (6) | O4—C24—C25 | 111.0 (9) |
| C1—C10—C5 | 107.0 (7) | O5—C24—C25 | 125.2 (9) |
| C1—C10—C9 | 110.7 (8) | C24—C25—C26 | 119.3 (9) |
| C1—C10—C19 | 111.3 (10) | C24—C25—C30 | 122.2 (9) |
| C5—C10—C9 | 112.3 (7) | C26—C25—C30 | 118.5 (9) |
| C5—C10—C19 | 106.6 (9) | C25—C26—C27 | 120.6 (10) |
| C9—C10—C19 | 109.0 (8) | C26—C27—C28 | 120.2 (10) |
| C9—C11—C12 | 111.1 (6) | C27—C28—C29 | 119.0 (11) |
| C11—C12—C13 | 112.9 (8) | C28—C29—C30 | 121.7 (11) |
| C12—C13—C14 | 107.9 (7) | C25—C30—C29 | 119.9 (10) |
| C12—C13—C17 | 103.8 (8) | | |

We thank Dr R. Ruel for helpful discussions while writing this paper.

Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and complete geometry, together with a stereoview of the unit-cell contents, have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71196 (18 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: CD1040]

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# Structure of 3-Epiryanodol: a Heptahydro Diterpene

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## Abstract

As part of an investigation of structure-activity relationships of ryanoids, the crystal structure of 3-epiryanodol was carried out in order to confirm its stereochemistry Ryanodol has 11 asymmetric C atoms. The C3 atom, which has *R* stereochemistry in the natural product, was inverted to the *S* stereochemistry to give this 3-epimer of ryanodol. The compound makes three inter- and four intramolecular hydrogen bonds.


## Comment

The natural compound ryanoidine (1) isolated from *Ryania speciosa* Vahl (Rogers, Koniuszy, Shavel & Folkers, 1948) is the ester of $\alpha$-pyrrolecarboxylic acid and the complex diterpene (+)-ryanodol (2). Its crystal structure was reported by Srivastava & Przybylska (1970). It is an interesting and important calcium-release channel modulator in mammalian muscle (Jenden & Fairhurst, 1969).