Data collection: *SMART* (Siemens, 1994). Cell refinement: *LSCELL* (Clegg, 1995). Data reduction: *SAINT* (Siemens, 1994). Program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997*c*). Program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997*b*). Molecular graphics: *PLATON* (Spek, 1999). Software used to prepare material for publication: *SHELXL*97 and *WordPerfect* macro *PRPKAPPA* (Ferguson, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1324). Services for accessing these data are described at the back of the journal.

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The 17-spiro lactide of cortienic acid: a probe for studying the active sites of steroidal receptors

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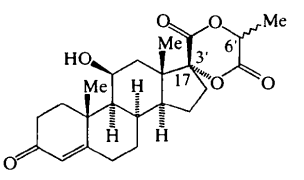
Abstract

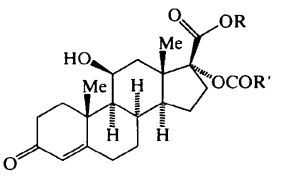
The steroid (5′*R*,17*R*)-11β-hydroxy-5′-methylspiro-[androst-4-ene-17,2′-[1,4]dioxane]-3,3′,6′-trione (cortienic acid lactide), $C_{23}H_{30}O_6$, adopts an arched conformation towards the β side of the molecule. The spiro lactide ring is in the half-chair conformation, with the two ester carbonyl groups aligned and directly opposing each other. A hydrogen bond between the hydroxyl group of ring *C* and the carbonyl group of ring *A* links the molecules, forming chains along **b**.

Comment

Soft drugs (Bodor, 1984) based on hydrocortisone (Little *et al.*, 1999) are important topical anti-inflammatory agents which are presently being tested in clinical trials (Hochhaus *et al.*, 1992; Bodor *et al.*, 1992). These compounds are of a structural type which is represented by scheme (II). In the process of developing these drugs, several candidates were considered, one of which is the subject of the present communication. This compound, (I), is an interesting cyclic modification in which the *R* groups of the 17α, 17β-diesters, (II), are joined into one alkyl group.



(I)



(II)

Although not active in *in vivo* tests, the spiro lactide, which was formed as a mixture of epimers which were separated by column chromatography, is useful as a probe of the active sites of steroidal receptors such as corticosteroid binding globulin (CBG) and the gluco-

corticoid receptor (GR). The epimers show markedly different activities in studies of binding to CBG (Little, 1983). The interaction of the DNA binding domain of steroid receptors to their sites of attachment on the DNA molecule has been extensively studied by X-ray crystallography (Härd & Gustafsson, 1993). However, the receptor domain responsible for binding steroid molecules suffers from the difficulty of crystallizing this highly hydrophobic portion of the protein, and there still exists much doubt as to the detailed intermolecular relations and their implications for biological activity (Zhang *et al.*, 1996). Thus, the accurately determined three-dimensional structure of compounds having high affinity for steroid receptors is still important in the establishment of quantitative relationships between structure and biological activity. Specifically, the isomer analyzed crystallographically in the present communication (chromatographic fraction 1) has the absolute configuration *R* at the 5′-position. (For convenience in the discussion of the crystallographic results, where it is necessary that each atom have an assigned number, we have used the traditional numbering system for the spiro ring. However, the official IUPAC name of the compound will be used in all other circumstances.) Its dissociation constant (K_i relative to hydrocortisone, K_i = 1.0 nM) was measured to be 68 nM, while that of its epimer was 20 nM, indicating a strong influence of the relative orientation of the 5′-methyl on the binding activity. In comparison, the K_i of diesters of type (II) are in the range of 10,000 to 50,000 nM.

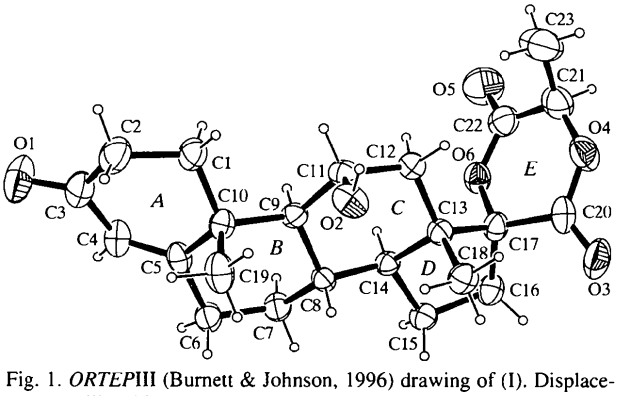


Fig. 1. *ORTEP*III (Burnett & Johnson, 1996) drawing of (I). Displacement ellipsoids are drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

As was mentioned above, the spiro lactide is closely related to the type (II) compounds, for one of which, the 17α-isobutyryloxy-17β-chloromethylcarboxylate derivative [type (II), R = $-CH_2Cl$, R' = $-CH(CH_3)_2$], we have some preliminary X-ray analysis data (Díaz de Delgado, 1998). A comparison of these structures shows two points of contrast (Fig. 2). With respect to the all-important conformation of the 17α-ester substituents, the respective alkyl groups are very differently oriented, with the isopropyl group of the isobutyrate oriented very much below the plane of the steroid-ring system, while the 5′-methyl of the *R*-lactide (I) is oriented toward the *D* ring and very much nearer the plane of the ring system. This observation can be made more concrete by comparing the respective torsional angles determined by C17—O6—C22—O5, which is $-176.5(4)^\circ$ in the lactides while only $18(6)^\circ$ in the open-chain derivative. It is also apparent that the two ester carbonyl groups are aligned in the type (II) compound, while being directly opposed in the lactide. This would necessarily produce a large difference in the observed dipole moment in the respective molecules. Since previous studies (Little, 1983) have shown that the presence of a 17α substituent is generally detrimental to binding in a series of cortienic acid derivatives to CBG, the higher binding affinity (lower K_i) of the 5′*S* epimer, which would necessarily have its methyl group more exposed, being thereby similar to the type (II) compounds, would imply that there is a hydrophobic contribution to binding even to CBG, but with the requirement that the hydrophobic group be much closer to the plane of the steroidal ring system than in the case of non-cyclic 17-α esters.

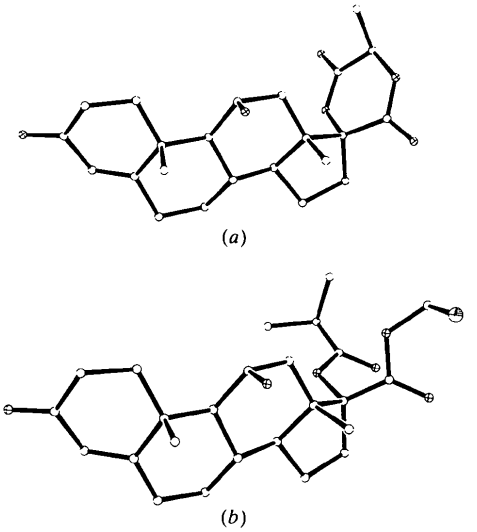


Fig. 2. View of the (*a*) 17-spiro lactide derivative (this work) and (*b*) 17α-isobutyryloxy-17β-chloromethylcarboxylate derivative (Díaz de Delgado, 1998).

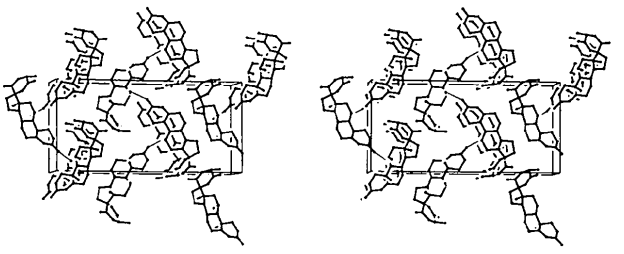


Fig. 3. Stereoview of packing down the *c* axis (H atoms have been omitted). Hydrogen bonds are indicated by dashed lines.

Fig. 3 shows a packing diagram of the structure. A two-dimensional zigzag pattern of hydrogen bonds involving the hydroxyl group of ring *C* and the terminal O1 atom of ring *A* at $2-x, \frac{1}{2}+y, \frac{1}{2}-z$ connects the molecules forming chains parallel to the (010) direction. The geometry of the hydrogen bond is detailed in Table 1.

Experimental

Melting points are uncorrected. Elemental analyses were performed by Atlantic Microlab of Atlanta, GA. Thin-layer chromatography analyses were performed using prepared plates, EM brand, SiO_2, thickness 200 μ, with UV_{254} indicator. Spots were visualized both by UV quenching and H_2SO_4/methanol charring. NMR spectra were obtained either on a Varian A-60 or EM-390. IR spectra were obtained on a Perkin–Elmer FX-1700. With the exception of α-bromopropionyl chloride, which was prepared by Vogel's (1948) procedure, chemical precursors and general laboratory reagents were purchased from either Sigma or Aldrich Chemical Co., Milwaukee, WI, USA. The synthesis of the spiro lactide began with the periodate oxidation of the dihydroxyacetone side chain of hydrocortisone to produce the corresponding 17β-carboxylic acid, cortienic acid, which was synthesized according to the literature procedure (Little *et al.*, 1999). This acid, upon reaction with two equivalents of α-bromopropionyl chloride, afforded the 17β-mixed anhydride-17α-ester, which was then selectively cleaved with diethylamine in acetone to give the 17α-ester-17β-acid exclusively. This ester, in the presence of anhydrous Cs_2CO_3 in the polar aprotic solvent hexamethylphosphoramide, spontaneously cyclized, forming the title compound as an unequal mixture of epimers, which were separated by column chromatography on silica gel (60 Å) with a solvent mixture of hexane/ethyl acetate. The two fractions isolated in this way were designated fractions 1 and 2, based on the order of elution. Fraction 1, analyzed crystallographically, had m.p. = 572–583 K; NMR (DMSO-d_6): δ 5.48 (*s*, 1, C=CH), 4.40 (*q*, J = 7 Hz, 1, $CHCH_3$), 1.48 (*d*, J = 7 Hz, 3, $CHCH_3$), 1.35 (*s*, 3, 19-CH_3), 1.17 (*s*, 3, 18-CH_3). Analysis calculated for $C_{23}H_{30}O_6 \cdot \frac{1}{2}H_2O$: C 67.13, H 7.59%; found: C 67.26, 67.29; H 7.62, 7.60%. IR (KBr cm^{-1}): 1740, 1650. Fraction 2 had m.p. = 535–541 K; NMR (DMSO-d_6): δ 5.51 (*s*, 1, C=CH), 4,25 (*q*, J = 7 Hz, 1, $CHCH_3$), 1.48 (*d*, J = 7 Hz, 3, $CHCH_3$), 1.36 (*s*, 3, 19-CH_3). Analysis calculated for $C_{23}H_{30}O_6$: C 68.63, H 7.51%; found: C 68.67, 68.65; H 7.52, 7.51%. IR (KBr, cm^{-1}): 1755, 1640.

Crystal data

$C_{23}H_{30}O_6$	Mo $K\alpha$ radiation
M_r = 402.49	λ = 0.71069 Å
Orthorhombic	Cell parameters from 54 reflections
$P2_12_12_1$	θ = 10–15°
a = 25.869 (8) Å	μ = 0.095 mm^{-1}
b = 12.494 (4) Å	T = 293 (2) K
c = 6.198 (2) Å	Plate
V = 2003. (1) $Å^3$	0.48 × 0.27 × 0.24 mm
Z = 4	Colourless
D_x = 1.334 Mg m^{-3}	
D_m not measured	

Data collection

Nicolet *P3/F* diffractometer	θ_{max} = 25°
$\theta/2\theta$ scans	$h = 0 \rightarrow 30$
Absorption correction: none	$k = 0 \rightarrow 14$
3775 measured reflections	$l = -7 \rightarrow 7$
2066 independent reflections	3 standard reflections
1640 reflections with $F^2 > 2\sigma(F^2)$	every 97 reflections
	intensity decay: <2%
R_{int} = 0.047	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0759P)^2 + 0.3744P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R(F)$ = 0.048	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2)$ = 0.154	$\Delta\rho_{max}$ = 0.30 e $Å^{-3}$
S = 1.151	$\Delta\rho_{min}$ = −0.33 e $Å^{-3}$
2066 reflections	Extinction correction: none
265 parameters	Scattering factors from *SHELXTL97* (Sheldrick, 1997)
H atoms treated by a mixture of independent and constrained refinement	

Table 1. *Hydrogen-bonding geometry (Å, °)*

D—H···A	D—H	H···A	D···A	D—H···A
O2—H1O2···O1^{i}	0.79 (6)	2.17 (6)	2.947 (5)	169 (6)

Symmetry code: (i) $2-x, \frac{1}{2}+y, \frac{1}{2}-z$.

All H atoms were placed in geometrically calculated positions and their isotropic displacement parameters were set to 1.2 times (1.5 times for CH_3 groups) the equivalent displacement parameter of their parent atoms. In the last cycle of refinements, the position of the H1O2 atom of the hydroxyl group was refined.

Program used to solve structure: *SHELXTL97* (Sheldrick, 1997). Program used to refine structure: *SHELXTL97*. Molecular graphics: *ORTEP*III (Burnett & Johnson, 1996) and *PLATON* (Spek, 1998). Software used to prepare material for publication: *SHELXTL97* and *PARST* (Nardelli, 1983).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK1456). Services for accessing these data are described at the back of the journal.

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1-[(1,3-Dihydro-2-benzothienyl)acetyl]-1*H*-indole *S*-oxide

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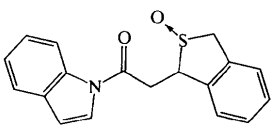
Abstract

The title compound, $C_{18}H_{15}NO_2S$, consists of two heterocycles, namely an indole and a 1,3-dihydro-2-benzothienyl *S*-oxide moiety, connected by an acetyl bridge. An S—O distance of 1.5007 (15) Å was observed and the two C—S distances differ, with S—CH_2 = 1.8217 (16) Å and S—CH = 1.8516 (16) Å.

Comment

The title compound, 1-[(1,3-dihydro-2-benzothienyl)-acetyl]-1*H*-indole *S*-oxide, (I), was synthesized according to a method reported previously (Bates & Xia, 1998). The present study was conducted in order to verify the assignment of relative stereochemistry assessed by ^{1}H NMR using aromatic solvent-induced shifts (Cooper *et al.*, 1969), and ^{1}H–^{1}H COSY (two-dimensional correlated spectroscopy) and NOE (nuclear Overhauser effect) difference spectra (Bates & Xia, 1998). The original assignments did agree with the general chromatographic order of elution observed for diastereomeric sulfoxides (Portoghese & Telang, 1971).



(I)

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Compound (I) crystallized with one molecule constituting the asymmetric unit. An *ORTEP*-3 (Farrugia, 1997) representation of the molecule and the atom-labeling scheme are shown in Fig. 1. The bond lengths and valence angles are all within the ranges expected for this type of compound. The H atom on C11 is clearly *trans* to the O atom of the sulfoxide group, as was predicted in the earlier report (Bates & Xia, 1998). Note that the crystal consists of a racemic mixture of these compounds and the opposite configuration is present in the unit cell. The molecule is not planar and the two ring systems (*i.e.* the indole and the benzothienyl rings) are bent towards the sulfoxide group, with an angle of 13 (3)° between these two planes. This would appear to be the first reported X-ray structure of a 1,3-dihydro-2-benzothienyl *S*-oxide fragment (Allen & Kennard, 1993). An S—O distance of 1.5007 (15) Å was observed and the two C—S distances differ, with S1—C18 = 1.8217 (16) Å and S1—C11 = 1.8516 (16) Å.

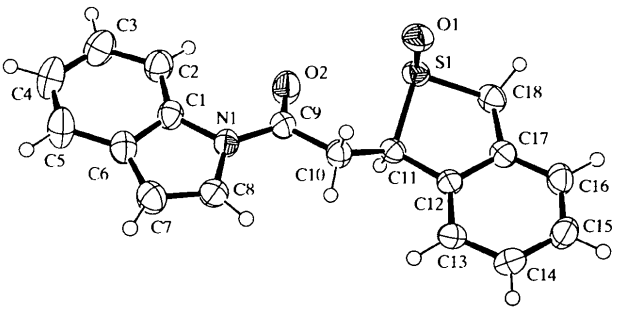

Fig. 1. View of (I) with ellipsoids at the 50% probability level. H atoms are shown as spheres of arbitrary radii.

Experimental

Crystals of the title compound (m.p. 471–474 K) were prepared as described previously (Bates & Xia, 1998) and were crystallized slowly from an ethyl acetate solution.

Crystal data

$C_{18}H_{15}NO_2S$
M_r = 309.38
Monoclinic
$P2_1/c$
a = 4.963 (1) Å
b = 10.458 (2) Å
c = 28.310 (4) Å
β = 94.716 (16)°
V = 1464.4 (5) Å^3
Z = 4
D_x = 1.403 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 25 reflections
θ = 8.19–13.96°
μ = 0.228 mm^{-1}
T = 293 (2) K
Prism
0.20 × 0.20 × 0.18 mm
White

Data collection

Enraf–Nonius CAD-4 diffractometer

2802 reflections with $I > 2\sigma(I)$