Données cristallines

$C_{15}H_{26}O_3$	Mo $K\alpha$ radiation
M_r = 254,36	λ = 0,71090 Å
Orthorhombique	Paramètres de la maille à l'aide de 25 réflexions
$P2_12_12_1$	θ = 7,1–11,2°
a = 7,449 (3) Å	μ = 0,081 mm^{-1}
b = 10,724 (4) Å	T = 293 (2) K
c = 17,733 (10) Å	Prisme
V = 1416,6 (11) Å^3	0,60 × 0,30 × 0,30 mm
Z = 4	Incolore
D_x = 1,193 Mg m^{-3}	
D_m non mesurée	

Collection des données

Diffractomètre Philips PW1100	1434 réflexions avec $I \geq 2\sigma(I)$
Balayage $\theta/2\theta$	θ_{max} = 25,99°
Pas de correction d'absorption	$h = 0 \rightarrow 9$
1621 réflexions mesurées	$k = 0 \rightarrow 13$
1621 réflexions indépendantes	$l = 0 \rightarrow 21$
	3 réflexions de référence
	fréquence: 120 min
	variation d'intensité: néant

Affinement

Affinement à partir des F^2	$(\Delta/\sigma)_{max}$ = −0,002
$R[F^2 > 2\sigma(F^2)]$ = 0,040	$\Delta\rho_{max}$ = 0,269 e Å^{-3}
$wR(F^2)$ = 0,133	$\Delta\rho_{min}$ = −0,178 e Å^{-3}
S = 1,090	Pas de correction d'extinction
1619 réflexions	Facteurs de diffusion des *International Tables for X-ray Crystallography* (Tome IV)
169 paramètres	
Les atomes d'H: voir ci-dessous	
$w = 1/[\sigma^2(F_o^2) + (0,0748P)^2 + 0,2158P]$ où $P = (F_o^2 + 2F_c^2)/3$	

Tableau 1. *Paramètres géométriques (°)*

C6—C1—C2—C3	62,5 (2)	C7—C9—C10—C11	50,1 (2)
C1—C2—C3—C4	−49,1 (2)	C9—C10—C11—C1	−42,7 (2)
C2—C3—C4—C5	37,1 (2)	C10—C11—C1—C6	50,1 (2)
C3—C4—C5—C6	−42,1 (2)	C6—C1—C2—O17	−64,5 (2)
C4—C5—C6—C1	56,8 (2)	C1—C2—O17—C13	54,2 (2)
C5—C6—C1—C2	−65,0 (2)	C2—O17—C13—C7	−42,2 (2)
C11—C1—C6—C7	−63,0 (2)	O17—C13—C7—C6	42,3 (2)
C1—C6—C7—C9	65,6 (2)	C13—C7—C6—C1	−54,9 (2)
C6—C7—C9—C10	−60,3 (2)	C7—C6—C1—C2	64,8 (2)

Les atomes d'H tous localisés sur séries-différence ont été recalculés en position théorique selon le modèle défini par *SHELXL*93 et affectés d'un facteur de température isotrope équivalent à celui de l'atome porteur × 1.2, ou × 1.4 pour les H des groupes méthyles et hydroxyles.

Collection des données: *PW*1100/20 *Software* (Philips, 1978). Affinement des paramètres de la maille: *PW*1100/20 *Software*. Réduction des données: *PHIL* (Riche, 1981). Programme(s) pour la solution de la structure: *SHELXS*86 (Sheldrick, 1985). Programme(s) pour l'affinement de la structure: *SHELXL*93 (Sheldrick, 1993). Graphisme moléculaire: *R3M* (Riche, 1983), *ORTEP* (Johnson, 1965). Logiciel utilisé pour préparer le matériel pour publication: *SHELXL*93.

Des documents complémentaires concernant cette structure peuvent être obtenus à partir des archives électroniques de l'UICr (Référence: GS1013). Les processus d'accès à ces archives sont donnés au dos de la couverture.

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Acta Cryst. (1998). C**54**, 1965–1968

Structure–Activity Relationships in 16- and 17-Substituted 5-Androstenes: 3β-Acetoxy-17β-picolyl-5-androsten-16-one

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(*Received 10 February 1998; accepted 9 July 1998*)

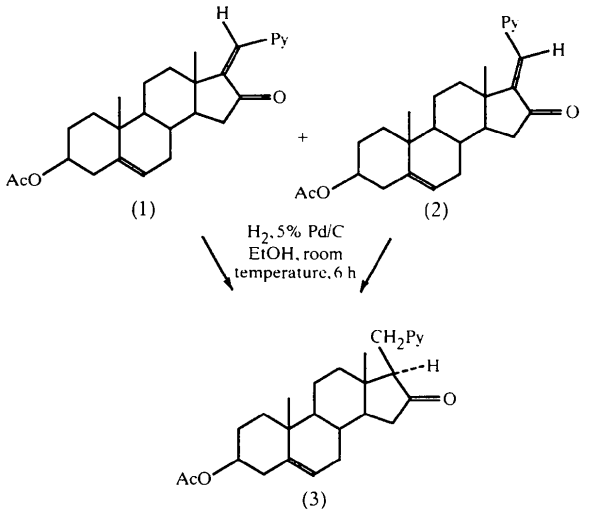
Abstract

The title compound, 3β-acetoxy-17β-picolyl-5-androsten-16-one, $C_{27}H_{35}NO_3$, was synthesized from a mixture of Z and E isomers of 3β-acetoxy-17-picolinylidene-5-androsten-16-one. The significant difference in these three compounds in the crystalline state lies in the conformation of the five-membered D ring, as well as in the orientation of the bulky substituent at C17. After molecular-mechanics calculations on the individual molecules, the conformational differences of the D ring disappeared, but the differences in the orientation of the

substituent at C17 increased. The remarkable differences in biological activity of these compounds could therefore be due to the different orientations of the bulky C17 substituent.

Comment

As a continuation of our study on the structure–activity relationships in 16- and 17-substituted estrane and androstane derivatives, we performed an investigation of 3β-acetoxy-17β-picolyl-5-androsten-16-one, (3). The compound was synthesized from the *Z* and *E* isomers of 3β-acetoxy-17-picolinylidene-5-androsten-16-one, (1) and (2), respectively. The structures of (1) and (2) have been reported previously (Stanković *et al.*, 1989). The structure of compound (3), deduced from chemical spectroscopic evidence, was confirmed by X-ray diffraction analysis. Molecular-mechanics calculations (MMC) for all three compounds were performed using the *PCMODEL* program (Serena Software, 1989), to establish possible changes in the conformations and distances between the functional groups in the molecules when released from interactions with surrounding molecules in the crystalline state.



Since the starting materials were synthesized from the natural androstene derivative 3β-hydroxy-5-androsten-17-one, the absolute stereochemistry of which is known (Fieser & Fieser, 1967), the X-ray structure of (3) is described for the appropriate enantiomer.

A perspective view of the molecule is shown in Fig. 1. Bond distances and angles of the steroid skeleton are in agreement with those of the two isomers, (1) and (2). The main differences appear in the distances, bond angles and torsion angles of the five-membered *D* ring, as a result of different conformations of this ring (Table 1). According to the ring-puckering parameters (Cremer & Pople, 1975) and asymmetry parameters (Duax *et al.*, 1976), the *D* ring in the title compound (3) adopts an ideal 13β-envelope conformation [the distance of C13 from the best plane of the remaining four atoms is 0.708 (4) Å]. In compound (1), ring *D* has a 13α,14β-half-chair conformation, while in compound (2), it exhibits a form intermediate between half-chair and envelope. The six-membered *A*, *B* and *C* rings in (3) have the usual conformations of 5-ene structures: rings *A* and *C* adopt chair conformations, while ring *B* exhibits an 8β,9α-half-chair conformation. The differences in the conformations of molecules (1), (2) and (3) in the crystalline state can be seen in Fig. 2(*a*).

After energy minimization there was a significant change in the conformation of the *D* ring of the title

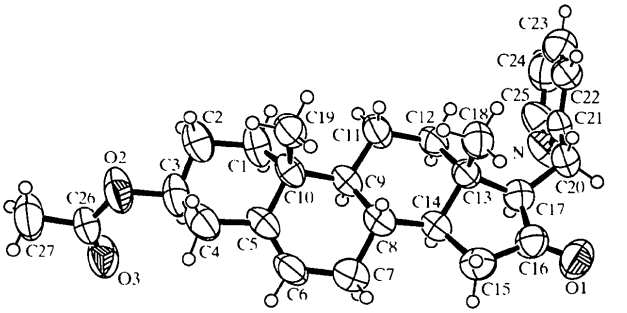


Fig. 1. A perspective view of the title molecule, with the atomic labelling. Displacement ellipsoids are shown at the 30% probability level and H atoms are drawn as spheres of arbitrary radii.

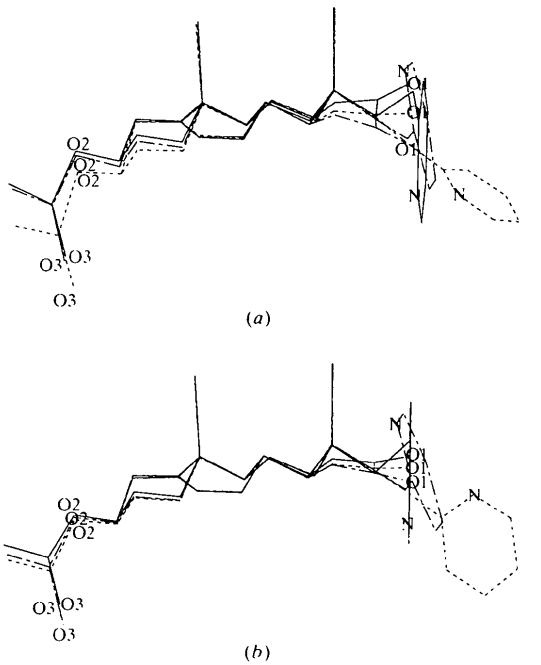


Fig. 2. The superimposed fits of the molecules of compounds (1) (dashed), (2) (dashed-dotted) and (3) (solid) (*a*) in the crystalline state and (*b*) after MMC.

compound, which became a 13β,14α-half-chair [similar to those of (1) and (2)], followed by a slight change in the orientation of the picolyl moiety. The superposition of the molecules after energy minimization (Fig. 2*b*) shows an improvement in the similarity of the steroid skeletons.

The potential antiandrogenic activity of compounds (1), (2) and (3) was tested *in vitro* (Marić *et al.*, 1996) by examining the inhibition of certain steroidogenic enzymes, as well as the competition for androgen receptors obtained from rat prostate (Martsche & Koritnik, 1987). It has been shown that compound (3) blocks the activity of 3β-hydroxy-steroid dehydrogenase (3β-HSD), while (1) and (2) have no effect. On the other hand, compound (2) inhibits the activity of 17α-hydroxylase/17,20-lyase (P450c17), while its isomer, (1), has no effect. The tested substances did not compete for androgen receptors in rat prostate.

The significant differences in the orientations of the C17 substituents could be the only reason for the remarkable differences observed in the biological activity of the compounds tested. It seems that the orientation of the bulky substituent at C17, relative to the length of the molecule, is of crucial importance in biological activity, not only of oestrogen derivatives (Duax *et al.*, 1985), but also of androgen compounds.

Experimental

The title compound, (3), was synthesized by catalytic hydrogenation at room temperature of both the *Z* and *E* isomers of 3β-acetoxy-17-picolinylidene-5-androsten-16-one, (1) and (2), with yields of 57 and 62%, respectively (Miljković *et al.*, 1985; Medić-Mijačević *et al.*, 1993).

Crystal data

$C_{27}H_{35}NO_3$
M_r = 421.56
Orthorhombic
$P2_12_12_1$
a = 9.727 (2) Å
b = 10.335 (2) Å
c = 24.177 (5) Å
V = 2430.5 (9) Å^3
Z = 4
D_x = 1.152 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 45 reflections
θ = 7.64–22.50°
μ = 0.074 mm^{-1}
T = 293 (2) K
Tablet
0.45 × 0.23 × 0.13 mm
Colourless

Data collection

Siemens *P*4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
4079 measured reflections
3185 independent reflections
1799 reflections with $I > 2\sigma(I)$
R_{int} = 0.029
θ_{max} = 22.5°
$h = -1 \rightarrow 10$
$k = 0 \rightarrow 11$
$l = -26 \rightarrow 26$
3 standard reflections
every 197 reflections
intensity decay: 4.44%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.057
$wR(F^2)$ = 0.190
S = 0.893
3135 reflections
282 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.1008P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.012
$\Delta\rho_{max}$ = 0.154 e Å^{-3}
$\Delta\rho_{min}$ = −0.127 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.004 (2)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

C13—C14	1.530 (7)	C15—C16	1.527 (8)
C13—C17	1.545 (7)	C16—C17	1.515 (8)
C14—C15	1.538 (7)		
C14—C13—C17	100.3 (4)	C17—C16—C15	108.5 (5)
C13—C14—C15	103.8 (4)	C16—C17—C13	101.3 (4)
C16—C15—C14	103.2 (5)		
C17—C13—C14—C8	177.9 (4)	C14—C15—C16—C17	−0.4 (6)
C12—C13—C14—C15	167.1 (4)	C15—C16—C17—C13	28.3 (6)
C13—C14—C15—C16	−28.2 (5)	C14—C13—C17—C16	−44.8 (5)
C8—C14—C15—C16	−158.1 (5)	C12—C13—C17—C16	−159.5 (5)

The crystals were very thin and their diffracting power was very low, so the data collection was stopped at θ = 22.5°. This was because only 106 of the 582 reflections collected in the range $21.0 < \theta < 22.5°$ had $I > 2\sigma(I)$, which meant that an extension of the data collection would only introduce noise. On the other hand, the high s.u.'s could be partly related to the θ cutoff. H atoms were generated and refined as riding groups with U(H) = 1.2U_{eq}(carrier atom) or 1.5U_{eq}(C_{methyl}).

Data collection: *XSCANS* (Siemens, 1991). Cell refinement: *XSCANS*. Data reduction: *XSCANS*. Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *CSU* (Vicković, 1988).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1052). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1998). C**54**, 1968–1970

Two 1-(Arylacetyl)-2-(aminomethyl)-piperidine Derivatives, a Novel Class of Highly Selective κ-Opioid Analgesics

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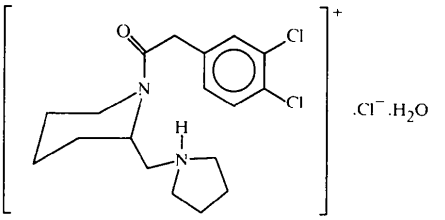
(Received 8 May 1998; accepted 10 June 1998)

Abstract

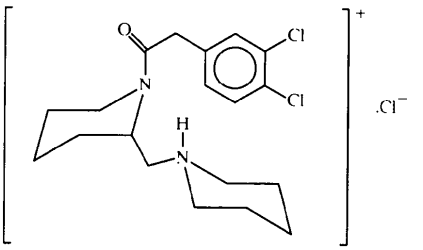
The single-crystal X-ray structures of (+)-1-{(2*R*)-1-[(3,4-dichlorophenyl)acetyl]piperidin-2-ylmethyl}-pyrrolidinium chloride monohydrate ($C_{18}H_{25}Cl_2N_2O^+.Cl^-.H_2O$; BRL-52536A) and (−)-1-{(2*S*)-1-[(3,4-dichlorophenyl)acetyl]piperidin-2-ylmethyl}piperidinium chloride ($C_{19}H_{27}Cl_2N_2O^+.Cl^-$; BRL-52781A) have been determined. BRL-52536A is the inactive stereoisomer of BRL-52537A, the highly selective and potent lead compound of the series. The pharmacophore N—C—C—N_{sp^2} torsion angle is (+)-synclinal in the 2*S* configuration.

Comment

Over the last decade, κ-opioid agonists have received increased interest as possible safe and effective analgesics for the treatment of acute and chronic pain (Rees, 1992). Vecchietti *et al.* (1991) described the synthesis and structure–activity relationships as κ-opioid analgesics of a novel class of 1-(arylacetyl)-2-(aminomethyl)piperidine derivatives. Antinociceptive activity and κ affinity were found to be extremely enantiospecific since only compounds with the 2*S* configuration displayed significant activity. Futhermore, it was concluded from computational studies and ^{1}H NMR spectroscopic analysis (Vecchietti *et al.*, 1991) that the pharmacophore N—C—C—N_{sp^2} torsion angle should be *ca* 60° in a low energy conformation. In order to confirm these results the crystal structures of two members of the series were determined, namely, (+)-1-{(2*R*)-1-[(3,4-dichlorophenyl)acetyl]piperidin-2-ylmethyl}pyrrolidinium chloride monohydrate (BRL-52536A) and (−)-1-{(2*S*)-1-[(3,4-dichlorophenyl)acetyl]piperidin-2-ylmethyl}piperidinium chloride (BRL-52781A).



BRL-52536A



BRL-52781A

The bond lengths do not display outstanding features. The internal angles of the phenyl ring reflect the substitution pattern (Domenicano & Murray-Rust, 1979). The piperidine ring has a chair conformation slightly flattened towards an envelope conformation, with the flap at C12, resulting in an enlarged C13—C14—C15 angle. The 2-substituent is in an axial position and in a *syn* conformation with respect to the carbonyl O atom. The global conformation of the molecules is futher determined by the torsion angles C3—C4—C7—C8, C4—C7—C8—N10, N10—C15—C16—N17 and C15—C16—N17—H17. In both crystal structures, the pharmacophore N10—C15—C16—N17 torsion angle and the C15—C16—N17—H17 torsion angle are synclinal, confirming the computational results. The observed conformation is probably a result of the electronic attraction between the charged N atom and the carbonyl group. The dihedral angle between the least-squares planes of the phenyl and amido groups is 101.0 (1) and 97.1 (1)° in BRL-52536A and BRL-52781A, respectively, indicating perpendicularity of the two planes. In both structures, the Cl^- anion is hydrogen bonded to N17 [N17···Cl 3.098 (3) and 3.097 (2), H17···Cl 2.22 and 2.21 Å, and N17—H17···Cl 162 and 166°, for BRL-52536A and BRL-