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Potential injectable contraceptive steroids: testosterone buciclate

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Key indicators

Single-crystal X-ray study
T = 180 K
Mean σ(C–C) = 0.007 Å
R factor = 0.073
wR factor = 0.162
Data-to-parameter ratio = 9.1

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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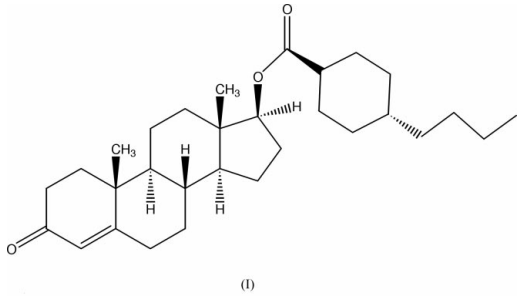
The buciclate ester of testosterone, $C_{30}H_{46}O_3$, whose structure is reported here, was synthesized as part of a World Health Organization programme for the development of injectable contraceptive steroids.

Comment

In the early 1970s, the World Health Organization (WHO) in collaboration with the National Institute of Child Health and Human Development (NICHD) embarked on a steroid ester synthesis programme (Hall *et al.*, 1984). The aim of this programme was to develop long-acting (up to six-month contraceptive activity from a single dose) injectable steroids for both men and women that retained an approximately constant pharmacokinetic profile. An additional aim was to reduce significantly the costs of the products to the public sector. The steroid synthesis programme focused on making new esters, oximes and ethers of steroids with known contraceptive activity. One of the results of this programme was the buciclate ester of testosterone, (I), whose structure is reported here. The dimensions and conformation of the molecule are as expected and match similar compounds already reported (Allen, 2002).



(I)

Experimental

trans-4-*n*-Butylcyclohexanecarboxylic acid (327.4 g, 1.777 *M*, 1.025 equivalents) was dissolved in a mixture of dry dichloromethane (1.5 l, 0.004% *w*/*w* water) and dry dimethylformamide (3 ml, 0.01% *w*/*w* water). Thionyl chloride (226.9 g, 1.907 *M*, 1.1 equivalents) was added to the stirred solution after 5 min at 288–293 K. The reaction mixture was heated gently to 308 K over a period of 0.5 h (a vigorous evolution of gas was observed at 293 K) and then heated at 308–313 K for a further 5 h. The solvent and excess thionyl chloride were removed by rotary evaporation below 313 K under vacuum. Care was taken to protect the resulting acid chloride from moisture at all times. Testosterone (500.0 g, 1.734 *M*) was dissolved in a mixture of dry dichloromethane (2.0 l, 0.004% *w*/*w* water) and dry pyridine (411.4 g, 5.201 *M*, 3.0 equivalents, 0.03% *w*/*w* water). The acid chloride, as prepared above (401.8 g), was dissolved in dry dichloromethane (500 ml, 0.004% *w*/*w* water) and was added dropwise, over a period of 0.5 h, to the testosterone solution at 273–278 K. This mixture was

stirred for a further 2 h at 273–278 K and was then allowed to warm slowly to ambient temperature (293 K) overnight (17 h). The resulting dichloromethane solution was washed with an aqueous 10% citric acid solution (1 l × 3), a saturated aqueous sodium bicarbonate solution (500 ml) and a saturated aqueous sodium chloride solution (500 ml). The resulting dichloromethane solution was dried with magnesium sulfate (300 g) and filtered, and the filtered solids were washed with more dichloromethane (500 ml). The combined dichloromethane filtrates were evaporated to dryness to give the crude testosterone ester (791.1 g). The crude ester was stirred with acetone (1.58 l) for 2.5 h. The resulting solid was filtered and washed with acetone (395 ml). The damp, partially purified, ester was then dissolved in hot methanol (5.5 l) and the hot solution was filtered through glass wool to remove a trace of insoluble material. This solution was stirred as it cooled and crystallized and was held at 283 K for 18 h. The precipitated ester was filtered, washed with methanol (625 ml × 2) and dried *in vacuo* below 313 K. A final purification of the testosterone ester was effected by dissolving it in warm ethanol (2.5 l) and then stirring the mixture at 283 K for 18 h. The recrystallized solid was filtered, washed with ethanol (500 ml) and dried *in vacuo* below 323 K, giving testosterone buciclate (613.5 g, 77.8% yield) as a white crystalline solid.

Crystal data

$C_{30}H_{46}O_3$
M_r = 454.67
Orthorhombic, $P2_12_12_1$
a = 6.2987 (13) Å
b = 10.500 (2) Å
c = 39.680 (8) Å
V = 2624.2 (9) Å^3
Z = 4
D_x = 1.151 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4739 reflections
θ = 3–15°
μ = 0.07 mm^{-1}
T = 180 (2) K
Plate, colourless
0.48 × 0.20 × 0.04 mm

Data collection

Siemens SMART diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.77, T_{max} = 0.96
12 882 measured reflections
2707 independent reflections
1700 reflections with $I > 2\sigma(I)$
R_{int} = 0.124
θ_{max} = 25.0°
$h = -7 \rightarrow 7$
$k = -12 \rightarrow 9$
$l = -44 \rightarrow 47$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.073
$wR(F^2)$ = 0.162
S = 1.05
2707 reflections
298 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0715P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.012
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

The temperature of the crystal was controlled using the Oxford Cryosystem Cryostream Cooler (Cosier & Glazer, 1986). H atoms were added at calculated positions and refined using a riding model (C—H distances in the range 0.95–1.00 Å), with U_{iso}(H) equal to 1.2 (or 1.5 for methyl H atoms) times U_{eq} of the carrier atom. Friedel pairs were merged and the absolute configuration was assigned from the known configuration of the steroid moiety of the molecule.

Data collection: *SMART* (Siemens, 1994); cell refinement: *SAINT* (Siemens, 1995); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXTL* (Sheldrick, 1997); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

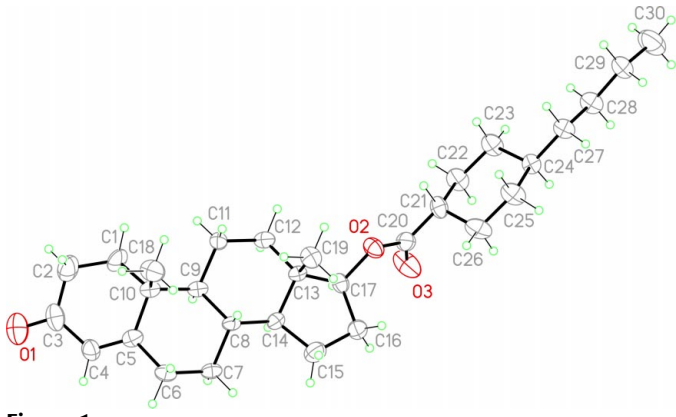


Figure 1
View of the title molecule, showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

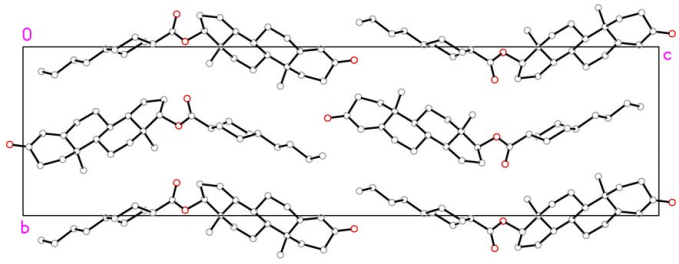


Figure 2
Packing diagram, viewed down the *a* axis. H atoms have been omitted.

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