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Anhydrous beclomethasone dipropionate

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Key indicators

Single-crystal X-ray study
T = 100 K
Mean σ(C–C) = 0.002 Å
R factor = 0.030
wR factor = 0.072
Data-to-parameter ratio = 14.5

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

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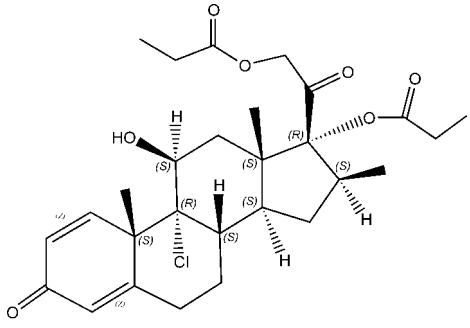
The anhydrous crystal structure of the title compound, 9α-chloro-16β-methyl-3,20-dioxo-1,4-pregnadiene-11β,17,21-triol 17,21-dipropionate, $C_{28}H_{37}ClO_7$, was determined by single-crystal X-ray diffractometry using direct methods. Beclomethasone dipropionate, BDP, is an important pharmaceutical steroid for the treatment of asthma. It is formulated for inhalation delivery either as a solution or as a suspension of crystals in liquefied halogenated-alkanes. The physicochemical properties of the crystals in suspension are of critical importance. Density will affect suspendability and settling rate, and different crystal forms may have significantly different dissolution rates *in vivo*. Until now, only the monohydrate form of BDP has been published [Duax *et al.* (1981). *Acta Cryst.* B**37**, 383–387]. This study presents the structure of the anhydrous form of BDP. The anhydrous form is intermolecularly hydrogen bonded and its efficient packing results in a more dense crystal (1.362 Mg m^{-3}) than the published monohydrate form (1.287 Mg m^{-3}).

Comment

Although the molecular structure of a pharmaceutical agent is ultimately responsible for its therapeutic effect, its crystalline structure can significantly alter its efficacy. Dissolution rate, solubility, chemical and physical stability, and physical characteristics, such as density and flow, are among the properties affected by the crystal form of a chemical. Thus, it is critical that thorough solid-state screenings and characterizations are performed on pharmaceutically relevant chemicals. All potential polymorphs and solvates/hydrates should be as well understood as possible to prevent later development problems.



(I)

Beclomethasone dipropionate, (I), is a well known therapeutic steroid, delivered *via* aerosol inhalation, for the treatment of chronic asthma. It is typically delivered as an aerosol suspension or solution out of pressurized chlorofluorocarbon

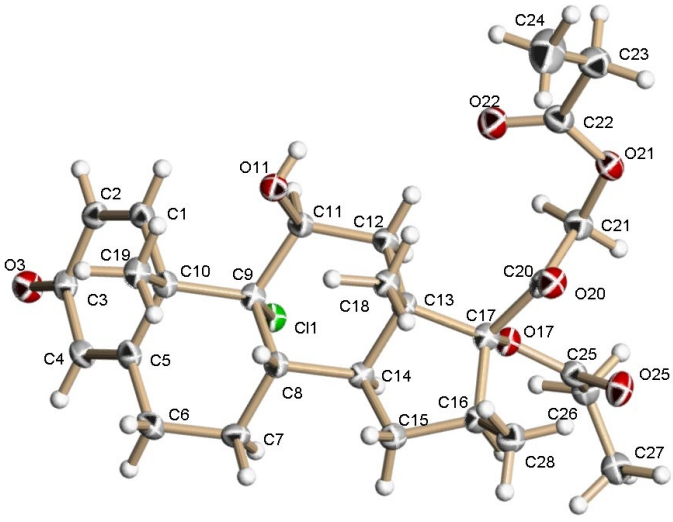


Figure 1
The molecular structure of anhydrous beclomethasone dipropionate, showing 50% probability displacement ellipsoids and standard steroid atomic numbering scheme. H atoms are drawn as spheres of arbitrary radii.

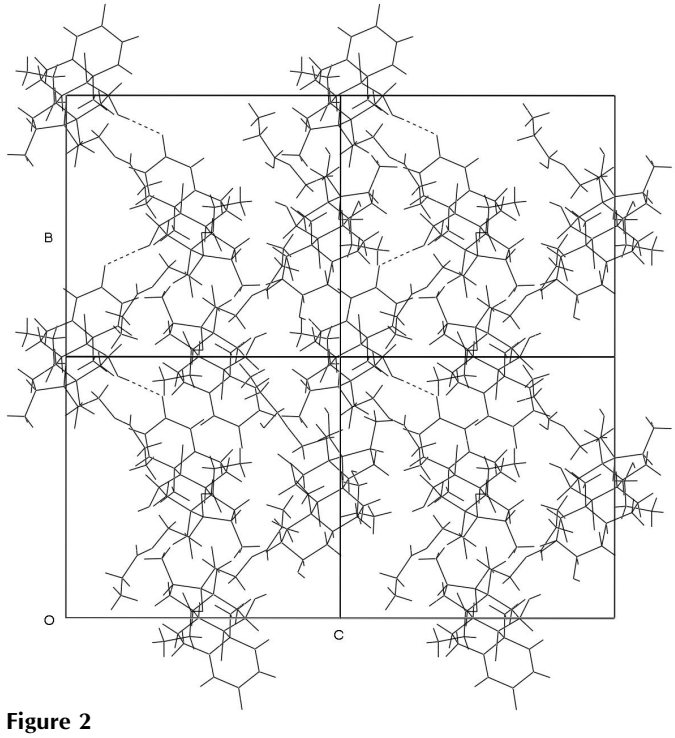


Figure 2
Packing diagram of four unit cells, viewed down the *a* axis. Hydrogen bonds are indicated by dashed lines. Note the upper left unit-cell hydrogen bond for clarity. The D—H···A hydrogen-bond angle agrees with expected carbonyl lone-pair geometry.

(CFC) or hydrofluoroalkane (HFA) propellants. While pressurized inhalers are sealed systems, subtle changes in the formulation's composition occur due to diffusion through seal materials. Therefore, the potential exists for the internal conversion of anhydrous BDP to other crystal forms such as the monohydrate.

The monohydrate form (Duax *et al.*, 1981) is more stable than the anhydrous form. Although both forms crystallize in space group $P2_12_12_1$, the anhydrous form has a density of 1.362 Mg m^{-3}, while that of the monohydrate form is 1.287 Mg m^{-3}. Since the densities of the various CFC and HFA propellants vary between 1.22 and 1.40 Mg m^{-3}, these density differences will affect how and to what extent the drug crystals tend to settle or cream in the propellant systems. This can dramatically alter the amount of drug delivered when the inhaler is actuated. It is also noteworthy that the anhydrous form will rapidly convert to the monohydrate in the presence of both high humidity and ethanol vapor, but rather slowly in solely a high humidity environment.

The monohydrate form was compared to the anhydrous form *via* the OFIT routine of *XP* (in *SHELXTL/PC*; Bruker, 1997)). The overall weighted r.m.s. deviation was 0.427 Å. The major differences were in the propionate groups, where the terminal C atoms, C24 and C27, had deviations of 1.38 and 1.45 Å, respectively. These large deviations were due to the significantly different torsion angles at the distal ends of the propionate groups. The O21—C22—C23—C24 torsion angle is −139.1° in the anhydrous form and 156.3° in the monohydrate, a difference of 64.6°. The O17—C25—C26—C27 torsion angle is −134.6° in the anhydrous form and 177.1° in the monohydrate, a difference of 48.3°. The rest of the atoms aligned reasonably well, with no r.m.s. differences of more than 0.6 Å.

The drug compound in this study was crystallized as described in the *Experimental* section, and its identity and purity were verified by HPLC UV diode-array assay and differential scanning calorimetry.

Experimental

Excellent crystals of the anhydrous form were obtained by programmed temperature cycling of beclomethasone dipropionate supersaturated soybean oil. Cycling was computer controlled from room temperature to 343 K and back to room temperature every 6 h for 48 h. Control of humidity was necessary to avoid monohydrate formation. A sharp melting point of the compound was observed at 486.7 K by differential scanning calorimetry and verified by hot-stage microscopy to be 485–487 K.

Crystal data

$C_{28}H_{37}ClO_7$
M_r = 521.03
Orthorhombic, $P2_12_12_1$
a = 12.1239 (15) Å
b = 14.1289 (17) Å
c = 14.8381 (18) Å
V = 2541.7 (5) Å^3
Z = 4
D_x = 1.362 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 5087 reflections
θ = 5.7–51.3°
μ = 0.20 mm^{-1}
T = 100 (2) K
Irregular block, colorless
0.40 × 0.30 × 0.25 mm

Data collection

Bruker CCD area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2000)
T_{min} = 0.923, T_{max} = 0.952
25323 measured reflections
4799 independent reflections
4507 reflections with $I > 2\sigma(I)$
R_{int} = 0.044
θ_{max} = 25.7°
$h = -14 \rightarrow 14$
$k = -17 \rightarrow 17$
$l = -18 \rightarrow 18$
287 standard reflections
every 1818 reflections
intensity decay: 0.1%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0386P)^2 + 0.3771P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.030$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.072$	$\Delta\rho_{max} = 0.25$ e Å^{-3}
$S = 1.07$	$\Delta\rho_{min} = -0.15$ e Å^{-3}
4799 reflections	Absolute structure: (Flack, 1983); 2086 Friedel pairs
331 parameters	Flack parameter = −0.01 (4)
H atoms treated by a mixture of independent and constrained refinement	

Table 1
Selected torsion angles (°).

O17—C25—C26—C27	−134.57 (16)	O21—C22—C23—C24	−139.05 (18)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O11—H11A···O3^{i}	0.79	2.02	2.7762 (17)	161

Symmetry code: (i) $-x, \frac{1}{2}+y, \frac{3}{2}-z$.

Most H atoms were refined as riding atoms with isotropic displacement parameters after being placed in ideal positions. The hydrogen-bonding H11*A* atom was refined using *AFIX* 147, with the *X*—O—H angle tetrahedral but with the torsion angle and bond distance free to refine.

Data collection: *SMART* (Bruker, 1997); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 2000); program(s) used to solve structure: *SHELXTL*/*PC* (Bruker, 1997); program(s) used to refine structure: *SHELXTL/PC*; molecular graphics: *SHELXTL/PC*; software used to prepare material for publication: *SHELXTL/PC*.

The structure was determined in the Molecular Structure Laboratory of the Department of Chemistry with assistance from Dr Michael Carducci, University of Arizona, Tucson, AZ 85721, USA. The SMART1000 diffractometer was gratefully obtained with funds provided by NSF grant CHE9610374.

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