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Polymorphism in Dethoxyprone, a Steroidal Anaesthetic. I. Structure of 11α-Dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one (Dethoxyprone Form I)

BY REX A. PALMER,* HILDA T. PALMER AND JOHN N. LISGARTEN†

Department of Crystallography, Birkbeck College, Malet Street, London WC1E 7HX, England

AND ROBERT LANCASTER

Glaxo Group Research, Greenford, England

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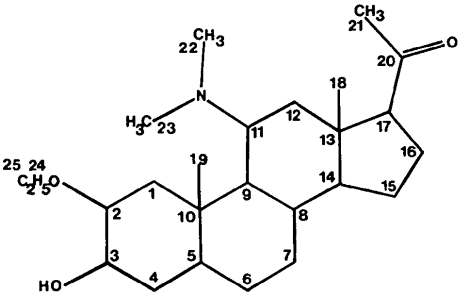
Abstract. $C_{25}H_{43}NO_3$, $M_r = 405$, monoclinic, $P2_1$, $a = 8.654$ (2), $b = 6.428$ (1), $c = 21.032$ (3) Å, $\beta = 95.7$ (2)°, $V = 1164$ (2) Å^3, $Z = 2$, $D_x = 1.16$ g cm^{-3}, λ(Cu $K\alpha$) = 1.5418 Å, $\mu = 5.05$ cm^{-1}, $F(000) = 448$, room temperature, $R = 0.042$ for 2185 observed reflections. All rings of the steroid skeleton are *trans* connected. Rings *A*, *B* and *C* are all in the chair conformation. Ring *D* is in a half-chair conformation. The molecules are hydrogen bonded in a head-to-head fashion through H(O3) and O(2) in a staggered arrangement linking molecules stacked along **b**.

Introduction. The anaesthetic properties of certain hormonal steroids have been known for over fifty years. The synthesis of Dethoxyprone [(2β,3α,5α,-11α)-11-dimethylamino-2-ethoxy-3-hydroxy-5-pregnan-20-one] was a direct response to the need for a soluble steroid with potent anaesthetic properties. Initial animal studies (Davies, 1978) have demonstrated that it produces rapid onset of and recovery from anaesthesia and is non-irritant on intravenous administration. Early clinical trials (Aveling, 1979; Dundee, 1979; Dunn, 1980) have shown equal promise. At present two polymorphic forms of dethoxyprone are known to exist: Form I (monoclinic, $P2_1$) and Form II (orthorhombic, $P2_12_12_1$). We report here the crystal and molecular structure of Form I as part of an investigation into the polymorphism of this compound.



Experimental. Sample provided by Glaxo Research Laboratories, UK. Colourless prisms by slow

* To whom correspondence should be addressed.

† Present address: Department of Ultrastructure, Instituut voor Molekulaire Biologie, Vrije Universiteit Brussel, Paardenstraat 65, B-1640 Sint-Genesius Rode, Belgium.

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Table 1. *Atomic positional parameters and equivalent isotropic temperature factors for non-H atoms with e.s.d.'s in parentheses*

$U_{eq} = (U_1U_2U_3)^{1/3}$.

	x	y	z	U_{eq}(Å^2)
C(1)	0.9961 (3)	0.1694 (7)	0.8690 (1)	0.037 (1)
C(2)	0.8932 (6)	0.2213 (7)	0.9215 (1)	0.040 (1)
C(3)	0.7956 (3)	0.4177 (8)	0.9058 (1)	0.046 (2)
C(4)	0.7128 (3)	0.4038*	0.8402 (1)	0.043 (1)
C(5)	0.8234 (3)	0.3673 (7)	0.7885 (1)	0.038 (2)
C(6)	0.7413 (4)	0.3867 (8)	0.7218 (1)	0.050 (2)
C(7)	0.8609 (4)	0.3888 (8)	0.6732 (1)	0.050 (2)
C(8)	0.9689 (3)	0.2001 (7)	0.6798 (1)	0.040 (1)
C(9)	1.0448 (3)	0.1655 (7)	0.7498 (1)	0.030 (1)
C(10)	0.9184 (3)	0.1632 (7)	0.7990 (1)	0.033 (1)
C(11)	1.1528 (3)	−0.0271 (7)	0.7491 (1)	0.034 (1)
C(12)	1.2767 (3)	−0.0007 (7)	0.7012 (1)	0.041 (1)
C(13)	1.2041 (3)	0.0368 (8)	0.6333 (1)	0.042 (2)
C(14)	1.0973 (4)	0.2252 (7)	0.6354 (1)	0.051 (2)
C(15)	1.0534 (4)	0.2781 (8)	0.5652 (1)	0.060 (2)
C(16)	1.2056 (4)	0.2377 (9)	0.5347 (2)	0.060 (2)
C(17)	1.3152 (4)	0.1179 (8)	0.5843 (1)	0.051 (2)
C(18)	1.1195 (4)	−0.1591 (8)	0.6060 (1)	0.050 (2)
C(19)	0.8175 (3)	−0.0328 (7)	0.7886 (1)	0.042 (2)
C(20)	1.4101 (4)	−0.0495 (9)	0.5561 (2)	0.070 (2)
C(21)	1.5546 (5)	−0.1194 (14)	0.5964 (2)	0.099 (4)
C(22)	1.2644 (4)	−0.3074 (8)	0.8175 (2)	0.054 (2)
C(23)	1.3543 (3)	0.0414 (9)	0.8384 (1)	0.050 (2)
C(24)	0.7384 (4)	0.0533 (8)	0.9935 (2)	0.058 (2)
C(25)	0.6466 (5)	−0.1394 (9)	1.0025 (2)	0.070 (2)
N(1)	1.2254 (3)	−0.0884 (7)	0.8129 (1)	0.040 (1)
O(2)	0.7933 (2)	0.0478 (7)	0.9318 (1)	0.045 (1)
O(3)	0.9042 (3)	0.5867 (6)	0.9124 (1)	0.053 (1)
O(20)	1.3760 (4)	−0.1216 (8)	0.5033 (1)	0.084 (2)

* Fixed to define the origin along **b**.

Table 2. *Bond lengths* (Å) *and bond angles* (°) *with e.s.d.'s in parentheses, selected torsion angles* (°) *for which e.s.d.'s are ca* 0.5° *and asymmetry parameters* (°) *for the title compound*

C(1)—C(2)	1.523 (3)	C(16)—C(17)	1.544 (5)
C(2)—C(3)	1.536 (4)	C(17)—C(13)	1.567 (4)
C(3)—C(4)	1.493 (4)	C(13)—C(18)	1.539 (4)
C(4)—C(5)	1.538 (4)	C(10)—C(19)	1.536 (4)
C(5)—C(6)	1.513 (4)	C(17)—C(20)	1.511 (5)
C(6)—C(7)	1.525 (4)	C(20)—C(21)	1.508 (6)
C(7)—C(8)	1.529 (4)	C(20)—O(20)	1.212 (4)
C(8)—C(9)	1.568 (3)	C(11)—N(1)	1.477 (3)
C(9)—C(10)	1.578 (3)	N(1)—C(22)	1.448 (4)
C(9)—C(11)	1.552 (4)	N(1)—C(23)	1.453 (4)
C(11)—C(12)	1.552 (3)	O(2)—C(2)	1.441 (4)
C(12)—C(13)	1.521 (4)	O(2)—C(24)	1.425 (3)
C(13)—C(14)	1.526 (4)	C(24)—C(25)	1.493 (5)
C(14)—C(8)	1.530 (4)	C(3)—O(3)	1.433 (4)
C(14)—C(15)	1.526 (4)	C(1)—C(10)	1.557 (3)
C(15)—C(16)	1.543 (4)	C(5)—C(10)	1.552 (4)

C(2)—C(1)—C(10)	117.5 (2)	C(7)—C(8)—C(14)	109.6 (2)
C(1)—C(2)—C(3)	111.9 (2)	C(8)—C(9)—C(11)	107.5 (2)
O(2)—C(2)—C(1)	110.0 (2)	C(10)—C(9)—C(11)	117.2 (2)
O(2)—C(2)—C(3)	110.1 (2)	C(9)—C(11)—C(12)	112.0 (2)
C(24)—O(2)—C(2)	112.2 (2)	C(11)—C(12)—C(13)	112.3 (2)
C(25)—C(24)—O(2)	109.0 (3)	C(12)—C(13)—C(14)	107.1 (2)
C(2)—C(3)—C(4)	110.6 (3)	C(13)—C(14)—C(8)	114.3 (2)
C(2)—C(3)—O(3)	105.1 (2)	C(9)—C(11)—N(1)	113.9 (2)
C(4)—C(3)—O(3)	112.6 (3)	C(12)—C(11)—N(1)	111.0 (2)
C(3)—C(4)—C(5)	112.8 (2)	C(11)—N(1)—C(22)	113.3 (3)
C(4)—C(5)—C(10)	112.7 (2)	C(11)—N(1)—C(23)	115.1 (2)
C(5)—C(10)—C(1)	106.6 (2)	C(13)—C(14)—C(15)	104.0 (2)
C(5)—C(10)—C(19)	112.8 (2)	C(8)—C(14)—C(15)	119.3 (3)
C(1)—C(10)—C(19)	110.0 (2)	C(14)—C(15)—C(16)	102.9 (3)
C(9)—C(10)—C(19)	109.6 (2)	C(15)—C(16)—C(17)	107.2 (2)
C(9)—C(10)—C(5)	106.9 (2)	C(16)—C(17)—C(13)	103.6 (2)
C(10)—C(5)—C(6)	113.2 (3)	C(17)—C(13)—C(14)	99.7 (2)
C(4)—C(5)—C(6)	112.1 (2)	C(12)—C(13)—C(18)	110.9 (3)
C(5)—C(6)—C(7)	109.5 (2)	C(17)—C(13)—C(18)	109.1 (2)
C(6)—C(7)—C(8)	112.4 (3)	C(13)—C(17)—C(20)	114.5 (3)
C(7)—C(8)—C(9)	113.2 (2)	C(16)—C(17)—C(20)	114.3 (3)
C(9)—C(8)—C(14)	109.1 (2)	C(17)—C(20)—C(21)	116.4 (4)
C(8)—C(9)—C(10)	111.3 (2)	C(17)—C(20)—O(20)	122.7 (4)

C(1)—C(2)—C(3)—C(4)	50.5	C(11)—C(12)—C(13)—C(14)	55.4
C(2)—C(3)—C(4)—C(5)	−56.4	C(12)—C(13)—C(14)—C(8)	−58.6
C(3)—C(4)—C(5)—C(10)	59.7	C(13)—C(14)—C(8)—C(9)	60.9
C(4)—C(5)—C(10)—C(1)	−52.1	C(14)—C(8)—C(9)—C(11)	−56.7
C(5)—C(10)—C(1)—C(2)	49.3	C(8)—C(9)—C(11)—C(12)	56.7
C(10)—C(1)—C(2)—C(3)	−49.8	C(9)—C(11)—C(12)—C(13)	−58.2
C(9)—C(10)—C(5)—C(6)	60.6	C(13)—C(17)—C(16)—C(15)	16.2
C(10)—C(5)—C(6)—C(7)	−61.4	C(17)—C(16)—C(15)—C(14)	17.8
C(5)—C(6)—C(7)—C(8)	54.7	C(16)—C(15)—C(14)—C(13)	−38.2
C(6)—C(7)—C(8)—C(9)	−51.3	C(15)—C(14)—C(13)—C(17)	47.9
C(7)—C(8)—C(9)—C(10)	51.5	C(14)—C(13)—C(17)—C(16)	−38.6
C(8)—C(9)—C(10)—C(5)	−53.8		

Ring *A*

$\Delta C_s^1 = 2.1$ $\Delta C_2^{1,2} = 3.2$

$\Delta C_s^2 = 6.0$ $\Delta C_2^{2,3} = 8.7$

$\Delta C_s^3 = 6.8$ $\Delta C_2^{3,4} = 6.7$

Ring B

$\Delta C_s^9 = 7.2$ $\Delta C_2^{9,10} = 10.1$

$\Delta C_s^{10} = 7.4$ $\Delta C_2^{5,10} = 5.8$

$\Delta C_s^8 = 1.0$ $\Delta C_2^{5,6} = 4.8$

Ring *C*

$\Delta C_2^{12} = 3.1$ $\Delta C_2^{11,12} = 1.6$

$\Delta C_s^{11} = 1.8$ $\Delta C_2^{11,9} = 4.0$

$\Delta C_s^9 = 2.4$ $\Delta C_2^{9,8} = 3.0$

Ring *D*

$\Delta C_2^{13,14} = 1.2$

evaporation from aqueous ethanol. Crystal 0.21 × 0.80 × 0.18 mm used for data collection. Precession and Weissenberg photographs yielded approximate cell dimensions and showed monoclinic (2/*m*) Laue symmetry. Space group $P2_1$, systematic absences: $0k0$, $k = 2n + 1$. Enraf–Nonius CAD-4 automated diffractometer. Accurate cell dimensions were determined from least-squares refinement of 25 reflections ($15 < \theta < 20°$); ω–2θ scan, scan width $(1.10 + 0.14\tan\theta)°$, vertical aperture = 4 mm; 5147 reflections measured ($-10 \le h \le 10$, $-7 \le k \le 7$, $0 \le l \le 26$), $R_{int} = 0.025$, 2584 unique reflections, 2185 with $I > 3\sigma(I)$ ($1 < \theta < 70°$), three intensity standards (112, 104 and $\bar{2}13$) showed no significant variations during data collection; intensity data corrected for Lorentz–polarization factors. No absorption correction applied. Structure solution by direct methods with *MULTAN*74 (Main, Woolfson, Lessinger, Germain & Declercq, 1974) and *SHELX*76 (Sheldrick, 1976). Atomic scattering factors from *SHELX*76; *E* map gave positions of all non-H atoms. Refinement by full-matrix least squares (*SHELX*76; Sheldrick, 1976) with anisotropic thermal factors for all the non-H atoms, isotropic for H atoms. The hydroxy hydrogen, H(O3), was located from a difference synthesis and fixed during subsequent refinement with an isotropic thermal parameter assigned as 0.09 Å^2; the remaining 42 H-atom positions were obtained by calculation and tied at a C—H distance of 1.08 Å. Function minimized was $\sum w(|F_o| - |F_c|)^2$, $w = 9.8066[\sigma^2(|F_o|) + 0.000194|F_o|^2]^{-1}$, $R = 0.042$, $wR = 0.047$, R (all data) = 0.052 for 304 variable parameters; max. $|\Delta/\sigma| = 0.518$. Final difference electron density ($\Delta\rho$) −0.15 to 0.17 e Å^{-3}. Calculations carried out on an Amdahl 470/8 computer. Geometrical calculations were performed with *XANADU* (Roberts & Sheldrick, 1975) and illustrations were drawn with *PLUTO* (Motherwell & Clegg, 1978).

Discussion. The final atomic coordinates and equivalent isotropic thermal parameters for the non-H

atoms are given in Table 1.* Bond distances and angles are listed in Table 2. Fig. 1 shows a stereoview of the molecule and Fig. 2 is a view of the crystal structure along **b**. Dethoxyprone is a fully saturated structure and most of the bond lengths are close to the expected values. The average C—C single-bond lengths in rings *A*, *B*, *C* and *D* are 1.533 (4), 1.544 (4), 1542 (4) and 1.541 (4) Å, respectively. The average value of all the C—C single-bond lengths in the molecule is 1.530 (4) Å. This is in agreement with the values found in similar steroid structures (Griffin, Duax & Weeks, 1984) and those cited by Allen, Kennard, Watson, Brammer, Orpen & Taylor (1987). The shortening in the C(3)—C(4) bond length [1.493 (4) Å] may be associated with the attachment of the hydroxy group to C(3) although this feature has not been observed in steroids with hydroxy moieties similarly positioned. All other bond lengths, *e.g.* C—N, C—O and C=O, show no significant deviations from the values given by Allen *et al.* (1987).

The average C—C—C bond angle within the steroid skeleton is 109.2°. Twelve of the angles are at least 5σ greater than this value [110.6 (3) to 114.3 (2)°] and nine are at least 10σ less [99.7 (2) to 107.2 (2)°]. The interior angle C(17)—C(13)—C(14) [99.7 (2)°] of ring *D* is significantly smaller than the other endocyclic valency angles. This effect has been observed in other pregnane steriods, *e.g.* 4-pregnene-3,20-dione (Serantoni, Krajewski, Mongiorgi, Riva di Sanseverino & Cameroni, 1975), 16β-methyl-4-pregnene-3,20-dione (Weeks, Strong & Osawa, 1976) and (20*R*)-5α-pregnano[3,4-*c*][1,2,5]oxadiazol-20-ol (Maes, Wyns, Lisgarten, Lisgarten & Palmer, 1992) which have angles having corresponding values of 99.0 (2), 99.1 (3) and 99.4 (1)°, respectively. Further examples may be found in Duax & Norton (1975) and Griffin, Duax & Weeks (1984). Conformational features of the molecule may be described in terms of (i) torsion angles (Table 2) and (ii) asymmetry parameters (Table 2). Rings *A*, *B* and *C* have low values for both ΔC_s and ΔC_2 showing good approximation to the ideal chair conformation. Ring junctions are all *trans* connected. The methyl and oxygen moieties of the 20-keto group are α and β oriented, respectively. One methyl of the *N*-dimethylamino group on C(11) is β oriented, the other having an α orientation. The ethoxy group on C(2) is prominently β oriented whilst the hydroxy group on C(3) is α. The molecule is typically β convex. Molecules are hydrogen-bonded head-to-head through H(O3) and O(2) in a staggered fashion linking molecules stacked down the *b* axis related by $(x, 1 + y, z)$. The intermolecular O(2)···O(3) distance is 3.154 (6) Å; the corresponding O(2)···H(O3) contact is 2.291 (4) Å; the O(3)—H(O3) bond length is 0.877 (4) Å, the C(3)—O(3)—H(O3) angle is 112.8 (3)° and O(3)—H(O3)···O(2) is 168.04 (44)°.

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55662 (15 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: AB1023]

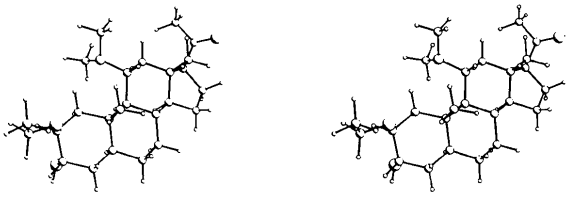

Fig. 1. Stereoview of the molecular conformation, viewed perpendicular to the steroid skeleton.

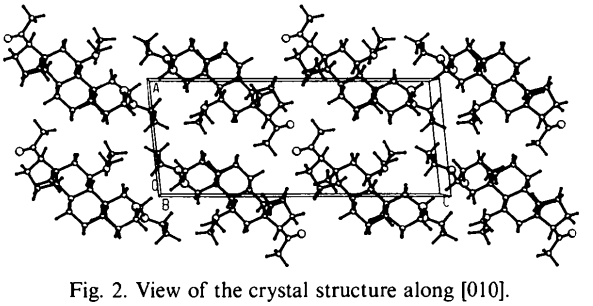

Fig. 2. View of the crystal structure along [010].

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