3β-Hydroxy-16β-morpholino-5-androsten-17-one

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Abstract. $C_{23}H_{35}NO_3$, monoclinic, $P2_1$, $a = 15\cdot200$ (1), $b = 6\cdot344$ (2), $c = 10\cdot786$ (1) Å, $\beta = 102\cdot23(1)°$, $V = 1016\cdot42$ Å^3, $Z = 2$, $M_r = 373\cdot54$, $D_c = 1\cdot29$ Mg m^{-3}. The crystal structure confirms the β assignment of the morpholino group. This is the first crystal structure report of a 16β-substituted 17-keto steroid. The conformation of the D ring is compared to D rings of other steroids with the 17-one substitution. The final R value is 0·049 for 2231 data.

Introduction. The mechanism of controlled alkaline hydrolysis of 16-bromo-17-keto steroids has recently been studied (Numazawa & Osawa, 1980). The crystal structure of 3β-hydroxy-16β-morpholino-5-androsten-17-one, (I), was undertaken to unambiguously determine the stereochemistry of this reaction product.

The single crystal used for X-ray measurements was 0·25 × 0·6 × 0·8 mm. The systematic absence 0*k*0 for $k = 2n + 1$ and intensity statistics indicated that the space group was $P2_1$. Cell constants were least-squares fitted to 34 diffractometer-centred reflections having $60° < 2\theta < 70°$ [measured at 293 K, $\lambda = 1\cdot54178$ Å (Cu $K\bar{\alpha}$)]. An Enraf–Nonius CAD-4 automated diffractometer with Cu $K\bar{\alpha}$ radiation was used to measure 2276 independent data with $2\theta < 150°$. Lorentz and polarization corrections were applied to the integrated intensities and normalized structure factor amplitudes were calculated and used in the computer program *MULTAN* (Germain, Main & Woolfson, 1971).
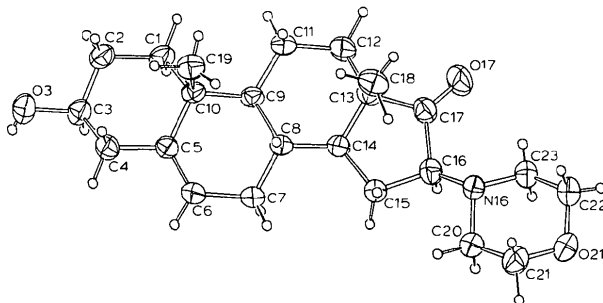
The most probable phase set from *MULTAN*, based on the negative quartet index generated by the computer program *NQEST* (DeTitta, Edmonds, Langs & Hauptman, 1975), gave an E map with peaks corresponding to all but two of the nonhydrogen atoms in the molecule. A Fourier map based on these 25 atoms revealed the coordinates of the remaining nonhydrogen atoms.
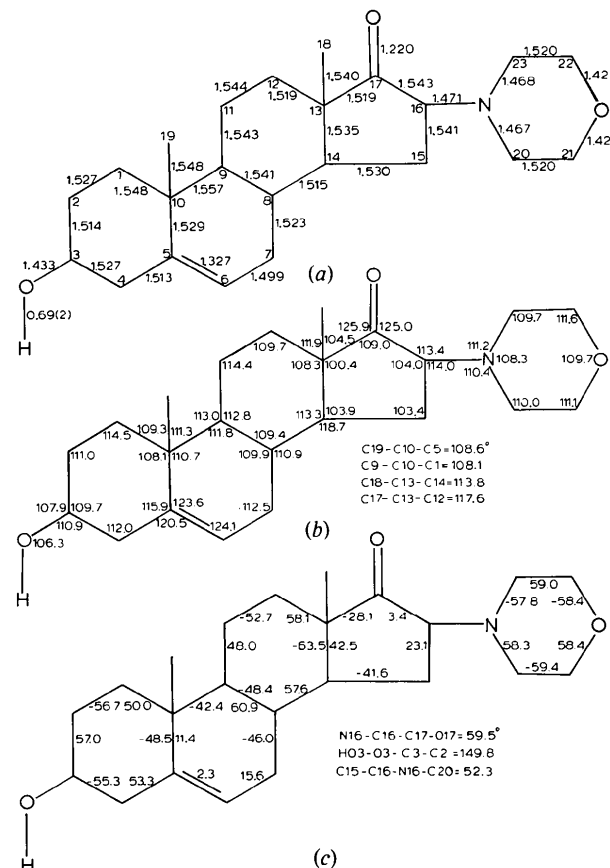

Fig. 1. Observed conformation of 3β-hydroxy-16β-morpholino-5-androsten-17-one. The atomic-numbering scheme and thermal vibrational ellipsoids of the nonhydrogen atoms are illustrated. The figure was drawn by *ORTEP* (Johnson, 1965), with ellipsoids scaled to the 50% probability level.

Fig. 2. Intramolecular geometry for 3β-hydroxy-16β-morpholino-5-androsten-17-one. (*a*) Bond distances (Å). (*b*) Bond angles (°). (*c*) Endocyclic torsion angles (*φ*). A torsion angle $\alpha-\beta-\gamma-\delta$ is positive if, when viewed down the $\beta-\gamma$ bond, the $\alpha-\beta$ bond will eclipse the $\gamma-\delta$ bond when rotated less than 180° in a clockwise direction. E.s.d.'s range from 0·002 to 0·004 Å for bond distances, 0·1 to 0·3° for bond angles and 0·5 to 0·7° for torsion angles.

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3β-HYDROXY-16β-MORPHOLINO-5-ANDROSTEN-17-ONE

Table 1. *Final atomic coordinates*

The estimated standard deviations are given in parentheses.* Atomic coordinates are $\times 10^5$ for non-hydrogen and $\times 10^3$ for H atoms. The H atoms are numbered according to the heavy atoms to which they are bonded.

	x	y	z		x	y	z
C(1)	37878 (11)	22238 (31)	57311 (15)	H(3α)	287 (1)	436 (6)	361 (2)
C(2)	41388 (12)	34510 (39)	47179 (16)	H(4α)	279 (1)	761 (5)	468 (2)
C(3)	34520 (11)	50471 (34)	40728 (15)	H(4β)	376 (1)	726 (6)	551 (2)
C(4)	32090 (12)	65333 (32)	50626 (16)	H(6)	172 (1)	676 (5)	587 (2)
C(5)	28847 (10)	53490 (30)	60980 (14)	H(7α)	117 (1)	387 (6)	696 (2)
C(6)	20966 (11)	58120 (36)	63747 (15)	H(7β)	146 (1)	573 (6)	785 (2)
C(7)	17305 (11)	47547 (38)	74011 (15)	H(8β)	285 (1)	460 (5)	877 (2)
C(8)	24485 (10)	35353 (–)	83243 (13)	H(9α)	261 (1)	132 (5)	694 (2)
C(9)	30148 (9)	22085 (30)	75850 (13)	H(11α)	388 (1)	−47 (7)	787 (2)
C(10)	35081 (10)	36128 (29)	67626 (14)	H(11β)	417 (–)	159 (–)	904 (–)
C(11)	36504 (12)	6518 (36)	84391 (17)	H(12α)	370 (–)	−156 (–)	997 (–)
C(12)	31969 (13)	−6601 (35)	93351 (16)	H(12β)	272 (–)	−173 (–)	878 (–)
C(13)	27169 (11)	7986 (31)	100925 (14)	H(14α)	164 (1)	103 (5)	856 (2)
C(14)	20251 (10)	20990 (32)	91565 (14)	H(15α)	83 (1)	337 (6)	950 (2)
C(15)	14313 (11)	30757 (37)	99865 (14)	H(15β)	173 (1)	415 (6)	1055 (2)
C(16)	12989 (12)	12560 (35)	108760 (14)	H(16α)	70 (1)	41 (5)	1038 (2)
C(17)	21108 (13)	−2050 (36)	108803 (15)	H(18A)	374 (1)	277 (6)	1061 (2)
C(18)	33837 (13)	21452 (47)	110457 (17)	H(18B)	297 (–)	322 (–)	1145 (–)
C(19)	43567 (11)	46546 (37)	75808 (17)	H(18C)	371 (1)	139 (6)	1161 (2)
C(20)	5288 (13)	35757 (44)	120672 (16)	H(19A)	468 (1)	569 (5)	712 (2)
C(21)	4583 (14)	42784 (49)	133898 (16)	H(19B)	420 (1)	520 (6)	826 (2)
C(22)	8951 (13)	9459 (49)	141955 (15)	H(19C)	475 (1)	377 (5)	780 (2)
C(23)	9793 (12)	1754 (40)	128918 (16)	H(20α)	−8 (1)	318 (6)	1163 (2)
N(16)	12218 (9)	19421 (32)	121517 (11)	H(20β)	73 (1)	492 (6)	1167 (2)
O(3β)	38395 (9)	61889 (33)	31738 (12)	H(21α)	−5 (1)	531 (7)	1343 (2)
O(17)	22364 (11)	−18999 (30)	114233 (13)	H(21β)	97 (1)	472 (7)	1377 (2)
O(21)	2330 (9)	25529 (37)	141107 (11)	H(22α)	67 (1)	−8 (7)	1460 (2)
H(1α)	324 (1)	137 (5)	522 (2)	H(22β)	154 (–)	163 (–)	1462 (–)
H(1β)	427 (1)	118 (5)	617 (2)	H(23α)	36 (1)	−37 (6)	1246 (2)
H(2α)	427 (1)	248 (6)	413 (2)	H(23β)	136 (1)	−63 (6)	1284 (2)
H(2β)	469 (1)	403 (5)	508 (2)	H(3O)	348 (1)	648 (5)	269 (2)

* For H atoms where no e.s.d. is given, that atom did not refine to a reasonable geometry and was fixed to a calculated position. C–H = 1·08 Å.

The atomic parameters were refined by full-matrix least-squares methods. After three iterations of aniso-tropic refinement, two successive difference electron density maps were computed and the H atom positions were located. All parameters were refined for the final four cycles with the isotropic temperature factor of each H atom set equal to 1·2 times the isotropic temperature factor of the atom to which it is bonded. Data where $I < 2\sigma_I$ were excluded from the refinement and the remaining data were weighted by $w = 1/\sigma_f^2$ where σ_f is as defined by Stout & Jensen (1968, eq. H14) with an instability correction of 0·06. The final R index, $R = \sum(\||F_o| - |F_c|\|)/\sum |F_o|$, was 0·049 for 2231 reflections and 333 parameters, and 0·050 for all data. The final positional parameters are given in Table 1.*

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35183 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Discussion. Fig. 1 illustrates the numbering scheme and shows that in this structure the morpholino group is attached at the 16β position. This is the first reported crystal structure of a 16β-substituted, 17-keto steroid. The bond distances, bond angles and endocyclic torsion angles are given in Fig. 2.

The A and C rings have normal chair conformations and the morpholino ring has a very symmetric chair conformation. The B ring is a 7α,8β half-chair, as are most 5-ene steroids. The asymmetry parameters for the B ring of (I), $\Delta C_s(6) = 25 \cdot 0°$ and $\Delta C_2(5-6) = 3 \cdot 9°$, are well within the range of values found in other 5-ene steroids [see *Atlas of Steroid Structure*, Vol. 1 (Duax & Norton, 1975), ch. 3, p. 31]. The conformational parameters $\Delta = -28 \cdot 5°$ and $\varphi_m = 43 \cdot 9°$ (Altona, Geise & Romers, 1968) for the D ring indicate a conformation close to a 14α-envelope. Fig. 3 shows the distribution of Δ and φ_m values for the D rings of 31 17-keto steroids found in *Atlas of Steroid Structure*, Vols. I and II. The average Δ and φ_m values are −22·3 and 43·1° respectively. The trigonal C atom at the 17
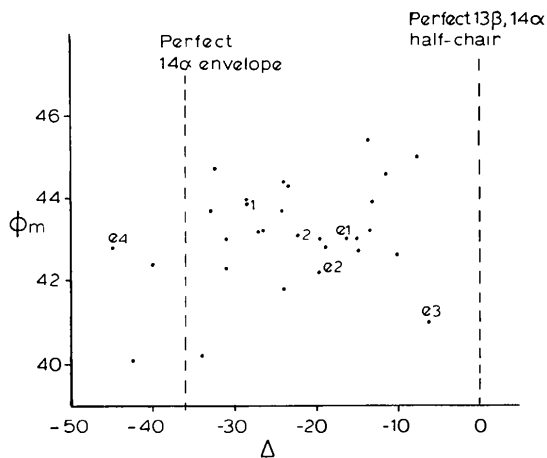
Fig. 3. Distribution of D-ring conformational parameters, Δ and φ_m (°), for 31 14α,17-one steroids found in Vols. I and II of *Atlas of Steroid Structure* (Duax & Norton, 1975). The location of the parameters for (I) is denoted by 1. The average of the distribution is denoted by 2. e1–4 denote the four different conformers of estrone found in the solid state (Busetta, Courseille & Hospital, 1973).

position prevents the D ring from adopting a 13β-envelope conformation but allows the conformation found in the solid state to range from a 13β,14α-half-chair to a 14α-envelope. The conformation of the D ring in (I) falls near the middle of this distribution.

The O(3β) atom is hydrogen bonded to the O(17) carbonyl O atom with an O(3β)—O(17) distance of 3·004 Å. There is only one intermolecular contact [H(13β)—H(8β) = 2·34 Å] shorter than the sum of the van der Waals radii.

In the reaction to form (I), the reactant 16α-bromo-3β-hydroxy-5-androsten-17-one, (II), exists in equilibrium with the 16β-bromo isomer, (III), in a ratio of approximately 1 : 1·2. Numazawa & Osawa's (1980) work indicates that the product is formed by S_N2 replacement of the Br atom by a nucleophile (OH⁻,C₄H₈NO). The fact that when the nucleophile is

hydroxide the product is 16α-substituted and when the nucleophile is morpholino the product is 16β-substituted suggests that steric factors must be considered when predicting which product, 16α or 16β, is formed.

The solid-state structure of (II) is known (Duax, Brennan, Weeks & Osawa, 1975) and has a D-ring conformation very similar to (I), $\Delta = -26\cdot6°$, $\varphi_m = 43\cdot2°$, indicating an unstrained conformation. The crystal structure determination of (III) is currently in progress to establish whether the conformation of the D ring in (III) is such as to sterically prohibit S_N2 replacement of the Br atom by the bulky morpholino group.

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