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Conformational Flexibility in Androgenic Steroids: The Structure of a New Form of (+)-17β-Hydroxy-19-nor-4-androsten-3-one (19-Nortestosterone), $C_{18}H_{26}O_2$

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Abstract. The structure and conformation of a second crystalline modification of 19-nortestosterone has been determined by X-ray methods. $M_r = 274$, monoclinic $P2_1$, $a = 9{\cdot}755$ (2), $b = 11{\cdot}467$ (3), $c = 14{\cdot}196$ (3) Å, $\beta = 101{\cdot}07$ (2)°, $V = 1558{\cdot}4$ (8) Å^3, $Z = 4$, $D_x = 1{\cdot}168$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}7107$ Å, $\mu = 0{\cdot}80$ cm^{-1}, $F(000) = 600$, $T = 300$ K. $R = 0{\cdot}060$ for 2158 observed reflections. The two molecules in the asymmetric unit show significant differences in the *A*-ring conformation from that of the previously reported form of the title compound [Precigoux, Busetta, Courseille & Hospital (1975). *Acta Cryst.* B**31**, 1527–1532]. The 1α,2β-half-chair conformation of the *A* ring increases its conformational freedom compared with testosterone.

Introduction. Testosterone (I), a testicular sex hormone, is a strong androgenic and anabolic agent, whereas 19-nortestosterone (II), identical to testosterone except for the absence of the angular methyl group on C(10), retains anabolic activity of the same order as (I) but androgenic activity is reduced considerably (Herschberger, Shipley & Meyer, 1953; Barnes, Stafford, Guild, Thole & Olson, 1954). It is of interest to determine the conformational features of 19-nortestosterone accurately and compare them with those of testosterone. Several crystallographic investigations of testosterone are known (Duax & Norton, 1975) but so far only one crystal structure of 19-nortestosterone has been studied (Precigoux *et al.*, 1975), where atoms of ring *A* are disordered. Since it is known from the literature that steroids often exhibit polymorphism depending on the solvent of crystallization (Busetta, Courseille, Leroy & Hospital, 1972; Roberts, Petterson, Sheldrick, Isaacs & Kennard, 1973; Busetta, Courseille, Fornies-Marquina & Hospital, 1972; Courseille, Precigoux, Leroy & Busetta, 1973), it was considered worthwhile to attempt crystallization of the title compound in different solvents, hopefully to obtain a new crystal form. Crystals obtained from ethanol solution were found to belong to a new crystalline modification. The X-ray crystallographic results of this form are presented here and the conformational flexibility of the title compound in two independent crystal environments is discussed.

Experimental. Colourless needles crystallized from saturated solution in ethanol kept at 273 K in the refrigerator. Unit-cell parameters in this paper differ from those reported by Precigoux *et al.* (1975). Cell parameters determined accurately on Nonius CAD-4 diffractometer by least-squares analysis of 25 reflections with $2\theta \geq 30°$. Intensity data collected on Nonius CAD-4 diffractometer, graphite-monochromated Mo $K\alpha$ radiation, $\omega/2\theta$ scan mode, scan speed 1° min^{-1}. Crystal dimensions $0{\cdot}2 \times 0{\cdot}3 \times 0{\cdot}5$ mm approx. Intensity variation monitored by frequently remeasuring 111 and 112, which varied only within 5%. 3136 reflections (including controls) measured (max. $2\theta = 45°$; h −11→11, k 0→13, l 0→16), 2158 considered observed [$|F_o| \geq 3\sigma(F_o)$]. No absorption correction. Structure solved by direct methods using *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). Full-matrix least-squares refinement for anisotropic O and C and isotropic H atoms using $w = [\sigma(|F_o|)^2 + 0{\cdot}002|F_o|^2]^{-1}$, final $R = 0{\cdot}060$ ($R_w = 0{\cdot}065$), $S = 1{\cdot}79$. $\sum w(|F_o| - |kF_c|)^2$ minimized using *SHELX*76 (Sheldrick, 1976). Δ/σ for nonhydrogen atoms ~0·01. Final difference Fourier map featureless. Atomic scattering factors of *SHELX* used.*

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates, bond angles, H-bonding parameters and intermolecular contacts <3·5 Å have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39577 (22 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Final positional parameters for nonhydrogen atoms* ($\times 10^4$) *with equivalent isotropic temperature factors* ($Å^2 \times 10^2$)

E.s.d.'s are given in parentheses. $U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	*y*	*z*	*U*
C(1)	2365 (5)	5688	−114 (4)	5·26 (19)
C(2)	880 (6)	5231 (6)	−288 (4)	5·71 (20)
C(3)	792 (6)	4183 (5)	340 (4)	2·62 (20)
O(3)	59 (5)	3337 (4)	44 (4)	6·97 (15)
C(4)	1556 (6)	4269 (5)	1314 (4)	2·18 (19)
C(5)	2465 (5)	5096 (5)	1601 (3)	3·92 (16)
C(6)	3126 (6)	5259 (6)	2653 (4)	5·33 (20)
C(7)	4735 (5)	5193 (5)	2813 (4)	4·90 (18)
C(8)	5290 (4)	6069 (4)	2172 (3)	3·48 (15)
C(9)	4606 (5)	5912 (5)	1109 (3)	3·74 (15)
C(10)	2994 (5)	5944 (5)	926 (3)	3·93 (16)
C(11)	5227 (5)	6778 (6)	476 (3)	4·91 (18)
C(12)	6813 (5)	6741 (6)	623 (4)	5·03 (19)
C(13)	7498 (5)	6888 (4)	1677 (4)	3·85 (16)
C(14)	6859 (5)	5966 (5)	2260 (3)	3·89 (15)
C(15)	7834 (5)	5997 (6)	3245 (4)	5·47 (20)
C(16)	9283 (5)	6294 (6)	3034 (4)	5·74 (20)
C(17)	9061 (5)	6568 (5)	1971 (4)	4·40 (17)
O(17)	10027 (3)	7440 (4)	1816 (3)	5·16 (13)
C(18)	7275 (6)	8136 (5)	1998 (4)	5·05 (20)
C(201)	7370 (6)	2548 (0)	2530 (4)	5·30 (19)
C(202)	8878 (6)	2797 (6)	2492 (5)	6·02 (23)
C(203)	9796 (6)	2762 (5)	3471 (5)	5·72 (22)
O(203)	10831 (5)	3371 (5)	3668 (4)	8·07 (19)
C(204)	9371 (6)	1934 (5)	4123 (4)	5·28 (19)
C(205)	8286 (6)	1229 (5)	3920 (4)	4·60 (18)
C(206)	8094 (6)	206 (6)	4525 (4)	5·91 (22)
C(207)	6616 (6)	80 (6)	4709 (4)	5·72 (21)
C(208)	5527 (5)	119 (5)	3766 (3)	4·01 (16)
C(209)	5667 (5)	1271 (5)	3235 (4)	3·97 (16)
C(210)	7171 (5)	1392 (4)	3029 (3)	3·99 (16)
C(211)	4558 (6)	1398 (5)	2340 (4)	5·31 (19)
C(212)	3077 (6)	1227 (5)	2522 (4)	5·18 (19)
C(213)	2939 (5)	53 (5)	2996 (4)	4·39 (17)
C(214)	4042 (6)	−7 (5)	3926 (4)	4·54 (18)
C(215)	3637 (7)	−1097 (7)	4432 (4)	6·58 (24)
C(216)	2040 (6)	−1109 (7)	4154 (5)	6·96 (25)
C(217)	1641 (5)	−149 (5)	3425 (4)	5·18 (20)
O(217)	355 (4)	−325 (4)	2763 (3)	6·19 (15)
C(218)	3068 (7)	−932 (5)	2287 (4)	5·63 (21)

Discussion. The final positional and thermal parameters of the nonhydrogen atoms are given in Table 1. A perspective view of the two molecules in the asymmetric unit with the numbering of atoms is shown in Fig. 1. Torsion angles within the rings for both forms of 19-nortestosterone and testosterone (Roberts *et al.*, 1973) are compared in Table 2. Values of ΔC_s and ΔC_2, the asymmetry parameters which measure the degree of departure from ideal mirror symmetry (C_s) and twofold symmetry (C_2) at various possible symmetry locations (Duax & Norton, 1975), are given in Table 3. The value of the asymmetry parameter is zero if the symmetry under consideration is present. In the present study, although ring *A* is predominantly a 1α,2β-half-chair for both independent molecules [Table 3, $\Delta C_2(1\text{–}2) = 9{\cdot}4$ and 9·5° for molecules *a* and *b*, respectively], significant differences are observed in the internal torsion angles (Table 2), particularly angle C(2)–C(3)–C(4)–C(5). In the earlier crystal form, one molecule of the asymmetric unit was found to exhibit disorder, atoms C(1) and C(2) taking two statistical positions. Ring *A* in this molecule takes the 1α,2β-half-chair and 1β,2α-half-chair conformations as seen from the reversal of signs in the torsion angles (Table 2) and asymmetry parameters $\Delta C_2(1\text{–}2)$. The other molecule in the asymmetric unit is midway between 1α,2β-half-chair [ΔC_2 (1–2) = 11·8°] and 1α-sofa [ΔC_s (1) = 13·8°]. In testosterone, ring *A* is essentially 1α-sofa for both the independent molecules (Table 3). The *A*-ring conformation observed in 19-nortestosterone clearly indicates the conformational freedom of this ring compared with testosterone. Rings *B* and *C* are in the chair form for both forms of 19-nortestosterone and testosterone, with some deviations from the ideal chair (Tables 2 and 3).

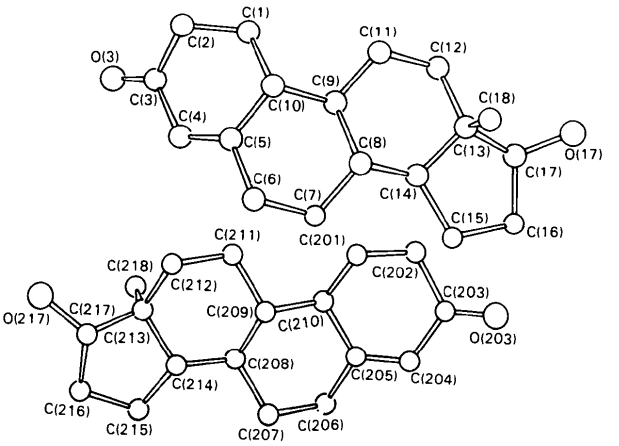

Fig. 1. Perspective view of the asymmetric unit.

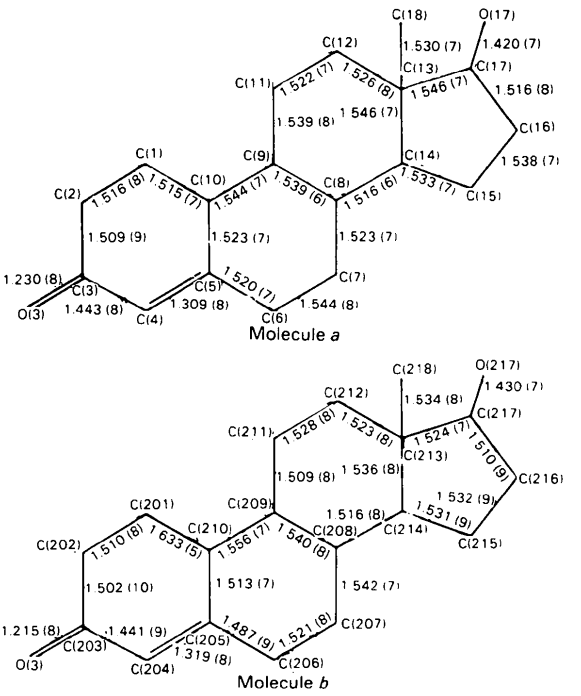

Fig. 2. Bond lengths involving non-hydrogen atoms (Å).

Table 2. *Internal torsion angles* (°) *in* 19-*nortestosterone and related steroids*

E.s.d.'s in the present study are 0·4–0·6°.

	19-Nortestosterone Present study Molecule		19-Nortestosterone Precigoux *et al.* (1975) Molecule			14-Dehydro-19-nortestosterone	Testosterone Molecule	
	a	*b*	(I)	(I)′	(II)		1	2
Ring *A*								
C(5)–C(10)–C(1)–C(2)	33·7	42·3	47·3	−43·2	45·9	37·1	47·8	47·3
C(10)–C(1)–C(2)–C(3)	−53·5	−54·9	−61·8	60·5	−56·7	−54·1	−55·7	−54·1
C(1)–C(2)–C(3)–C(4)	42·0	33·1	44·2	−50·4	34·1	40·3	33·4	29·2
C(2)–C(3)–C(4)–C(5)	−11·8	0·8	−10·9	23·7	−2·1	−9·7	−5·2	0·0
C(3)–C(4)–C(5)–C(10)	−9·9	−13·4	−5·0	−5·0	−9·0	−7·8	−1·8	−5·1
C(4)–C(5)–C(10)–C(1)	−1·5	−9·0	−14·7	−14·7	−13·9	−6·0	−19·6	−18·5
Ring *B*								
C(9)–C(10)–C(5)–C(6)	52·3	46·7	52·1		45·4	52·2	44·9	45·0
C(10)–C(5)–C(6)–C(7)	−55·3	−46·3	−56·1		−49·2	−55·0	−48·1	−50·1
C(5)–C(6)–C(7)–C(8)	55·0	51·5	56·2		55·7	55·1	53·6	54·4
C(6)–C(7)–C(8)–C(9)	−54·5	−57·9	−54·9		−60·8	−56·0	−58·7	−56·5
C(7)–C(8)–C(9)–C(10)	54·1	58·0	51·9		59·0	54·3	57·6	54·5
C(8)–C(9)–C(10)–C(5)	−51·3	−52·3	−49·2		−49·7	−50·9	−49·4	−46·8
Ring *C*								
C(14)–C(8)–C(9)–C(11)	−54·5	−51·7	−57·8		−54·5	−56·3	−50·1	−53·2
C(8)–C(9)–C(11)–C(12)	53·2	52·6	56·2		53·8	62·7	49·9	52·2
C(9)–C(11)–C(12)–C(13)	−53·4	−55·5	−53·8		−54·5	−58·7	−53·4	−54·4
C(11)–C(12)–C(13)–C(14)	53·6	56·6	53·8		54·9	47·7	57·1	56·4
C(12)–C(13)–C(14)–C(8)	−59·6	−59·4	−60·2		−60·6	−46·1	−61·5	−61·4
C(13)–C(14)–C(8)–C(9)	60·4	56·4	62·0		60·0	50·6	57·6	59·7
Ring *D*								
C(17)–C(13)–C(14)–C(15)	44·2	46·9	49·3		46·5	15·9	46·0	45·8
C(13)–C(14)–C(15)–C(16)	−32·2	−33·9	−34·7		−33·4	0·0	−32·7	−35·2
C(14)–C(15)–C(16)–C(17)	6·9	7·0	6·2		6·6	−15·0	6·2	10·1
C(15)–C(16)–C(17)–C(13)	21·2	22·6	23·6		22·5	23·8	22·4	18·5
C(16)–C(17)–C(13)–C(14)	−40·3	−42·3	−44·1		−42·0	−24·2	−41·6	−38·9

Table 3. *Asymmetry parameters* (°) *for* 19-*nortestosterone*

	Molecule *a*	Molecule *b*		Molecule *a*	Molecule *b*
Ring *A*					
$\Delta C_s(1)$	28·9	17·3	$\Delta C_2(1-2)$	9·4	9·5
$\Delta C_s(2)$	11·6	30·7	$\Delta C_2(2-3)$	42·7	43·4
$\Delta C_s(3)$	44·6	48·0	$\Delta C_2(3-4)$	52·0	47·2
Ring *B*					
$\Delta C_s(5)$	2·8	0·5	$\Delta C_2(5-6)$	3·0	5·2
$\Delta C_s(6)$	2·1	7·9	$\Delta C_2(6-7)$	1·4	11·4
$\Delta C_s(7)$	0·9	8·4	$\Delta C_2(7-8)$	1·6	6·2
Ring *C*					
$\Delta C_s(8)$	5·0	4·8	$\Delta C_2(8-9)$	6·7	3·9
$\Delta C_s(9)$	5·4	1·8	$\Delta C_2(8-11)$	3·6	6·8
$\Delta C_s(11)$	0·7	3·7	$\Delta C_2(9-11)$	4·9	2·7

The conformation of ring *D* can be expressed by two parameters: a pseudorotation angle Δ and a maximum torsion angle φ_m (Altona, Geise & Romers, 1968). For a perfect envelope (C_s symmetry) Δ is 36°, whereas it is 0° for a half-chair. In the present case as well as in the earlier one, ring *D* is midway between 13β-envelope and 13β,14α-half-chair with Δ values of 18·7 and 18·9° for molecules *a* and *b* respectively. The φ_m values are 44·8 and 47·6° for the independent molecules. In testosterone ring *D* is also in between 13β-envelope and 13β,14α-half-chair ($\Delta = 20{\cdot}1°$, $\varphi_m = 47{\cdot}2°$) for one molecule and distorted 13β,14α-half-chair for the other ($\Delta = 9{\cdot}8°$, $\varphi_m = 46{\cdot}0°$). Thus, the two independent crystallographic observations for 19-nortestosterone reveal that ring *A* shows greater flexibility than rings *B*, *C* and *D*, which could be attributed to the absence of the angular methyl group on C(10). Ring junctions *A*/*B*, *B*/*C* and *C*/*D* are quasi-*trans*, *trans* and *trans* respectively as in testosterone and give rise to a topographically 'flat' molecule.

Bond distances involving non-H atoms are shown in Fig. 2. All the bond distances in molecule *a* are equal to the corresponding distances (within 3σ) in molecule *b*, with the exceptions of C(5)–C(6) and C(9)–C(11) distances. The C(9)–C(10) bond tends to be longer in several derivatives of testosterone. For example, it is 1·590 (7) and 1·580 (8) Å for the two molecules in 8-isotestosterone (Chakrabarti, Banerjee & Venkatesan, 1981). No such lengthening is observed in the present structure, the value of this bond being 1·544 (7) and 1·556 (7) Å for molecules *a* and *b* respectively. The observed lengthening may be attributed to steric strain present at the quaternary C(10) atom. Most of the bond angles in molecule *a* of 19-nortestosterone agree within experimental error with the corresponding angles in molecule *b* except for the angles involving C(5) and C(10).

The packing of the molecules viewed down **b** is shown in Fig. 3. O–H···O-type intermolecular hydrogen bonding stabilizes the structure in the present as well as in the earlier crystal structure of 19-nortestosterone. However, the hydrogen-bonding patterns are entirely different. In the present study, the hydroxyl group O(17) of molecule *a* acts as a donor [2·82 (1) Å] as well as an acceptor [2·88 (1) Å]; it donates its H atom to O(3) of molecule *a* and accepts

one from O(217) of molecule *b*. The carbonyl group O(203) of molecule *b* does not take part in any H bonding (Fig. 3). The packing arrangement and H bonding are very similar to that observed in 8-isotestosterone (Chakrabarti *et al.*, 1981). The earlier form of 19-nortestosterone exhibits 'head-to-tail' O–H···O-type intermolecular hydrogen bonding, which is common in many steroids, between carbonyl O(3) of molecule (I) and hydroxyl O(17) of molecule (II) and *vice versa*.

19-Nortestosterone and other 19-nor analogues exhibit relatively weak androgenic activity but the protein anabolic effects are of the same order as for testosterone (Herschberger *et al.*, 1953; Barnes *et al.*, 1954). Various hypotheses have been put forward to explain the specificities involved in steroid and androgenic-receptor binding on the basis of X-ray data, geometry minimization and synthetic analogues of androgens (Busetta, Courseille, Precigoux & Hospital, 1977; Liao, Liang, Fang, Castaneda & Shao, 1973; Schimit, Quiry & Rousseau, 1980; Toth & Hertelendy, 1979; Chan, Smythe & Liao, 1979). From these studies it was concluded that the overall shape of the molecule plays an important role in the receptor binding rather than the electronic structure of ring *A*. From a superposition of testosterone and all the five conformations of 19-nortestosterone viewed down C(12)···C(14), it is observed that the flatness of both molecules is very similar except for ring *A*, which shows significant variations. The distance O(3)···O(17), which is of significance in connection with the biological activity, is 10·93 Å for both molecules of testosterone whereas it varies from 10·58 to 10·94 Å in the observed conformations of 19-nortestosterone. The androgen-binding studies in rat seminal vesicles show that the binding indices of 19-nortestosterone and testosterone are in the ratio 0·44: 1 and 0·40:1 for cystosol receptor binding and nuclear retention respectively (Toth & Hertelendy, 1979). It seems likely that androgenic receptor protein, situated in specific target cells, imposes strict stereospecific requirements unlike anabolic receptors, which are situated in several tissues (Liao, 1976).

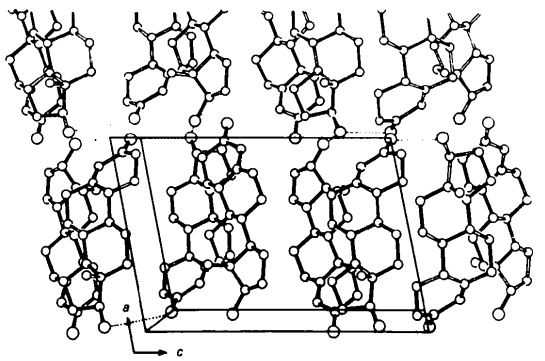

Fig. 3. Packing of molecules in 19-nortestosterone.

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