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STEROID CONFORMATIONS IN SOLID AND SOLUTION

THE STRUCTURE OF 2β-METHYL-19-NORTESTOSTERONE *p*-BROMOBENZENESULFONATE

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Abstract—Crystals of 2β-methyl-19-nortestosterone *p*-bromobenzenesulfonate ($C_{25}H_{31}O_4BrS$) are orthorhombic, space group $P2_12_12_1$ with unit cell dimensions $a = 9{\cdot}127(5)$Å, $b = 36{\cdot}15(3)$Å, $c = 7{\cdot}162$(Å). The structure was solved by the heavy atom technique and refined by block diagonal least squares to a final R of 0·06. The overall conformations of this and a previously studied 19-nor steroid are much flatter than the normally observed conformations of 4-en-3-one steroids. The A-ring of the steroid is found to be in the typical half-chair conformation in contrast to the twist conformation previously assigned for 2β-methyl-19-nortestosterone from the interpretation of ORD data. In light of the apparent stability of the observed structure and CD measurements subsequent to the X-ray determination, a reinterpretation of the ORD spectra giving greater attention to its fine structure is suggested in order to resolve the ambiguity between solid structure determination and previous solution structure assignment.

THE ORD, CD, and NMR spectra of some 2β-substituted testosterone derivatives have been interpreted as indicating twist, half-boat, or "nonsteroidal" half-chair conformations of the A-ring.[1–4] Because X-ray studies of over twenty 4-en-3-one steroids showed the A-ring to be in normal half-chair conformations, investigations of the structures of 2β-substituted derivatives were begun in order to verify the existence and determine the nature of twist and half-boat conformations. The first 2β-substituted steroid in the series, 2,2,6β-trichloro-17β-acetoxy-4-androsten-3-one[5] which was reported to have a half-boat conformation of the A-ring in solution,[4] was found to have the normal half-chair conformation in the solid and it was possible to reinterpret the ORD and CD spectra on the basis of the observed structure.[6] In the crystal structures of 2β,17β-diacetoxy-4-androsten-3-one *p*-bromophenol (1:1),[7] 2β-acetoxy-17β-chloroacetoxy-4-androsten-3-one methanol (1:1),[7,8] and 2β,17β-diacetoxy-4-androsten-3-one,[9] the A-ring was determined to be in a previously unobserved inverted half-chair conformation rather than the twist or half-boat form suggested on the basis of the ORD and CD spectra. This paper describes structure analysis of 2β-methyl-19-nortestosterone,§ the ORD spectrum of which has been interpreted to indicate a twist conformation of the A-ring.[3]

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§ Abbreviations used are: 2β-methyl-19-nortestosterone, 17β-hydroxy-2β-methyl-4-estrene-3-one; 2β-methyl-19-nortestosterone *p*-bromobenzenesulfonate, 2β-methyl-17β-*p*-bromobenzenesulfonyloxy-4-estren-3-one; 2β-acetoxy-19-nortestosterone acetate, 2β,17β-diacetoxy-4-estren-3-one.

RESULTS AND DISCUSSION

The A-ring of 2β-methyl-19-nortestosterone *p*-bromobenzenesulfonate (Fig 1) was determined to be in the normal half-chair conformation for steroids containing the 4-en-3-one system in conflict with the interpretation of the ORD spectra.

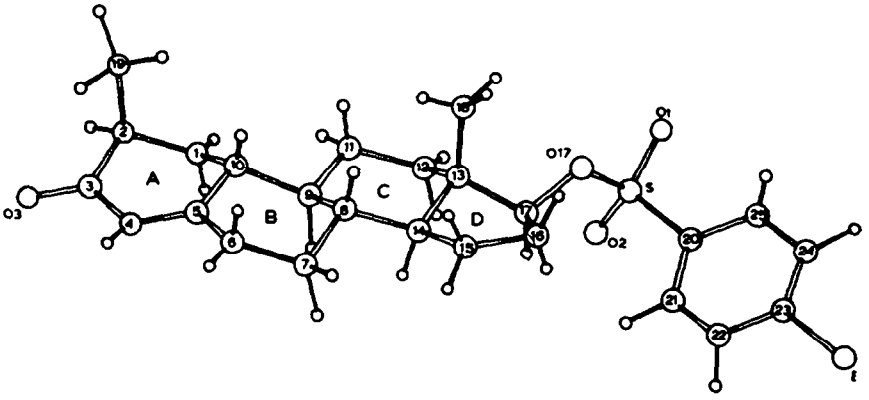

FIG 1. A view of the molecular conformation of 2β-methyl-19-nortestosterone *p*-bromobenzenesulfonate prepared from the observed atomic coordinates with steroid atomic numbering and ring designations indicated.

In Fig 2, a projection of the entire molecule parallel to the least-squares plane through atoms C(5) to C(17) is shown in which the 3-oxygen atom is 0·6 Å below the plane (Fig 2a). The A-rings of similarly oriented projections of testosterone[10] (Fig 2c) and 7α-methyl-19-nortestosterone[11] (Fig 2b) are also illustrated for purposes of comparison. In the two 19-nor structures the average of the C(1)—C(10)—C(5), C(1)—C(10)—C(9), and C(5)—C(10)—C(9) angles is 110·9°, 1·3° larger than the normal tetrahedral value and there is considerable flattening of the steroid nucleus at the

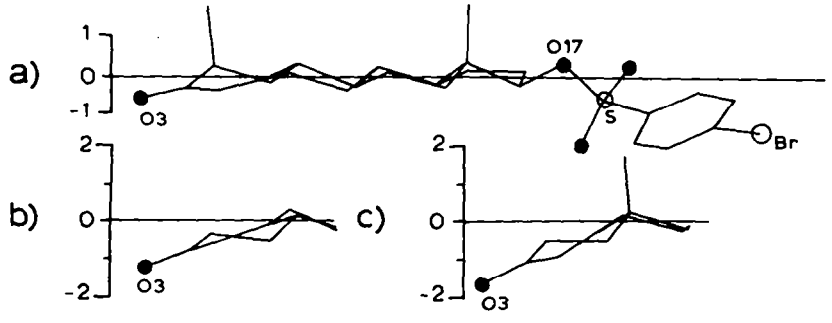

FIG 2. Projections perpendicular to the least-squares planes through steroid atoms C(5) to C(17) illustrating the relative orientation of the A-rings in 2β-methyl-19-nortestosterone *p*-bromobenzenesulfonate (a), 7α-methyl-19-nortestosterone, (b), and testosterone (c).

A/B-ring junction. With 19-methyl substitution steric crowding prohibits such severe flattening and the 108·3° average of these angles is 1·3° less than the normal tetrahedral value. An unusual feature of the 2β-methyl structure is the position of C(2) above the least-square plane through atoms C(5) to C(17) of the steroid nucleus (Fig 2a). This occurs because the 2β-methyl substitution promotes a fully staggered conformation across the C(1)—C(2) bond. The C(10)—C(1)—C(2)—C(3) torsional angle is 60° in 2β-methyl-19-nortestosterone as compared to 52° in 7α-methyl-19-nortestosterone[11] and this 8° rotation about the C(1)—C(2) bond moves the C(2) atom above the least-squares plane. Most conformational differences among 2β-substituted 19-nor steroids and 2β-unsubstituted 19-methyl steroids having Δ4-3-one configurations are seen to be subtle variations of normal half-chair conformations. However, the relationship between these structures and 2β-substituted 19-methyl steroids is more complicated as suggested by the observed structure of 2β,17β-diacetoxy-4-androsten-3-one in which the A-ring is in an inverted half-chair conformation. Unfavourable 2β-substituent-19-methyl interactions that might occur if the A-ring were in the normal half-chair conformation are avoided in the observed conformation. The only other 2β-substituted-19-methyl structure for which the X-ray crystal structure has been

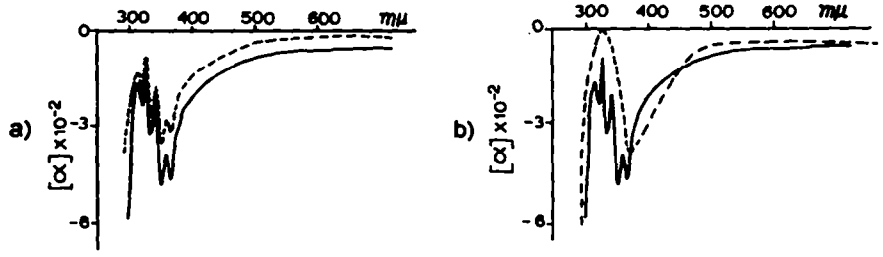

FIG 3. The ORD spectra of 2β-methyl-19-nortestosterone (———) is compared to that of 2β-methyl-19-nortestosterone *p*-bromobenzenesulfonate (– – – –, a) and 2β-acetoxy-19-nortestosterone diacetate (– – – –, b).

completed is 2,2,6β-trichloro-17β-acetoxy-4-androsten-3-one in which the A-ring is in the normal half-chair conformation despite close 2β-chloro-19-methyl contacts.

The torsional angles for the steroid nucleus (Table 1) are the most sensitive index of ring conformation. The B- and C-rings have the normal chair conformation. The D-ring is a β-envelope as reflected by the parameters $\Delta = 37{\cdot}9$ and $\phi_m = 50{\cdot}2$.[12]

The ORD spectra of 2β-methyl-19-nortestosterone and its *p*-bromobenzenesulfonate are nearly identical (Fig 3a). The similarity of ORD spectra of 2β-acetoxy-19-nortestosterone acetate and 2β-methyl-19-nortestosterone shown in Fig 3b was interpreted[3] to indicate a twist conformation of the A-ring thought to exist in 2β-acetoxytestosterone and its derivatives.[1,2,7,8] The ORD of 2β-methyl-19-nortestosterone in dioxane, however, has a characteristic fine structure in the region of 330 to 370 nm very similar to that of testosterone and 19-nortestosterone. 2β-Acetoxytestosterone and its derivatives are shown by X-ray crystallography to have the inverted

TABLE 1. TORSIONAL ANGLES IN THE RINGS[a,b]

Ring A		Ring B		Ring C		Ring D	
Bond	ϕ(A–B)	Bond	ϕ(A–B)	Bond	ϕ(A–B)	Bond	ϕ(A–B)
C(1)—C(2)	−60·0	C(5)—C(6)	−41·7	C(8)—C(9)	−51·1	C(13)—C(14)	47·5
C(2)—C(3)	34·7	C(6)—C(7)	49·1	C(9)—C(11)	50·0	C(14)—C(15)	−29·9
C(3)—C(4)	−4·5	C(7)—C(8)	−62·0	C(11)—C(12)	−54·5	C(15)—C(16)	−0·3
C(4)—C(5)	−3·7	C(8)—C(9)	66·9	C(12)—C(13)	59·3	C(16)—C(17)	31·3
C(5)—C(10)	−19·0	C(9)—C(10)	−56·4	C(13)—C(14)	−64·1	C(13)—C(17)	−48·5
C(1)—C(10)	50·8	C(5)—C(10)	44·4	C(8)—C(14)	59·6		

[a] The sign convention for torsional angles is that of W. Klyne and V. Prelog, *Experientia* **16**, 521 (1960)
[b] ϕ(A–B) is the torsional angle about the A–B bond, in which the other two atoms required to define the angle are those attached to either end of the bond and are in the ring in question.

half-chair conformation of the A-ring[7,9] and their spectroscopic data are consistent with the 5β-like conformation of the A-ring.[6,8] The loss of fine structure in ORD of this α,β-unsaturated ketone may be correlated with an observed breakdown of the conjugation of the 4-en-3-one system which accompanies the formation of the inverted half-chair.[7] After X-ray structure determination, the CD spectrum of 2β-methyl-19-nortestosterone *p*-bromobenzenesulfonate was measured and found to be similar to that of testosterone in agreement with the concept that the steroid ring conformation is the same in solid and solution.[6]

While it is possible that the structure in solution may be different from and is certainly more flexible than the structure in the solid, the observed crystalline conformation does not involve any unusually close intermolecular contacts that would suggest molecular instability leading to drastic conformational change in solution. The closest intramolecular contact between the hydrogen atoms of the 2β-methyl substituent and H(10) is 2·21 Å. Although this is a closer contact than that observed between the nearest 19-methyl hydrogen and the 2β-hydrogen atom in a 4-en-3-one A-ring (2·4Å)[13] the distance is greater than hydrogen-hydrogen van der Waals contact.

EXPERIMENTAL*

2β-Methyl-19-nortestosterone p-bromobenzenesulfonate. *p*-Bromobenzenesulfonyl chloride (37 mg) was added to a solution of 2β-methyl-19-nortestosterone (20 mg) in pyridine (0·2 ml) in an ice–water bath with stirring. After 18 h in the dark at room temp the whole was poured into water. The precipitates were collected by filtration and dried with a stream of N_2. Recrystallization of the amorphous powder (31 mg, m.p. 146–148°) from acetone–hexane gave the sulfonate (26 mg, m.p. 148–151°). Two further recrystallizations from C_6H_6–MeOH yielded an analytical sample as colourless platelets, m.p. 153–155°, $\lambda_{max}^{95\%\,EtOH}$ 235 nm (ε 34,300); ν_{max}^{KBr} 1665, 1610, 1575, 1194, 1188, 745, 620 cm^{-1}. $\delta_{ppm}^{CDCl_3}$ (TMS 0 ppm, 60 MHz): 0·87 18-CH_3), 1·10 (d, 2β-CH_3, *J* 7 Hz), 4·38 (m, 17α-H, *W* ½ 16 Hz), 5·77 (s, 4-H), 7·81 (s, aromatic H): ORD (*c* 0·10, dioxane at 25°): $[\alpha]_{700}$ −20°, $[\alpha]_{400}$ −140°, $[\alpha]_{368}$ −320°, $[\alpha]_{360}$ −280°, $[\alpha]_{353}$ −360°, $[\alpha]_{344}$ −180°, $[\alpha]_{337}$ −280°, $[\alpha]_{327}$ −80°, $[\alpha]_{322}$ −200°, $[\alpha]_{317}$ −140°, $[\alpha]_{300}$ −300°, $[\alpha]_{280}$ −700°. CD (*c* 0·10, dioxane at 25°): $[\theta]_{422}$ 0°, $[\theta]_{368}$ −670°, $[\theta]_{360}$ −535°, $[\theta]_{348}$ −1340°, $[\theta]_{342}$ −740°, $[\theta]_{330}$ −1400°, $[\theta]_{326}$ −600°, $[\theta]_{321}$ −875°, $[\theta]_{300}$ 0°. (Calc. for $C_{25}H_{31}O_4BrS$: C, 59·17; H, 6·16. Found: C, 59·40; H, 6·38%). Lattice parameters (a = 9·127(5)Å, b = 36·15(3)Å, c = 7·162(1)Å, $P2_12_12_1$, Z = 4) were determined from a least-squares fit of 36 measurements of three dimensional vectors with $2\theta > 50°$.