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A Novel Bridged-*A*-Ring Steroid

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Abstract. 2,10-Ethano-10-norandrost-4-ene-3,17-dione, $C_{20}H_{26}O_2$, $M_r = 298\cdot43$, orthorhombic, $P2_12_12_1$, $a = 7\cdot566$ (3), $b = 11\cdot478$ (7), $c = 18\cdot681$ (7) Å, $V = 1622\cdot5$ (13) Å^3, $Z = 4$, D_m (flotation in aqueous $ZnCl_2$) $= 1\cdot21$ (2), $D_x = 1\cdot222$ Mg m^{-3}, $\lambda(Mo\ K\overline{\alpha}) = 0\cdot71073$ Å, $\mu = 0\cdot0716$ mm^{-1}, $F(000) = 648$, $T = 293$ K, $R = 0\cdot038$, $wR = 0\cdot052$ for 1629 observations. The title molecule was prepared as part of synthetic efforts in the design of inhibitors for steroid 5α-reductase. Based upon a desire to lift the *A* ring in the β direction, relative to the parent androst-4-ene-3,17-dione, this novel steroid contains an ethano bridge between atoms C(2) and C(10). The *A* ring displays a highly distorted 1α-sofa conformation with C(1) disposed 0·844 (2) Å below the plane defined by atoms C(2), C(3), C(4), C(5) and C(10). Mirror symmetry is dominant in the *A* ring with $\Delta C_s^1 = 9\cdot0$. The remainder of the steroid nucleus displays a normal conformation including a flattened 14α-envelope for the *D* ring. Relative to androst-4-ene-3,17-dione the position of atom O(3) is lifted 0·151 Å toward the β face. The observed structure is consistent with molecular modeling predictions.

Introduction. The enzyme steroid 5α-reductase converts the substrate testosterone into dihydrotestosterone (Brooks, Berman, Hichens, Primka, Reynolds & Rasmussen, 1982). Inhibition of this enzyme is of considerable interest (Rasmussen, Reynolds, Utne, Jobson, Primka, Berman & Brooks, 1984) since elevated levels of dihydrotestosterone have been linked to such undesirable androgenic activities in man as acne, male-pattern baldness and benign prostatic hypertrophy (Peterson, Imperato-McGinley, Gautier & Sturla, 1977; Price, 1975). In connection with an interest in inhibition of steroid 5α-reductase, the report of Rasmussen *et al.* (1984) regarding the inhibitory activity of a 19-nor analog in a series of 4-aza steroids was intriguing. In the testosterone series, the solid-state structure of the 19-nor analog shows the steroidal *A* ring arched towards the β face relative to the parent testosterone molecule (Duax & Norton, 1975). Our *MM*2 (Burkert & Allinger, 1982) calculations supported the anticipation that incorporation of a bridge between atoms C(2) and C(10) also would promote β arching of the *A* ring, relative to the parent, while simultaneously reducing the known flexibility of 19-nor steroids (Duax, Weeks & Rohrer, 1976). Since androst-4-ene-3,17-dione also is a substrate for steroid 5α-reductase, compound (1) was prepared to test these structural hypotheses and their biological effects. We report here the solid-state structure of (1), as determined by X-ray diffraction, and compare this structure to relevant analogs, such as (2) (Bussetta, Comberton, Courseille & Hospital, 1972).

(1)   (2)
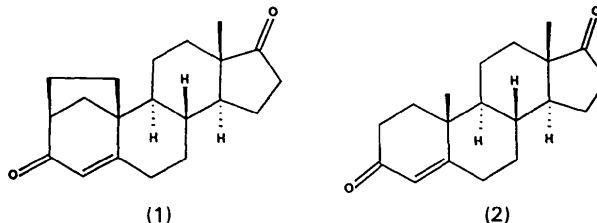
Experimental. The synthetic pathway leading to (1) has been reported previously (Lan-Hargest, Elliott, Eggleston, Holt, Levy & Metcalf, 1987). Colorless prism, approximately $0\cdot30 \times 0\cdot30 \times 0\cdot35$ mm on edge,

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mounted with epoxy on a glass fiber. Cell constants from a least-squares analysis of 25 reflections [$30 \leq 2\theta(\text{Mo}) \leq 35°$] measured on the diffractometer. Data collection on an Enraf–Nonius CAD-4 diffractometer equipped with graphite monochromator; variable-speed ω–2θ scans. Systematic absences: $h00$, $0k0$, $00l$ for h, k, l odd, respectively. 2239 measured intensities, $2\theta \leq 56°$, $0 \leq h \leq 9$, $0 \leq k \leq 15$, $0 \leq l \leq 24$; Lorentz–polarization correction, no systematic fluctuations in reflections $4\bar{5}9$; $3,\bar{3},13$; $36\bar{7}$, monitored at the beginning, end and each 3 h during data collection (12 times); max. deviations in $|F_o|$ from mean 0·6, 2·8 and 1·2%, respectively; mean values of $|F_o|$ 257·9 (9), 166·0 (13) and 140·5 (7), respectively; no absorption correction. Structure solution by direct methods using *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) after temporary removal of reflection 038, the highest E value, which was complicating origin definition. The highest combined-figure-of-merit set from *RANTAN* (Yao Jia-xing, 1981) phase assignment gave an image of the complete molecule. Anisotropic least-squares refinement (on F) of non-H-atom positions led to conventional $R = 0·09$; weights $4F_o^2/\sigma^2(I)$ with $\sigma(I) = [\sigma(I)^2 + (pF_o)^2]^{1/2}$ with $p = 0·06$. Difference Fourier synthesis revealed positions for all the H atoms; these atoms were refined also, with isotropic thermal parameters. An extinction coefficient (Zachariasen, 1963) included in the later stages refined to $9·11$ (8) $\times 10^{-7}$; final $wR = 0·0519$, $R = 0·0379$, $S = 1·34$; 1629 observations with $I \geq 3·0\sigma(I)$, 304 variables; convergence indicated by max. $(\Delta/\sigma) = 0·06$; final difference map showed maximum positive excursion of $0·176$ e Å^{-3}. Refinement using 2025 observations with $I \geq 0·01 \sigma(I)$, gave $R = 0·049$, $wR = 0·056$. All programs from the locally modified Enraf–Nonius (1987) CAD-4 *SDP*; neutral-atom scattering factors from *International Tables for X-ray Crystallography* (1974), for H from Stewart, Davidson & Simpson (1965).

Discussion. Fig. 1 displays an *ORTEP* (Johnson, 1976) drawing of the solid-state molecular structure of (1). Positional parameters are listed in Table 1 along with their standard deviations as estimated from the inverse least-squares matrix.* The crystallographic results confirm the double bond between atoms C(4) and C(5) [C(4)—C(5) = 1·337 (3) Å] and the ethano bridge between the 2 and 10 positions [C(19)—C(20) = 1·537 (4) Å] (Table 2).

Geometric requirements of the bicyclo[3.2.1.]octene system created by the ethano bridge in this molecule are

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* Lists of structure factors, H-atom positions, principal bond distances and angles and anisotropic librational parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44864 (21 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.
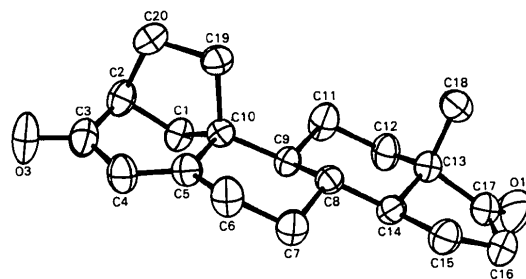

Fig. 1. View of (1) with H atoms omitted. Atoms are depicted as primary ellipses at the 50% probability level.

Table 1. *Positional and thermal parameters*

$$B_{eq} = \tfrac{4}{3}[B_{11} + B_{22} + B_{33}].$$

	x	y	z	$B_{eq}(\text{Å}^2)$
O(3)	0·6850 (3)	1·1001 (2)	0·7525 (1)	5·95 (5)
O(17)	0·7938 (4)	0·3212 (2)	1·0550 (1)	7·46 (6)
C(1)	0·5843 (3)	0·8309 (2)	0·8365 (1)	3·09 (4)
C(2)	0·5784 (3)	0·9052 (2)	0·7691 (1)	3·72 (5)
C(3)	0·7118 (4)	1·0019 (2)	0·7756 (1)	4·04 (5)
C(4)	0·8793 (4)	0·9680 (2)	0·8081 (1)	4·05 (5)
C(5)	0·9094 (3)	0·8589 (2)	0·8301 (1)	3·11 (4)
C(6)	1·0936 (3)	0·8192 (2)	0·8479 (1)	3·96 (5)
C(7)	1·1016 (3)	0·7337 (2)	0·9098 (1)	3·70 (5)
C(8)	0·9783 (3)	0·6308 (2)	0·8966 (1)	2·68 (4)
C(9)	0·7868 (3)	0·6749 (2)	0·8880 (1)	2·63 (4)
C(10)	0·7626 (3)	0·7684 (2)	0·8287 (1)	2·58 (4)
C(11)	0·6540 (3)	0·5748 (2)	0·8818 (1)	4·00 (5)
C(12)	0·6663 (3)	0·4873 (2)	0·9444 (1)	3·76 (5)
C(13)	0·8533 (3)	0·4424 (2)	0·9506 (1)	3·28 (4)
C(14)	0·9812 (3)	0·5459 (2)	0·9591 (1)	3·09 (4)
C(15)	1·1551 (3)	0·4897 (2)	0·9834 (1)	4·32 (5)
C(16)	1·0919 (5)	0·3937 (2)	1·0349 (2)	5·23 (6)
C(17)	0·8964 (5)	0·3758 (2)	1·0188 (1)	4·52 (6)
C(18)	0·9013 (4)	0·3607 (2)	0·8883 (1)	4·20 (5)
C(19)	0·7515 (4)	0·7254 (2)	0·7495 (1)	3·47 (4)
C(20)	0·6390 (4)	0·8174 (2)	0·7108 (1)	4·49 (6)

Table 2. *Selected principal bond distances (Å) and angles (°)*

C(1)–C(2)	1·522 (3)	C(2)–C(1)–C(10)	102·0 (2)
C(1)–C(10)	1·536 (3)	C(1)–C(2)–C(3)	109·0 (2)
C(2)–C(3)	1·505 (4)	C(1)–C(2)–C(20)	102·0 (2)
C(2)–C(20)	1·552 (4)	C(3)–C(2)–C(20)	109·7 (2)
C(3)–O(3)	1·224 (3)	O(3)–C(3)–C(2)	122·6 (3)
C(3)–C(4)	1·458 (4)	O(3)–C(3)–C(4)	122·5 (3)
C(4)–C(5)	1·337 (3)	C(2)–C(3)–C(4)	114·8 (2)
C(5)–C(6)	1·504 (3)	C(3)–C(4)–C(5)	121·7 (3)
C(5)–C(10)	1·521 (3)	C(4)–C(5)–C(6)	120·6 (2)
C(6)–C(7)	1·517 (3)	C(4)–C(5)–C(10)	120·7 (2)
C(7)–C(8)	1·526 (3)	C(6)–C(5)–C(10)	118·3 (2)
C(8)–C(9)	1·543 (3)	C(5)–C(6)–C(7)	113·7 (2)
C(9)–C(10)	1·553 (3)	C(6)–C(7)–C(8)	110·7 (2)
C(9)–C(11)	1·531 (3)	C(7)–C(8)–C(9)	109·7 (2)
C(10)–C(19)	1·562 (3)	C(7)–C(8)–C(14)	111·3 (2)
C(11)–C(12)	1·544 (3)	C(9)–C(8)–C(14)	107·7 (2)
C(12)–C(13)	1·510 (4)	C(8)–C(9)–C(10)	114·3 (2)
C(13)–C(14)	1·540 (3)	C(8)–C(9)–C(11)	112·2 (2)
C(13)–C(17)	1·521 (3)	C(10)–C(9)–C(11)	112·8 (2)
C(13)–C(18)	1·538 (3)	C(1)–C(10)–C(5)	108·7 (2)
C(14)–C(15)	1·534 (3)	C(1)–C(10)–C(9)	111·0 (2)
C(15)–C(16)	1·539 (4)	C(1)–C(10)–C(19)	101·0 (2)
C(16)–C(17)	1·524 (5)	C(5)–C(10)–C(9)	111·9 (2)
C(17)–O(17)	1·205 (4)	C(5)–C(10)–C(19)	105·8 (2)
C(19)–C(20)	1·537 (4)	C(10)–C(19)–C(20)	104·9 (2)
		C(2)–C(20)–C(19)	106·3 (2)

reflected in the angular compression about C(1) [C(2)–C(1)–C(10) = 102·0 (2)°] as compared to the parent androstenedione [C(2)–C(1)–C(10) = 112·7°]. Similar distortions have been observed in related [3.2.1.] systems (Stevens, Treat, Pillai, Schmonsees & Glick, 1973; Schomburg & Landry, 1981; Gillon, Ovadia, Kapon & Bien, 1982). The endocyclic angles involving C(1) and the bridging C atoms, C(1)–C(2)–C(20) = 102·0 (3), C(1)–C(10)–C(19) = 101·0 (2)°, also are compressed relative to normal tetrahedral values.

The six-membered A ring adopts a highly distorted 1α-sofa conformation with C(1) disposed 0·844 (2) Å below the plane defined by atoms C(2), C(3), C(4), C(5) and C(10), from which no atom deviates by more than 0·045 (2) Å. Mirror symmetry is dominant with an approximate C_s plane passing through C(1) and C(4). The A-ring asymmetry parameters (Duax & Norton, 1975) are $\Delta C_s^1 = 9·0$ (7), $\Delta C_2^{1,2} = 25·7$ (8). The average of the endocyclic A-ring dihedral angles is 34·7 (9)°. For the sake of comparison, numbers for the parent molecule, androst-4-ene-3,17-dione, (2), are $\Delta C_s^1 = 9·0$, $\Delta C_2^{1,2} = 17·6$, average dihedral angle = 26·0°. The differences in these values primarily arise from the larger out-of-plane distortion at C(1) in (1) and from a shift in the position of C(10) in (1) relative to the parent, (2), see below. Interestingly, as compared to the parent (2), the presence of the ethano bridge and concomitant A-ring buckling cause no additional distortion from planarity about the site of unsaturation, the C(3)–C(4)=C(5)–C(10) torsion being −6·2 (8) versus −6·4° for (2).

The seven-membered ring defined by atoms C(2)–C(3)–C(4)=C(5)–C(10)–C(19)–C(20) displays a buckled shape characteristic of bicyclo[3.2.1]cyclo-octene systems. This L shape is denoted by the dihedral
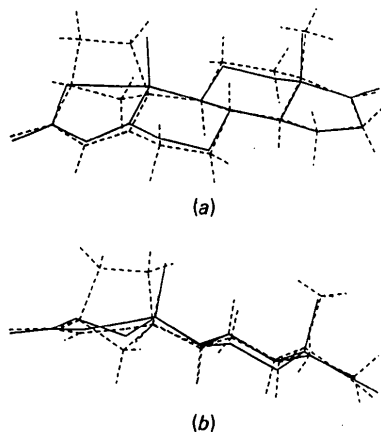

(a)

(b)

Fig. 2. Views of the least-squares overlap between (1) and (2) looking (a) onto and (b) into the side of the steroid rings. The structure of (1) is represented by dashed lines and includes the H atoms; the solid lines represent (2).

angle of 108·4 (7)° between the four- and five-atom planes defined by C(2)–C(20)–C(19)–C(10) and C(2)–C(3)–C(4)=C(5)–C(10), respectively. The five-membered ring defined by atoms C(1)–C(2)–C(20)–C(19)–C(10) displays an envelope conformation with C(1) displaced 0·707 (4) Å out of the plane defined by the remaining four atoms, from which no atom deviates by more than 0·022 (4) Å.

Both the B and C rings of (1) adopt chair conformations; mirror symmetry is dominant in both cases. The D-ring conformation is a flattened 14α-envelope; atom C(14) sits 0·644 (2) Å out of the plane defined by atoms C(13), C(17), C(16) and C(15), from which no atom deviates by more than 0·059 (2) Å. Interatomic distances between functional groups are O(3)···O(17) = 10·610 (4), O(3)···C(18) = 9·009 (4), C(18)···C(19) = 5·052 (4) Å.

Structural consequences of the ethano bridge may be evaluated by comparison to the observed structure of androst-4-ene-3,17-dione. Fig. 2 displays two views of an overlay of (1) and (2) as generated with the $SYBYL$ molecular modeling system (SYBYL, 1985) by requir-ing atoms C(9), C(15) and C(17) to overlap and least-squares fitting the rest of the atoms of the bridged structure to the static structure of the parent molecule. The r.m.s. fit for this overlay was 0·024 Å. As may be seen from these drawings, there is a close corre-spondence between the B, C and D rings of (1) and (2) in the solid state. In contrast, there are dramatic differences between features of the A rings. In particu-lar, the position of C(1) in (1) is displaced 0·405 Å toward the α face compared to its location in (2). Additionally, the ethano-bridge distance appears to constrain C(19) to a location directed more towards the center of the A ring as compared to the parent molecule. The computed difference is 0·588 Å. Concurrently, atom C(10) also is pulled toward the ring center, by 0·258 Å, compared to the analogous position in (2). As to the orientation of the oxygen substituent at C(3), there is a difference of 0·151 Å in these two locations with O(3) of (1) lying above (towards the β face) relative to the analogous atom in (2). The difference in O-atom orientation is apparent despite a near cor-respondence between the positions of C(3) in both molecules, i.e. only a 0·026 Å disparity in the relative locations of these two atoms. The crystallographic results thus confirmed our predictions based on $MM2$ calulations, which in turn substantiated the hypo-thesized β arching of the A ring from consideration of the structure of 19-nortestosterone relative to the structure of testosterone.

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Structure of *cis-cisoid-cis-* and *cis-transoid-cis*-Tricyclo[9.3.0.0⁴,⁸]tetradecane-2,9-dione and *cis-cisoid-cis-* and *trans-cisoid-trans*-Tricyclo[9.3.0.0³,⁷]tetradecane-2,9-dione

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Abstract. $C_{14}H_{20}O_2$, $M_r = 220.3$, Mo $K\alpha$, $\lambda = 0.71073$ Å, $F(000) = 480$ or 240, $T = 295$–299 (1) K. *cis-cisoid-cis*-Tricyclo[9.3.0.0⁴,⁸]tetradecane-2,9-dione (m.p. 477.2–477.7 K) (I): monoclinic, $C2/c$, $a = 11.994$ (2), $b = 5.451$ (1), $c = 18.306$ (2) Å, $\beta = 91.49$ (2)°, $V = 1196.4$ (3) Å³, $Z = 4$, $D_m = 1.21$ (2), $D_x = 1.22$ Mg m⁻³, $\mu = 0.07$ mm⁻¹, $R = 0.040$ for 745 observed unique reflections. *cis-transoid-cis*-Tricyclo[9.3.0.0⁴,⁸]tetradecane-2,9-dione (m.p. 415.2–416.2 K) (II): monoclinic, $P2_1/n$, $a = 11.761$ (3), $b = 9.208$ (1), $c = 5.594$ (1) Å, $\beta = 98.02$ (2)°, $V = 599.9$ (2) Å³, $Z = 2$, $D_m = 1.19$ (2), $D_x = 1.22$ Mg m⁻³, $\mu = 0.07$ mm⁻¹, $R = 0.048$ for 603 reflections. *cis-cisoid-cis*-Tricyclo[9.3.0.0³,⁷]tetradecane-2,9-dione (m.p. 369.2–370.2 K) (III): monoclinic, $P2_1/n$, $a = 12.316$ (2), $b = 17.833$ (3), $c = 5.390$ (1) Å, $\beta = 90.06$ (2)°, $V = 1183.8$ (4) Å³, $Z = 4$, $D_m = 1.23$ (2), $D_x = 1.24$ Mg m⁻³, $\mu = 0.08$ mm⁻¹, $R = 0.052$ for 1293 reflections. *trans-cisoid-trans*-Tricyclo[9.3.0.0³,⁷]-tetradecane-2,9-dione (m.p. 393.2–394.2 K) (IV): monoclinic, $P2_1/c$, $a = 11.625$ (3), $b = 5.306$ (1), $c = 21.108$ (3) Å, $\beta = 104.18$ (1)°, $V = 1262.3$ (4) Å³, $Z = 4$, $D_m = 1.14$ (3), $D_x = 1.16$ Mg m⁻³, $\mu = 0.07$ mm⁻¹, $R = 0.038$ for 601 reflections. The 5-8-5 compounds (I), (II) and (III) synthesized by a photochemical reaction have ring junctions all *cis*. (I) and (II) are geometrical isomers having different relative configuration of two ring junctions, *cisoid* and *transoid*. In an alkaline solution (III) was changed to the geometrical isomer (IV). The central eight-membered rings in