Acta Cryst. (1996). C**52**, 2892–2894

3β,4α-Dihydroxy-5β-androstan-17-one

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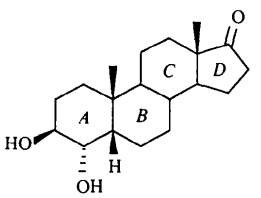
(*Received 29 August 1995; accepted 2 July 1996*)

Abstract

The crystal structure of the title compound, $C_{19}H_{30}O_3$, is reported. This steroid was obtained as an intermediate in the synthesis of formestane. The molecules are held together by a network of hydrogen bonds involving the carbonyl and hydroxyl groups.

Comment

As part of a study directed towards developing an efficient strategy for the synthesis of formestane, an irreversible aromatase inhibitor, (I), which has been shown to be very effective in the treatment of oestrogen-dependent breast cancer, has been synthesized as an intermediate.



(I)

Rings *A*, *B* and *C* all have chair conformations which are slightly flattened (all torsion angles within each ring are less than 60°). The conformation of ring *D* is 14α-envelope. The 5β configuration produces a *cis* junction between rings *A* and *B*. The bowing angle of ring *A* relative to the remainder of the steroid is 58.91 (6)°, showing the strong bending typical of 5β steroids. The distance between the terminal O atoms, O3 and O17, is 9.966 (4) Å. An average value of 1.527 (16) Å was computed for the 20 C_{sp^3}—C_{sp^3} bonds, which agrees well with the expected overall value of 1.530 Å (*International Tables for Crystallography*, 1992, Vol. C). The C2—C3 and C3—C4 bonds, however, are significantly shorter than the average value; this shortening can be attributed to the presence of the hydroxyl groups bonded to ring *A* and has been observed in other related steroid crystal structures (Weeks, Cooper, Norton, Hauptman & Fisher, 1971; Banerjee, Das & Saenger, 1978). The geometry of ring *D* is very similar to that found by Weeks, Cooper, Norton, Hauptman & Fisher (1971) for epiandrosterone, a similar structure having one of the C atoms, C17, sp^2 hybridized.

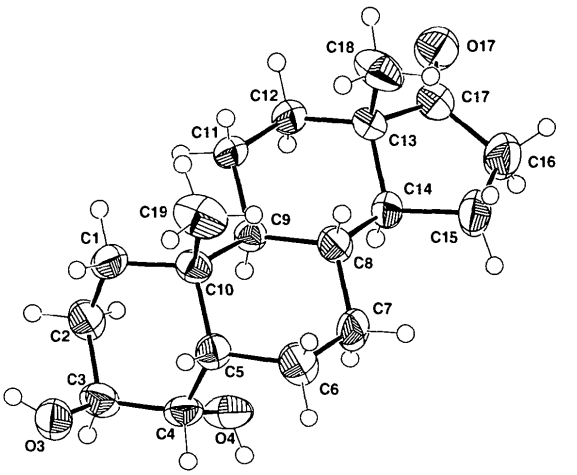


Fig. 1. *ORTEP*II (Johnson, 1976) plot of the title compound. Displacement ellipsoids are drawn at the 50% probability level, except for H atoms which are spheres of arbitrary radii.

The 3β-hydroxyl group takes part in two hydrogen bonds, one as a donor towards the carbonyl group, the other as an acceptor from the 4α-hydroxyl group. The 3β-hydroxyl to 4α-hydroxyl intermolecular bond is shorter and links two molecules in a head-to-head fashion; the weaker bond is a head-to-tail link *via* the 3β-hydroxyl and carbonyl groups. The single-crystal melting point of the title compound was determined to be 494 (2) K, higher by about 100 K than the corresponding value for androstan-17-one (Banerjee, Das & Saenger, 1978) which has no hydrogen bonds. The molecular volume is 419.3 Å^3, a value similar to those found in other related steroids (Weeks, Cooper, Norton, Hauptman & Fisher, 1971). It should be pointed out that the absolute configuration known from chemical studies of the molecule could not be determined from our data because none of the atoms is a strong enough anomalous scatterer at the Mo $K\alpha$ wavelength.

Experimental

Oxidation of 5β-androst-3-en-17-one, easily prepared from available androst-4-ene-3,17-dione in the presence of Zn/AcOH under ultrasonic irradiation (Salvador, Sá e Melo & Campos Neves, 1993), was carried out with performic acid generated *in situ*. The main product of this reaction has been isolated and identified from IR, ^{1}H NMR and ^{13}C NMR spectra as the title compound 3β,4α-dihydroxy-5β-androstan-17-one. Good quality transparent crystals suitable for X-ray experiments were obtained by slow evaporation of a solution of the steroid in a mixture of ethyl acetate and *n*-hexane.

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Crystal data

$C_{19}H_{30}O_3$
M_r = 306.43
Orthorhombic
$P2_12_12_1$
a = 6.3280 (10) Å
b = 13.208 (2) Å
c = 20.069 (5) Å
V = 1677.4 (6) Å^3
Z = 4
D_x = 1.213 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 7.84–16.85°
μ = 0.080 mm^{-1}
T = 293 (2) K
Needle
0.48 × 0.07 × 0.07 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
Profile data from ω scans
Absorption correction: none
6517 measured reflections
2901 independent reflections
1510 observed reflections [$I > 2\sigma(I)$]

R_{int} = 0.047
θ_{max} = 25°
$h = -7 \rightarrow 3$
$k = -15 \rightarrow 15$
$l = -23 \rightarrow 23$
3 standard reflections
frequency: 120 min
intensity decay: 4.7%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.0424
$wR(F^2)$ = 0.1204
S = 1.004
2898 reflections
203 parameters
H atoms riding
$w = 1/[\sigma^2(F_o^2) + (0.0527P)^2 + 0.0364P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.164 e Å^{-3}
$\Delta\rho_{min}$ = −0.143 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
O3	0.4054 (4)	0.6098 (2)	0.47989 (11)	0.0608 (7)
O4	0.0482 (4)	0.7286 (2)	0.59497 (11)	0.0587 (7)
O17	−0.0519 (4)	0.5953 (2)	0.95499 (11)	0.0678 (8)
C1	0.4169 (6)	0.5221 (2)	0.61565 (15)	0.0483 (9)
C2	0.2250 (7)	0.5244 (2)	0.57144 (15)	0.0516 (10)
C3	0.2303 (6)	0.6138 (2)	0.52490 (14)	0.0469 (9)
C4	0.2469 (6)	0.7108 (2)	0.56376 (15)	0.0425 (8)
C5	0.4284 (5)	0.7113 (2)	0.61422 (14)	0.0398 (8)
C6	0.4353 (7)	0.8099 (2)	0.6541 (2)	0.0598 (11)
C7	0.2844 (7)	0.8120 (2)	0.7131 (2)	0.0577 (11)
C8	0.3086 (5)	0.7198 (2)	0.75779 (14)	0.0411 (8)
C9	0.2808 (5)	0.6224 (2)	0.71682 (13)	0.0326 (7)
C10	0.4458 (5)	0.6160 (2)	0.65929 (13)	0.0369 (7)
C11	0.2746 (6)	0.5259 (2)	0.76022 (14)	0.0453 (9)
C12	0.1323 (5)	0.5332 (2)	0.82120 (14)	0.0439 (9)
C13	0.1806 (5)	0.6273 (2)	0.86063 (14)	0.0390 (8)
C14	0.1528 (5)	0.7198 (2)	0.81476 (14)	0.0424 (8)
C15	0.1398 (7)	0.8092 (2)	0.8628 (2)	0.0705 (13)
C16	0.0068 (8)	0.7672 (2)	0.9201 (2)	0.0782 (14)
C17	0.0321 (6)	0.6534 (3)	0.9171 (2)	0.0505 (9)
C18	0.3991 (6)	0.6206 (3)	0.8931 (2)	0.0664 (12)
C19	0.6725 (5)	0.6107 (3)	0.6877 (2)	0.0669 (11)

Table 2. *Selected geometric parameters (Å, °)*

O3—C3	1.430 (4)	C8—C9	1.536 (4)
O4—C4	1.424 (4)	C9—C11	1.544 (4)
O17—C17	1.204 (4)	C9—C10	1.559 (4)
C1—C2	1.504 (5)	C10—C19	1.545 (4)
C1—C10	1.529 (4)	C11—C12	1.523 (4)
C2—C3	1.507 (4)	C12—C13	1.506 (4)
C3—C4	1.504 (4)	C13—C17	1.512 (4)
C4—C5	1.531 (4)	C13—C18	1.531 (4)
C5—C6	1.530 (4)	C13—C14	1.539 (4)
C5—C10	1.553 (4)	C14—C15	1.527 (4)
C6—C7	1.522 (4)	C15—C16	1.528 (5)
C7—C8	1.520 (4)	C16—C17	1.513 (4)
C8—C14	1.510 (4)		
C2—C1—C10	114.7 (3)	C19—C10—C5	108.6 (3)
C1—C2—C3	111.3 (3)	C1—C10—C9	112.8 (3)
O3—C3—C4	107.8 (3)	C19—C10—C9	110.5 (2)
O3—C3—C2	112.3 (3)	C5—C10—C9	109.9 (3)
C4—C3—C2	110.4 (2)	C12—C11—C9	114.6 (3)
O4—C4—C3	107.9 (3)	C13—C12—C11	110.7 (3)
O4—C4—C5	111.8 (2)	C12—C13—C17	117.1 (3)
C3—C4—C5	113.5 (3)	C12—C13—C18	111.0 (3)
C6—C5—C4	111.8 (3)	C17—C13—C18	104.8 (2)
C6—C5—C10	112.5 (2)	C12—C13—C14	108.5 (2)
C4—C5—C10	115.8 (3)	C17—C13—C14	101.4 (2)
C7—C6—C5	113.8 (3)	C18—C13—C14	113.8 (3)
C8—C7—C6	112.4 (3)	C8—C14—C15	120.9 (3)
C14—C8—C7	112.4 (3)	C8—C14—C13	112.2 (3)
C14—C8—C9	109.3 (2)	C15—C14—C13	104.0 (2)
C7—C8—C9	110.1 (2)	C14—C15—C16	102.9 (3)
C8—C9—C11	113.1 (2)	C17—C16—C15	105.9 (3)
C8—C9—C10	111.4 (2)	O17—C17—C13	127.1 (3)
C11—C9—C10	113.0 (2)	O17—C17—C16	124.2 (3)
C1—C10—C19	106.6 (3)	C13—C17—C16	108.7 (3)
C1—C10—C5	108.3 (2)		

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3···O17^i	0.82	2.09	2.906 (4)	171
O4—H4···O3^{ii}	0.82	1.96	2.762 (4)	167

Symmetry codes: (i) $\frac{1}{2} - x, 1 - y, z - \frac{1}{2}$; (ii) $x - \frac{1}{2}, \frac{3}{2} - y, 1 - z$.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *SDP-Plus* (Frenz, 1985). Program(s) used to solve structure: *MULTAN*11/82 (Main *et al.*, 1982). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *SHELXL*93.

One of us (MRS) would like to thank Junta Nacional de Investigacao Científica e Tecnológica (Programa PRAXIS XXI) for the award of a research scholarship. We are indebted to the Cultural Service of the German Federal Republic Embassy, the Deutscher Akademischer Austauschdienst (DAAD) and the German Agency for Technical Cooperation (GTZ) for the loan of the diffractometer which enabled the experimental work to be carried out. This work was also supported by the JNICT-CIÊNCIA program.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: FG1119). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1996). C**52**, 2894–2896

5-Phenylindazole

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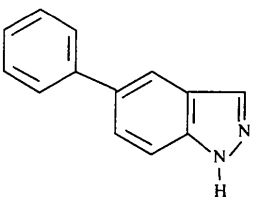
(*Received 21 March 1996; accepted 30 May 1996*)

Abstract

The title compound, $C_{13}H_{10}N_2$, packs in chains along the *a* axis *via* N—H···N hydrogen bonds that are stronger and more linear than those observed in unsubstituted indazole. These chains are linked by C—H···N and C—H···phenyl contacts along **b**, giving rise to a wave-like structure.

Comment

We are interested in the proton tautomerism (prototropy) and the intermolecular hydrogen bonding of NH-pyrazoles (Llamas-Saiz, Foces-Foces & Elguero, 1994; Aguilar-Parrilla *et al.*, 1995; Elguero, Jagerovic *et al.*, 1995); the NH-indazoles are a subgroup of these compounds (Llamas-Saiz, Foces-Foces & Elguero, 1994). With regard to tautomerism, the literature suggests that only the 1*H*-tautomer is present in NH-indazoles, the 2*H*-tautomer being much less stable (Catalan, de Paz & Elguero, 1996). Two types of hydrogen-bonding network are possible for NH-indazoles, catemers and trimers. In the first group, indazole molecules (Escande & Lapasset, 1974) are linked by N—H···N hydrogen bonds while in 1*H*-indazole-3-carboxylic acid (Benetollo & Del Pra, 1993), the molecules are bonded through N—H···O bonds reinforced by O—H···N interactions. Trimers are formed *via* N—H···N bonds in 3-phenyl-5-methyl-1*H*-indazole (Dvorkin *et al.*, 1989) and *via* N—H···O/N three-centre bonds in 3-methoxycarbonyl-1*H*-indazole (Glaser, Mummert, Horan & Barnes, 1993).



(I)

The molecular structure of the title compound (I) (Fig. 1) compares well with that reported for indazole itself (Escande & Lapasset, 1974). There are no significant differences in terms of the achieved precision as tested by half-normal probability plots (Abrahams & Keve, 1971). There is also good agreement with the results of the *ab initio* calculation at MP2/6-31G** level for the 1*H*-indazole (Catalan, de Paz & Elguero, 1996), but some differences are worth noting. The free molecule presents a greater degree of charge delocalization in the five-membered ring. The N1—N2 and N2—C3 bonds appear to be longer and shorter, respectively, in the present compound. The differences in the C5—C6 and C6—C7 bonds, however, could be due to the phenyl ring attached to C5 which is twisted by 23.8 (4)° with respect to the indazole plane. The *ipso* angle at the phenyl ring as well as the C4—C5—C6 angle (Table 2) in the indazole moiety reflects the σ-withdrawing influence of the indazole and phenyl moieties (Domenicano & Vaciago, 1979).

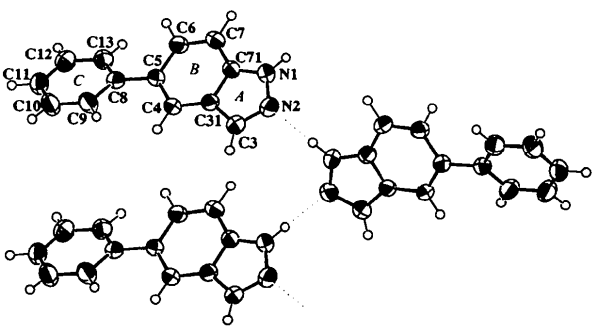


Fig. 1. The structure of 5-phenylindazole as projected along the *c* axis showing the atom labelling and the hydrogen-bonding system. Displacement ellipsoids are drawn at 50% probability level. The ring centroids are denoted by *A*, *B* and *C*. Dotted lines indicate hydrogen bonds.

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