Conformational Studies. Part 11.[1] Crystal and Molecular Structure of the Anaesthetic, 3α-Hydroxy-5α-pregnane-11,20-dione

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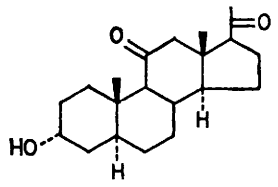
The title compound (1), $C_{21}H_{32}O_3$, forms orthorhombic crystals, space group $P2_12_12_1$, with $Z = 4$ in a cell of dimensions $a = 7.372(3)$, $b = 13.561(5)$, $c = 18.493(7)$ Å. The structure was determined by direct methods and refined by full-matrix least-squares calculations to R 0.063 for 1 167 observed reflections. The conformation of each of the six-membered rings is a chair; that of the five-membered ring D is mid-way between a half-chair and a C(13) envelope. In the crystal the molecules are linked together in chains parallel to the b axis by weak O–H · · · O hydrogen bonds [O · · · O 2.95(1) Å].

A NUMBER of 2α- and 2β-substituted derivatives of 3α-hydroxy-5α-pregane-11,20-dione (1) exhibit anaesthetic activity.[2] One of the active members of this group is the parent compound itself, which comprises the main component of the now widely, clinically used anaesthetic, 'Althesin'.[3] In view of our interest in the correlation

[1] Part 10, G. Ferguson, R. J. Restivo, G. A. Lane, J. M. Midgley, and W. B. Whalley, preceding paper.
[2] G. H. Phillipps, *J. Steroid Biochem.*, 1975, **6**, 607.
[3] B. Davis and D. R. Pearce, *Postgrad. Medicin. J.*, 1972, **48**, Suppl. (2), 13; K. J. Child, J. P. Currie, B. Davis, M. G. Dodds, D. R. Pearce, and D. J. Twissell, *Br. J. Anaesth.*, 1971, **43**, 2.

between structure, conformation, and various physical parameters of steroids it seemed of interest to investigate the structure of (1) by *X*-ray crystallography.



(1)

EXPERIMENTAL

Crystal Data.—$C_{21}H_{32}O_3$, $M = 332.5$. Orthorhombic, $a = 7.372(3)$, $b = 13.561(5)$, $c = 18.493(7)$ Å, $U = 1\,848.8$ Å^3, $D_m = 1.20$ g cm^{-3}, $Z = 4$, $D_c = 1.19$, $F(000) = 728$. Space group $P2_12_12_1$ (D_2^4, No. 19) uniquely from systematic absences. Mo-K_α radiation, $\lambda = 0.710\,69$ Å; μ(Mo-K_α) = 0.83 cm^{-1}.

The crystal employed for data collection had dimensions 0.40 × 0.20 × 0.18 mm. Intensities were measured on a Hilger and Watts Y290 PDP 8I controlled four-circle diffractometer, by use of approximately monochromatic zirconium-filtered Mo-K_α radiation as described previously.[4] Data were corrected for Lorentz and polarzation effects but not for absorption, which is negligible. Of the 1 498

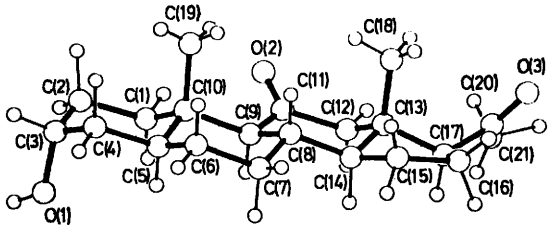


FIGURE 1 3α-Hydroxy-5α-pregnane-11,20-dione (1) showing the atom numbering scheme

unique reflections with $\theta \leqslant 23°$, 1 167 having intensities $>3.0\ \sigma(I)$ were employed in the subsequent structure analysis and refinement.

The structure was solved by use of the program MULTAN [5] with the 267 *E* values greater than 1.30 as input. The solution with the highest figure-of-merit and lowest residual yielded an *E* map, the top 24 peaks of which corresponded to the atomic positions in the molecule. The structure was refined by full-matrix least-squares calculations with the hydrogen atoms (in positions located from a difference-Fourier synthesis) included in the structure-factor calculation but excluded from the refinement. The carbon and oxygen atoms were allowed anisotropic vibration with the scattering factors of ref. 6; hydrogen atoms were only allowed isotropic thermal parameters with the scattering factors of ref. 7. The function minimised was $\Sigma w(|F_o| - |F_c|)^2$, with $w = 1/\sigma^2(F_o)$ derived from counting statistics. The final R was 0.082 for all reflections and 0.063 for the 1 167 reflections with non-zero weight; the final value of $R'\{[\Sigma w(F_o - F_c)^2/\Sigma wF_o^2]^{\frac{1}{2}}\}$ was 0.063. A final difference-Fourier synthesis was essentially featureless with maximum fluctuations of ± 0.25 eÅ^{-3}.

A view of the molecule is presented in Figure 1. Final positional parameters are in Table 1 and the main interatomic distances and angles derived from these are in Table 2. Thermal parameters, C–H distances and a listing of structure factors have been deposited as Supplementary Publication No. SUP 22269 (14 pp., 1 mircofiche).*

TABLE 1

Final positional parameters (carbon and oxygen ×10^4, hydrogen ×10^3), with estimated standard deviations in parentheses for (1)

Atom	*x*	*y*	*z*
O(1)	2 600(10)	4 944(4)	2 788(3)
O(2)	−307(8)	856(4)	3 334(3)
O(3)	1 737(9)	−2 301(4)	5 609(3)
C(1)	992(11)	2 854(5)	2 885(4)
C(2)	1 364(11)	3 486(6)	2 216(4)
C(3)	2 966(13)	4 156(6)	2 285(5)
C(4)	4 636(12)	3 605(6)	2 562(5)
C(5)	4 219(10)	2 986(5)	3 244(4)
C(6)	5 923(11)	2 492(6)	3 530(4)
C(7)	5 566(11)	1 939(6)	4 237(4)
C(8)	4 047(10)	1 183(5)	4 142(4)
C(9)	2 303(10)	1 694(5)	3 839(4)
C(10)	2 675(10)	2 240(5)	3 113(3)
C(11)	703(10)	1 001(5)	3 852(4)
C(12)	353(11)	426(5)	4 555(4)
C(13)	2 078(10)	−115(5)	4 782(4)
C(14)	3 601(11)	659(6)	4 848(4)
C(15)	5 157(11)	72(6)	5 226(4)
C(16)	4 151(12)	−671(7)	5 724(5)
C(17)	2 129(12)	−560(5)	5 561(4)
C(18)	2 502(12)	−924(5)	4 223(4)
C(19)	3 170(13)	1 482(6)	2 518(4)
C(20)	1 008(12)	−1 499(5)	5 639(4)
C(21)	−994(12)	−1 397(6)	5 748(5)
H(01)	175(18)	542(9)	265(6)
H(11)	−19(14)	236(7)	279(5)
H(12)	86(9)	326(4)	329(3)
H(21)	154(9)	300(4)	172(3)
H(22)	38(9)	383(5)	211(3)
H(3)	308(9)	449(4)	183(3)
H(41)	506(10)	309(5)	213(3)
H(42)	552(9)	406(5)	268(3)
H(5)	376(8)	345(4)	361(3)
H(61)	646(11)	205(5)	317(4)
H(62)	685(7)	297(4)	361(3)
H(71)	648(11)	167(5)	441(4)
H(72)	500(12)	251(6)	466(4)
H(8)	449(10)	75(5)	379(4)
H(9)	197(7)	216(3)	417(3)
H(121)	−3(8)	80(4)	490(3)
H(122)	−84(12)	−5(6)	452(4)
H(14)	314(9)	117(5)	526(3)
H(151)	584(9)	−20(5)	487(3)
H(152)	596(10)	60(5)	547(3)
H(161)	476(16)	−132(8)	575(6)
H(162)	408(13)	−41(7)	626(5)
H(17)	168(7)	−2(4)	588(3)
H(181)	147(12)	−139(6)	417(4)
H(182)	264(10)	−67(5)	375(3)
H(183)	370(10)	−129(5)	433(4)
H(191)	213(10)	108(5)	253(4)
H(192)	318(13)	170(6)	216(4)
H(193)	418(11)	103(6)	261(4)
H(211)	−134(13)	−78(7)	598(5)
H(212)	−162(19)	−207(9)	601(6)
H(213)	−151(14)	−153(7)	528(5)

DISCUSSION

In the molecule rings A, B, and C have the expected chair conformation; the values of the *cis*-torsion angles

* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1977, Index issue.

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TABLE 2

Interatomic distances (Å) and angles (°) for (1)

(*a*) Bond lengths

C(1)–C(2)	1.530(11)	C(10)–C(19)	1.550(11)
C(1)–C(10)	1.553(11)	C(11)–O(2)	1.223(9)
C(2)–C(3)	1.495(12)	C(11)–C(12)	1.539(10)
C(3)–O(1)	1.442(10)	C(12)–C(13)	1.526(11)
C(3)–C(4)	1.529(12)	C(13)–C(14)	1.542(11)
C(4)–C(5)	1.546(11)	C(13)–C(17)	1.563(10)
C(5)–C(6)	1.518(11)	C(13)–C(18)	1.540(10)
C(5)–C(10)	1.542(10)	C(14)–C(15)	1.562(11)
C(6)–C(7)	1.530(12)	C(15)–C(16)	1.553(12)
C(7)–C(8)	1.528(11)	C(16)–C(17)	1.528(12)
C(8)–C(9)	1.564(11)	C(17)–C(20)	1.525(11)
C(8)–C(14)	1.522(10)	C(20)–O(3)	1.216(9)
C(9)–C(10)	1.557(10)	C(20)–C(21)	1.496(12)
C(9)–C(11)	1.508(10)		

(*b*) Bond angles

C(2)–C(1)–C(10)	112.2(6)	C(5)–C(10)–C(19)	109.7(6)
C(1)–C(2)–C(3)	114.4(7)	O(2)–C(11)–C(9)	124.4(6)
O(1)–C(3)–C(2)	111.0(7)	O(2)–C(11)–C(12)	118.2(6)
O(1)–C(3)–C(4)	107.3(7)	C(9)–C(11)–C(12)	117.4(6)
C(2)–C(3)–C(4)	111.6(7)	C(11)–C(12)–C(13)	109.6(6)
C(3)–C(4)–C(5)	112.2(7)	C(12)–C(13)–C(14)	107.6(6)
C(4)–C(5)–C(6)	111.0(6)	C(12)–C(13)–C(17)	117.3(6)
C(4)–C(5)–C(10)	112.0(6)	C(12)–C(13)–C(18)	109.1(6)
C(6)–C(5)–C(10)	112.1(6)	C(14)–C(13)–C(17)	99.9(6)
C(5)–C(6)–C(7)	111.8(6)	C(14)–C(13)–C(18)	112.9(6)
C(6)–C(7)–C(8)	110.9(6)	C(17)–C(13)–C(18)	109.8(6)
C(7)–C(8)–C(9)	110.3(6)	C(8)–C(14)–C(13)	114.0(6)
C(7)–C(8)–C(14)	111.9(6)	C(8)–C(14)–C(15)	117.6(6)
C(9)–C(8)–C(14)	109.6(6)	C(13)–C(14)–C(15)	102.9(6)
C(8)–C(9)–C(10)	112.0(6)	C(14)–C(15)–C(16)	104.2(6)
C(8)–C(9)–C(11)	111.2(6)	C(15)–C(16)–C(17)	106.6(7)
C(10)–C(9)–C(11)	116.6(6)	C(13)–C(17)–C(16)	104.1(6)
C(1)–C(10)–C(5)	106.3(6)	C(13)–C(17)–C(20)	113.4(6)
C(1)–C(10)–C(9)	110.4(6)	C(16)–C(17)–C(20)	115.3(7)
C(1)–C(10)–C(19)	110.5(6)	O(3)–C(20)–C(17)	120.3(8)
C(5)–C(10)–C(9)	107.9(5)	O(3)–C(20)–C(21)	121.6(7)
C(5)–C(10)–C(19)	111.9(6)	C(17)–C(20)–C(21)	118.1(7)

(*c*) Shorter intermolecular contacts

O(2) · · · H[O(1^{I})]	2.19	H(72) · · · H(121^{II})	2.43
O(2) · · · O(1^{I})	2.948	H(183) · · · H(212^{III})	2.33

Roman numeral superscripts refer to the following equivalent positions:

I $-x, -\frac{1}{2}+y, \frac{1}{2}-z$ III $\frac{1}{2}+x, -\frac{1}{2}-y, 1-z$
II $\frac{1}{2}+x, \frac{1}{2}-y, 1-z$

in ring B (Figure 2) are close to standard values [8] whereas rings A and C exhibit some slight flattening in the region

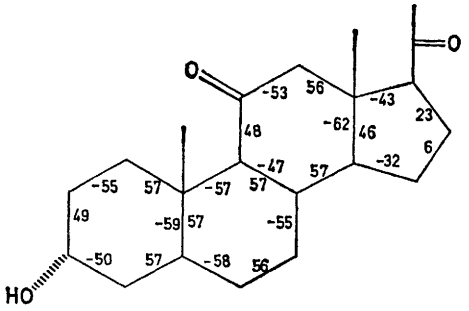

FIGURE 2 Details of *cis*-torsion angles

of C(3) and C(9). There are no unusually short intramolecular contacts but the shortest intermolecular contacts in the crystal structure (Figure 3) involve the axial hydroxy-group at C(3) with the carbonyl at C(11) on an adjacent molecule (O · · · O 2.95, H · · · O 2.19 Å; O–H · · · O 137°). Almost certainly this weak intermolecular interaction is responsible for the slight flattening of ring A as an increase in the O–H · · · O distance would lead to a more puckered (*i.e.* normal) ring A conformation. The same arguments can be applied

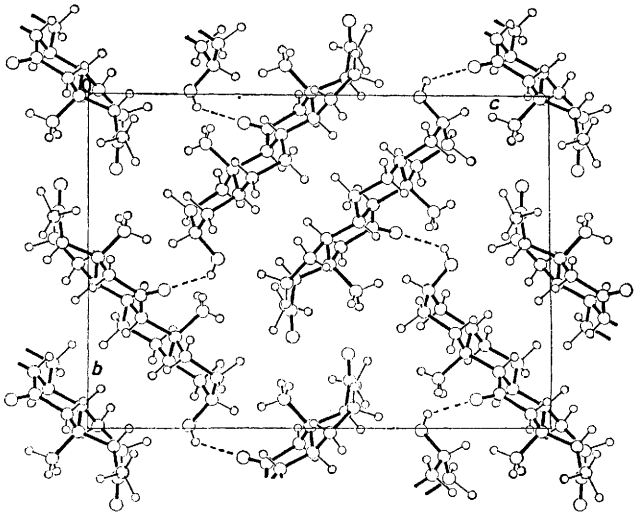

FIGURE 3 The molecular packing diagram for (1); dashed lines indicate O–H · · · O hydrogen bonds

to the ring C conformation but here the sp^2 hybridized atom C(11) will also be partly responsible for the slight flattening found. That relatively weak intermolecular interactions can cause small changes in steroid ring conformations has been noted previously in 17β-bromoacetoxy-19-nor-5α-androstan-3-one and 17β-bromoacetoxy-5α-androstan-3-one.[4] The *cis*-torsion angles in ring D are consistent with a conformation intermediate between a half-chair and a C(13) envelope. In more quantitative terms the conformation may be expressed [9] in terms of the phase angle, Δ, which is 22.4° and the angle of puckering ϕ_m, 47.1°.

The bond lengths do not differ significantly from expected values.[10] Mean bond lengths are: C(sp^3)–C(sp^3) 1.539, C(sp^2)–C(sp^3) 1.517, C(sp^2)–O 1.220, and C(sp^3)–O 1.442 Å, C–H 0.99 Å.

The steroid (1) is thus devoid of unusual conformational features in both the solid state, and in solution.[3] However, the energy of binding of (1) to the receptor is probably sufficient to modify the conformation of ring A and thus it may not be assumed that the presently defined conformation is necessarily that at the site of biological activity. Additionally the uniquely specific requirement for the 3α-hydroxy-group [3] indicates the possibility that this substituent fits closely into a cavity on the receptor, to which point it is guided by the ' template ' action of the steroid.

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[7/1962 *Received*, 7*th November*, 1977]

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