

Conformational Studies. Part 13.¹ ¹H N.m.r. and X-Ray Analyses of 2 β -Bromo-3 α -hydroxy-5 α -pregnane-11,20-dione, 3 α -Hydroxy-2 β -methoxy-5 α -pregnane-11,20-dione, and 3 α -Hydroxy-2 α -methyl-5 α -pregnane-11,20-dione

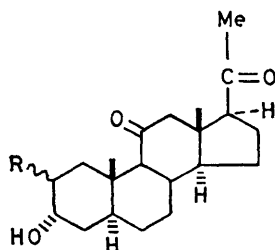
By John M. Midgley and W. Basil Whalley,* The School of Pharmacy, The University, London WC1N 1AX
Barry E. Ayres and Gordon H. Phillipps, Glaxo Research, Greenford, Middlesex UB6 0HE
George Ferguson * and Masood Parvez, Department of Chemistry, The University, Guelph, Ontario, Canada N1G 2W1

To investigate the potential relationship between structure and anaesthetic activity, the title steroids have been analysed by ¹H n.m.r. spectroscopy, and by X-ray crystallography. The three compounds crystallise in the monoclinic space group *P*2₁ with two molecules per unit cell. Crystals of the 2 β -bromo-derivative (2) have *a* = 10.288(4), *b* = 7.480(5), *c* = 13.646(4) Å, β = 107.78(2)°. The structure was solved by the heavy-atom method and refined by full-matrix least-squares calculations: *R* = 0.083 for 1 428 reflections. The 2 β -methoxy-derivative (3) has *a* = 10.814(3), *b* = 7.207(2), *c* = 13.963(3) Å, β = 106.73(1)°. Structure solution was by direct methods and refinement as for (2) lowered *R* = 0.052 for 1 505 reflections. Crystals of the 2 α -methyl derivative (4) are isomorphous with those of (2) with *a* = 10.183(8), *b* = 7.552(7), *c* = 13.772(9) Å, β = 106.73(4)°; refinement by full-matrix least-squares calculations lowered *R* to 0.072 for 698 reflections.

The torsion angles in ring A of (2) involving atom C(2) are smaller than standard values because of a slight flattening of the ring. In (3) this flattening is marginally less marked whereas in (4) the ring A conformation is close to a 'normal' chair. The ¹H n.m.r. (solution) data are compatible with these observations.

THE anaesthetic activities of many derivatives of 3 α -hydroxy-5 α -pregnane-11,20-dione [Alphaxalone, (1)] have been reported,² and particular attention has been paid to the pharmacological effect of substitution at the 2-position. It has been postulated² that the enhancement of anaesthetic activity is associated with the presence of a bulky 2 β -substituent with the consequent distortion of ring A by the resultant 1,3-diaxial interaction between the 2 β -substituent and the C-19 angular methyl group. Although the biological significance of such distortion would be limited to the conformation of the molecule in the vicinity of the biological 'target', laboratory evidence for the flattening of ring A would support the theory.

Thus, three derivatives of (1), which has already been



- (1) R = H
(2) R = β -Br
(3) R = β -MeO. Monohydrate
(4) R = α -Me

examined³ by X-ray crystallography, namely (i) 2 β -bromo-3 α -hydroxy-5 α -pregnane-11,20-dione (2), which contains a bulky 2 β -substituent, (ii) 3 α -hydroxy-2 β -methoxy-5 α -pregnane-11,20-dione (3), which has a

medium-sized 2 β -substituent, and (iii) 3 α -hydroxy-2 α -methyl-5 α -pregnane-11,20-dione (4), with no β -substituent, were examined by X-ray crystallography and ¹H n.m.r. spectroscopy.

DISCUSSION

The ¹H n.m.r. spectra (see Experimental) clearly show that all three derivatives exhibit only slight broadening of the 3 β -proton multiplet, and hence that this C-H

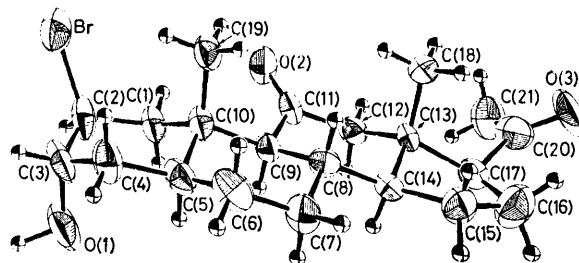


FIGURE 1 Perspective view of the molecule of (2)

bond retains an essentially unperturbed equatorial conformation in agreement with only a marginal conformational change of ring A from a 'classical' chair.

Molecular dimensions for (2), (3), and (4), derived from the X-ray crystallographic examination are given in Tables 1, 2, and 3. Table 4 contains the torsion angles for the molecules. Figures 1, 2, and 3 are ORTEP drawings of (2), (3), and (4), and Figures 4, 5, and 6 are views of the respective unit cell packing.

The molecular dimensions of (2), (3), and (4) are normal and in each case rings A, B, and C have the expected chair conformations as found³ in 3 α -hydroxy-5 α -pregnane-11,20-dione (1) (see Table 4 for details of torsion angles). The torsion angles in ring A of the 2 β -bromo-derivative

involving atom C(2) are smaller than the standard values because of a slight flattening of the ring. In the 2 β -methoxy-derivative the flattening of ring A is marginally less marked, whereas in the 2 α -methyl derivative and in (1) the ring conformation is close to a 'normal' chair.

TABLE 1

2 β -Bromo-3 α -hydroxy-5 α -pregnane-11,20-dione:
interatomic distances (Å) and angles (°)

(a) Bond lengths

Br—C(2)	1.97(2)	C(9)—C(11)	1.53(3)
C(1)—C(2)	1.57(2)	C(10)—C(19)	1.55(3)
C(1)—C(10)	1.54(3)	C(11)—C(12)	1.56(2)
C(2)—C(3)	1.51(4)	C(11)—O(2)	1.19(2)
C(3)—C(4)	1.55(4)	C(12)—C(13)	1.54(3)
C(3)—O(1)	1.43(3)	C(13)—C(14)	1.54(3)
C(4)—C(5)	1.53(3)	C(13)—C(17)	1.56(2)
C(5)—C(6)	1.52(3)	C(13)—C(18)	1.55(3)
C(5)—C(10)	1.56(3)	C(14)—C(15)	1.54(3)
C(6)—C(7)	1.51(3)	C(15)—C(16)	1.55(3)
C(7)—C(8)	1.50(3)	C(16)—C(17)	1.58(4)
C(8)—C(9)	1.57(3)	C(17)—C(20)	1.53(3)
C(8)—C(14)	1.54(2)	C(20)—C(21)	1.41(5)
C(9)—C(10)	1.56(2)	C(20)—O(3)	1.24(3)

(b) Bond angles

C(2)—C(1)—C(10)	116(2)	C(5)—C(10)—C(19)	115(2)
C(1)—C(2)—C(3)	113(2)	C(9)—C(10)—C(19)	109(1)
C(1)—C(2)—Br	113(1)	C(9)—C(11)—C(12)	116(2)
C(3)—C(2)—Br	109(2)	C(9)—C(11)—O(2)	125(2)
C(2)—C(3)—C(4)	112(1)	C(12)—C(11)—O(2)	120(2)
C(2)—C(3)—O(1)	108(2)	C(11)—C(12)—C(13)	110(2)
C(4)—C(3)—O(1)	106(2)	C(12)—C(13)—C(14)	108(1)
C(3)—C(4)—C(5)	112(2)	C(12)—C(13)—C(17)	115(2)
C(4)—C(5)—C(6)	113(2)	C(12)—C(13)—C(18)	109(1)
C(4)—C(5)—C(10)	111(2)	C(14)—C(13)—C(17)	100(1)
C(6)—C(5)—C(10)	113(1)	C(14)—C(13)—C(18)	114(2)
C(5)—C(6)—C(7)	110(2)	C(17)—C(13)—C(18)	110(1)
C(6)—C(7)—C(8)	113(2)	C(8)—C(14)—C(13)	114(1)
C(7)—C(8)—C(9)	112(1)	C(8)—C(14)—C(15)	117(2)
C(7)—C(8)—C(14)	113(2)	C(13)—C(14)—C(15)	104(1)
C(9)—C(8)—C(14)	109(1)	C(14)—C(15)—C(16)	103(2)
C(8)—C(9)—C(10)	112(2)	C(15)—C(16)—C(17)	107(2)
C(8)—C(9)—C(11)	113(1)	C(13)—C(17)—C(16)	103(2)
C(10)—C(9)—C(11)	116(2)	C(13)—C(17)—C(20)	115(2)
C(1)—C(10)—C(5)	107(1)	C(16)—C(17)—C(20)	115(2)
C(1)—C(10)—C(9)	108(2)	C(17)—C(20)—C(21)	119(2)
C(1)—C(10)—C(19)	111(2)	C(17)—C(20)—O(3)	118(3)
C(5)—C(10)—C(9)	107(2)	C(21)—C(20)—O(3)	124(2)

Primed atom is related to the unprimed atom by the transformation $x, y, 1+z$.

$$O(1) \cdots O(3)' \quad 2.77$$

(c) Intermolecular contacts

Thus, the flattening of ring A in (2) and to a lesser extent in (3) can be attributed to intramolecular steric effects involving the bulky C(2) β -substituents.

The torsion angles in ring B in (1)—(4) are close to the

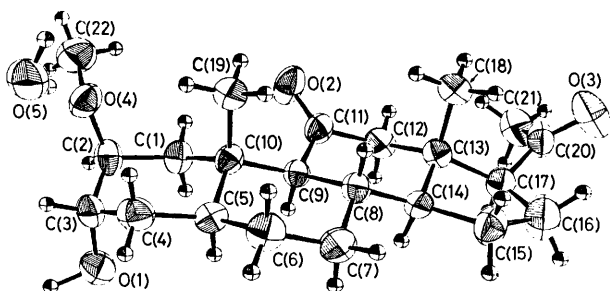


FIGURE 2 Perspective view of the molecule of (3)

expected values; the sp^2 hybridisation of C(11) causes a slight flattening of ring c in each compound. The torsion angles in ring D in the derivatives are consistent

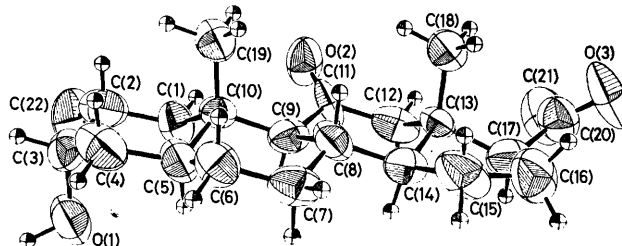


FIGURE 3 Perspective view of the molecule of (4)

with a conformation intermediate between a half-chair and a C(13) envelope

In the crystal structures of (2), (3), and (4) (Figures 4, 5, and 6 respectively) the molecules are linked by hydro-

TABLE 2

3 α -Hydroxy-2 β -methoxy-5 α -pregnane-11,20-dione
hydrate: interatomic distances (Å) and angles (°)

(a) Bond lengths

C(1)—C(2)	1.527(5)	C(10)—C(19)	1.546(5)
C(1)—C(10)	1.557(5)	C(11)—C(12)	1.516(6)
C(2)—C(3)	1.535(5)	C(11)—O(2)	1.204(4)
C(2)—O(4)	1.426(5)	C(12)—C(13)	1.527(5)
C(3)—C(4)	1.506(6)	C(13)—C(14)	1.527(5)
C(3)—O(1)	1.410(5)	C(13)—C(17)	1.558(5)
C(4)—C(5)	1.540(6)	C(13)—C(18)	1.532(5)
C(5)—C(6)	1.511(6)	C(14)—C(15)	1.539(6)
C(5)—C(10)	1.547(5)	C(15)—C(16)	1.535(7)
C(6)—C(7)	1.513(6)	C(16)—C(17)	1.540(8)
C(7)—C(8)	1.533(6)	C(17)—C(20)	1.514(6)
C(8)—C(9)	1.565(5)	C(20)—C(21)	1.481(7)
C(8)—C(14)	1.519(5)	C(20)—O(3)	1.209(5)
C(9)—C(10)	1.548(5)	C(22)—O(4)	1.403(6)
C(9)—C(11)	1.524(5)		

(b) Bond angles

C(2)—C(1)—C(10)	115.8(3)	C(9)—C(10)—C(19)	110.4(3)
C(1)—C(2)—C(3)	112.0(3)	C(9)—C(11)—C(12)	117.1(3)
C(1)—C(2)—O(4)	113.8(3)	C(9)—C(11)—O(2)	123.3(4)
C(3)—C(2)—O(4)	106.8(3)	C(12)—C(11)—O(2)	119.6(4)
C(2)—C(3)—C(4)	111.5(3)	C(11)—C(12)—C(13)	110.5(3)
C(2)—C(3)—O(1)	109.5(3)	C(12)—C(13)—C(14)	107.8(3)
C(4)—C(3)—O(1)	108.4(3)	C(12)—C(13)—C(17)	116.9(3)
C(3)—C(4)—C(5)	111.1(4)	C(12)—C(13)—C(18)	108.8(3)
C(4)—C(5)—C(6)	112.6(3)	C(14)—C(13)—C(17)	100.1(3)
C(4)—C(5)—C(10)	112.7(3)	C(14)—C(13)—C(18)	112.5(3)
C(6)—C(5)—C(10)	112.3(3)	C(17)—C(13)—C(18)	110.5(3)
C(5)—C(6)—C(7)	110.5(3)	C(8)—C(14)—C(13)	114.2(3)
C(6)—C(7)—C(8)	112.1(3)	C(8)—C(14)—C(15)	118.3(4)
C(7)—C(8)—C(9)	110.5(3)	C(13)—C(14)—C(15)	104.5(3)
C(7)—C(8)—C(14)	111.8(3)	C(14)—C(15)—C(16)	103.6(4)
C(9)—C(8)—C(14)	109.0(3)	C(15)—C(16)—C(17)	107.1(3)
C(8)—C(9)—C(10)	112.7(3)	C(13)—C(17)—C(16)	104.3(4)
C(8)—C(9)—C(11)	109.7(3)	C(13)—C(17)—C(20)	114.4(3)
C(10)—C(9)—C(11)	117.5(3)	C(16)—C(17)—C(20)	114.5(4)
C(1)—C(10)—C(5)	106.9(3)	C(17)—C(20)—C(21)	118.4(4)
C(1)—C(10)—C(9)	109.7(3)	C(17)—C(20)—O(3)	121.2(4)
C(1)—C(10)—C(19)	110.6(3)	C(21)—C(20)—O(3)	120.4(4)
C(5)—C(10)—C(9)	107.2(3)	C(2)—O(4)—C(22)	113.9(4)
C(5)—C(10)—C(19)	112.0(3)		

(c) Short intermolecular contacts

O(4) \cdots O(5)	2.880	O(5) \cdots H(01')	1.939
O(5) \cdots O(1')	2.729	H(051) \cdots O(3'')	1.919
O(5) \cdots O(3'')	2.855	H(052) \cdots O(4)	1.920

Primed and double primed atoms are related to the unprimed atoms by the transformations $1-x, y-\frac{1}{2}, 2-z$ and $-x, y-\frac{1}{2}, 1-z$ respectively.

TABLE 3

3 α -Hydroxy-2 α -methyl-5 α -pregnane-11,20-dione:
interatomic distances (Å) and angles (°)

(a) Bond lengths			
C(1)–C(2)	1.533(13)	C(9)–C(11)	1.537(12)
C(1)–C(10)	1.627(13)	C(10)–C(19)	1.471(11)
C(2)–C(3)	1.522(14)	C(11)–C(12)	1.484(12)
C(2)–C(22)	1.538(15)	C(11)–O(2)	1.220(10)
C(3)–C(4)	1.506(14)	C(12)–C(13)	1.524(12)
C(3)–O(1)	1.450(10)	C(13)–C(14)	1.504(12)
C(4)–C(5)	1.500(13)	C(13)–C(17)	1.635(11)
C(5)–C(6)	1.503(13)	C(13)–C(18)	1.495(10)
C(5)–C(10)	1.569(12)	C(14)–C(15)	1.507(13)
C(6)–C(7)	1.483(12)	C(15)–C(16)	1.573(15)
C(7)–C(8)	1.558(13)	C(16)–C(17)	1.541(15)
C(8)–C(9)	1.572(13)	C(17)–C(20)	1.476(13)
C(8)–C(14)	1.522(12)	C(20)–C(21)	1.590(16)
C(9)–C(10)	1.514(11)	C(20)–O(3)	1.182(11)
(b) Bond angles			
C(2)–C(1)–C(10)	114.2(8)	C(5)–C(10)–C(19)	112.5(8)
C(1)–C(2)–C(3)	110.6(8)	C(9)–C(10)–C(19)	112.4(7)
C(1)–C(2)–C(22)	111.2(9)	C(9)–C(11)–C(12)	118.2(9)
C(3)–C(2)–C(22)	111.7(8)	C(9)–C(11)–O(2)	119.2(8)
C(2)–C(3)–C(4)	112.0(7)	C(12)–C(11)–O(2)	122.6(8)
C(2)–C(3)–O(1)	110.3(8)	C(11)–C(12)–C(13)	109.7(7)
C(4)–C(3)–O(1)	104.0(9)	C(12)–C(13)–C(14)	109.6(5)
C(3)–C(4)–C(5)	114.6(9)	C(12)–C(13)–C(17)	115.5(8)
C(4)–C(5)–C(6)	113.1(10)	C(12)–C(13)–C(18)	108.2(7)
C(4)–C(5)–C(10)	114.0(9)	C(14)–C(13)–C(17)	99.8(7)
C(6)–C(5)–C(10)	111.2(7)	C(14)–C(13)–C(18)	114.4(7)
C(5)–C(6)–C(7)	113.1(8)	C(17)–C(13)–C(18)	109.3(6)
C(6)–C(7)–C(8)	113.2(7)	C(8)–C(14)–C(13)	112.4(7)
C(7)–C(8)–C(9)	111.5(7)	C(8)–C(14)–C(15)	119.2(9)
C(7)–C(8)–C(14)	112.9(8)	C(13)–C(14)–C(15)	104.6(7)
C(9)–C(8)–C(14)	111.2(8)	C(14)–C(15)–C(16)	106.1(9)
C(8)–C(9)–C(10)	111.0(8)	C(15)–C(16)–C(17)	105.3(8)
C(8)–C(9)–C(11)	109.1(7)	C(13)–C(17)–C(16)	102.8(9)
C(10)–C(9)–C(11)	119.8(8)	C(13)–C(17)–C(20)	114.3(8)
C(1)–C(10)–C(5)	102.7(6)	C(16)–C(17)–C(20)	113.5(9)
C(1)–C(10)–C(9)	109.4(7)	C(17)–C(20)–C(21)	116.3(10)
C(1)–C(10)–C(19)	109.7(7)	C(17)–C(20)–O(3)	123.0(10)
C(5)–C(10)–C(9)	109.6(7)	C(21)–C(20)–O(3)	120.5(11)
(c) Short intermolecular contacts			
O(1) \cdots O(3')	2.772		

Primed atom is related to the unprimed atom by the transformation $1 + x, y, z$.

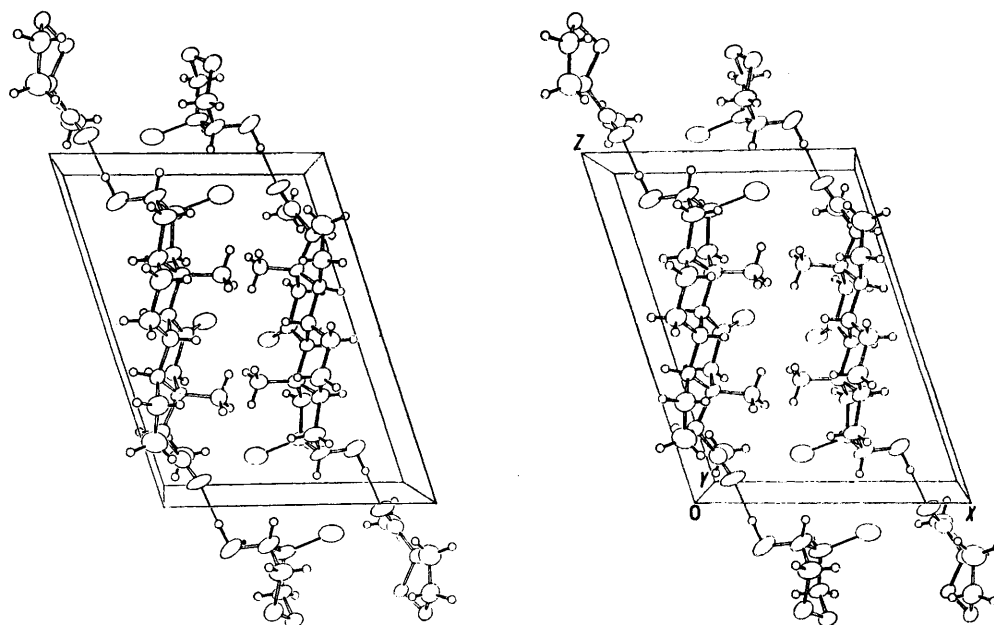


FIGURE 4 Stereoview of (2) showing the hydrogen bonding

gen bonds involving in all cases the C(3) α -hydroxy-group whose proton is in the same general orientation in each structure [e.g. H–C(3)–O(3)–H torsion angles of -16° , $+33$ and $+3$ in (2), (3), and (4) respectively]. In the isomorphous structures (2) and (4) the molecules are linked head-to-tail fashion by O–H \cdots O hydrogen

TABLE 4
cis-Torsion angles (ϕ) in the rings A, B, and C compared with the standard values

	(2)	(3)	(4)	(1)	Standard * value
C(10)C(1)–C(2)C(3)	–47	–51	–58	–55	–56
C(1)C(2)–C(3)C(4)	46	51	51	49	52
C(2)C(3)–C(4)C(5)	–55	–56	–52	–50	–53
C(3)C(4)–C(5)C(10)	62	60	57	57	57
C(4)C(5)–C(10)C(1)	–58	–55	–56	–59	–55
C(5)C(10)–C(1)C(2)	51	51	57	57	55
C(9)C(10)–C(5)C(6)	58	59	59	57	58
C(10)C(5)–C(6)C(7)	–59	–60	–56	–58	–57
C(5)C(6)–C(7)C(8)	56	56	52	56	53
C(6)C(7)–C(8)C(9)	–54	–53	–49	–55	–52
C(7)C(8)–C(9)C(10)	54	54	52	57	55
C(8)C(9)–C(10)C(5)	–55	–55	–57	–57	–57
C(14)C(8)–C(9)C(11)	–48	–50	–47	–47	–53
C(8)C(9)–C(11)C(12)	48	50	47	48	54
C(9)C(11)–C(12)C(13)	–53	–53	–53	–53	–55
C(11)C(12)–C(13)C(14)	57	55	57	56	56
C(12)C(13)–C(14)C(8)	–63	–62	–62	–62	–59
C(13)C(14)–C(8)C(9)	58	59	57	57	57
C(17)C(13)–C(14)C(15)	45	48	46	46	
C(13)C(14)–C(15)C(16)	–34	–38	–34	–32	
C(14)C(15)–C(16)C(17)	10	13	7	6	
C(15)C(16)–C(17)C(13)	18	16	20	23	
C(14)C(13)–C(17)C(16)	–38	–38	–41	–43	

* H. J. Geise, C. Altona, and C. Romers, *Tetrahedron*, 1967, **23**, 439; C. Altona, H. J. Geise, and C. Romers, *ibid.*, 1968, **24**, 13.

bonds between the C(3) α -hydroxy- and carbonyl oxygen O(3) with O \cdots O 2.77 and 2.772 respectively. In (3), the addition of the water of crystallisation causes a significant change in the packing but not in the conformation of the steroid.

The water molecule, with oxygen O(5), has one of its hydrogen atoms hydrogen bonded to the methoxy-oxygen O(4) of one molecule [$O(5)-H \cdots O(4)$ 2.880 Å], and the second hydrogen bonded to the keto-oxygen O(3)

Although the conformation of a molecule in the crystalline state (*X*-ray analysis) may not necessarily be the same as in solution (1H n.m.r.) the congruence between the results of the two techniques in this investigation

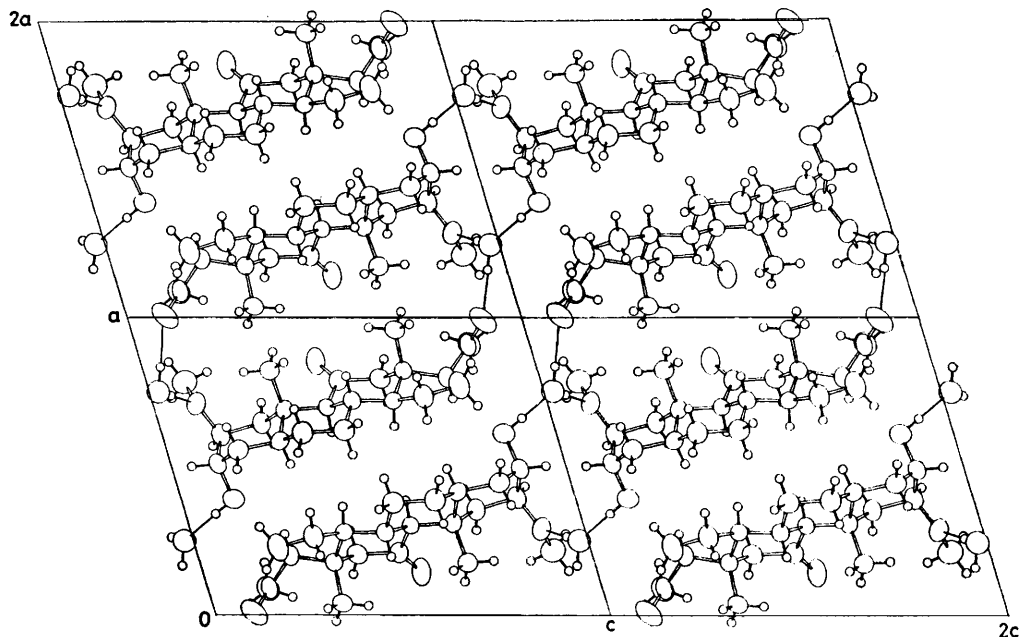


FIGURE 5 View of four unit cells of (3) showing the hydrogen bonding involving the water molecules

of another molecule [$O(5)-H \cdots O(3)$ 2.855 Å]. Additionally, O(5) of the same water molecule is simultaneously hydrogen bonded to the hydrogen of the C(3) α -hydroxy-group [$O(1)-H \cdots O(5)$ 2.729 Å]. In this way spirals of inter-linked molecules are developed along *b* (Figure 5).

indicates the close similarity of the conformations of (2), (3), and (4) with each other and in both the solid and solution states. Although this investigation provides only minimal support for the suggested relationship² between anaesthetic activity and the bulk of the C(2) β -substituents it does not preclude a more substantial

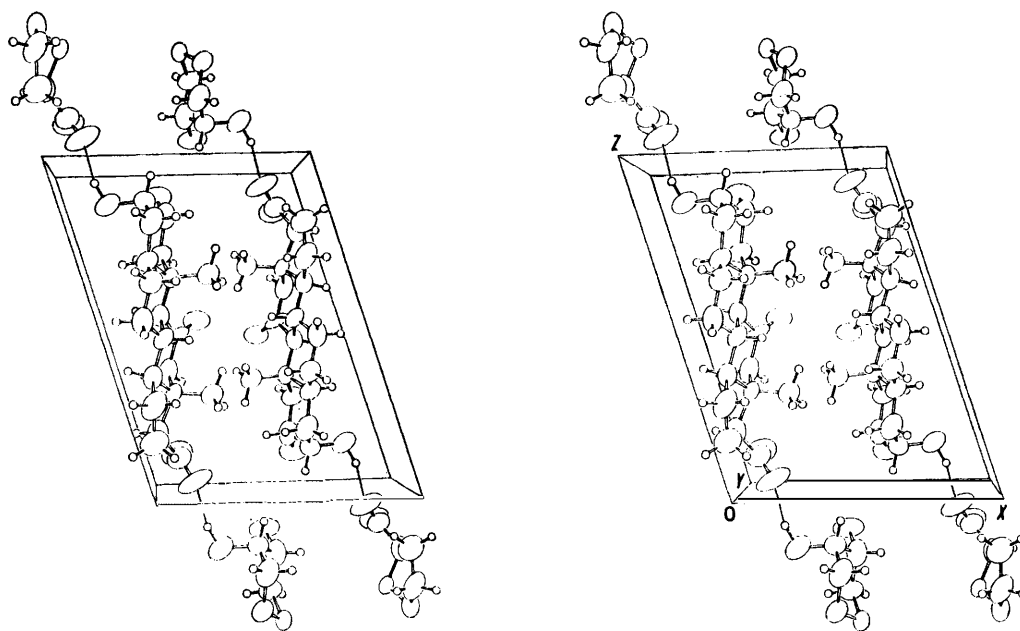


FIGURE 6 Stereoview of (4) showing the hydrogen bonding

modification of the conformation of ring A occurring when the substrate is adsorbed onto the 'target' site.

EXPERIMENTAL

2 β -Bromo-3 α -hydroxy-5 α -pregnane-11,20-dione (2).—Prepared by the previous route,⁴ the dione separated from methanol as thick prisms, m.p. 183—184 °C. The ¹H n.m.r. spectrum (100 MHz, CDCl₃) showed signals at τ 9.43 (s, 13-CH₃, 3 H), 8.73 (s, 10-CH₃, 3 H), 7.90 (s, 21-CH₃, 3 H), 7.40 and 7.56 (ABq, *J* 12 Hz, 12-CH₂, 2 H), and 5.77 (m, 2-CH and C-3-CH, *W*₁ 9 Hz), indicating that both protons were predominantly equatorial.

Mono-3 α -hydroxy-2 β -methoxy-5 α -pregnane-11,20-dione

Hydrate (3).—Prepared as previously⁴ the monohydrate recrystallised from methyl acetate as prisms, m.p. 173—174 °C (Found: C, 69.5; H, 9.6. C₂₂H₃₄O₄·H₂O requires C, 69.5; H, 9.6%). The presence of one mole of water was confirmed by the ¹H n.m.r. (singlet at τ 8.2) and i.r. (3 730 and 1 600 cm⁻¹ in bromoform) spectra. The ¹H n.m.r. spectrum (60 MHz, CDCl₃) had signals at τ 9.42 (s, 13-CH₃, 3 H), 8.86 (s, 10-CH₃, 3 H), 7.91 (s, 21-CH₃, 3 H), 7.48 (s, 12-CH₂, 2 H), 6.71 (m, 2-CH, 2 H), 6.62 (s, OCH₃, 3 H), and 6.03 (m, *W*₁ 8 Hz, 3-CH, H).

3 α -Hydroxy-2 α -methyl-5 α -pregnane-11,20-dione (4).—The compound⁵ separated from ethyl acetate—light petroleum (b.p. 60—80 °C) as small needles, m.p. 174—180 °C. The ¹H n.m.r. spectrum (100 MHz, CDCl₃) had the following characteristic signals; τ 9.42 (s, 18-CH₃, 3 H), 9.07 (d, *J* 7 Hz, 2 α -CH₃, 3 H), 8.99 (s, 19-CH₃, 3 H), 7.91 (s, 21-CH₃, 3 H), 7.47 (centre of ABq, 12-CH₂, 2 H), 6.20 (m, *W*₁ 7 Hz, 3-CH, H).

X-Ray Analysis.—Crystals of (2) and (3) were elongated prisms with well-defined faces; (4) crystallised as very thin plates. Crystals of (3) gave fairly satisfactory diffraction patterns, but those of (2) and (4) did not diffract well.

Crystal data for (2). C₂₁H₃₁BrO₃, *M* = 411.4, Monoclinic, *a* = 10.228(4), *b* = 7.480(5), *c* = 13.646(4) Å, β = 107.78(2)°, *U* = 994.1 Å³, *Z* = 2, *F*(000) = 432, ρ (calc.) = 1.373 g cm⁻³, μ (MoK α) = 20.15 cm⁻¹. Space group *P*2₁ (*C*₂², No. 4) from systematic absences: 0*h*0 when *h* is odd.

Crystal Data for (3). C₂₂H₃₆O₅, *M* = 380.5. Monoclinic *a* = 10.814(3), *b* = 7.207(2), *c* = 13.963(3) Å, β = 106.73(1)°, *U* = 1 042.2 Å³, *Z* = 2, *F*(000) = 396, ρ (calc.) = 1.212 g cm⁻³, μ (MoK α) = 0.49 cm⁻¹. Space group *P*2₁(*C*₂², No. 4) from systematic absences: 0*h*0 when *h* is odd.

Crystal Data for (4). C₂₂H₃₄O₃, *M* = 346.5. Monoclinic, *a* = 10.183(8), *b* = 7.552(7), *c* = 13.772(9) Å, β = 106.73(4)°, *U* = 1 010.2 Å³, *Z* = 2, *F*(000) = 380, ρ (calc.) = 1.134 g cm⁻³, μ (MoK α) = 0.40 cm⁻¹. Space group *P*2₁ (*C*₂², No. 4) from systematic absences: 0*h*0 when *h* is odd.

On the basis of precession and Weissenberg photographs taken with Mo-K α and Cu-K α radiation respectively, all three compounds were uniquely assigned to the monoclinic space group *P*2₁; the alternative space group *P*2₁/*m* could be rejected immediately because of the optically active nature of the samples. Lattice parameters were obtained from a least-squares analysis of the setting angles of reflections with θ (Mo-K α) in the range of 10—15° measured on a Hilger and Watts Y290 diffractometer.

Intensity data were collected using graphite monochromatised Mo-K α radiation and processed in the usual way.⁶ In each case a one-quarter sphere of intensities was collected by the θ —2 θ scanning procedure. The number of reflections measured, those with *I* > 3 σ (*I*), and θ_{\max} were

respectively 1 900, 1 428, 25° for (2); 1 997, 1 505, 25° for (3); and 1 049, 698, 20° for (4). The stability of the crystals was checked by measurement of three reflections every 100 measurements. There was no evidence of crystal decay

TABLE 5

2 β -Bromo-3 α -hydroxy-5 α -pregnane-11,20-dione: final positional parameters (bromine, carbon, and oxygen $\times 10^4$, hydrogen $\times 10^3$) with estimated standard deviations in parentheses

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>
Br	4 127(2)	2 500	1 037(1)
O(1)	8 078(10)	988(20)	1 300(7)
O(2)	6 238(9)	3 865(13)	4 713(6)
O(3)	8 458(11)	1 430(19)	9 390(6)
C(1)	6 711(11)	2 623(21)	2 770(7)
C(2)	6 143(13)	2 420(22)	1 572(7)
C(3)	6 654(14)	758(22)	1 180(8)
C(4)	6 561(14)	-909(19)	1 830(8)
C(5)	7 295(11)	-615(18)	2 972(8)
C(6)	7 423(12)	7 685(21)	3 598(9)
C(7)	8 293(12)	8 016(15)	4 697(8)
C(8)	7 762(10)	-485(15)	5 197(7)
C(9)	7 558(10)	1 269(15)	4 539(7)
C(10)	6 634(11)	949(16)	3 408(7)
C(11)	7 166(11)	2 872(16)	5 091(7)
C(12)	8 066(10)	3 165(15)	6 224(8)
C(13)	8 129(10)	1 424(16)	6 835(7)
C(14)	8 685(10)	-60(15)	6 295(7)
C(15)	8 992(13)	-1 613(19)	7 069(9)
C(16)	9 555(15)	-662(23)	8 125(10)
C(17)	9 230(11)	1 395(19)	7 921(8)
C(18)	6 693(11)	1 022(16)	6 936(8)
C(19)	5 139(12)	607(18)	3 412(8)
C(20)	8 814(12)	2 359(27)	8 766(8)
C(21)	8 788(16)	4 243(26)	8 760(10)
H(01)	822	116	65
H(11)	623	360	296
H(12)	766	299	291
H(2)	643	349	132
H(3)	621	49	51
H(41)	694	-190	160
H(42)	561	-109	174
H(5)	822	-24	303
H(61)	782	-324	331
H(62)	653	-270	360
H(71)	921	-162	470
H(72)	839	-304	510
H(8)	687	-93	525
H(9)	844	162	448
H(121)	776	413	652
H(122)	900	343	621
H(14)	950	30	615
H(151)	967	-241	695
H(152)	820	-229	703
H(161)	1 052	-80	839
H(162)	912	-106	858
H(17)	1 004	209	793
H(181)	641	194	727
H(182)	607	84	626
H(183)	674	-9	731
H(191)	480	159	369
H(192)	455	42	272
H(193)	509	-45	380
H(211)	785	460	866
H(212)	933	465	941
H(213)	909	465	823

for (4) but the intensities of the reference reflections for (2) and (3) decreased by 22 and 8% respectively during the data collection, and the intensities were appropriately scaled to compensate for this. Absorption corrections were applied to the data from (2) (transmission coefficients 0.37—0.65); no absorption corrections were needed for the data from crystals (3) and (4).

Determination of the Structures.—The structure of (2) was

solved by the heavy-atom method. A Fourier synthesis based on the heavy-atom phases revealed the positions of the non-hydrogen atoms.

TABLE 6

3 α -Hydroxy-2 β -methoxy-5 α -pregnane-11,20-dione hydrate: final positional parameters (carbon and oxygen $\times 10^4$, hydrogen $\times 10^3$) with estimated standard deviations in parentheses

Atom	x/a	y/b	z/c
O(1)	6 101(3)	8 587	8 672(3)
O(2)	1 451(4)	5 990(9)	5 539(3)
O(3)	73(4)	7 908(9)	988(3)
O(4)	2 886(3)	7 984(8)	8 901(2)
O(5)	2 489(4)	11 485(9)	9 766(3)
C(1)	3 538(5)	7 174(9)	7 393(3)
C(2)	3 939(5)	7 540(9)	8 519(3)
C(3)	4 913(4)	9 128(10)	8 815(3)
C(4)	4 446(5)	10 842(10)	8 189(4)
C(5)	4 146(4)	10 398(9)	7 067(3)
C(6)	3 861(5)	12 126(10)	6 421(4)
C(7)	3 785(5)	11 659(9)	5 347(4)
C(8)	2 771(4)	10 151(9)	4 921(3)
C(9)	3 012(4)	8 411(9)	5 618(3)
C(10)	3 086(4)	8 903(9)	6 714(3)
C(11)	2 101(4)	6 845(9)	5 121(3)
C(12)	2 045(4)	6 371(9)	4 054(4)
C(13)	1 772(4)	8 101(9)	3 397(3)
C(14)	2 786(4)	9 557(10)	3 877(3)
C(15)	2 638(5)	11 062(11)	3 072(4)
C(16)	2 272(7)	9 959(13)	2 086(4)
C(17)	1 993(5)	7 950(11)	2 346(3)
C(18)	393(4)	8 770(10)	3 302(4)
C(19)	1 757(4)	9 583(10)	6 780(4)
C(20)	910(5)	7 014(11)	1 564(3)
C(21)	889(6)	4 953(12)	1 525(4)
C(22)	2 160(6)	6 444(13)	9 032(5)
H(1)	662	792	924
H(11)	285	628	725
H(12)	426	663	723
H(21)	432	637	880
H(31)	500	928	949
H(41)	510	1 175	836
H(42)	368	1 126	831
H(51)	492	986	696
H(61)	454	1 299	668
H(62)	307	1 262	646
H(71)	461	1 122	531
H(72)	355	1 273	494
H(81)	196	1 065	490
H(91)	385	790	568
H(121)	138	548	380
H(122)	285	584	404
H(141)	365	908	404
H(151)	344	1 169	317
H(152)	199	1 190	310
H(161)	296	997	178
H(162)	152	1 047	162
H(171)	272	715	235
H(181)	-21	782	301
H(182)	32	905	395
H(183)	21	984	289
H(191)	114	862	657
H(192)	182	990	746
H(193)	150	1 063	637
H(211)	38	430	95
H(212)	60	452	207
H(213)	175	455	162
H(221)	182	582	839
H(222)	270	556	947
H(223)	148	679	927
H(051)	165	195	952
H(052)	261	31	948

Direct methods were used to solve the structure of (3). The phases of the 209 largest E values were determined by the program SHELX,⁷ and the resulting E -map revealed

17 of the 27 non-hydrogen atoms. The remaining non-hydrogen atoms were found in a subsequent Fourier synthesis phased with the contributions from these 17 atoms; this map also revealed the presence of a molecule of water of crystallisation in the asymmetric unit, in agreement with other analytical procedures (see Experimental section).

TABLE 7

3 α -Hydroxy-2 α -methyl-5 α -pregnane-11,20-dione: final positional parameters (carbon and oxygen $\times 10^4$, hydrogen $\times 10^3$) with estimated standard deviations in parentheses

Atom	x/a	y/b	z/c
O(1)	8 171(11)	894	1 375(7)
O(2)	6 202(12)	3 659(22)	4 755(7)
O(3)	8 286(15)	1 366(27)	9 405(8)
C(1)	6 811(17)	2 482(29)	2 801(11)
C(2)	6 124(17)	2 189(33)	1 667(15)
C(3)	6 737(16)	584(32)	1 289(11)
C(4)	6 755(17)	-1 023(32)	1 941(14)
C(5)	7 395(16)	-728(30)	3 055(12)
C(6)	7 514(16)	-2 395(27)	3 670(12)
C(7)	8 277(15)	-2 138(25)	4 753(12)
C(8)	7 723(17)	-568(31)	5 256(12)
C(9)	7 551(13)	1 158(25)	4 592(10)
C(10)	6 708(13)	795(28)	3 511(9)
C(11)	7 164(19)	2 707(27)	5 180(10)
C(12)	7 967(15)	2 960(25)	6 255(13)
C(13)	7 999(12)	1 236(28)	6 837(9)
C(14)	8 584(14)	-217(29)	6 340(11)
C(15)	8 862(17)	-1 712(28)	7 097(14)
C(16)	9 305(20)	-819(32)	8 174(14)
C(17)	9 081(15)	1 181(29)	7 973(12)
C(18)	6 584(15)	879(25)	6 906(10)
C(19)	5 261(15)	428(25)	3 430(10)
C(20)	8 604(17)	2 112(32)	8 752(13)
C(21)	8 648(22)	4 216(33)	8 728(14)
C(22)	6 215(20)	3 860(31)	1 052(12)
H(01)	839	93	74
H(11)	640	349	304
H(12)	776	276	291
H(2)	519	183	164
H(3)	622	40	58
H(41)	724	-200	172
H(42)	583	-144	185
H(5)	834	-22	313
H(61)	796	-336	341
H(62)	663	-285	367
H(71)	923	-180	475
H(72)	836	-319	512
H(8)	681	-95	531
H(9)	842	147	445
H(121)	757	388	658
H(122)	893	334	637
H(14)	943	9	617
H(151)	958	-256	704
H(152)	806	-249	704
H(161)	1 024	-117	852
H(162)	875	-131	858
H(17)	991	191	799
H(181)	628	178	728
H(182)	593	80	624
H(183)	654	-25	724
H(191)	480	137	365
H(192)	470	17	271
H(193)	514	-63	380

Compounds (2) and (4) were isomorphous. Co-ordinates of the steroidal skeleton C(1)-C(17) from (2) were used to calculate phases for a Fourier synthesis with the data from (4). The resulting electron-density map revealed the position of all non-hydrogen atoms.

Refinement of the Structures.—All three structures were refined by full-matrix least-squares calculations employing the data classified as 'observed' [$I \geq 3\sigma(I)$], with aniso-

tropic thermal parameters for the non-hydrogen atoms. Difference Fourier synthesis calculated at various stages of the refinement located all hydrogen atoms in (2) and (3); the hydrogen atoms bonded to methyl carbons C(21) and C(22) could not be located for (4) but the remaining hydrogen atoms were clearly visible in the difference maps. In all relevant cases the hydrogen atoms were fixed with the appropriate idealised geometry at 0.95 Å from the atom to which they were bonded. The hydrogen atoms were allowed for (with $U_{\text{iso}} = 0.06 \text{ \AA}^2$), but not refined, in all subsequent refinement cycles. Atomic scattering factors for carbon, oxygen, and bromine were taken from International Tables, Vol. IV;⁸ those for hydrogen were those of Stewart *et al.*⁹ At the conclusion of the refinements, difference electron density syntheses were essentially featureless. During the refinements a weighting scheme of the form $w^{\frac{1}{2}} = 1/[\sigma^2(F) + (0.001)F^2]^{\frac{1}{2}}$ was employed. At the conclusion of the refinements the values of R and $R' = [\Sigma w\Delta^2/\Sigma wF_o^2]^{\frac{1}{2}}$ were 0.083 and 0.088 respectively for (2), 0.052 and 0.062 respectively for (3), and 0.072 and 0.077 respectively for (4). The final atomic fractional coordinates and standard deviations for (2), (3), and (4) are in Tables 5, 6, and 7 respectively and molecular dimensions are in Tables 1, 2, and 3. Tables of temperature factors

together with observed and calculated structure factors for all three structures have been deposited as Supplementary Publications SUP 22766 (20 pp.).*

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* For details of the Supplementary Publications scheme, see Notice to Authors No. 7, *J.C.S. Perkin I*, 1979, Index issue.

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