Crystal and Molecular Structure of 20(*S*)-Hydroxypregn-4-en-3-one [20(*S*)-Hydroxyprogesterone]

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Crystals of the steroid 20(*S*)-hydroxyprogesterone are tetragonal, $a = 9{\cdot}422(1)$, $c = 20{\cdot}789(3)$ Å, $Z = 4$, space group $P4_1$. The structure has been determined by direct methods from diffractometer data and refined by full-matrix least-squares to a final R of 0·047 for 1462 observed reflections. All the ring junctions are *trans/trans*. The conformation of ring A is half-chair while that of rings B and C is chair. The cyclopentane ring D is a distorted C(13) envelope. The molecules are linked in the crystal structure ' head-to-tail ' by a hydrogen bond between the C(20) hydroxy-group and the C(3) keto-group.

20(*S*)-HYDROXYPROGESTERONE is a metabolite of progesterone. Although it is only a weak progestational agent, with about one third to one half the progestational activity of progesterone, it seems to have important biological functions. The interrelationship of 20(*S*)-hydroxyprogesterone and progesterone was found [1,2] to be closely connected with the maintenance of pregnancy in some species, particularly the rat and rabbit. In these species a high blood-level of 20(*S*)-hydroxyprogesterone, characteristic of early pregnancy, apparently reinforces the release of pituitary luteinising hormone, thus causing ovulation by a positive feedback mechanism. The ratio of 20(*S*)-hydroxyprogesterone and progesterone varies throughout pregnancy and decreases markedly towards term. It has been suggested [3,4] that in the rat the total progestational activity of ovarian secretion is controlled by the extent to which progesterone is metabolised to 20(*S*)-hydroxyprogesterone. As part of a study of the detailed stereochemistry of steroid hormones we are undertaking the *X*-ray diffraction analysis of these compounds and report here the crystal structure of 20(*S*)-hydroxyprogesterone.

EXPERIMENTAL

Crystal Data.—$C_{21}H_{32}O_2$, $M = 316$. Tetragonal, $a = 9{\cdot}422(1)$, $c = 20{\cdot}789(3)$ Å, $U = 1845{\cdot}2(1)$ Å^3, $D_m = 1{\cdot}13$ (gradient column), $D_c = 1{\cdot}15$, $F(000) = 696$. Cu-K_α radiation, $\lambda = 1{\cdot}5418$ Å; μ(Cu-K_α) = 5·55 cm^{-1}. Space group $P4_1$ or $P4_3$ from systematic absences: $00l$ for $l = 4n + 1$; the former space group was used throughout the analysis, and was confirmed by the known chirality of the molecule.

The crystal used for data collection was a rectangular prism (0·18 × 0·10 × 0·40 mm) mounted with the c axis parallel to the ϕ axis of a Picker four-circle automatic diffractometer equipped with a graphite monochromator. Cell dimensions were derived from a least-squares fit of the measured 2θ angles of ten axial reflections. Intensity data were collected with Cu-K_α radiation. The θ—2θ scanning mode was used, with a speed of 1° min^{-1} for reflections with $\sin\theta \leq 0{\cdot}50$ and a speed of 0·5° min^{-1} for the higher-angle data. Background values were derived from a background curve measured over the full range of 2θ. Of the 3602 intensities measured with $\sin\theta \leq 0{\cdot}896$, 1584 were unique and 122 of these were considered to be unobserved $[I < \sqrt{2}\sigma(I)]$. The agreement factor between measurements of equivalent reflections was 1·3% based on F. Twelve monitor reflections measured *ca.* every 20 h showed no signs of decay over the period of the data collection. The data were corrected for Lorentz and polarisation effects, but not for absorption.

Determination of the Structure.—The structure was solved by direct methods. Normalised structure factors $|E|$ were obtained in the usual way after the structure amplitudes had been corrected for thermal motion using an overall temperature factor obtained from a Wilson plot. The data were then scaled so that the average value of $|E|^2$ was 1·00; the $|E|$ statistics obtained are compared with the theoretical values [5] in Table 1.

TABLE 1

$|E|$ statistics

		Calc.*	
	Obs.	Centro	Non-centro
$\langle\lvert E\rvert\rangle$	0·860	0·798	0·886
$\langle\lvert E\rvert^2\rangle$	1·000	1·000	1·000
$\langle\lvert E^2 - 1\rvert\rangle$	0·823	0·968	0·736
$\lvert E\rvert \geq 1{\cdot}0(\%)$	34·1	32·00	36·80
$\lvert E\rvert \geq 2{\cdot}0(\%)$	2·6	5·00	1·80
$\lvert E\rvert \geq 3{\cdot}0(\%)$	0·2	0·30	0·01

* From ref. 5.

TABLE 2

Starting set of reflections together with final refined values for symbolic phases

h	k	l	$\lvert E\rvert$	Φ Initial	Φ Final
9	2	0	2·96	0	Fixed for origin Definition
3	7	1	3·02	0	
2	4	3	2·39	$a(\pm\pi/4, \pm3\pi/4)$	262°
9	3	5	2·09	$b(\pi/4, 3\pi/4)$	24°

Table 2 lists the starting set of reflections used in the multisolution tangent-formula calculations. This method is a modification of the procedure by Karle and Karle [6] and Germain and Woolfson [7] and has been fully described by us previously.[8] The origin-defining reflections were

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chosen with due regard to limitations imposed by the space group.[9] The symbolic starting reflections were selected from the 25 highest $|E|$ values with acceptance criteria of 2·0 for $E_{\text{min.}}$ and 3·0 for $\alpha_{\text{min.}}$ using a program developed in this laboratory.[10] In the tangent-formula calculations the first hundred reflections with highest $|E|$ values were refined for 10 cycles and then all data (143 terms; $|E| > 1{\cdot}58$) for 20 cycles. The values of $E_{\text{min.}}$, $\alpha_{\text{min.}}$, and $t_{\text{min.}}$ were 2·0, 2·5, and 0·25. The initial phase assigned to one of the symbols [(*b*), Table 2] was restricted to the range 0—π thus effectively defining the enantiomorph. Of the eight resultant phase sets one, with phases calculated for 137 of the 143 reflections with $|E| > 1{\cdot}58$ had a significantly low R_K value of 23%. The phases from this set were used to estimate phases for 294 of the 317 reflections with $|E| > 1{\cdot}25$ by the method of the tangent-formula extension. A Karle map, computed with these phased E values as coefficients indicated the position of a 14-atom fragment of the structure. A structure-factor calculation based on these 14 atoms gave R 0·41. The calculated phases of those reflections with $|E| > 1{\cdot}40$ and $|F_c| > 0{\cdot}6|F_o|$ were used in a further cycle of tangent-formula refinement to generate phases for 493 of the 554 reflections with $|E| > 1{\cdot}00$. A Karle map based on these phased E values displayed the complete structure with the 23 largest peaks in the map corresponding to the 23 non-hydrogen atoms.

TABLE 3

Final fractional co-ordinates for the non-hydrogen atoms

Atom	x	y	z
C(1)	0·7176(4)	−0·0672(4)	0·0885
C(2)	0·5958(4)	−0·1674(4)	0·0714(3)
C(3)	0·4639(4)	−0·0846(4)	0·0595(3)
C(4)	0·4796(4)	0·0516(4)	0·0275(3)
C(5)	0·6056(4)	0·1115(4)	0·0156(2)
C(6)	0·6124(4)	0·2465(4)	−0·0222(3)
C(7)	0·6994(4)	0·3599(4)	0·0119(3)
C(8)	0·8483(4)	0·3037(3)	0·0274(2)
C(9)	0·8377(4)	0·1682(3)	0·0685(2)
C(10)	0·7454(4)	0·0490(4)	0·0377(3)
C(11)	0·9858(4)	0·1152(4)	0·0884(3)
C(12)	1·0778(5)	0·2302(4)	0·1200(3)
C(13)	1·0897(4)	0·3623(4)	0·0781(2)
C(14)	0·9376(4)	0·4128(3)	0·0628(2)
C(15)	0·9562(4)	0·5597(4)	0·0337(3)
C(16)	1·0895(4)	0·6193(4)	0·0681(3)
C(17)	1·1482(4)	0·4986(4)	0·1108(2)
C(18)	1·1744(4)	0·3315(5)	0·0164(3)
C(19)	0·8187(5)	−0·0194(4)	−0·0207(3)
C(20)	1·3080(4)	0·5128(4)	0·1231(3)
C(21)	1·3740(5)	0·3969(5)	0·1623(3)
O(22)	1·3320(3)	0·6418(3)	0·1585(2)
O(23)	0·3451(3)	−0·1296(4)	0·0733(3)

Two cycles of full-matrix least-squares refinement using isotropic temperature factors and unit weights, followed by one cycle with anisotropic temperature factors reduced R from 0·23 to 0·13. The positions of all the hydrogen atoms except those of the methyl and hydroxy-groups were located from a difference electron-density synthesis. The hydrogen atoms were assigned isotropic temperature factors equal to the largest B (B_{11}, B_{22}, or B_{33}) value of the atoms to which they were bonded, and included in the structure-factor calculation. A cycle of anisotropic refinement of the non-hydrogen atoms reduced R to 0·075. As this cycle produced large shifts in some of the carbon atom positions, a difference electron-density map was computed (excluding the contribution of the hydrogen atoms) from which the positions of all hydrogens could be located. Two further cycles of refinement gave a final R of 0·047

TABLE 4

Anisotropic thermal parameters * ($\beta_{ij} \times 10^4$)

Atom	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	127(5)	105(5)	22(1)	−20(4)	−8(2)	12(2)
C(2)	126(5)	99(4)	32(1)	−23(4)	−5(2)	13(2)
C(3)	115(5)	113(5)	31(1)	−19(4)	−3(2)	0(2)
C(4)	95(4)	107(5)	30(1)	−5(4)	0(0)	4(2)
C(5)	105(4)	90(4)	20(1)	−2(4)	−2(5)	5(2)
C(6)	112(5)	120(5)	30(1)	−8(4)	−17(2)	21(2)
C(7)	110(5)	95(5)	30(1)	−1(4)	−6(2)	15(2)
C(8)	96(4)	89(4)	17(1)	−6(3)	−3(1)	5(1)
C(9)	107(4)	88(4)	17(1)	−5(3)	−3(1)	5(1)
C(10)	99(4)	92(4)	17(1)	−4(3)	−1(1)	6(1)
C(11)	124(5)	98(5)	32(1)	−15(4)	−24(2)	13(2)
C(12)	139(6)	113(5)	28(1)	−24(4)	−23(2)	14(2)
C(13)	96(4)	92(4)	20(1)	−9(3)	−2(2)	2(2)
C(14)	99(4)	86(4)	19(1)	−5(3)	4(2)	2(1)
C(15)	131(5)	93(4)	29(1)	−12(4)	−7(2)	9(2)
C(16)	137(5)	96(4)	26(1)	−14(4)	−3(2)	1(2)
C(17)	121(5)	102(4)	18(1)	−19(4)	0(2)	−1(1)
C(18)	120(5)	137(5)	26(1)	9(4)	2(2)	−12(2)
C(19)	137(5)	135(5)	21(1)	−15(5)	3(2)	−8(2)
C(20)	129(5)	131(5)	25(1)	−31(4)	−2(2)	1(2)
C(21)	134(6)	158(7)	41(2)	−13(5)	−24(3)	9(3)
O(22)	161(4)	135(4)	31(1)	−49(3)	−12(2)	−4(1)
O(23)	136(4)	156(5)	62(1)	−46(4)	6(2)	22(2)

* In the form: $\exp -(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)$.

TABLE 5

Final fractional co-ordinates and isotropic thermal parameters (B) for the hydrogen atoms

Atom	x	y	z	B/A^2
H(1C1)	0·810	−0·125	0·096	4·8
H(2C1)	0·701	−0·017	0·128	4·8
H(1C2)	0·592	−0·244	0·104	7·1
H(2C2)	0·599	−0·218	0·023	7·1
H(C4)	0·386	0·091	0·016	4·8
H(1C6)	0·530	0·282	−0·036	5·2
H(2C6)	0·661	0·225	−0·069	5·2
H(1C7)	0·649	0·381	0·054	5·8
H(2C7)	0·698	0·447	−0·011	5·8
H(C8)	0·895	0·279	−0·017	4·3
H(C9)	0·788	0·197	0·108	4·2
H(1C11)	1·034	0·075	0·038	6·0
H(2C11)	0·975	0·028	0·118	6·0
H(1C12)	1·166	0·195	0·140	5·8
H(2C12)	1·043	0·250	0·157	5·8
H(C14)	0·882	0·422	0·100	3·7
H(1C15)	0·851	0·634	0·040	5·8
H(2C15)	0·969	0·552	−0·014	5·8
H(1C16)	1·060	0·703	0·098	5·3
H(2C16)	1·165	0·660	0·032	5·3
H(C17)	1·113	0·500	0·157	4·3
H(1C18)	1·134	0·254	−0·009	5·1
H(2C18)	1·164	0·413	−0·014	5·1
H(3C18)	1·276	0·308	0·027	5·1
H(1C19)	0·912	−0·065	−0·009	6·2
H(2C19)	0·758	−0·077	−0·045	6·2
H(3C19)	0·850	0·038	−0·049	6·2
H(C20)	1·347	0·527	0·081	6·5
H(1C21)	1·374	0·293	0·136	8·2
H(2C21)	1·305	0·363	0·202	8·2
H(3C21)	1·453	0·416	0·187	8·2
H(O22)	1·318	0·739	0·138	6·4

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and a weighted factor R' of 0·063 $\{R' = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{\frac{1}{2}}\}$ excluding unobserved data. A final difference electron-density map showed no peaks $>0{\cdot}3$ eÅ^{-3}. The quantity minimised throughout the refinement was $\Sigma w(F_o - F_c)^2$ where the weights were assigned to the various observations according to counting statistics. Scattering factors for carbon and oxygen were taken from ref. 11 and for hydrogen from ref. 12. Final atomic co-ordinates of the non-hydrogen atoms are listed in Table 3 and thermal parameters in Table 4. Hydrogen atom parameters are given in Table 5. A list of observed and calculated structure amplitudes appears in Supplementary Publication No. 20524 (10 pp., 1 microfiche).*

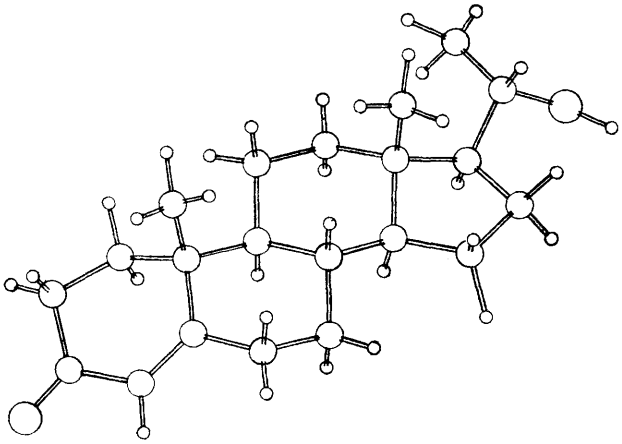

FIGURE 1 A perspective view of the molecule

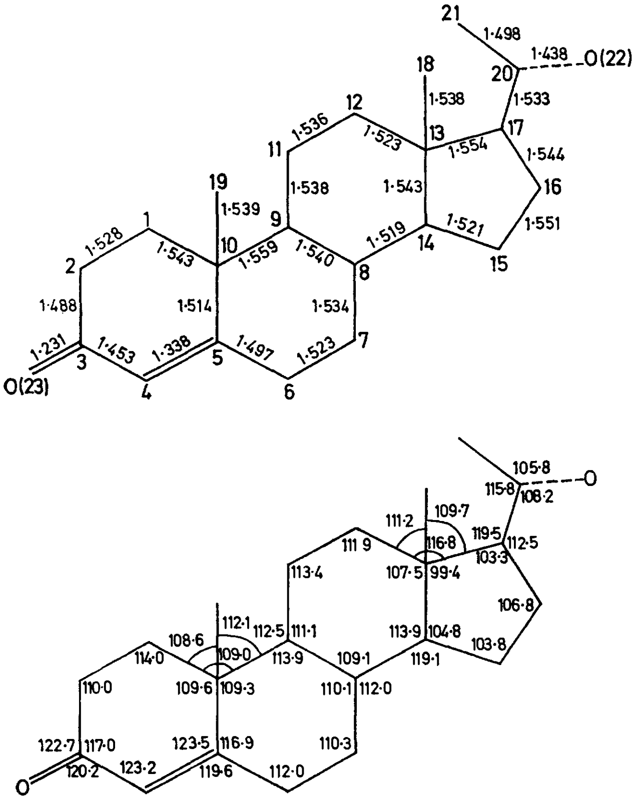

FIGURE 2 Observed bond distances and angles, showing the numbering of the atoms used in the discussion; C(14)–C(13)–C(18) is 111·6, and C(5)–C(10)–C(19) is 108·3°

DISCUSSION

Description of the Molecule.—Figure 1 shows a view of the molecule and conforms to the known chirality of the molecule and the space group ($P4_1$). The bond distances and angles are summarised in Figure 2. The program-estimated standard deviations are 0·006 Å for bond lengths and 0·3° for angles for non-hydrogen atoms. The C–H bond distances range from 0·85—1·22 Å and (tetrahedral) angles involving hydrogen from 91—120°. The O(22)–H(O22) distance is 1·02 Å and the angle C(20)–O(22)–H(O22) 122°. The mean C(sp^3)–C(sp^3) bond length is 1·535 Å in good agreement with the commonly observed value.[13] The valence angles are generally larger than expected for tetrahedral carbon atoms (mean values: ring B 111·1, ring C 111·2°), but are in accord with similar angles found in other steroids.[14]

TABLE 6

Intra-annular torsion angles (ω) compared with theoretical values from minimum-energy calculations. Standard deviations were computed by use of the formula of ref. 15

Ring A			Ring B		
Bond	ω_{obs}	ω_{calc} [a]	Bond	ω_{obs}	ω_{calc} [b]
1–2	−55·8(8)	−62	9–10	−48·8(4)	−46
2–3	36·8(5)	45	10–5	47·4(5)	42·5
3–4	−8·1(7)	−15	5–6	−52·2(5)	−48
4–5	−4·0(7)	0	6–7	55·3(5)	59
5–10	−14·1(6)	−15	7–8	−57·2(4)	−62
10–1	43·9(5)	45	8–9	55·5(4)	56
	' Half-chair '			' Chair '	

Ring C			Ring D		
Bond	ω_{obs}	ω_{calc} [c]	Bond	ω_{obs}	ω_{calc} [d]
12–11	−53·9(5)	−56	13–14	46·2(4)	43·0
11–9	52·0(5)	56	14–15	−32·0(4)	−29·8
9–8	−53·0(4)	−58	15–16	4·9(4)	5·0
8–14	59·2(4)	58	16–17	23·5(4)	21·8
14–13	−59·8(4)	−59	17–13	−41·8(4)	−40·0
13–12	55·0(5)	58			
	' Chair '			' Envelope '	

[a] From ref. 16. [b] From Table 12, col. 7, of ref. 14. [c] From Table 4, col. 7, of ref. 14. [d] From ref. 17.

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* For details see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20.

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The values of the torsion angles in the rings, all of which are *trans*-fused, are listed in Table 6 and compared with appropriate theoretical values. The results of various least-squares planes calculations are given in Table 7.

TABLE 7

Least-squares planes calculations. The perpendicular distance (d) (Å) of an atom from the plane, is given followed in parentheses by d/σ where σ is the mean standard deviation of the atomic position obtained from least-squares refinement. Atoms marked (*) were not included in the mean plane calculation

Plane (1): Ring A
C(2) −0·016 (2·0), C(3) 0·033 (4·1), C(4) −0·036, (4·5), C(5) 0·019 (2·7), C(1)* 0·744 (124·0), C(10)* 0·246 (30·8), O(23)* 0·074 (9·3)

Plane (2): Ring A
C(3) −0·024 (3·0), C(4) −0·026 (3·3), C(5) 0·024 (3·4), O(23) 0·026 (3·3), C(1)* 0·611 (101·8), C(2)* −0·150 (18·8), C(10)* 0·176 (22·0)

Plane (3): Ring B
C(5) −0·037 (5·3), C(10) 0·036 (4·5), C(7) 0·036 (4·5), C(8) −0·035 (5·8), C(6)* −0·626 (78·3), C(9)* 0·628 (104·7)

Plane (4): Ring C
C(9) −0·025 (4·2), C(11) 0·024 (3·0), C(13) −0·024 (3·4), C(14) 0·025 (4·2), C(8)* −0·679 (113·2), C(12)* 0·653 (72·6)

Plane (5): Ring D
C(14) −0·019 (3·2), C(15) 0·029 (3·6), C(16) −0·029 (3·6), C(17) 0·019 (2·7), C(13)* 0·699 (100·0), C(20)* 0·602 (75·3)

Equations of planes where X, Y, Z are co-ordinates in Å

Plane (1): $0{\cdot}0395X + 0{\cdot}4130Y + 0{\cdot}9099Z = 0{\cdot}9359$
Plane (2): $0{\cdot}0099X + 0{\cdot}4579Y + 0{\cdot}8890Z = 0{\cdot}8020$
Plane (3): $-0{\cdot}2172X + 0{\cdot}1448Y + 0{\cdot}9653Z = -0{\cdot}7372$
Plane (4): $-0{\cdot}1978X + 0{\cdot}1520Y + 0{\cdot}9684Z = 0{\cdot}0839$
Plane (5): $-0{\cdot}5467X + 0{\cdot}3648Y + 0{\cdot}7537Z = -2{\cdot}4455$

The A/B junction involves one trigonal [C(5)] and one tetrahedral [C(10)] carbon atom. Ideally, because of the planarity of the conjugated 4-en-3-one system, ring A should be in the sofa-form with C(1) out of plane of the remaining atoms. As discussed by Geise, *et al.*[14] for a similar junction between rings B and C in ecdysone (2β,3β,14α,22β,25-pentahydroxy-5β-cholest-7-en-6-one) the sum of the torsion angles ($\Phi_A + \Phi_B$) at such a junction should be 180° − δ (see Figure 3). In the present structure the value of δ is *ca.* 120° since C(10) is a quaternary carbon atom.[14] For an ideal sofa-form the torsion angle Φ_A (4–5–10–1) would be *ca.* 27° and hence the corresponding angle Φ_B (9–10–5–6) would be *ca.* 33°. However, this value would lead to a considerable flattening of ring B and in 20(*S*)-hydroxyprogesterone, as in ecdysone, it appears energetically more favourable to allow for some puckering of the 4-en-3-one system (see Table 7). As a result, ring A is changed into an unsymetrically distorted half-chair with $\Phi_A - 14{\cdot}1°$; Φ_B is 47·4° and the sum of the angles larger than 180° − δ.

Rings B and C are in the chair conformation and show good agreement between the observed and theoretical torsion angles. Ring D is a distorted C(13) envelope with a phase angle[18] Δ of 22·6°. The best four-atom least-squares plane contains C(14), C(15), C(16), C(17) which are planar to within 0·03 Å. The configuration at C(20) is (*S*) with a torsion angle C(16)–C(17)–C(20)–O(22) of 63·5(5)°. [See Figure 1 for the chirality (*S*) at C(20)]. The steroid skeleton is convex towards the methyl groups C(18) and C(19), with an angle of 14·0° between the vectors C(10)–C(19) and C(13)–C(18). The bending of the molecule is caused by interactions between the methyl groups and the axial hydrogen atoms on C(8) and C(11).

Newman projections down the ring junctions A/B, B/C, and C/D are shown in Figure 3. The A/B junction has already been discussed. The sum of the torsion angles around the B/C junction is 108·5° and the decrease from the expected value[14] of 115° may be attributed to the steric interactions between the methyl groups and axial hydrogens. The sum of the torsion angles around the C/D junction is 106·0° which is close to the empirical value.[14]

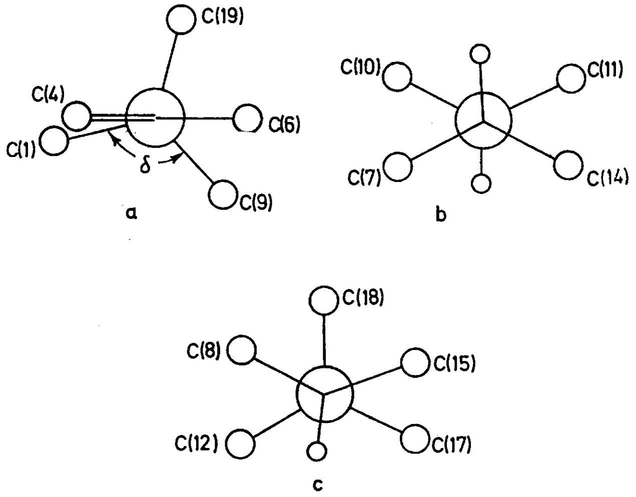

FIGURE 3 Newman projections down the three ring-junctions; a, A/B junction C(5)–C(10); b, B/C junction C(8)–C(9); and c, C/D junction C(14)–C(13)

TABLE 8

Interatomic distances <4·0 Å

C(2) · · · O(22^{I})	3·563	C(2) · · · O(22^{III})	3·749
C(3) · · · O(22^{I})	3·525	C(4) · · · C(17^{III})	3·948
O(23) · · · C(16^{I})	3·378	C(7) · · · O(22^{IV})	3·653
O(23) · · · C(20^{I})	3·542	C(19) · · · C(16^{III})	3·897
C(18) · · · C(4^{II})	3·908	C(19) · · · O(22^{III})	3·690

Roman numerals as superscripts refer to the following equivalent positions relative to the reference molecule at x, y, z:

I $x - 1, y - 1, z$
II $x - 1, y, z$
III $\bar{y}, x + 1, 3/4 + z - 1$
IV $\bar{y}, x + 2, 3/4 + z - 1$

Packing of the Molecules.—A hydrogen bond between the 20-hydroxy-group and the 3-keto-group

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[18] C. Altona, H. J. Geise, and C. Romers, *Tetrahedron*, 1968, **24**, 13.

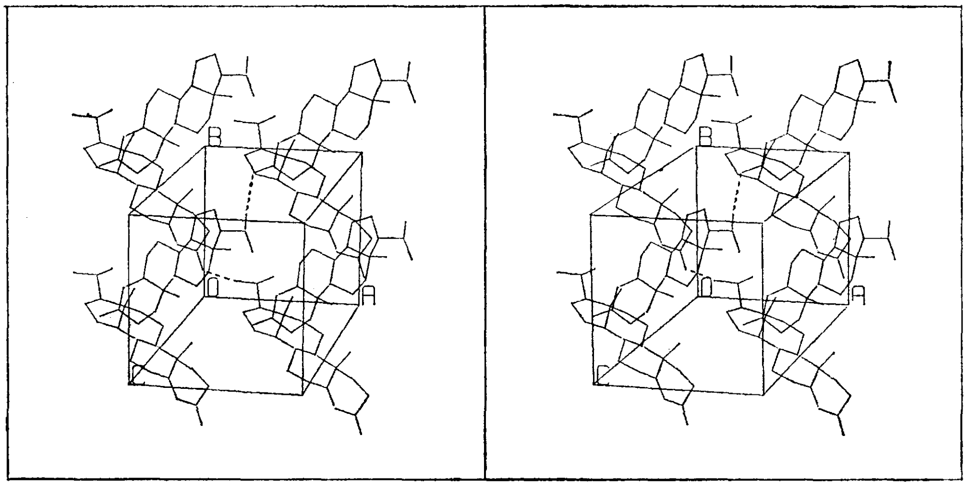

FIGURE 4 A stereo packing-diagram; the hydrogen bond is shown in dotted lines

[O(22) · · · O(23) 2·792 Å; H(O22)–O(22) · · · O(23) 19·4°] links the molecules 'head-to-tail' to form ribbons extending through the crystal parallel to the (110) and ($\bar{1}\bar{1}0$) planes (see Figure 4). The steroid nuclei lie almost parallel to the *ab* plane with some overlap of the A and D rings of symmetry-related molecules. Apart from the hydrogen bond there are only ten intermolecular distances <4·0 Å (Table 8). The closest points of contacts are between the A and D rings of hydrogen bonded molecules and the A and D rings of overlapping molecules.

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