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18. The Molecular and Crystal Structure of ψ-Retroprogesterone

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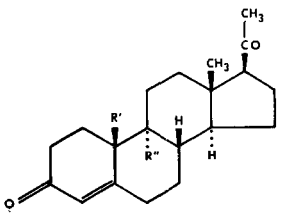
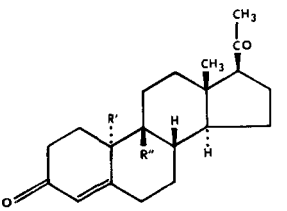
(24. X. 73)

Summary. The crystal structure of synthetic, racemic ψ-retroprogesterone (9α-methyl-19-norprogesterone) has been determined by X-ray analysis and refined to R = 0.050. The analysis was carried out to establish the relative configuration at positions 9, 10 and 17 in connection with the biological activity of the compound.

An important chapter in the history of steroids [1] grew out from the recognition that the steric 'bulk', represented by the 10β-methyl group (*i.e.*, C(19)) of *corpus luteum* hormone progesterone (**1**) is actually detrimental to what has been defined as



1: R′ = CH_3; R″ = H: progesterone
2: R′ = H; R″ = H: 19-norprogesterone
4: R′ = H; R″ = CH_3: ψ = retroprogesterone



3: R′ = CH_3; R″ = H: retroprogesterone

Table 1. *Crystal Data and Intensity Statistic*

ψ-Retroprogesterone, $C_{21}H_{30}O_2$, M = 314,469	
Monoclinic, space group: $P2_1/c$	
Cell dimensions:	**a** = 7.55(1), **b** = 22.93(3), **c** = 10.63(2) Å
	β = 107.5(1)°, **V** = 1755 Å³
	D_m = 1.18(1), D_x = 1.19 Z = 4
Intensities:	total number of observations: 2734 ($\sin\theta/\lambda \leqslant 0.56$ Å^{-1})
	number of significant reflexions: 1494 ($I \geqslant 3\sigma(I)$)
	$\overline{B}$ (overall) = 4.3 Å²
	$\langle\|E\|\rangle = 0.789$ $\langle\|E^2-1\|\rangle = 1.057$ $\langle E^2\rangle = 1.050$

'progestational activity'. Two types of structural modification aiming at diminution of this bulk led to compounds with significantly higher biological potency. One consisted in simply substituting hydrogen for the 10β-methyl group, leading to the class of *19-norsteroids* [1], *e.g.*, to **2**. The other involved inversion of the configurations at C(9) and C(10) to yield an 'unnatural' skeleton that, without drastic changes in overall geometry, contained the 10-methyl group on the α-side. Compounds in this class are called *'retrosteroids'* [2], *e.g.*, **3**, 'retroprogesterone'.

Table 2. *Coordinates and anisotropic temperature factors for C- and O-atoms of ψ-retroprogesterone.* (In brackets the LS-calculated e.s.d.'s).

	X	Y	Z
C1	-.1514(5)	-.1758(1)	.7136(3)
C2	-.2072(5)	-.2166(2)	.5959(4)
C3	-.1008(6)	-.2025(1)	.5022(4)
C4	.0927(5)	-.1867(1)	.5601(3)
C5	.1707(5)	-.1772(1)	.6890(3)
C6	.3771(5)	-.1711(1)	.7450(4)
C7	.4400(5)	-.1261(1)	.8541(4)
C8	.3360(4)	-.1336(1)	.9556(3)
C9	.1233(4)	-.1271(1)	.8888(3)
C10	.0587(4)	-.1767(1)	.7851(3)
C11	.0235(5)	-.1338(1)	.9940(3)
C12	.0977(5)	-.0936(1)	1.1149(3)
C13	.3048(4)	-.1026(1)	1.1789(3)
C14	.4022(4)	-.0928(1)	1.0732(3)
C15	.6091(5)	-.0912(1)	1.1508(4)
C16	.6135(5)	-.0617(1)	1.2814(4)
C17	.4095(5)	-.0566(1)	1.2821(3)
O18	-.1699(4)	-.2066(1)	.3824(2)
C19	.0744(6)	-.0674(1)	.8200(4)
C20	.3433(5)	-.1638(1)	1.2416(3)
C21	.3835(5)	-.0618(1)	1.4167(3)
C22	.2013(6)	-.0434(1)	1.4311(4)
O23	.5037(4)	-.0801(1)	1.5113(2)

	B(11)	B(22)	B(33)	B(12)	B(13)	B(23)
C1	1572(95)	359(11)	977(50)	122(27)	142(54)	-79(20)
C2	1899(106)	414(13)	1008(54)	141(30)	115(60)	-176(22)
C3	3005(126)	328(12)	886(52)	407(32)	111(65)	-58(19)
C4	2787(117)	253(10)	1033(51)	143(28)	832(64)	48(18)
C5	2139(98)	186(8)	972(47)	98(23)	611(55)	27(16)
C6	1974(101)	288(10)	1338(58)	-96(27)	904(62)	-116(20)
C7	1902(101)	285(10)	1466(58)	-140(27)	962(63)	-105(20)
C8	1255(81)	191(8)	1090(48)	-4(21)	499(49)	14(16)
C9	1300(84)	203(8)	878(44)	112(21)	364(48)	42(15)
C10	1324(85)	226(8)	819(45)	106(21)	307(49)	22(16)
C11	1258(85)	328(11)	951(48)	71(25)	331(50)	-53(18)
C12	1480(89)	307(10)	915(47)	56(24)	381(52)	-57(17)
C13	1309(81)	184(8)	912(45)	-8(20)	267(47)	22(15)
C14	1412(84)	181(8)	1088(48)	-23(21)	436(51)	-11(16)
C15	1527(95)	298(11)	1566(60)	-171(26)	450(59)	-131(21)
C16	1845(98)	280(10)	1476(60)	-221(27)	320(61)	-146(21)
C17	1773(91)	189(8)	974(46)	-16(23)	277(52)	7(16)
O18	3995(107)	573(12)	931(37)	624(29)	33(50)	-114(17)
C19	3229(127)	218(10)	1171(55)	270(28)	459(66)	59(18)
C20	2388(111)	215(9)	1028(52)	-113(25)	191(60)	57(17)
C21	2586(109)	192(8)	1042(50)	-72(26)	109(58)	-16(17)
C22	2984(127)	303(11)	1068(56)	29(30)	579(67)	-51(20)
O23	3165(86)	372(9)	1241(39)	77(22)	-41(46)	135(14)

A third class can be derived by shifting the methyl group from the 10β-position to the 9α. It would then be sterically analogous to the 10α-methyl group in retrosteroids while preserving the configuration of the carbon skeleton. It is appropriate to give the name *ψ-(pseudo)-retrosteroids* to this class of 9α-methyl-19-nor-derivatives and, to compound **4**, ψ-retroprogesterone.

The preparation of these compounds has now been reported [3]. While the configuration at C(9) could be firmly established, that at C(17) and, more importantly, at C(10), rested only on mechanistic considerations and analogy. An X-ray analysis of racemic ψ-retroprogesterone, prepared for this purpose by total synthesis [3], was therefore undertaken to establish the structure unequivocally.

1. Crystallographic Data. – Racemic ψ-retroprogesterone was recrystallized from methanol as colorless, prismatic needles. Symmetry and cell dimensions were determined from precession photographs; intensities were measured on a Linear Diffractometer [4] with graphite monochromatized MoKα-radiation and reduced to absolute values by the *Wilson*-method [5]. Absorption corrections were not applied. Crystal data and intensity statistics are summarized in Table 1.

2. Structure Analysis. – The phases (signs) of 481 reflexions with $|E| \geqslant 1.1$ were determined by an automated symbolic addition procedure [6]. The structure was clear-

Table 3. *Coordinates and isotropic temperature factors for H-atoms in ψ-retroprogesterone.* (In brackets the LS-calculated e.s.d.'s)

	X	Y	Z	B
H1A	-.183(4)	-.134(1)	.683(3)	2.45(81)
H1B	-.223(4)	-.188(1)	.781(3)	2.89(86)
H2A	-.180(5)	-.260(1)	.627(3)	3.43(90)
H2B	-.344(5)	-.217(1)	.555(3)	3.91(96)
H4	.179(5)	-.181(1)	.500(3)	3.60(93)
H6A	.435(4)	-.212(1)	.785(3)	2.40(82)
H6B	.433(4)	-.161(1)	.664(3)	3.15(88)
H7A	.422(4)	-.085(1)	.819(3)	2.78(84)
H7B	.576(4)	-.132(1)	.900(3)	3.19(87)
H8	.359(4)	-.177(1)	.996(3)	1.31(72)
H10	.092(4)	-.218(1)	.836(2)	1.40(73)
H11A	.038(4)	-.178(1)	1.027(3)	2.11(79)
H11B	-.112(4)	-.124(1)	.952(3)	3.14(87)
H12A	.031(4)	-.103(1)	1.183(3)	2.76(85)
H12B	.074(4)	-.052(1)	1.085(3)	2.00(77)
H14	.367(4)	-.052(1)	1.034(3)	2.17(79)
H15A	.653(4)	-.132(1)	1.169(3)	2.59(83)
H15B	.677(4)	-.068(1)	1.097(3)	3.03(89)
H16A	.686(5)	-.089(1)	1.363(3)	3.26(89)
H16B	.666(4)	-.023(1)	1.291(3)	2.97(87)
H17	.360(4)	-.016(1)	1.247(3)	2.56(82)
H20A	.297(4)	-.196(1)	1.167(3)	2.02(78)
H20B	.475(4)	-.172(1)	1.293(3)	3.01(87)
H20C	.274(4)	-.169(1)	1.303(3)	3.28(90)
H19A	.133(5)	-.064(1)	.748(3)	3.62(89)
H19B	-.064(4)	-.063(1)	.780(3)	3.55(90)
H19C	.123(4)	-.034(1)	.885(3)	3.48(92)
H22A	.196(4)	-.049(1)	1.524(3)	3.86(92)
H22B	.180(5)	-.002(1)	1.409(3)	3.98(94)
H22C	.099(5)	-.067(1)	1.371(3)	3.72(91)

ly indicated in the resultant electron density map. The position of the heavier atoms were refined with anisotropic temperature factors, those of the hydrogens – located from a difference *Fourier*-map – with isotropic temperature factors in a number of LS-cycles. A scale factor and a isotropic extinction factor [7] were also included in the pa-

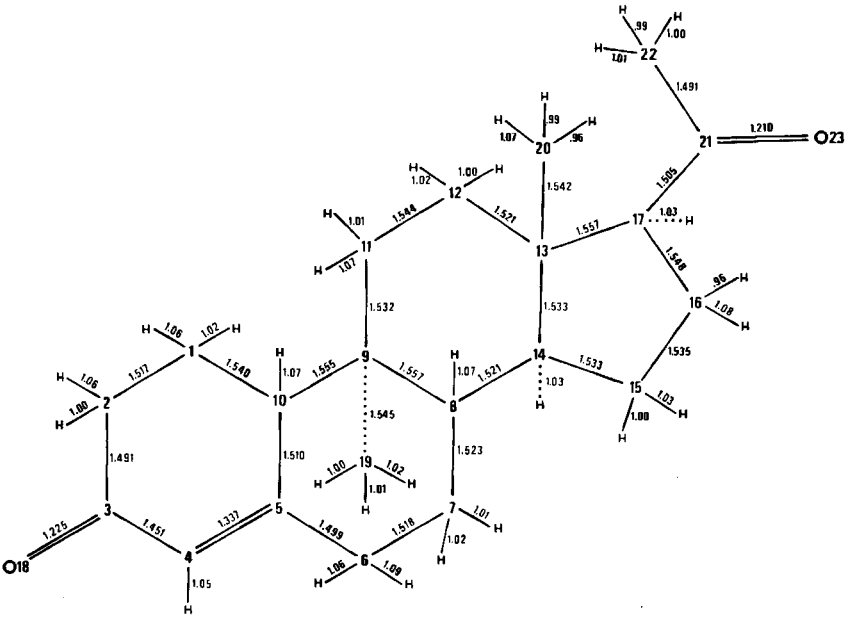


Fig. 1. *Bond lengths in ψ-retroprogesterone. E.s.d. for C—C bonds is about 0.014* Å.

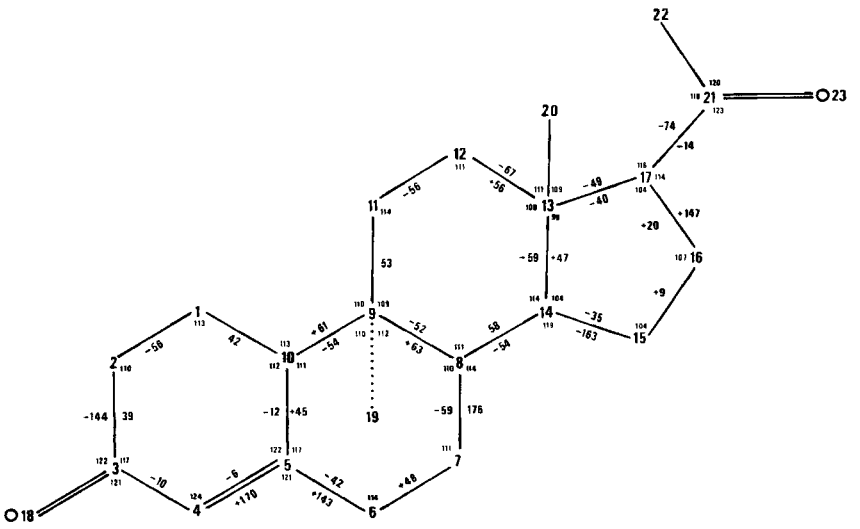


Fig. 2. *Bond angles and torsion angles in ψ-retroprogesterone. E.s.d. for (C—C—C) angles is about 0.8°, for torsion angles 1°.*

rameter set. Complete convergence of all parameters was reached at R = 0.050 (329 parameters, 1494 significant observations). A list of structure factors can be obtained upon request from the authors (HPW).

3. Results. – A list of the refined atomic parameters with standard deviations is given in Tables 2 and 3. The atom numbering and some geometrical parameters of the molecular structure are shown in Fig. 1 and 2. The mean of the 16 C(sp^3)–C(sp^3) bond lengths is 1.536 Å with standard deviation 0.014[1]). This is about twice the standard deviation of a single bond length according to the e.s.d.'s listed in Table 2. If bond lengths are assumed equal, this would suggest that the LS e.s.d.'s are underestimated. Realistic standard deviations for geometrical parameters involving C and O are then about 0.014 Å for bonds, 0.8° for bond angles and about 1° for torsion angles.

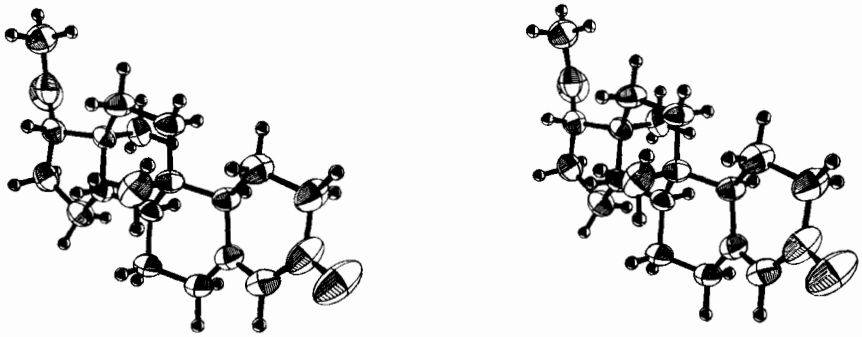


Fig. 3. *Stereoscopic view of the molecule.* The 50%-thermal vibration ellipsoids are drawn for carbon and oxygen atoms. Hydrogens have been given a common isotropic temperature factor of 1 Å^2 for the purpose of this drawing.

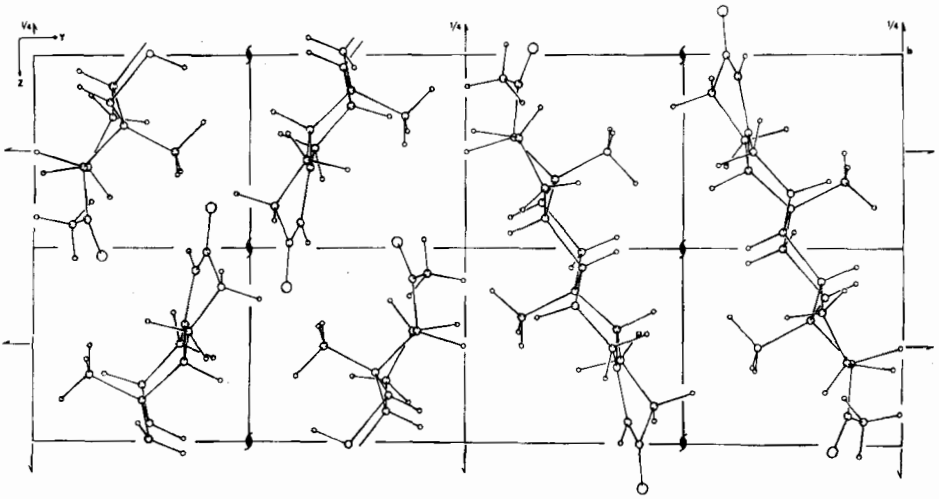


Fig. 4. *Packing diagram.*

[1]) $\sigma(b) = \left[\sum_{i=1}^{16}(b^i - \bar{b})^2/(n-1)\right]^{1/2}$ for individual bond length.

The principal axes of the 50%-thermal vibration ellipsoids for C- and O-atoms vary between 0.18 and 0.35 Å. A qualitative impression of the relative orientation of the ellipsoids can be obtained from the stereoscopic drawing of the molecule in Fig. 3[2]), which also shows the overall conformation of the steroid. The A-ring has a 'twist'-conformation with an approximate twofold-axis through the middle of the 4,5-double bond and C(1)–C(2). The B-ring has a chair conformation slightly distorted due to the sp^2-character of C(5); the C-ring is an almost undistorted chair conformation, with torsion angles slightly less than the ideal 60°, $\langle|\tau|\rangle = 56°$, and the five-membered D-ring is in an envelope conformation with C(13) as flap (for torsion angles see Fig. 2). The β-acetyl substituent at C(17) has the keto group almost *syn*-planar with C(16)–C(17), which brings O(23) to a distance of about 2.4 Å from the β-hydrogen on C(16). A calculation of all intra- and intermolecular distances revealed no abnormally close contacts. A packing diagram is shown in Fig. 4.

The authors express sincere thanks to Dr. *R. V. Coombs* and co-workers at *Sandoz-Wander Inc.*, Hanover, N.J., who prepared the rac-ψ-retroprogesterone by total synthesis.

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[2]) This drawing has been calculated with the program ORTEP (*C. K. Johnson*, Oak Ridge (1965)), adapted to an U-1108 Computer, plotted on a *Benson-Lehner* Plotter.

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19. A Chemical Study of *Burley* Tobacco Flavour (*Nicotiana tabacum* L.) IV. Identification of Seven New Solanone Metabolites Including 7,8-Dioxabicyclo[3.2.1.]octane- and 4,9-Dioxabicyclo[3.3.1]nonane Derivatives[1])

Preliminary Communication

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(28. XI. 73)

To date, our continuing study of *Burley tobacco condensate*[2]) has already lead to the isolation and identification of more than 300 constituents of this flavour [1], including new chemical entities such as *solanofuran* and *spiroxabovolide* [1c]. Investi-

[1]) For the 3rd publication of this series see [1c].
[2]) *Burley* tobacco condensate and fractions B1, B2 and B3 were prepared as previously described [1a–b].