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19-Norpregn-4-ene-3,20-dione*

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Abstract. $C_{20}H_{28}O_2$, $M_r = 300{\cdot}4$, $\rho_x = 1{\cdot}17$ Mg m^{-3}, orthorhombic, $P2_12_12_1$, $Z = 4$, $a = 14{\cdot}539$ (3), $b = 15{\cdot}457$ (2), $c = 7{\cdot}579$ (1) Å, $V = 1703{\cdot}2$ Å^3. Final $R = 0{\cdot}055$ for 1456 independent reflections. The *A* ring is observed in a 1α,2β-half-chair conformation. A comparison with the structure of progesterone suggests that in the title compound the conjugation of the 4-ene-3-one system has been destabilized and the *A* ring may be more susceptible to conversion to the conformer postulated to enhance binding to the progesterone receptor.

Introduction. A specific *A*-ring conformation has been shown to be common to a number of steroids with high affinity for the progesterone receptor (Duax, Cody, Griffin, Rohrer & Weeks, 1978). The high-affinity conformation (which we have called the inverted *A* ring) is one in which the 2β-hydrogen atom assumes an equatorial rather than an axial position. Enhanced binding of 19-norprogesterone to the progesterone receptor has been attributed to removal of an unfavorable hydrophobic interaction between the methyl group and the receptor. The crystallographic observation of an equilibrium between the normal and inverted *A*-ring conformation in 19-nortestosterone (Precigoux, Busetta, Courseille & Hospital, 1975), suggests an alternative possibility that 19-methyl removal stabilizes the high affinity (inverted) conformer. In order to test this hypothesis the X-ray crystal structure of 19-norprogesterone was undertaken.

Crystallographic data were measured on a specimen crystal of dimensions 0·2 × 0·4 × 0·6 mm with an Enraf–Nonius CAD-4 automated diffractometer using Ni-filtered Cu $K\alpha$ radiation at room temperature. The crystals showed systematic absences in the diffraction data consistent with the orthorhombic space group $P2_12_12_1$. Lattice dimensions were refined by a least-squares fit to a set of measured θ values [λ(Cu $K\alpha$) = 1·54051 Å] for 40 reflections in the interval $20° < \theta < 30°$. Integrated relative intensities for 2015 independent reflections accessible with $\theta < 75°$ were measured by ω–2θ scans; 1456 of these reflections were measured to be observed above background ($I > 2\sigma_I$).

The intensities were reduced to structure-factor amplitudes, and phase angles sufficient to locate the nonhydrogen atoms were obtained using the direct-methods program *MULTAN* (Germain, Main & Woolfson, 1971). All but one of the H atoms were located in a difference electron-density map prepared at an intermediate stage in the least-squares refinement of structural parameters. In the final cycles of full-matrix least-squares refinement, positional parameters for all atoms, anisotropic thermal vibration parameters for the nonhydrogen atoms and isotropic thermal vibration parameters for the H atoms were varied. The quantities $(1/\sigma_F^2)$ were used to weight the least-squares differences for the observed data, where σ_F was as defined by Stout & Jensen (1968, p. 457, equation H14) but with an instability factor of 0·06 (instead of 0·01); unobserved data were given zero weight. The final values of the residual, $R = \sum ||F_o| - |F_c|| / \sum |F_o|$, were 0·055 for the observed data and 0·080 for all the measured data. The final weighted residual was 0·075. The scattering factors used throughout the refinement were generated from the coefficients given in *International Tables for X-ray Crystallography* (1974). Final positional parameters are listed in Table 1.‡

Discussion. The crystallographically observed conformation of the steroid molecule is illustrated in Fig. 1 and the molecular packing is illustrated in Fig. 2. Fig. 3 shows the atom numbering and the intramolecular dimensions involving the nonhydrogen atoms; estimated standard deviations range from 0·002 to 0·004 Å for the bond distances, from 0·1 to 0·2° for the bond angles, and from 0·1 to 0·4° for the torsion angles. Although the *A* ring is observed to be in the normal conformation, a comparison with the structure of progesterone suggests that the ring may be somewhat destabilized relative to the inverted (high-affinity) conformer.

The crystallographic studies of two polymorphs of progesterone (Campsteyn, Dupont & Dideberg, 1972; Serantoni, Krajewski, Mongiorgi & Riva di San-

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‡ Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34514 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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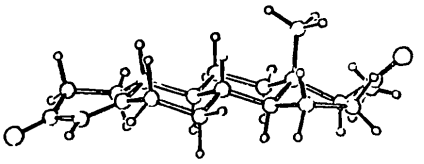

Fig. 1. *ORTEP* (Johnson, 1965) drawing of the structure.

Table 1. *Atomic coordinates of* 19-*norpregn*-4-*ene*-3,20-*dione*

	x	*y*	*z*
C(1)	0·7810 (2)	0·7985 (2)	0·6163 (5)
C(2)	0·8596 (2)	0·7364 (3)	0·6454 (6)
C(3)	0·9158 (2)	0·7598 (3)	0·8043 (7)
C(4)	0·8656 (2)	0·7974 (2)	0·9514 (6)
C(5)	0·7756 (2)	0·8180 (2)	0·9468 (4)
C(6)	0·7245 (3)	0·8460 (3)	1·1106 (5)
C(7)	0·6671 (2)	0·9267 (3)	1·0780 (4)
C(8)	0·6012 (2)	0·9122 (2)	0·9241 (4)
C(9)	0·6569 (2)	0·8904 (2)	0·7571 (4)
C(10)	0·7197 (2)	0·8113 (2)	0·7789 (4)
C(11)	0·5929 (2)	0·8810 (2)	0·5963 (4)
C(12)	0·5294 (2)	0·9588 (2)	0·5680 (4)
C(13)	0·4741 (2)	0·9787 (2)	0·7347 (4)
C(14)	0·5421 (2)	0·9913 (2)	0·8892 (4)
C(15)	0·4829 (3)	1·0282 (3)	1·0384 (5)
C(16)	0·4100 (2)	1·0854 (3)	0·9411 (5)
C(17)	0·4235 (2)	1·0693 (2)	0·7405 (5)
C(18)	0·4039 (2)	0·9063 (2)	0·7704 (5)
C(20)	0·3383 (2)	1·0752 (2)	0·6325 (6)
C(21)	0·3494 (3)	1·0870 (3)	0·4368 (6)
O(3)	0·9986 (2)	0·7459 (2)	0·8120 (5)
O(20)	0·2628 (2)	1·0704 (2)	0·6940 (4)
H(1*A*)	0·807 (2)	0·861 (2)	0·587 (5)
H(1*B*)	0·745 (2)	0·774 (3)	0·530 (6)
H(2*A*)	0·902 (3)	0·732 (3)	0·533 (6)
H(2*B*)	0·834 (2)	0·672 (3)	0·660 (5)
H(4)	0·901 (2)	0·809 (2)	1·065 (6)
H(6*A*)	0·783 (2)	0·858 (3)	1·191 (5)
H(6*B*)	0·685 (2)	0·785 (2)	1·142 (5)
H(7*A*)	0·713 (2)	0·983 (2)	1·058 (5)
H(7*B*)	0·626 (2)	0·943 (3)	1·175 (5)
H(8*B*)	0·561 (2)	0·864 (2)	0·951 (4)
H(9*A*)	0·699 (2)	0·942 (2)	0·739 (4)
H(10*B*)	0·683 (2)	0·749 (2)	0·780 (6)
H(11*A*)	0·615 (2)	0·877 (3)	0·497 (5)
H(11*B*)	0·549 (2)	0·824 (2)	0·626 (4)
H(12*A*)	0·570 (2)	1·008 (2)	0·540 (4)
H(12*B*)	0·495 (2)	0·941 (2)	0·484 (4)
H(14*A*)	0·591 (2)	1·034 (2)	0·850 (4)
H(15*A*)	0·535 (2)	1·066 (2)	1·122 (5)
H(15*B*)	0·457 (4)	0·974 (4)	1·104 (9)
H(16*A*)	0·401 (2)	1·148 (3)	0·979 (6)
H(16*B*)	0·342 (2)	1·065 (3)	0·972 (5)
H(17*A*)	0·458 (2)	1·114 (2)	0·700 (5)
H(18*A*)	0·429 (2)	0·844 (2)	0·796 (4)
H(18*B*)	0·358 (2)	0·926 (3)	0·870 (7)
H(18*C*)	0·360 (2)	0·907 (2)	0·673 (5)
H(21*A*)	0·314 (2)	1·129 (2)	0·391 (4)
T(21*B*)*	0·419	1·113	0·435
H(21*C*)	0·354 (2)	1·033 (2)	0·374 (6)

* *T* = theoretical hydrogen positions.

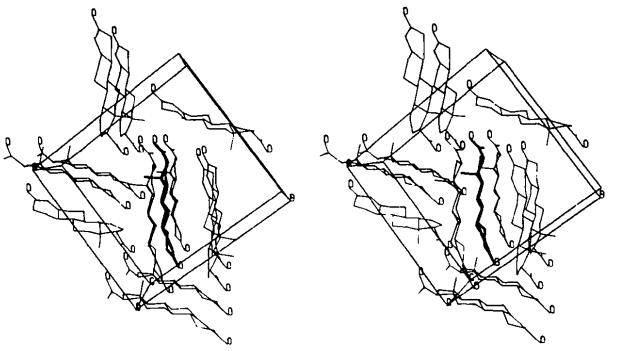

Fig. 2. Stereodiagram of the crystal packing viewed parallel to the width of the steroid.

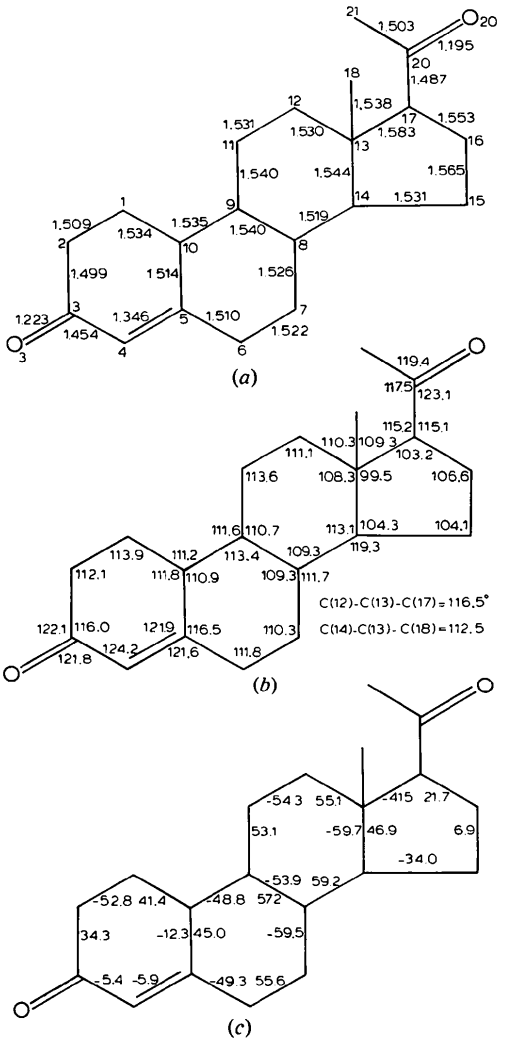

Fig. 3. Intramolecular dimensions of the steroid molecule. (*a*) Bond distances (Å), (*b*) bond angles (°), (*c*) endocyclic torsion angles (°). A torsion angle $\alpha-\beta-\gamma-\delta$ is positive if, when viewed down the $\beta-\gamma$ bond, the $\alpha-\beta$ bond will eclipse the $\gamma-\delta$ bond when rotated less than 180° in a clockwise direction.

Table 2. *Comparison of asymmetry parameters and torsion angles for progesterone and related compounds*

	$\Delta C_s(1)$	$\Delta C_2(1,2)$	O(3)–C(3)–C(4)–C(5)	C(13)–C(17)–C(20)–O(20)	Reference
Progesterone (1)	7·8°	18·5°	−177·3°	115·8°	*a*
(2)	11·5	12·6	179·5	106·1	*b*
(3)	19·3	4·0	175·8	114·6	*c*
19-Norprogesterone	15·7	7·0	176·6	101·5	*d*
Medroxyprogesterone acetate	21·1	4·0	180·0	100·3	*e*

References: (*a*) Campsteyn, Dupont & Dideberg (1972). (*b*) Serantoni, Krajewski, Mongiorgi & Riva di Sanseverino (1975). (*c*) Dideberg, Dupont & Campsteyn (1975). (*d*) This paper. (*e*) Duax, Cody, Griffin, Rohrer & Weeks (1978).

severino, 1975) and a progesterone–resorcinol complex (Dideberg, Dupont & Campsteyn, 1975) have illustrated that the principal regions of flexibility in progesterone are the *A* ring and the progesterone side chain. In Table 2 the asymmetry parameters that define the ring conformation (Duax, Weeks & Rohrer, 1976) and torsion angles that define the 3-ene-4-one conjugation and side-chain conformation are compared for the three progesterone molecules and for 19-norprogesterone.

A correlation has been observed between *A*-ring conformation and 3-ene-4-one conjugation (Duax, Cody, Griffin, Rohrer & Weeks, 1978). Perfect conjugation [O(3)–C(3)–C(4)–C(5) = 180°] is favored when the *A* ring has a conformation midway between the symmetric 1α-sofa and 1α,2β-half-chair conformations [progesterone (2) in Table 2]. In over 40 examples, the O(3)–C(3)–C(4)–C(5) torsion angle rarely differs from 180° by more than 7° (Duax & Norton, 1975). Steric influences that distort the O(3)–C(3)–C(4)–C(5) torsion angle further than this may induce ring inversion if it is accompanied by restoration of full conjugation, as in the case of medroxyprogesterone acetate (Duax, Cody, Griffin, Rohrer & Weeks, 1978). The *A* ring of progesterone is seen to vary on either side of the midpoint, the O(3)–C(3)–C(4)–C(5) torsion angle being negative as the ring moves toward a 1α-sofa conformation and positive as it moves toward the 1α,2β-half-chair conformation. The largest deviation of the 4-ene-3-one group from planarity is achieved in the resorcinol complex where the 3-carbonyl is hydrogen bonded. This is the only structure in Table 2 having a hydrogen bond to O(3).

The *A* ring of 19-norprogesterone is seen to be most similar to that observed for progesterone in the resorcinol complex. It is conceivable that hydrogen bonding to the 3-carbonyl of 19-norprogesterone could induce or permit an additional distortion of the O(3)–C(3)–C(4)–C(5) torsion angle sufficient to alter the relative conformational stability of the *A* ring in favor of the inverted (high-affinity binding) form. It should be noted that the observed structure remains compatible with the possibility that the 19-methyl group has an unfavorable interaction with the receptor and that its removal permits better binding.

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