The Crystal and Molecular Structure of *d*-Norgestrel, a Progestational Steroid

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dl-Norgestrel is a highly active, totally synthetic progestational steroid in widespread use for fertility control. The crystal and molecular structure of the *d* enantiomorph, the biologically active portion, has been determined by single-crystal X-ray diffraction analysis using direct methods. The space group is $P2_12_12_1$, with $a = 20\cdot673$ (6), $b = 12\cdot797$ (4), and $c = 6\cdot567$ (1) Å; $Z = 4$. 1628 reflections were collected ($2\theta < 127°$) on a Picker FACS-1 four-circle diffractometer, and 1594 were considered observed. Hydrogen atoms were located, and refinement was carried out on all the data with full-matrix least-squares calculations to an R of 0·048. The molecules are linked together in the crystal lattice by hydrogen bonding.

Introduction

The widespread use of progestational steroids for fertility control purposes has resulted in an ever-increasing need for readily available supplies of highly effective, safe steroid substances. Suitable compounds derivable from natural sources could not fill the need, and the only practical solution was the development of commercially feasible, totally synthetic routes of preparation. Herschel Smith and his coworkers (1964) designed one of the more successful approaches, and prepared a wide variety of new 13-alkylgonane derivatives, one of which *dl*-13β-ethyl-17α-ethynyl-17β-hydroxygon-4-en-3-one (*dl*-norgestrel), had outstanding clinical effectiveness, being nine times as active as the naturally occurring hormonal steroid, progesterone (Buzby, Walk & Smith, 1966).

dl-Norgestrel is one of the active ingredients of the oral contraceptive, Ovral®, but it is only the *d* enantiomorph that is biologically active (Edgren, Smith, Hughes, Smith & Greenspan, 1963). The total synthesis of *d*-norgestrel was achieved (Edgren *et al.*, 1963), and it has been found that both *dl* and *d* norgestrel crystallize in the same space group with identical cell dimensions (DeAngelis, 1974). *dl*-Norgestrel crystallizes in a mixture of *d* crystals and *l* crystals, and hence is a racemic mixture (Eliel, 1962).

Because norgestrel is an important synthetic hormone that exhibits an unusually high progestational activity, the determination of the molecular structure of the biologically active *d* enantiomorph (and consequently the *dl* racemic mixture) was carried out.

Experimental

d-Norgestrel was obtained as clear, transparent rectangular crystals by recrystallization from ethyl acetate. Crystal symmetry was determined from precession photographs, and unit-cell dimensions were obtained from a least-squares treatment of 12 general reflections with $2\theta > 30°$ on a Picker FACS-1 diffractometer

Crystal data

d-Norgestrel, $C_{21}H_{28}O_2$, M.W. 312·46. Space group $P2_12_12_1$. Cell dimensions at $20°C \pm 1°C$: $a = 20\cdot673(6)$, $b = 12\cdot797(4)$, $c = 6\cdot567(1)$ Å. $V = 1737$ Å³. $D_x = 1\cdot194$, D_m (flotation) $= 1\cdot190$ g cm⁻³.

A crystal of dimensions $0\cdot30 \times 0\cdot20 \times 0\cdot25$ mm was used for all intensity measurements made by the θ–2θ scan technique with Cu $K\alpha$ graphite-monochromated radiation. Of the 1628 accessible reflections collected ($2\theta < 127°$), 1594 were considered observed by the criterion $I > 2\cdot33\sigma(I)$, where $\sigma(I)$ includes the possibility of error in the peak and background counts, and in the attenuators. The usual Lorentz–polarization factors were applied, but no absorption corrections were made; the data were scaled by means of a Wilson plot.

Structure determination and refinement

The solution to the structure was arrived at by direct methods, the data being phased by the multi-solution technique, *MULTAN* (Germain, Main & Woolfson, 1971). An E map generated from the phase set with the highest figure of merit (1·24) located an 18-atom fragment which was expanded by phase extension (Karle, 1968) and difference Fourier techniques to the full 23-atom structure.

Initial structure refinement was carried out by full matrix least-squares analysis [minimizing $\sum w(F_o - F_c)^2$] with isotropic thermal parameters for the non-hydrogen atoms, Four cycles reduced R [$\sum||F_o| - |F_c||/\sum|F_o|$] from 0·30 to 0·15, and three additional cycles with anisotropic temperature factors reduced R to 0·11. The hydrogen atoms were located from a difference map, and the final refinement was done with isotropic thermal parameters for the hydrogen atoms, and ani-

sotropic ones for the non-hydrogen atoms. Refinement converged at $R=0.048$ for the 1628 measured reflections, and a three-dimensional difference map gave no significant peaks. The standard deviations were estimated from inversion of the matrices in the last least-squares cycle.*

Discussion

The coordinates and thermal parameters for all atoms are given in Tables 1 and 2, with the numbering system shown in Fig. 1. The intermolecular bond distances and angles are given in Fig. 2 for all the non-hydrogen atoms.

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* Tables of structure factors, bond distances and angles, least-squares planes, and contact distances have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30975 (33 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.
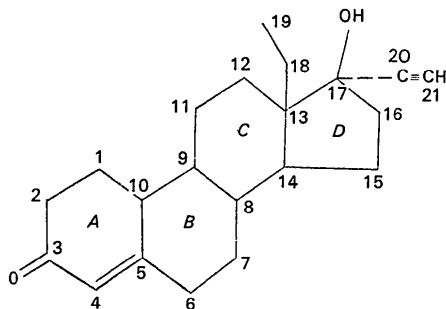

Fig. 1. *d*-Norgestrel.

Table 2. *Final coordinates* ($\times 10^3$) *and isotropic temperature factors* ($\times 10$) *for hydrogen atoms*

	x	y	z	β
H(1A)	4038 (1)	849 (3)	-26 (5)	33 (7)
H(1B)	4115 (1)	718 (2)	-115 (5)	33 (7)
H(2A)	3187 (2)	810 (3)	-236 (6)	38 (8)
H(2B)	2860 (2)	842 (3)	31 (6)	47 (8)
H(4)	2693 (2)	563 (3)	163 (5)	32 (7)
H(6A)	3290 (2)	532 (3)	451 (6)	53 (9)
H(6B)	3392 (1)	643 (2)	546 (5)	33 (6)
H(7A)	4276 (2)	535 (2)	621 (5)	31 (6)
H(7B)	4310 (2)	500 (2)	381 (5)	39 (7)
H(8)	4708 (2)	713 (2)	549 (5)	34 (7)
H(9)	4797 (1)	638 (2)	127 (5)	22 (6)
H(10)	3895 (2)	792 (3)	298 (7)	63 (10)
H(11A)	5032 (1)	846 (2)	276 (4)	9 (4)
H(11B)	5058 (1)	809 (2)	39 (4)	13 (5)
H(12A)	5907 (1)	690 (2)	123 (4)	10 (4)
H(12B)	6149 (1)	801 (2)	188 (5)	23 (6)
H(14)	5544 (1)	566 (2)	371 (4)	6 (4)
H(15A)	5508 (1)	613 (2)	804 (4)	16 (5)
H(15B)	5501 (2)	496 (3)	701 (6)	45 (8)
H(16A)	6629 (1)	631 (2)	802 (5)	19 (5)
H(16B)	6660 (2)	514 (2)	685 (6)	39 (7)
H(18A)	5952 (1)	770 (3)	730 (5)	34 (7)
H(18B)	5395 (2)	811 (3)	616 (6)	44 (8)
H(19A)	6682 (2)	892 (3)	509 (6)	37 (8)
H(19B)	6006 (2)	940 (4)	426 (9)	76 (12)
H(19C)	6289 (2)	951 (5)	655 (9)	75 (14)
H(21)	7045 (2)	457 (3)	88 (7)	52 (9)
H(O17)	7388 (2)	749 (3)	384 (7)	58 (10)

The average length of the $C(sp^3)-C(sp^3)$ bond is $1.536(4)$ Å, in good agreement with the generally accepted value of 1.533 Å (Bartell, 1959). Five bond distances differ by more than 3σ from this mean value [C(9)–C(11), C(8)–C(14), C(13)–C(18), C(16)–C(17), C(17)–C(13)]; however the short C(8)–C(14) and the long C(17)–C(13) bonds are commonly encountered

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Table 1. *Final coordinates and anisotropic thermal parameters for non-hydrogen atoms with standard deviations* ($\times 10^4$)

Thermal parameters are of the form $\exp(-h^2\beta_{11}-k^2\beta_{22}-l^2\beta_{33}-hk\beta_{12}-hl\beta_{13}-kl\beta_{23})$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	3854 (1)	7778 (2)	-125 (5)	21 (1)	68 (2)	339 (8)	8 (2)	64 (4)	77 (7)
C(2)	3142 (1)	7901 (2)	-699 (6)	22 (1)	67 (2)	426 (11)	-4 (2)	85 (5)	5 (8)
C(3)	2785 (1)	6880 (2)	-443 (4)	16 (0)	67 (2)	293 (7)	-11 (2)	20 (4)	-63 (6)
C(4)	2967 (1)	6261 (2)	1322 (4)	18 (0)	74 (2)	273 (8)	1 (2)	-13 (4)	-28 (6)
C(5)	3463 (1)	6498 (2)	2525 (4)	12 (0)	78 (2)	237 (6)	-3 (1)	-19 (3)	-23 (6)
C(6)	3571 (1)	5926 (3)	4498 (5)	19 (1)	133 (3)	245 (8)	27 (2)	-26 (4)	57 (8)
C(7)	4276 (1)	5619 (3)	4851 (4)	19 (1)	105 (2)	230 (6)	20 (2)	-3 (3)	114 (8)
C(8)	4745 (1)	6534 (2)	4527 (3)	17 (0)	71 (2)	155 (5)	2 (2)	-12 (3)	3 (6)
C(9)	4648 (1)	6977 (2)	2364 (4)	16 (0)	56 (1)	166 (5)	-4 (1)	-4 (3)	2 (5)
C(10)	3951 (1)	7358 (2)	2045 (4)	18 (0)	57 (1)	234 (6)	-7 (1)	12 (3)	-45 (6)
C(11)	5140 (1)	7826 (2)	1872 (4)	16 (0)	57 (1)	210 (6)	-3 (1)	5 (3)	21 (6)
C(12)	5840 (1)	7458 (2)	2197 (3)	13 (0)	57 (1)	167 (5)	2 (1)	-3 (3)	3 (5)
C(13)	5940 (1)	7073 (2)	4386 (3)	15 (0)	60 (2)	143 (5)	-3 (1)	-5 (2)	-18 (5)
C(14)	5444 (1)	6201 (2)	4798 (3)	18 (0)	62 (1)	139 (5)	-4 (1)	-8 (3)	10 (5)
C(15)	5658 (1)	5748 (2)	6853 (4)	22 (1)	88 (2)	165 (6)	0 (2)	0 (3)	44 (6)
C(16)	6405 (1)	5839 (2)	6802 (4)	23 (1)	86 (2)	165 (5)	-10 (2)	9 (3)	34 (6)
C(17)	6577 (1)	6452 (2)	4822 (4)	13 (0)	69 (2)	168 (5)	-5 (1)	6 (3)	-7 (5)
C(18)	5883 (1)	7980 (2)	5951 (4)	20 (0)	75 (2)	201 (6)	-2 (2)	-14 (3)	-69 (6)
C(19)	6225 (1)	9005 (2)	5397 (5)	31 (1)	72 (2)	329 (9)	7 (2)	-19 (5)	-115 (7)
C(20)	6729 (1)	5701 (2)	3181 (4)	15 (0)	62 (2)	186 (6)	-6 (1)	-6 (3)	23 (6)
C(21)	6894 (1)	5092 (2)	1921 (4)	23 (1)	70 (2)	238 (7)	-10 (2)	-17 (4)	-18 (7)
O(3)	2371 (1)	6615 (2)	-1650 (3)	19 (0)	91 (1)	341 (6)	6 (1)	50 (3)	-33 (6)
O(17)	7134 (1)	7070 (1)	5212 (3)	18 (0)	84 (1)	245 (5)	7 (1)	28 (2)	-20 (5)

in similar steroids (Cooper & Norton, 1968; Dideberg & Dupont, 1972; Dupont, Dideberg & Campsteyn, 1973). All other bond lengths involving C–C or C–O are consistent with previously observed values with the exception of the C(5)–C(10) sp^3–sp^2 bond, which is

5σ longer than the mean value of 1·505 Å (Bartell & Bonham, 1960). The C–H bond distances are all equivalent to within 3σ of the mean [1·02(4) Å], and bond angles involving hydrogen atoms range from 95° to 120° with a σ of 2°. Complete tables of bond dis-
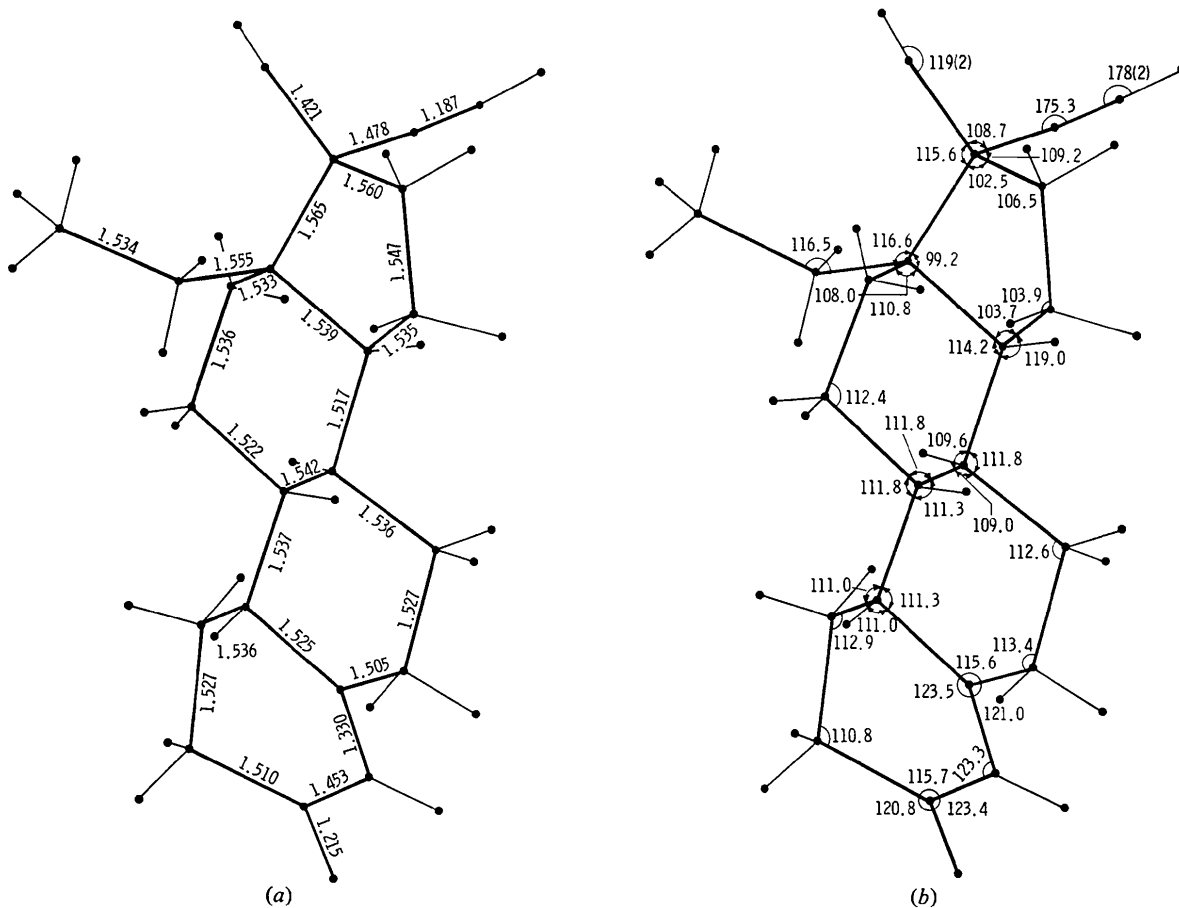
Fig. 2. Intermolecular bond lengths (*a*) and bond angles (*b*). σ's are 0·004 Å and 0·2°.
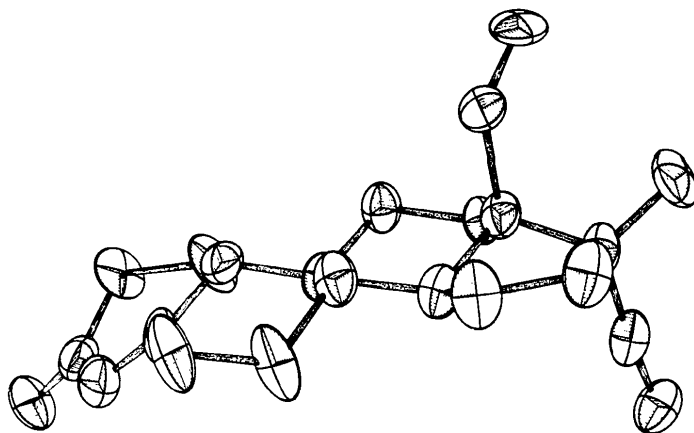
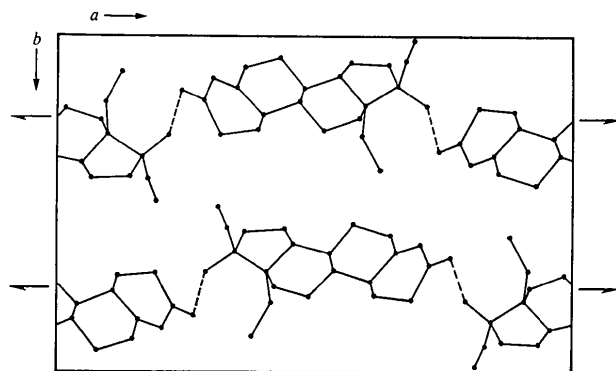Fig. 3. *ORTEP* plot of molecule parallel to plane of the ring structure.

Fig. 4. c-axis projection of molecular packing.

tances and angles for all atoms have been deposited.*

The interatomic bond angles are not unusual when compared to similar steroids. The strain in the five-membered D ring, and in the Δ^4A ring, results in an enlargement of the C(3)–C(4)–C(5) and C(4)–C(5)–C(10) angles, and a closing of the C(14)–C(13)–C(17) angle. This strain is further transmitted to the B ring, and to a small extent to the C ring, as evidenced by the enlargement of the angles in the B and C rings where they are joined to the A and D rings. The C(17)–C(20)–C(21) ethynyl bond angle is not quite linear (175·3°); however, a similar result was obtained by Lepicard, Delettré & Mornon (1973) for a steroid with the same D ring substituents.

The ORTEP drawing (Johnson, 1965) in Fig. 3 is a view of the molecule parallel to a plane running through the ring structure, showing the configuration of the molecule and the 50% probability thermal ellipsoids of the carbon and oxygen atoms. The stereochemistry of the 13 and 17 substituents is particularly evident in this view. The four rings are trans-fused, with the A ring inclined at an angle of 18·1° to the least-squares plane through the B ring. Rings B, C, and D are almost coplanar, the least-squares planes through each of these rings making angles of 4·5° and 5·3°, respectively, with each other. Rings B and C are in the chair conformation, ring D has a distorted envelope configuration, and ring A is a distorted half chair. The equations of the least-squares planes through the atoms in the steroid skeleton, and the deviations of the individual atoms from these planes, have been deposited.*

The torsion angles within the steroid nucleus are listed in Table 3. The low values of the torsion angles in the B ring at the A–B junction reflect the strain in this portion of the molecule (Altona, Geise & Romers, 1968). There is no indication of strain in the C ring based on the magnitude of the torsion angles.

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* See footnote on p. 2041.

Table 3. Torsion angles in the steroid ring structure

Ring A		Ring B	
C(1)—C(2)	−56·0°	C(5)–C(6)	−45·1°
C(2)—C(3)	38·8	C(6)–C(7)	49·5
C(3)—C(4)	−7·5	C(7)–C(8)	−56·3
C(4)—C(5)	−8·3	C(8)–C(9)	59·2
C(5)—C(10)	−9·0	C(9)–C(10)	−54·6
C(10)—C(1)	40·8	C(5)–C(10)	47·6

Ring C		Ring D	
C(8)—C(9)	−52·3°	C(13)–C(14)	48·6°
C(9)—C(11)	54·1	C(14)–C(15)	−34·3
C(11)—C(12)	−56·8	C(15)–C(16)	6·1
C(12)—C(13)	56·6	C(16)–C(17)	23·6
C(13)—C(14)	−58·4	C(13)–C(17)	−43·6
C(8)—C(14)	56·1		

The molecules in the crystal lattice are joined together by intermolecular hydrogen bonds (2·92 Å long) formed between the hydroxyl and keto groups. Fig. 4 is the c-axis projection of the molecular packing. The molecules form a zigzag chain parallel to the a edges of the unit cell and centered on the a screw axes. There are 27 intermolecular contacts less than 4·0 Å, comprising the van der Waals attraction forces that stabilize the molecules in the unit cell, the shortest distance being 3·40 Å. The complete table has been deposited.

References

ALTONA, C., GEISE, H. J. & ROMERS, C. (1968). Tetrahedron, 24, 13–32.
BARTELL, L. S. (1959). J. Amer. Chem. Soc. 81, 3497–3498.
BARTELL, L. S. & BONHAM, R. A. J. (1960). J. Chem. Phys. 32, 824–827.
BUZBY, G. C. JR, WALK, C. R. & SMITH, H. (1966). J. Med. Chem. 9, 782–784.
COOPER, A. & NORTON, D. A. (1968). Acta Cryst. B24, 811–824.
DEANGELIS, N. J. (1974). Thesis, Villanova Univ.
DIDEBERG, O. & DUPONT, L. (1972). Acta Cryst. B28, 3014–3022.
DUPONT, L., DIDEBERG, O. & CAMPSTEYN, H. (1973). Acta Cryst. B29, 205–214.
EDGREN, R. A., SMITH, H., HUGHES, G. A., SMITH, L. L. & GREENSPAN, G. (1963). Steroids, 2, 731–737.
ELIEL, E. L. (1962). Stereochemistry of Carbon Compounds, p. 44. New York: McGraw Hill.
GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). Acta Cryst. A27, 368–376.
JOHNSON, C. K. (1965). ORTEP. Oak Ridge National Laboratory Report ORNL 3794.
KARLE, J. (1968). Acta Cryst. B24, 182–186.
LEPICARD, G., DELETTRÉ, J. & MORNON, J. P. (1973). Acta Cryst. B29, 1723–1725.
SMITH, H., HUGHES, G. A., DOUGLAS, G. H., WENDT, G. R., BUZBY, G. C. JR, EDGREN, R. A., FISHER, J., FOELL, T., GADSBY, B., HARTLEY, D., HERBST, D., JANSEN, A. B. A., LEDIG, K., McGLOUGHLIN, B. J., McMENAMIN, J., PATTISON, T. W., PHILLIPS, T. C., REES, R., SIDDALL, J., SINDRA, J., SMITH, L. L., TOKOLICS, J. & WATSON, D. H. P. (1964). J. Chem. Soc. pp. 4472–4492.