

The Conformation of Non-Aromatic Ring Compounds. LXXV.*

The Crystal and Molecular Structure of the 3,20-Bis(ethylenedioxy) Analogue of Vitamin D

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Crystals of 3,20-bis(ethylenedioxy)-9,10-seco-pregna-5,7,10(19)-triene are monoclinic, space group $P2_1$. The lattice constants are $a = 7.134$, $b = 12.281$, $c = 12.746$ Å, $\beta = 93.00^\circ$ and $Z = 2$. The structure was solved by simultaneous application of direct methods and Patterson-image-seeking methods. The refinement of the structure, using diffractometer data, resulted in an R value of 7.15%. The triene system of atoms 4, 5, 6, 7, 8, 9, 10, 14, 19, 1 is not planar, but consists of a nearly planar diene system 4, 5, 6, 7, 8, 9, 10, 14 enclosing a dihedral angle with the planar ene system 1, 5, 10, 19. The triene system is *cis* relative to C(10)–C(5) and *trans* with respect to C(6)–C(7), C(6) opposing C(9). The chair conformation of ring *A* is modified from the conformation of this ring in the 4-iodo-5-nitrobenzoate ester of ergocalciferol. C(19) is 0.69 Å above the diene system while being 1.2 Å below this system in the ester. The conformations of rings *A*, *C*, *D* and the dioxolane rings are described by means of torsion angles and Newman projections.

Introduction

The present study is a continuation of structure determinations of steroids (*cf.* Portheine & Romers, 1970; Portheine, Romers & Rutten, 1972; Braun, Hornstra & Leenhouts, 1969, 1970) and forms part of an investigation into the physicochemical properties of isomers occurring in the calciferol series (Sanders, Pot & Havinga, 1969).

The spatial arrangement of atoms of the 4-iodo-5-nitrobenzoate ester of ergocalciferol (hereafter INC) has been elucidated by Hodgkin, Rimmer, Dunitz & Trueblood (1963), but, owing to the poor quality of the eye-estimated photographic data, no full information concerning the geometry of the molecule was given. We felt that a detailed description of the conformation of calciferol, precalciferol and tachysterol might help in arriving at the correct interpretation of ultraviolet and n.m.r. spectra of these and related isomers (Allinger & Miller, 1963; Lugtenburg & Havinga, 1969).

As it is difficult to obtain stable single crystals from pure crystalline ergo or cholecalciferol (vitamin D_2 or D_3), the 3,20-bis(ethylenedioxy) analogue (Rappoldt & Rix, 1971) was chosen. According to the IUPAC–IUB rules (1969) the systematic name (see Fig. 1) is 3,20-bis(ethylenedioxy)-9,10-seco-pregna-5,7,10(19)-triene

(hereafter ECF). With the exception of the atoms occurring in the dioxolane rings the atoms are numbered according to chemical convention (Fig. 1).

Experimental

ECF forms colourless, monoclinic, nearly square plates (001) which retain their appearance even after several months' exposure to air at room temperature. The crystals were not single. Cut specimens sealed in capillaries were used for both photographic and diffractometer measurements. About 35 crystals were photographed before a suitable cut single crystal was obtained: a triangular plate with edges parallel to [011], $[0\bar{1}1]$, [001] and [100] and having dimensions 0.5, 0.5, 1.0 and 0.35 mm, respectively. The lattice constants at room temperature were measured with a

Table 1. *Crystallographic data of ECF at 20°C*

Quoted errors are estimated standard deviations.

3,20-Bis(ethylenedioxy)-9,10-seco-pregna-5,7,10(19)-triene
 $C_{25}O_4H_{36}$, $M = 400.5$ g.mol⁻¹, melting point 123°C.
 Space group $P2_1$, two molecules per unit cell.

$a = 7.1345$ (20) Å	$c = 12.7460$ (16) Å
$b = 12.2815$ (21)	$\beta = 93.00$ (12) ^o
$d_{obs} = 1.203$ g.cm ⁻³	$d_x = 1.192$ g.cm ⁻³ .

Mo $K\alpha$, radiation, $\lambda = 0.71069$ Å, $\mu(\text{Mo } K\alpha) = 0.87$ cm⁻¹.

Data sets	$h k l$	$h \bar{k} l$
Number of reflexions	1893	1782
$\langle E^2 - 1 \rangle$	0.897	0.762
$\langle E \rangle$	0.845	0.885

* Part LXXIV: de Graaff, Giesen, Rutten & Romers (1972).
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three-circle diffractometer using Cu $K\alpha$ radiation ($\lambda=1.54178$ Å). The reflexions $0k0$ are absent for $k=\text{odd}$. Since ECF is optically active the space group is $P2_1$. Crystallographic data for ECF are given in Table 1.

The reflexion intensities were recorded at room temperature with a three-circle diffractometer using zirconium-filtered Mo $K\alpha$ radiation to a maximum $\theta=30^\circ$. The $\theta-2\theta$ scan was applied according to the previously described technique (Verschoor & Keulen, 1971; Portheine, Romers & Rutten, 1972). A number of standard reflexions was used in order to correct for the decrease in scattering intensity as a polynomial function of exposure time. The crystal was oriented about c^* . During two consecutive runs with $k \geq 0$ and $k < 0$, 3361 reflexions were measured and 1893 and 1782 were considered observed in the hkl and $h\bar{k}l$ data sets respectively.

Reflexions with measured intensities smaller than twice the standard deviations from counting statistics were classified as 'not observed'. Since the random scatter in the measurements was greater than any absorption, the correction for this effect was omitted. The reflexion intensities were reduced to structure factor moduli in the usual way. Normalized structure factors E were also calculated, using the value $B=3.2$ Å² obtained from a Wilson curve. Clearly this value is too low, but because of the very high percentage of non-observed reflexions (45% in a sphere of radius $2 \sin \theta/\lambda=1.4$ Å⁻¹), the Wilson plot is not strictly applicable.

Structure determination

The $h\bar{k}l$ data set was analysed by Patterson search methods by P.B.B. and J. H. The hkl data set was subjected to direct methods by the first two authors.

(a) Direct methods

The analysis was performed according to the method proposed by Karle & Hauptman (1956) and performed by Karle & Karle (1964). However, no symbolic addition (Kennard *et al.*, 1971) was used before expansion of the obtained phases by the tangent formula (Karle & Karle, 1966). It was necessary to consider a number of different starting sets of phases. The two most promising sets with phases initially considered in multiples of $\pi/4$ or π are listed in Table 2. From these sets three phase combinations, namely 0, 0, 0, $\pi/4$, $\pi/4$, $\pi/4$ (set Ia), 0, 0, 0, $\pi/4$, $5\pi/4$, $7\pi/4$ (set Ib) and 0, 0, 0, $\pi/4$, $\pi/4$, 0 (set II) emerged which yielded 194, 192 and 194 phases, respectively, for $E's > 1.8$. The

corresponding E Fourier maps contained a number of peaks having chemically acceptable configurations and occurring at least twice in the three computed maps. With the exception of the hydrogen atoms and the atoms of the dioxolane rings, 23 peaks could be recognized as belonging to rings A , C , D and to the triene system.

The remaining heavy atoms were subsequently located in ordinary F Fourier maps. At this stage the agreement between calculated and observed structure factors was still bad ($R=42\%$) and after three cycles of least squares, R dropped only to 36%. It was then discovered that a very short distance of 2.8 Å existed between C(11) and C(28) in two symmetry-related molecules. A shift $\Delta x = -0.05$ and $\Delta z = -0.05$ applied to the whole molecule enlarged this intermolecular distance to 3.6 Å. After three cycles of block-diagonal least-squares refinement of 29 heavy atoms, one scale factor and an overall isotropic temperature factor, an R value of 24% was obtained.

Continuation of the refinement with individual B parameters resulted in an R value of 14.4%.

Disregarding the time for searching for a good crystal and for measuring and processing the experimental data, it took four weeks to produce a properly phased E map and three weeks to reduce the disagreement index to the last-mentioned value. All calculations so far mentioned were executed on a IBM 360/50 computer and required eight hours c.p.u. time.

(b) Patterson-search methods

The applied Patterson search, assuming the geometry of (part of) the molecule to be known, has been described in detail elsewhere (Braun, Hornstra & Leenhouts, 1969). The known part was considered to be the framework of nine atoms constituting the rings C and D . A first search yielded a list of possible orientations. For each of these orientations a small number of probable positions with respect to the screw axis are selected by a second search. The correct set of positional and orientational parameters of the search part emerges after a refinement of each selected set in Patterson space. The atoms not belonging to the search model are now located and added to the molecule one after the other by a third automated search. Thirty minutes c.p.u. time were required using a C.D. 3600 computer. Within another thirty minutes the structure was refined to an R value of 11.6%. The whole procedure was straightforward and was executed automatically without human intervention.

At this stage the positional parameters obtained *via*

Table 2. Two starting sets, I and II

Set	$h k l$	E	Orig. def. phase	Set	$h k l$	E	Considered phases
I, II	5 0 5	3.92	0	I, II	1 2 1	3.38	$\pi/4, 3\pi/4, 5\pi/4, 7\pi/4$
I, II	1 0 $\bar{2}$	3.10	0	I, II	4 1 15	3.57	same
I, II	1 3 6	3.34	0	I	2 6 10	3.05	same
				II	2 0 6	3.35	0, π

Table 3. Fractional coordinates of ECF chosen in conformity with the accepted absolute configuration and with respect to a right-handed reference system

The estimated standard deviations are given in parentheses.

	x	y	z
C(1)	-0.1755 (46)	0.8181 (52)	0.5267 (45)
C(2)	-0.0803 (44)	0.7996 (50)	0.6344 (42)
C(3)	0.1067 (43)	0.7449 (46)	0.6285 (37)
C(4)	0.0918 (42)	0.6411 (48)	0.5648 (39)
C(5)	-0.0107 (41)	0.6549 (42)	0.4568 (36)
C(6)	0.0619 (39)	0.6197 (47)	0.3697 (37)
C(7)	-0.0202 (37)	0.6266 (43)	0.2640 (39)
C(8)	0.0676 (36)	0.6058 (40)	0.1740 (34)
C(9)	0.2680 (41)	0.5736 (52)	0.1702 (40)
C(10)	-0.1928 (43)	0.7134 (50)	0.4666 (40)
C(11)	0.2961 (40)	0.4769 (52)	0.0971 (43)
C(12)	0.1957 (39)	0.4917 (48)	-0.0129 (37)
C(13)	-0.0134 (39)	0.5161 (39)	-0.0024 (39)
C(14)	-0.0286 (36)	0.6188 (42)	0.0681 (35)
C(15)	-0.2335 (42)	0.6527 (43)	0.0538 (37)
C(16)	-0.2836 (43)	0.6261 (49)	-0.0634 (40)
C(17)	-0.1200 (35)	0.5573 (40)	-0.1048 (33)
C(18)	-0.1132 (42)	0.4197 (42)	0.0479 (36)
C(19)	-0.3561 (49)	0.6747 (63)	0.4309 (44)
C(20)	-0.1840 (40)	0.4770 (45)	-0.1900 (36)
C(21)	-0.0249 (48)	0.4108 (55)	-0.2317 (43)
O(22)	-0.3265 (30)	0.4064 (33)	-0.1575 (26)
C(23)	-0.4562 (62)	0.3853 (82)	-0.2418 (48)
C(24)	-0.4167 (59)	0.4732 (64)	-0.3196 (55)
O(25)	-0.2726 (30)	0.5398 (34)	-0.2729 (27)
O(26)	0.1823 (31)	0.7194 (38)	0.7297 (28)
C(27)	0.3567 (50)	0.7697 (61)	0.7463 (49)
C(28)	0.3458 (49)	0.8613 (61)	0.6726 (52)
O(29)	0.2393 (31)	0.8158 (34)	0.5845 (29)

the two methods (after shifting to the same origin) differed by at most 0.03 Å, the difference Δz for C(1) being, however, 0.06 Å.

Refinement

Since it had been measured first and since it contained more observed reflexions, the hkl data set was thought to be somewhat better. Therefore the refinement was mainly carried out with this set. The atomic scattering values of carbon (C-valence) and oxygen were taken from *International Tables for X-ray Crystallography* (1962) and for hydrogen the scattering factor values of Stewart, Davidson & Simpson (1965) were adopted. The weighting scheme was derived from the counting statistics as described by Portheine, Romers & Rutten (1972). In the present work we apply, as measures of convergence, the ordinary disagreement index $R = \sum |F_o - F_c| / \sum F_o$ and the weighted index $R_w = \{ \sum w(F_o - F_c)^2 / \sum wF_o^2 \}^{1/2}$, w being the weight of an observation. The refinement was carried out in a block-diagonal approximation to the matrix of normal equations. The blocks were 4×4 for 'isotropic' atoms and 9×9 for 'anisotropic' atoms.

The hydrogen atoms were located by means of difference Fourier maps. In general their coordinates agreed rather well with calculated positions assuming standard bond length C-H=1.0 Å and standard tetragonal or trigonal (the latter for sp^2 hybridization) valency angles H-C-H and C-C-H. The methyl

Table 4. Vibrational parameters U_{ij} of ECF and their standard deviations (10^4 \AA^2)The temperature factor is defined as $\exp[-2\pi^2 \sum_i \sum_j h_i h_j a_i^* a_j^* U_{ij}]$, $i, j=1, 2, 3$.

	U_{11}	U_{22}	U_{33}	$2U_{12}$	$2U_{23}$	$2U_{13}$
C(1)	761 (31)	708 (33)	624 (28)	416 (60)	-46 (50)	171 (45)
C(2)	743 (31)	723 (34)	518 (26)	8 (54)	-71 (49)	374 (44)
C(3)	678 (29)	641 (31)	435 (23)	-69 (49)	78 (45)	96 (40)
C(4)	682 (29)	632 (31)	513 (24)	213 (50)	55 (47)	-138 (40)
C(5)	592 (26)	462 (26)	532 (24)	7 (42)	55 (43)	-74 (40)
C(6)	585 (25)	501 (24)	466 (22)	154 (45)	-136 (42)	17 (36)
C(7)	537 (25)	371 (23)	681 (26)	69 (42)	0 (44)	-105 (39)
C(8)	518 (24)	436 (23)	430 (21)	28 (41)	-168 (40)	69 (34)
C(9)	546 (27)	869 (37)	570 (26)	-88 (52)	-131 (51)	4 (40)
C(10)	603 (27)	735 (32)	488 (25)	163 (51)	156 (50)	-67 (40)
C(11)	451 (25)	857 (36)	686 (28)	339 (52)	10 (56)	47 (40)
C(12)	519 (25)	738 (32)	456 (23)	191 (48)	13 (46)	195 (37)
C(13)	439 (21)	413 (22)	427 (19)	0 (37)	37 (38)	52 (32)
C(14)	460 (22)	402 (22)	533 (23)	-78 (41)	42 (42)	99 (35)
C(15)	594 (25)	504 (26)	492 (23)	194 (42)	-141 (43)	21 (38)
C(16)	666 (28)	534 (27)	629 (26)	166 (49)	-94 (49)	-153 (42)
C(17)	505 (23)	442 (23)	366 (20)	-12 (40)	85 (37)	126 (35)
C(18)	752 (29)	414 (23)	414 (21)	15 (44)	85 (40)	124 (39)
C(19)	753 (34)	1212 (50)	580 (30)	151 (67)	55 (62)	-79 (49)
C(20)	639 (27)	532 (26)	382 (21)	23 (45)	163 (41)	106 (36)
C(21)	961 (37)	737 (36)	565 (27)	286 (61)	-153 (54)	-111 (50)
O(22)	879 (22)	726 (23)	538 (17)	-570 (38)	19 (35)	24 (30)
C(23)	1319 (49)	1590 (65)	531 (31)	-1239 (98)	-83 (75)	-78 (60)
C(24)	1212 (47)	991 (34)	838 (37)	-73 (83)	-159 (72)	-932 (65)
O(25)	816 (21)	673 (21)	559 (17)	84 (35)	65 (33)	-313 (30)
O(26)	861 (23)	998 (27)	490 (17)	-285 (41)	28 (37)	-284 (30)
C(27)	759 (33)	963 (40)	770 (33)	-2 (62)	-746 (64)	-42 (51)
C(28)	784 (35)	908 (41)	995 (40)	-363 (64)	-556 (70)	429 (57)
O(29)	821 (21)	792 (23)	629 (20)	-307 (39)	44 (35)	313 (31)

hydrogen atoms gave some trouble. Their off-staggered positions were ultimately taken from hkl - and $h\bar{k}l$ -derived difference Fourier maps. The 36 hydrogen atoms were kept fixed at calculated positions, with isotropic B values being 2 \AA^2 larger than those of the carbon atoms to which they are bonded. The 29 heavy atoms were now subjected to anisotropic refinement: $R=8\%$.

Due to the large thermal vibrations of the molecule, attempts to refine the coordinates and the isotropic B values of the hydrogen atoms failed. The refinement of the heavy atoms was therefore continued by using both data sets and maintaining the constraints on the light atoms. The disagreement indices obtained were $R=6.87\%$ and $R_w=6.42\%$ for hkl reflexions and $R=6.57\%$ and $R_w=6.79\%$ for $h\bar{k}l$ reflexions. The difference between the parameters of the two sets did not exceed 2σ .

At this point we merged the two data sets by taking weighted averages of structure factors $F(hkl)$ and $F(h\bar{k}l)$ and designating them as $F(hkl)$. This procedure, of course, excludes the determination of the absolute configuration, but is justified because the dispersion correction for Mo K radiation is extremely small. With the combined set, comprising 2088 observed reflexions, the refinement with constrained hydrogen atoms converged after three cycles at $R=7.15\%$ and $R_w=6.34\%$. For all 3361 reflexions, these indices are $R=10.8\%$ and $R_w=6.47\%$. The reflexion 041 was omitted because of background noise difficulties during the measurement. A list of observed and calculated structure factors is available upon request. The final coordinates

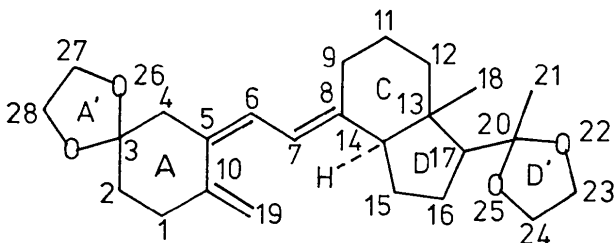


Fig. 1. The numbering of atoms and nomenclature of rings in 3,20-bis(ethylenedioxy)-9,10-seco-pregna-5,7,10(19)-triene.

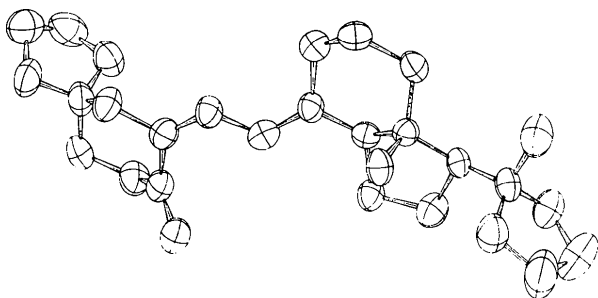


Fig. 2. A perspective view of ECF. The orientations of vibrational ellipsoids are scaled to include 50% probability (Johnson, 1971).

and vibrational parameters of the heavy atoms together with their estimated standard deviations are listed in Tables 3 and 4.

Inspection of Table 4 reveals that a number of atoms, specially C(19) and those of rings A' and D' , have rather high U_{ij} values. Attempts to explain the vibrational parameters in terms of a rigid body motion according to the method of Schomaker & Trueblood (1968) were unsatisfactory and resulted in poor agreement between observed and calculated U_{ij} values. For this reason, thermal motion corrections to the geometrical entities of the molecule are omitted. The mean estimated standard deviations of bond lengths, valency and torsion angles are about 0.006 \AA , 0.4 and 0.6° . In this case, these flattering numbers should perhaps be multiplied by a factor of two.

Molecular geometry

The molecule ECF is elongated. Its shape is illustrated in Fig. 2. The longest heavy-atom intramolecular distance between C(24) and C(27) amounts to 14.84 \AA . The intramolecular bond lengths, valency and a number of torsion angles are shown in Fig. 3(a), (b) and (c). The relevant torsion angles of INC are indicated in Fig. 3(d). Since the parameters of the light atoms could not be refined, we have omitted all information of geometrical entities involving hydrogen atoms.

Force-field calculations (Portheine, 1971) clearly show that sp^3 - sp^3 distances between carbon atoms in steroids undergo small variations due to repulsive 1-4 interactions and unfavourable off-staggered conformations of the methyl groups. However, in view of the accuracy obtained a detailed discussion of intramolecular bond lengths and valency angles of ECF is hardly warranted. The difference in length (0.042 \AA) between the double bonds C(10)-C(19) and C(7)-C(8) is probably significant. The distances C(23)-C(24) and C(27)-C(28) are too short. In all these cases atoms with large thermal parameters are involved and the observed deviations are not alarming.

Inspection of the distribution of endocyclic torsion angles indicates [Fig. 3(c)] that rings A and C are rather regular, somewhat flattened chairs. The regularity of A is surprising, since the two exocyclic double bonds should exercise a distortive influence. The mean torsion angles of A and C (52.5 and 53.8°) are significantly smaller than for cyclohexane (55.9° ; Geise, Buys & Mijlhoff, 1972). Ring D [Fig. 4(d)] is trans-fused with C ; its conformation is a nearly ideal half chair with C_2 symmetry. The exact point on the pseudorotational pathway (Altona, Geise & Romers, 1968) can be characterized by the maximum puckering angle $\varphi(\max)=46.5^\circ$ and phase angle $\Delta=3.8^\circ$.

Although the two dioxolane rings are C_s envelopes their conformations differ both in degree of puckering and in orientation of the 'flaps', *i.e.* C(28) for A' and C(20) for D' . We find $\varphi(\max)=37.6$, $\Delta=32.0^\circ$ for ring A' and $\varphi(\max)=30.3$, $\Delta=35.4^\circ$ for ring D' . For methyl

Table 5. Displacements (\AA) of atoms from four least-squares planes in ECF and in INC

Plane through atoms 4, 5, 6, 7, 8, 9, 10 and 14

	ECF	INC		ECF	INC
C(4)	0.02	-0.02	C(9)	-0.15	-0.07
C(5)	0.01	0.01	C(10)	-0.15	-0.10
C(6)	0.11	0.10	C(14)	0.01	0.01
C(7)	0.13	0.13	C(19)	0.69	-1.17
C(8)	0.02	-0.04			

Plane 6, 7, 8, 9, 14

	ECF	INC
C(6)	0.01	-0.02
C(7)	-0.01	0.04
C(8)	-0.02	0.04
C(9)	0.00	0.02
C(14)	0.01	-0.00

Plane 4, 5, 6, 7, 10

	ECF	INC
C(4)	-0.00	-0.00
C(5)	-0.01	0.00
C(6)	0.01	-0.00
C(7)	-0.00	-0.00
C(10)	0.00	-0.00

Plane 1, 5, 10, 19

	ECF	INC
C(1)	0.01	-0.03
C(5)	0.01	-0.02
C(10)	-0.02	0.07
C(19)	0.01	-0.03

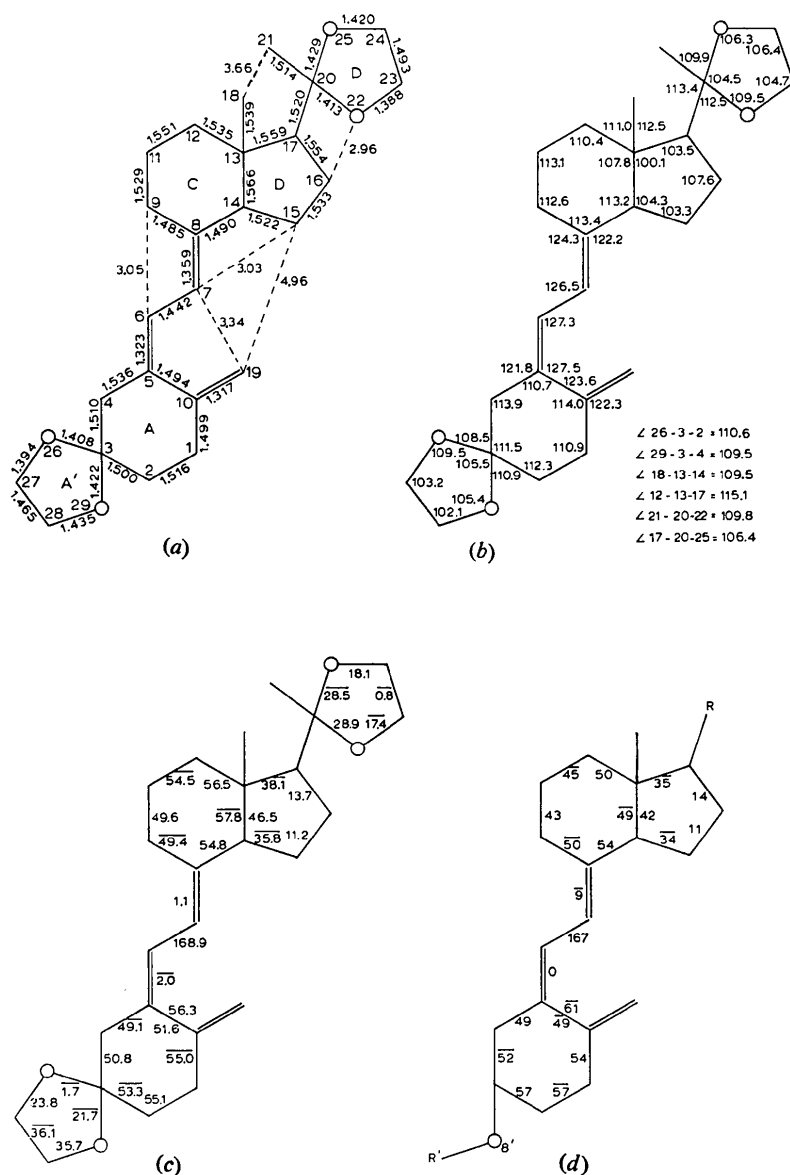


Fig. 3. Intramolecular bond lengths (a), valency angles (b), and torsion angles (c); torsion angles of part of the molecule INC are depicted in (d).

the reference molecule I at x, y, z is surrounded by 12 molecules at

II	$1+x,$	$y,$	z
III	$-1+x,$	$y,$	z
IV	$x,$	$y,$	$1+z$
V	$x,$	$y,$	$-1+z$
VI	$-x,$	$\frac{1}{2}+y,$	$-z$
VII	$-x,$	$\frac{1}{2}+y,$	$1-z$
VIII	$-x,$	$-\frac{1}{2}+y,$	$1-z$
IX	$-x,$	$-\frac{1}{2}+y,$	$-z$
X	$-1-x,$	$\frac{1}{2}+y,$	$-z$
XI	$-1-x,$	$-\frac{1}{2}+y,$	$-z$
XII	$1+x,$	$y,$	$1+z$
XIII	$-1+x,$	$y,$	$-1+z$

The smallest intermolecular distance is 3.53 Å between C(7) of the reference molecule and C(21) of molecule VI.

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