

Determination of the Molecular Packing in the Crystal of 5 α -Androstan-3,17-dione by Means of Potential-Energy Calculations

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Crystals of 5 α -androstan-3,17-dione are monoclinic, space group $C2$, $Z=4$, $a=12.70$, $b=6.19$, $c=21.34$ Å, $\beta=91^{\circ}16'$. The structure was solved by potential-energy calculations coupled with a minimum residual phasing technique. Three-dimensional X-ray data were used in the refinement, which was carried out by least-squares methods. The crystal packing is characterized by molecular layers, normal to the b axis, tied together by van der Waals, dipole-dipole and π - π interactions.

Introduction

Semi-empirical potentials describing inter- and intramolecular interactions have been used in our laboratory to determine the molecular packing in crystals by means of potential-energy calculations (Coiro, Giacomello & Giglio, 1971; Coiro, Giglio & Quagliata, 1972, and references quoted therein). This approach has been employed previously (Damiani, Giglio, Liquori & Mazzarella, 1967) to solve the phase problem in the crystal of 5 α -androstan-3,17-dione (hereafter referred to as ANDR) by using $h0l$ and $0kl$ reflexions. ANDR (see Fig. 1) was chosen because up to that time for only one steroid, 5 α -androstan-3 α -ol-17-one, had the crystal structure been determined without introduction of heavy atoms (High & Kraut, 1966). Moreover the average complexity of the ANDR crystal structure was considered suitable for testing the potential-energy method.

To be certain that the more likely molecular packing found for ANDR (Damiani, Giglio, Liquori & Mazzarella, 1967) is the correct one, three-dimensional intensity data have been collected. In this paper we report a three-dimensional study of the ANDR crystal structure.

Experimental

Crystals of ANDR were grown by slow evaporation from n-hexane as very thin plates showing a moderate amount of bending. The colourless crystals, melting point 133°C , are monoclinic, with $a=12.70 \pm 0.02$; $b=6.19 \pm 0.01$; $c=21.34 \pm 0.03$ Å; $\beta=91^{\circ}16' \pm 6'$, (λ for Cu $K\alpha=1.542$ Å).

These values coincide with those reported by Ohrt, Haner & Norton (1965). The experimental density, 1.14 g cm^{-3} , determined by flotation in an aqueous

solution of barium chloride, agrees with the calculated one, 1.14 g cm^{-3} , on the basis of four ANDR molecules per unit cell. Oscillation, precession and Weissenberg photographs established the space group as $C2$, Cm or $C2/m$, since the hkl reflexions were absent for $h+k$ odd. The space groups Cm and $C2/m$ must be discarded because a mirror plane is incompatible with a non-racemic compound.

The intensities of 1193 independent reflexions ($h0l$ - $h5l$ and $0kl$) were collected on multiple-film equi-inclination Weissenberg photographs, using Cu $K\alpha$ radiation and two crystals of different sizes. The intensities were of very poor quality and were estimated visually and corrected for Lorentz, polarization and change of spot shape on upper layers. No absorption factor was applied. The scaling factors of the various layers were determined subsequently as adjustable parameters during the least-squares refinement. An attempt to put the data on the same scale was made by using 170 intensities measured with the ω -scan technique by Dr T. Furnas on a Picker diffractometer, but the result was unsatisfactory, probably because of the high degree of mosaicity of the ANDR crystals.

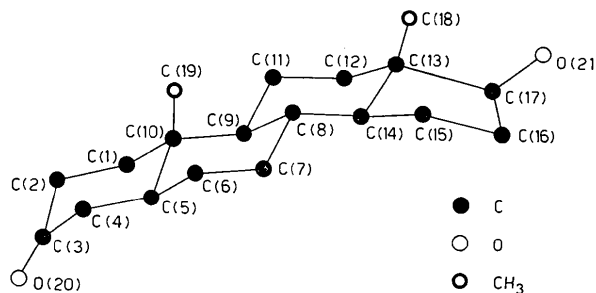
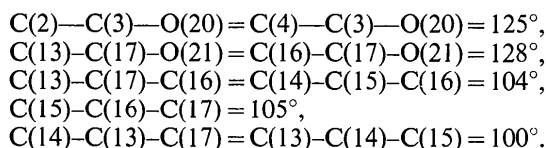


Fig. 1. Atomic numbering of ANDR molecule.

Molecular packing determination

The packing energy in the crystal of ANDR depends on three rotations (ψ_1, ψ_2, ψ_3) and two translations (t_x, t_z) along the a and c axes. The starting model of the ANDR molecule was derived using bond lengths C—C=1.54, C—O=1.23 and C—H=1.08 Å and tetrahedral bond angles except for the following:



The atomic fractional coordinates of the molecule at $\psi_1 = \psi_2 = \psi_3 = 0^\circ$ and $t_x = t_z = 0$ Å are reported in Table 1. The hydrogen atoms, when included in the calculations, were at the expected positions.

Table 1. Fractional coordinates ($\times 10^5$) of carbon and oxygen atoms of the ANDR molecule in the starting positions

The origin is placed halfway between C(8) and C(9).

	x	y	z
C(1)	14849	-4148	-11712
C(2)	14849	4148	-18516
C(3)	4950	-4148	-22049
C(4)	-4950	4148	-18777
C(5)	-4950	-4148	-11973
C(6)	-14849	4148	-8700
C(7)	-14849	-4148	-1896
C(8)	-4950	4148	1636
C(9)	4950	-4148	-1636
C(10)	4950	4148	-8440
C(11)	14849	4148	1896
C(12)	14849	-4148	8700
C(13)	4950	4148	11973
C(14)	-4950	-4148	8440
C(15)	-13542	4148	12803
C(16)	-9054	0	19471
C(17)	2755	-4148	18619
C(18)	4950	29043	11973
C(19)	4950	29043	-8440
O(20)	4950	-15625	-26756
O(21)	9043	-12274	22399

The ANDR molecule was rotated in a right-handed orthogonal framework $Oxyz$ oriented with respect to the monoclinic crystallographic system $Oabc$ in such a way that Oy and Oz coincide with Ob and Oc respectively and the positive Ox and Oa semi-axes are on the same side of the yz plane. ψ_1, ψ_2 and ψ_3 stand for clockwise rotations about Oz, Ox and Oz , provided that they are performed in the order given, moving the orthogonal system and keeping the molecule fixed.

The first calculation (Damiani, Giglio, Liquori & Mazzarella, 1967) was performed on an IBM 7040 computer by means of semi-empirical potential functions employed in the conformational analysis of helical macromolecules (De Santis, Giglio, Liquori & Ripa-

monti, 1963). The coefficients of the atom-atom potentials in the generalized form:

$$V(r) = \frac{a \exp(-br)}{r^d} - cr^{-6}$$

are reported in Table 2. Angular and translational increments of 20° and 1 Å were given in the first run, assuming a cut-off distance of 5.5 Å and neglecting the hydrogen atoms. The broad regions of minima of the potential energy were subsequently explored by decreasing the angular and translational increments to 10° and 0.5 Å and including the hydrogen atoms. All the minima were tested by computing the agreement index R for 151 $h0l$ and $0kl$ reflexions as a function of two rotational or translational degrees of freedom at once because at that time only an IBM 1620 computer was available. The two deepest minima (hereafter referred to as I and II and characterized by equal values of the parameters, except for the ψ_3 angles, which differ by 170° of rotation) were considered promising. The parameters $\psi_1, \psi_2, \psi_3, t_x$ and t_z are respectively as follows:

- (I) 350, 340, 190° , 3.2, 5.3 Å;
 (II) 350, 340, 20° , 3.2, 5.3 Å.

The minimum I corresponding to the lowest R value was analysed by three-dimensional Fourier synthesis and structure-factor calculations and then refined by least-squares methods. The refinement led to an unsatisfactory agreement index and the minimum I was discarded after many trials had been performed. At this stage a UNIVAC 1108 computer became available and the minimum residual technique was again applied to explore I and II as a function of $\psi_1, \psi_2, \psi_3, t_x$ and t_z taking into account 71 reflexions with $\sin \theta/\lambda \leq 0.2$ Å $^{-1}$. The best R values were 0.31 and 0.22 for I and II respectively and it was therefore decided to start the refinement of II.

Table 2. The coefficients of the potential functions used for the conformational analysis of polymers

The energy is in kcal per atom pair if the interatomic distance is in Å.

Interaction	$a \times 10^{-3}$	b	c	d
H—H	3.7	3.071	89.5	0
H—C	33.5	1.535	589.0	6
H—O	19.8	3.840	497.6	0
H—CH ₃	31.9	3.200	2089.0	0
C—C	301.2	0.000	327.2	12
C—O	178.5	2.304	202.2	6
C—CH ₃	287.9	1.665	1235.0	6
O—O	105.7	4.608	125.1	0
O—CH ₃	170.2	3.969	796.2	6
CH ₃ —CH ₃	273.9	3.329	2942.0	0

Refinement of the structure

The structure was refined by a set of programs written for a UNIVAC 1108 computer by Domenicano, Spagna & Vaciago (1969) together with a structure-factor

least-squares program by J. R. Carruthers. The atomic scattering factors employed for the carbon and oxygen atoms were those given by Cromer & Mann (1968) and for the hydrogen atom the values were taken from Hanson, Herman, Lea & Skillman (1964).

Refinement proceeded by isotropic and anisotropic block-diagonal least-squares methods, initially with unit weights and then with $w = (a + |F_o| + b|F_o|^2)^{-1}$. The hydrogen atoms were generated at the expected positions (C-H = 1.08 Å), those of the two methyl groups

being in staggered conformation with respect to the bonds of C(10) and C(13), and were included in the last two cycles with an isotropic B of 4 Å². The refinement was considered to be complete when the parameter shifts were less than 50% of the estimated standard deviations. The final R value and the weighted discrepancy index were 0.12 and 0.17 respectively for the observed reflexions. The final atomic coordinates and anisotropic thermal parameters are reported in Tables 3 and 4 with their standard deviations. The bond lengths and bond angles are given in Figs. 2 and 3. A list of the observed and calculated structure factors is available.*

Table 3. Final values of the fractional atomic coordinates ($\times 10^4$) of ANDR with their standard deviations in parentheses

	<i>x</i>	<i>y</i>	<i>z</i>
C(1)	3525 (7)	597 (22)	1285 (4)
C(2)	3491 (9)	1660 (28)	619 (4)
C(3)	2494 (9)	1615 (26)	289 (4)
C(4)	1535 (8)	1771 (26)	662 (5)
C(5)	1586 (7)	583 (22)	1307 (4)
C(6)	602 (7)	958 (23)	1668 (5)
C(7)	653 (7)	-327 (23)	2283 (5)
C(8)	1644 (6)	184 (21)	2680 (4)
C(9)	2631 (6)	-194 (18)	2286 (4)
C(10)	2601 (7)	1240 (0)*	1680 (4)
C(11)	3656 (7)	67 (23)	2676 (4)
C(12)	3657 (7)	-1340 (27)	3291 (4)
C(13)	2694 (7)	-758 (21)	3664 (4)
C(14)	1719 (7)	-1225 (23)	3260 (4)
C(15)	827 (8)	-1177 (27)	3725 (5)
C(16)	1330 (8)	-2420 (25)	4320 (5)
C(17)	2497 (8)	-2336 (24)	4212 (4)
C(18)	2764 (9)	1469 (28)	3938 (4)
C(19)	2655 (7)	3673 (22)	1837 (4)
O(20)	2421 (7)	1628 (18)	-289 (3)
O(21)	3137 (7)	-3285 (21)	4519 (3)

* This coordinate was kept fixed during the refinement.

Results and discussion

The rather large standard deviations of the atomic coordinates and the high final R value may be ascribed to the poor quality of the intensity data.

The average C-C distance is 1.53 Å. Two bond lengths, C(2)-C(3) and C(3)-C(4), are rather below the average and below the shortened values found in androsterone (High & Kraut, 1966) and epiandrosterone (Weeks, Cooper, Norton, Hauptman & Fisher, 1971) probably because of the delocalized π electrons in the nearly planar group C(2), C(3), C(4), O(20) [O(20) is 0.11 Å out of the plane passing through the other three atoms]. A similar, smaller, shortening was found in 17 β -hydroxyandrostan-3-one monohydrate by Bu-

* This table has been deposited with the National Lending Library, England, as Supplementary Publication No. SUP 30083. Copies may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester, CH1 1NZ, England.

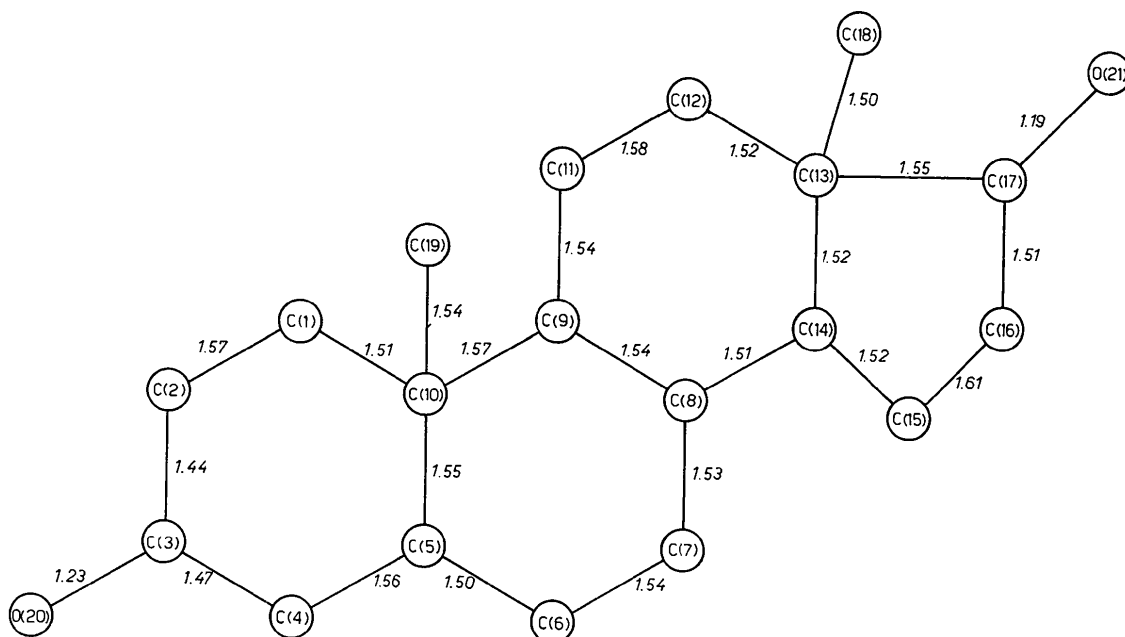


Fig. 2. Schematic drawing of ANDR showing bond distances (Å).

setta, Courseille, Fornies-Marquina & Hospital (1972). In addition, dipole-dipole and π - π interactions may be present between the two parallel C(3)-O(20) bonds of the ANDR molecules at (x, y, z) and $(\frac{1}{2}-x, \frac{1}{2}+y, \bar{z})$ (see Fig. 4), the two C(3)···O(20) intermolecular distances being 3.1 Å. The torsion angles C(1)-C(2)-C(3)-C(4) and C(2)-C(3)-C(4)-C(5) in ring *A* are 33 and -37° according to the sign convention of Klyne & Prelog (1960), and are significantly less than, for example, the corresponding angles of 17 β -hydroxyandrostan-3-one, 49 and -51° . This causes ring *A* of

ANDR to assume an unusual flattened conformation, which is very important for the determination of the actual potential energy minimum, as will be seen later. Thus it may be supposed that the intermolecular dipole-dipole and π - π interactions are responsible for the conformational change of ring *A*. The average bond angle of the *B* and *C* rings is 110° , while in ring *A* this value increases to 113° because of the C(3) trigonal hybridization. Moreover the angles C(1)-C(2)-C(3) and C(3)-C(4)-C(5) are greater than the expected tetrahedral value.

Table 4. *Thermal parameters* ($\times 10^4$) for ANDR with their standard deviations in parentheses

The form of the temperature factor is:

$$\exp [-(b_{11}h^2 + b_{12}hk + b_{13}hl + b_{22}k^2 + b_{23}kl + b_{33}l^2)].$$

	b_{11}	b_{12}	b_{13}	b_{22}	b_{23}	b_{33}
C(1)	74 (6)	29 (30)	9 (6)	322 (40)	18 (18)	32 (2)
C(2)	117 (9)	-72 (38)	18 (7)	373 (42)	-4 (21)	29 (2)
C(3)	124 (8)	34 (36)	2 (7)	297 (37)	26 (19)	27 (2)
C(4)	101 (8)	-49 (35)	-20 (7)	344 (45)	1 (21)	35 (3)
C(5)	82 (6)	-25 (29)	-7 (6)	288 (38)	11 (16)	28 (2)
C(6)	79 (7)	-17 (32)	-7 (6)	432 (59)	22 (21)	36 (3)
C(7)	69 (6)	-71 (31)	-1 (6)	430 (52)	26 (20)	34 (2)
C(8)	71 (6)	-34 (27)	-8 (5)	247 (35)	1 (16)	29 (2)
C(9)	59 (5)	14 (23)	0 (4)	255 (37)	-1 (14)	26 (2)
C(10)	71 (6)	-26 (27)	-7 (5)	263 (40)	-14 (16)	26 (2)
C(11)	69 (5)	-22 (31)	-3 (5)	434 (49)	43 (18)	27 (2)
C(12)	70 (6)	22 (34)	7 (6)	532 (55)	30 (20)	30 (2)
C(13)	83 (6)	31 (28)	-7 (5)	309 (42)	-8 (16)	23 (2)
C(14)	87 (6)	-46 (32)	8 (6)	302 (40)	2 (17)	29 (2)
C(15)	100 (8)	-69 (41)	12 (7)	454 (53)	51 (24)	37 (3)
C(16)	96 (7)	-35 (38)	24 (7)	390 (49)	48 (23)	40 (3)
C(17)	105 (8)	-71 (35)	-7 (6)	372 (42)	16 (18)	27 (2)
C(18)	116 (8)	-209 (40)	6 (6)	464 (51)	-39 (21)	25 (2)
C(19)	80 (6)	-93 (30)	-4 (6)	289 (38)	-19 (17)	32 (2)
O(20)	173 (8)	-25 (30)	5 (6)	300 (26)	11 (14)	28 (1)
O(21)	142 (7)	68 (34)	15 (6)	530 (39)	123 (20)	39 (2)

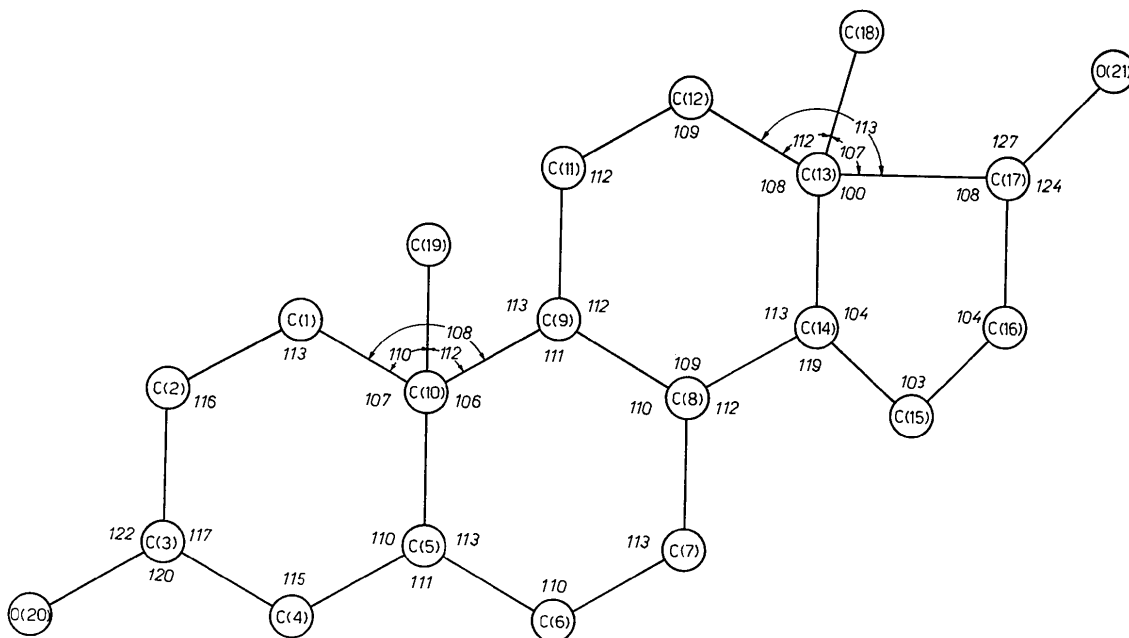


Fig. 3. Schematic drawing of ANDR showing bond angles ($^\circ$).

The geometry of the five-membered *D* ring of steroids, with an sp^2 hybridized carbon atom, is characterized in comparison with the 17- β -substituted steroids by an enlargement of the C(13)–C(17)–C(16) angle (about 108° *vs.* 104–105°) and by a decrease of the C(13)–C(17) and C(16)–C(17) torsion angles. In fact, the maximum deviation from the best plane through C(13), C(15), C(16) and C(17) is only 0.06 Å. C(17) and the atoms bound to it are nearly coplanar, O(21) being 0.04 Å from the plane passing through C(13), C(16) and C(17). The torsion angles of ring *D* of some 17-keto-steroids are given in Table 5. Epiandrosterone (I) and androsterone (II), which differ from ANDR only in the orientation of the C(3) hydroxyl group, show the same approximate half-chair conformation as ANDR. Androstenedione (IV) (Busetta, Comberton, Courseille & Hospital, 1972) adopts a conformation approaching a β -envelope, the parameters Δ and φ_m being -22 and 42° respectively (Altona, Geise & Romers, 1968). Since the sole difference between (III) and (IV) is the presence of the C(4)–C(5) double bond in (IV) instead of a single bond in (III), it is reasonable to suppose that the change in the conformation of ring *D* may be due to long range conformation–transmission effects or to the packing forces in the crystals. This last cause may sometimes be more important than has previously been assumed (Altona, Geise & Romers, 1968) in view of the structural variations occurring in the *A* and *D* rings of the ANDR molecule.

Table 5. Torsion angles ($^\circ$) in the ring *D*, and parameters Δ and φ_m of I: 5 α -androstan-3 β -ol-17-one, II: 5 α -androstan-3 α -ol-17-one, III: ANDR and IV: androst-4-en-3,17-dione

	I	II	III	IV
C(13)–C(14)	44	45	47	41
C(14)–C(15)	–39	–39	–41	–38
C(15)–C(16)	18	17	18	21
C(16)–C(17)	10	12	11	4
C(13)–C(17)	–34	–34	–35	–28
Δ	–11	–8	–11	–22
φ_m	45	45	47	42

The ANDR molecules are held together by van der Waals, dipole–dipole and π – π interactions. The outstanding feature of the molecular packing (see Figs. 4 and 5) is the overlap of the C–O bonds along the *b* axis. Other intermolecular contacts appear to be normal.

The search for the minimum potential energy in the ANDR crystal is a point of interest. This is so far the only crystal structure studied by us which does not correspond to the deepest energy minimum, even if the minima I and II differ by a partial transposition of atoms, mainly in the *ac* projection. It was therefore decided to analyse the influence of both the potentials and the molecular model used. First the energy calculation was repeated using coefficients subsequently chosen by us for solving the phase problem in crystals (see Table 6). The result was the same as before, the

order of the minima I and II being unchanged. Thus a second run was performed with the coefficients of Table 6 and with the positional parameters of Table 3. The final rotational and translational increments were 3° and 0.1 Å and the energy reached the values of -38.4 and -41.9 kcal per ANDR molecule for I and II respectively.

Table 6. The coefficients of the potentials at present used by us in packing-energy calculations

The energy is in kcal per atom pair if the interatomic distance is in Å.

Interaction	$a \times 10^{-3}$	b	c	d
H—H	6.6	4.080	49.2	0
H—C	44.8	2.040	125.0	6
H—O	42.0	2.040	132.7	6
H—CH ₃	49.1	3.705	380.5	0
C—C	301.2	0.000	327.2	12
C—O	278.7	0.000	342.3	12
C—CH ₃	291.1	1.665	981.1	6
O—O	259.0	0.000	358.0	12
O—CH ₃	272.7	1.665	1026.3	6
CH ₃ –CH ₃	273.9	3.329	2942.0	0

In addition the agreement between the lowest energy minimum and the actual structure was surprisingly good, the *x* atomic coordinates differing by 0.01 Å and the *z* by -0.06 Å from those of Table 3. Because the

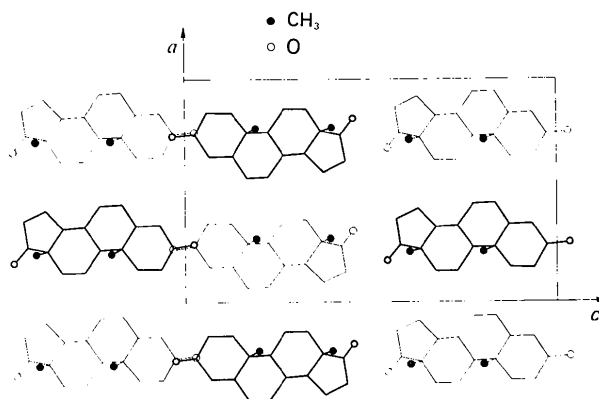


Fig. 4. Molecular packing of the ANDR molecules viewed along the *b* axis.

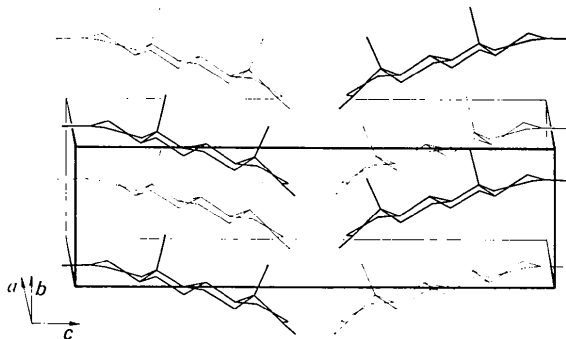


Fig. 5. View of the packing of the ANDR molecules in the crystal.

two ANDR molecules defined by the atomic coordinates of Tables 1 and 3 are similar enough with the exception of ring *A*, it is reasonable to suppose that the geometry found for this ring is substantially correct.

In conclusion the determination of the ANDR crystal structure, in spite of the unfavourable molecular model chosen for the energy computation, leads us to believe that the coupling of the potential energy calculation with the minimum residual analysis (Damiani, Giglio, Liquori & Ripamonti, 1967) is a useful tool in solving the crystal structures of complicated compounds without heavy atoms. This method is particularly useful when the replacement of a light atom with a heavy one (to solve the phase problem) changes the molecular geometry.

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Structure Determination of 2,6-Anhydro- β -D-fructofuranose

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2,6-Anhydro- β -D-fructofuranose crystallizes in space group $P2_12_12_1$ with lattice constants $a = 21.445$, $b = 10.732$ and $c = 5.874$ Å with two molecules in the asymmetric unit. The phase problem was solved by a multiresolution method. Because of the remarkable influence of extinction, the last refinement included an isotropic extinction parameter. The residual, R , is 2.8% and the standard deviations in heavy-atom bond lengths are 0.003 Å. The molecular shape can be described by two five-membered rings with three common atoms and a boat-shaped six-membered ring. The furanosyl ring can be described by an E_c -conformation. The torsional angle between the two hydroxyl groups is about 123°. Each OH group takes part in two hydrogen bonds, one as a donor, the other as an acceptor, yielding a total of six intermolecular hydrogen bonds.

Introduction

2,6-Anhydro- β -D-fructofuranose, $C_6O_5H_{10}$, hereinafter called fructose anhydride, is a decomposition product of sucrose on dry heating (Bollmann, 1964). This monomeric fructose anhydride was first described by Goldschmid & Perlin (1960). The conventional form of the structural formula is shown in Fig. 1(a), and a different form in Fig. 1(b). In the latter, two five-membered

rings can clearly be detected having three common atoms. Hence, one six-membered ring is formed which must have a boat form because of the oxygen bridge. This conformation has already been suggested (Goldschmid & Perlin, 1960). To prove this proposal, a three-dimensional X-ray structure analysis was carried out. Crystals of fructose anhydride were supplied by the Institut für Zuckerindustrie der Technischen Universität Berlin.