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The Crystal and Molecular Structure of Lithocholic Acid

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The crystal and molecular structure of lithocholic acid ($C_{24}H_{40}O_3$) has been determined from three-dimensional X-ray diffractometer data. The structure was solved by direct methods. The crystals are orthorhombic, $P2_12_12_1$, with $a=6{\cdot}807$ (2), $b=12{\cdot}178$ (3), $c=26{\cdot}779$ (4) Å and $Z=4$. The atomic parameters were refined by full-matrix least-squares to an R value of 0·049. The structure and hydrogen bonding are compared to other similar type steroids. All the oxygen atoms are involved in hydrogen bonding.

Introduction

The chemistry and physiological action of the bile acids, reviewed in the classic text of Fieser & Fieser (1959), continue to be the subject of much study. The structure determination of lithocholic acid was undertaken as a continuation of a program of study of bile acid molecular conformation and intermolecular interaction (Schaefer & Reed, 1972; Johnson & Schaefer, 1972). The ultimate goal of such studies is to relate molecular structure to physiological function.

Experimental

Lithocholic acid was obtained from Nutritional Biochemical Co. and was crystallized as needles from acetic acid. The cell parameters were determined by a least-squares fit to the settings for four angles of ten reflections on a Picker FACS I diffractometer. Table 1 gives the crystal data. A crystal measuring 0·4 × 0·3 × 0·15 mm, mounted along the a axis was used for recording crystal data and intensities. Intensity data were collected using a scintillation counter with pulse-height analyzer, θ–2θ scan, 2° min^{-1} scan rate, 10 s background counts, attenuators when scan rate exceeded 10000 counts s^{-1}, and 2·2° scan range, with a dispersion factor allowing for α_1–α_2 splitting at large 2θ values. Of 2090 unique reflections measured, $1841 > 2\sigma(I)$ were considered. Three standard reflections were monitored every 50 measurements; no decrease in the intensity of standards was observed. Lorentz and polarization corrections were applied to the data but no correction was made for absorption.

Table 1. *Crystal data for lithocholic acid*

Orthorhombic	Space group: $P2_12_12_1$
$a=$ 6·807 (2) Å	$D_x=1{\cdot}125$ g cm^{-3}
$b=12{\cdot}178$ (3)	$D_m=1{\cdot}121$
$c=26{\cdot}779$ (4)	$Z=4$
	$\mu=5{\cdot}7$ cm^{-1}

Radiation used: Cu $K\alpha$ ($\lambda=1{\cdot}54178$ Å) with graphite monochromator.
Intensity data: 2090 unique reflections measured.

Structure solution and refinement

Normalized structure factors were calculated and the reflections with E values $>1{\cdot}4$ were used to solve the structure using the program *MULTAN* (Germain, Main & Woolfson, 1971). A six-atom fragment from the first E map generated a twelve-atom fragment *via* tangent extension. All non-hydrogen atoms were located *via* subsequent tangent extension. Full-matrix least-squares refinement in which positional and isotropic thermal parameters of non-hydrogen atoms were varied reduced R to 0·127. Two more cycles of full-matrix least-squares refinement with anisotropic temperature factors reduced R to 0·102. All the 40 H atoms were located in a difference map. Two more cycles of least-squares refinement with anisotropic temperature factors for non-hydrogen atoms and isotropic temperature factors for H atoms reduced R to 0·049. The refinement was terminated at this stage since the ratios of shifts in parameters to estimated standard deviations were all less than 0·3. The refinement was based on F_o, the quantity minimized being $\sum w(F_o-F_c)^2$. Unit weights were used throughout the refinement. The scattering factors used were those of Hanson, Herman, Lea & Skillman (1964).*

Results and discussion

The final atomic positional and thermal parameters are given in Table 2. Fig. 1 shows the thermal ellipsoid probability plot of the molecule (Johnson, 1965). Fig. 2

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31191 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

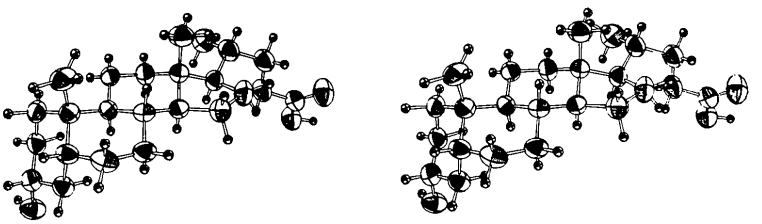

Fig. 1. Stereoscopic view of the molecule. Hydrogen atoms are shown as spheres, and other atoms as 50% probability ellipsoids.

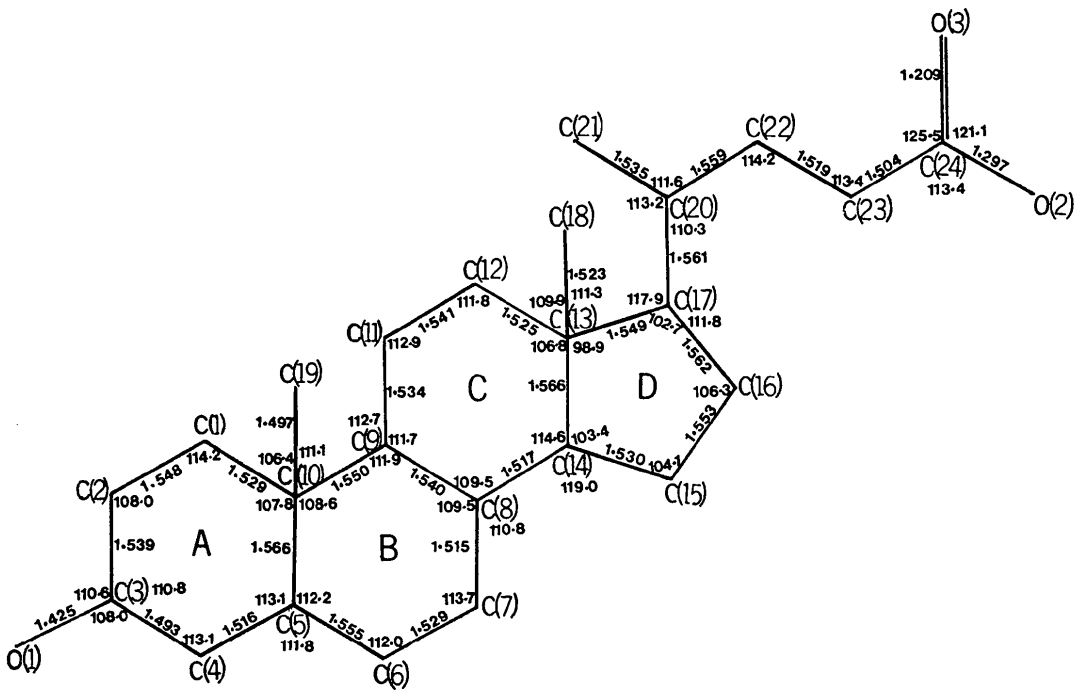

Fig. 2. Bond lengths (Å) and angles (°) in the molecule.

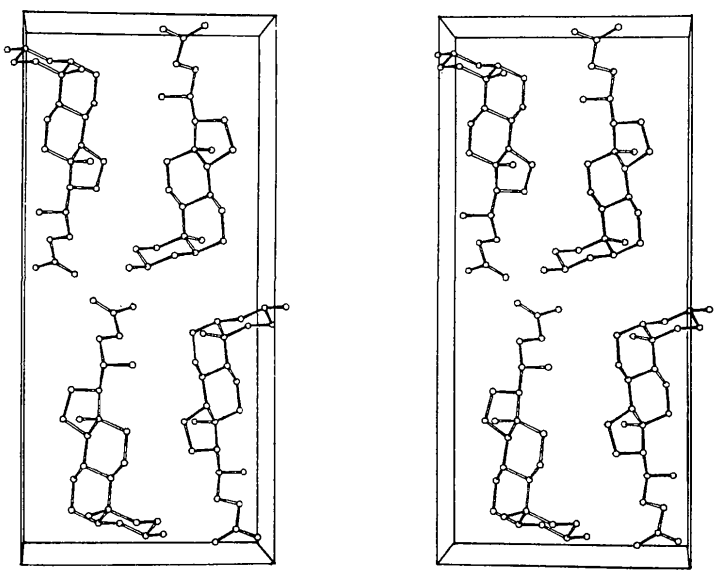

Fig. 3. Stereoscopic view of the unit cell, *a* axis projection with *c* axis vertical and *b* axis horizontal.

gives the bond lengths and angles between non-hydrogen atoms in the molecule. The C–H distances vary between 0·8 to 1·2 Å. The average standard deviations in C–O, C–C, and C–H bond lengths are 0·006, 0·008, and 0·05 Å respectively. The corresponding estimated standard deviations in C–C–O, C–C–C and C–C–H bond angles are 0·2, 0·2 and 1·5° respectively. Comparing the bond lengths in the *A*, *B* and *C* rings in lithocholic acid (I) with those in 5β-androstan-3α,17β-diol (Weeks, Cooper, Norton, Hauptman & Fisher, 1971) denoted (II) and 3α,6α-dihydroxy-5β-cholan-24-oic acid (Hall, Maslen & Cooper, 1974) denoted (III), the significant differences are in bonds C(1)–C(2), C(4)–C(5), C(5)–C(6), C(10)–C(19), and C(13)–C(18). The r.m.s. deviations between the angles in rings *A*, *B* and *C* in structures (I), (II) and (III) are 1·05° and 1·2° respectively. The geometry of the rings was as expected with the *A*/*B*-ring juncture *cis* while the *B*/*C*- and *C*/*D*-ring junctures are *trans*. The torsion angles are given in Table 3 and show that the rings *A*, *B* and *C* have normal chair conformations with torsion angles all less than 60°.

In the cyclopentane *D* ring, the bond lengths in (I) agree well with those in (III) but differ significantly from those in (II). This is due to the presence of the hydroxyl group at C(17) in (II). The r.m.s. deviations in bond angles in ring *D* are (II) 1·05°, and (III) 0·8°. The r.m.s. deviations between the torsion angles are large (I) and (II) 1·7°, (I) and (III) 4·4°. This is expected because of the flexibility of the cyclopentane ring. The conformation of the cyclopentane ring can be described by the parameters Δ and φ_m (Altona, Geise & Romers, 1968) where Δ is the phase angle and φ_m is the maximum torsional angle attainable in this conformation ($\Delta = +36°$, β-envelope; $\Delta = 0°$, half chair; $\Delta = -36°$, α-envelope). The *D* ring of lithocholic acid has a β-envelope conformation, defined by parameters $\Delta = +36{\cdot}1°$ and $\varphi_m = 50{\cdot}9°$.

Fig. 3 shows the packing diagram of the cell. The hydrogen-bond network is centered on O(1) which is

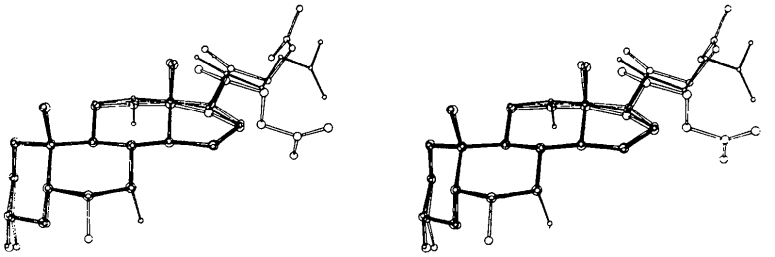

Fig. 4. A stereo view comparing (I) (large atoms), (III) (medium atoms) and (VI) (small atoms) after least-squares fitting of the *B* rings.

Table 2. *Final atomic parameters and standard deviations (in parentheses) in lithocholic acid*

Thermal parameters are of the form $\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+\beta_{12}hk+\beta_{13}hl+\beta_{23}kl) \times 10^{-4}]$. Hydrogen atoms were given isotropic temperature factors of atoms to which they were attached.

	x	*y*	*z*	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
O(1)	−0·0420 (7)	0·4201 (3)	−0·4665 (2)	305 (13)	77 (3)	26 (1)	−6 (6)	−20 (3)	−4 (1)
O(2)	−0·1982 (7)	0·5445 (3)	−0·0357 (1)	414 (13)	80 (3)	23 (1)	−50 (6)	25 (3)	−2 (1)
O(3)	−0·0968 (7)	0·7125 (3)	−0·0236 (1)	511 (16)	83 (3)	27 (1)	−42 (7)	44 (3)	−7 (1)
C(1)	0·4413 (10)	0·5448 (6)	−0·4275 (2)	253 (17)	135 (7)	14 (1)	56 (10)	1 (3)	−2 (2)
C(2)	0·2818 (10)	0·4545 (5)	−0·4308 (2)	309 (19)	98 (6)	16 (1)	44 (9)	−5 (4)	−12 (2)
C(3)	0·1141 (10)	0·4980 (5)	−0·4639 (2)	279 (18)	87 (5)	16 (1)	−1 (9)	1 (4)	−3 (2)
C(4)	0·0328 (10)	0·6024 (5)	−0·4431 (2)	266 (17)	69 (4)	16 (1)	5 (8)	−8 (4)	−3 (2)
C(5)	0·1866 (9)	0·6915 (5)	−0·4371 (2)	222 (15)	88 (5)	13 (1)	−19 (8)	−7 (3)	7 (2)
C(6)	0·0969 (10)	0·7992 (5)	−0·4158 (2)	292 (19)	72 (5)	18 (1)	−10 (8)	−19 (4)	9 (2)
C(7)	0·0535 (9)	0·7902 (4)	−0·3599 (2)	225 (16)	72 (5)	19 (1)	24 (8)	−12 (4)	0 (2)
C(8)	0·2274 (8)	0·7520 (4)	−0·3292 (2)	193 (14)	64 (4)	14 (1)	−8 (7)	−5 (3)	3 (2)
C(9)	0·3051 (9)	0·6427 (4)	−0·3502 (2)	221 (15)	76 (4)	11 (1)	4 (7)	−3 (3)	2 (2)
C(10)	0·3685 (9)	0·6535 (5)	−0·4057 (2)	225 (16)	96 (5)	14 (1)	−27 (8)	3 (3)	1 (2)
C(11)	0·4667 (9)	0·5938 (5)	−0·3171 (2)	218 (16)	107 (6)	16 (1)	50 (9)	−11 (4)	−8 (2)
C(12)	0·4044 (9)	0·5833 (5)	−0·2620 (2)	298 (19)	81 (5)	13 (1)	5 (8)	−8 (4)	0 (2)
C(13)	0·3385 (8)	0·6931 (4)	−0·2404 (2)	211 (14)	72 (4)	15 (1)	−8 (7)	0 (3)	−2 (2)
C(14)	0·1696 (8)	0·7367 (4)	−0·2749 (2)	199 (14)	69 (4)	15 (1)	−9 (7)	2 (3)	0 (2)
C(15)	0·0877 (9)	0·8347 (5)	−0·2459 (2)	282 (18)	82 (5)	20 (1)	14 (9)	−2 (4)	−8 (2)
C(16)	0·1128 (10)	0·8014 (5)	−0·1903 (2)	342 (20)	96 (5)	17 (1)	4 (10)	2 (4)	6 (2)
C(17)	0·2253 (9)	0·6897 (4)	−0·1903 (2)	246 (16)	81 (5)	13 (1)	−13 (8)	9 (3)	−2 (2)
C(18)	0·5123 (10)	0·7717 (6)	−0·2378 (2)	278 (18)	130 (7)	17 (1)	−46 (10)	−3 (4)	5 (2)
C(19)	0·5338 (10)	0·7337 (6)	−0·4113 (2)	249 (18)	161 (9)	22 (1)	−78 (11)	12 (4)	4 (2)
C(20)	0·3464 (9)	0·6732 (5)	−0·1414 (2)	355 (22)	122 (7)	12 (1)	−39 (11)	3 (4)	−3 (2)
C(21)	0·4548 (10)	0·5627 (6)	−0·1395 (2)	405 (22)	160 (7)	17 (1)	20 (12)	−8 (4)	10 (2)
C(22)	0·2126 (9)	0·6896 (5)	−0·0947 (2)	359 (19)	117 (6)	16 (1)	−37 (10)	6 (4)	−6 (2)
C(23)	0·0485 (10)	0·6057 (5)	−0·0901 (2)	385 (19)	99 (5)	15 (1)	−25 (9)	10 (4)	−3 (2)
C(24)	−0·0822 (9)	0·6278 (5)	−0·0471 (2)	343 (18)	80 (4)	15 (1)	−2 (8)	0 (3)	3 (2)

Table 2 (*cont.*)

	x	*y*	*z*
H(O1)	0·023 (7)	0·341 (3)	−0·470 (1)
H(O2)	−0·274 (7)	0·556 (3)	−0·004 (1)
H(1α)	0·528 (6)	0·508 (3)	−0·408 (1)
H(1β)	0·487 (6)	0·564 (3)	−0·468 (1)
H(2α)	0·267 (6)	0·444 (3)	−0·391 (1)
H(2β)	0·333 (6)	0·389 (3)	−0·444 (1)
H(3β)	0·148 (6)	0·516 (3)	−0·499 (1)
H(4α)	−0·002 (6)	0·583 (3)	−0·407 (1)
H(4β)	−0·062 (6)	0·631 (3)	−0·467 (1)
H(5β)	0·216 (6)	0·714 (3)	−0·470 (1)
H(6α)	−0·005 (6)	0·822 (3)	−0·440 (1)
H(6β)	0·179 (6)	0·869 (3)	−0·421 (1)
H(7α)	−0·038 (6)	0·739 (3)	−0·357 (1)
H(7β)	0·005 (6)	0·869 (3)	−0·349 (1)
H(8β)	0·335 (6)	0·821 (3)	−0·330 (1)
H(9α)	0·195 (6)	0·583 (3)	−0·345 (1)
H(11α)	0·505 (6)	0·517 (3)	−0·329 (1)
H(11β)	0·564 (6)	0·631 (3)	−0·316 (1)
H(12α)	0·494 (6)	0·552 (3)	−0·246 (1)
H(12β)	0·303 (6)	0·525 (3)	−0·258 (1)
H(14α)	0·072 (7)	0·674 (3)	−0·273 (1)
H(15α)	−0·049 (6)	0·854 (3)	−0·258 (1)
H(15β)	0·155 (6)	0·900 (3)	−0·254 (1)
H(16α)	−0·003 (6)	0·792 (3)	−0·171 (1)
H(16β)	0·115 (6)	0·868 (3)	−0·169 (1)
H(17α)	0·133 (6)	0·621 (3)	−0·194 (1)
H(18*A*)	0·547 (6)	0·801 (3)	−0·268 (1)
H(18*B*)	0·474 (6)	0·853 (3)	−0·221 (1)
H(18*C*)	0·602 (6)	0·747 (3)	−0·211 (1)
H(19*A*)	0·547 (6)	0·750 (3)	−0·455 (1)
H(19*B*)	0·506 (6)	0·821 (3)	−0·407 (1)
H(19*C*)	0·615 (6)	0·750 (3)	−0·407 (1)
H(20)	0·427 (6)	0·744 (3)	−0·141 (1)
H(21*A*)	0·350 (6)	0·494 (3)	−0·152 (1)
H(21*B*)	0·565 (6)	0·567 (3)	−0·168 (1)
H(21*C*)	0·442 (7)	0·531 (3)	−0·112 (1)
H(22*A*)	0·153 (6)	0·766 (3)	−0·094 (1)
H(22*B*)	0·314 (6)	0·689 (3)	−0·061 (1)
H(23*A*)	0·075 (6)	0·521 (3)	−0·087 (1)
H(23*B*)	−0·051 (6)	0·614 (3)	−0·119 (1)

Table 3. *Endocyclic torsional angles* (°) *for the rings of lithocholic acid*

Ring	Bond	Angle	Ring	Bond	Angle
	C(1)—C(2)	59·1		C(8)—C(9)	−51·9
	C(2)—C(3)	−57·6		C(9)—C(11)	52·7
A	C(3)—C(4)	57·1	*C*	C(11)–C(12)	−56·1
	C(4)—C(5)	−53·9		C(12)–C(13)	55·9
	C(5)—C(10)	50·5		C(13)–C(14)	−58·7
	C(10)–C(1)	−54·7		C(14)–C(8)	56·9
	C(5)—C(6)	−52·3		C(13)–C(14)	48·5
	C(6)—C(7)	52·5		C(14)–C(15)	−33·1
B	C(7)—C(8)	−54·7	*D*	C(15)–C(16)	4·9
	C(8)—C(9)	58·7		C(16)–C(17)	25·3
	C(9)—C(10)	−59·3		C(17)–C(13)	−44·4
	C(10)–C(5)	55·2			

the donor in the O–H···O bond to O(3) at ($\bar{x}$, $-\frac{1}{2}+y$, $-\frac{1}{2}-z$) of length 2·712 (5) Å and is acceptor in a similar bond from O(2) at ($-\frac{1}{2}-x$, $1-y$, $-\frac{1}{2}+z$), length 2·597 (5) Å. The angles O(1)–H···O(3) and O(2)–H···O(1) are 171·0 and 160·9° respectively. All the O atoms in the molecule are involved in hydrogen bonding. The type of hydrogen bonding affects the bond C(3)–O(1) of length 1·425 Å, which agrees very well with (II) 1·424 Å, while differing significantly from (III), 1·452 Å, in which not all of the O atoms are involved in hydrogen bonding. Table 4 gives the intermolecular distances less than 3·8 Å.

Table 4. *Intermolecular distances less than* 3·8 Å *between non-hydrogen atoms in lithocholic acid*

Symmetry code

None	x	y	z	(iii)	$-\frac{1}{2}+x$	$1\frac{1}{2}-y$	$-z$
(i)	$1+x$	y	z	(iv)	$-x$	$-\frac{1}{2}+y$	$-\frac{1}{2}-z$
(ii)	$-\frac{1}{2}-x$	$1-y$	$-\frac{1}{2}+z$	(v)	$\frac{1}{2}-x$	$1-y$	$\frac{1}{2}+z$

C(21)–O(2^{i})	3·655 (6)	O(3)–O(3^{iii})	3·744 (6)
O(1)—O(2^{ii})	2·597 (5)	O(3)–C(22^{iii})	3·626 (6)
O(1)—O(3^{ii})	3·316 (5)	O(1)–O(3^{iv})	2·712 (5)
O(1)—C(24^{ii})	3·366 (6)	O(1)–C(22^{iv})	3·452 (6)
C(3)—O(2^{ii})	3·461 (6)	O(2)–C(6^{iv})	3·330 (6)
O(2)—C(1^{v})	3·555 (6)	C(2)–C(3^{iv})	3·429 (7)

The conformation of the side chain in cholanic acids is related to the biological activity. The configuration of the ring skeleton is similar to that determined absolutely for 3α,12α-dihydroxy-5β-cholan-24-*p*-bromoanilide (Schaefer & Reed, 1972) denoted (IV), C(20) has the usual *R* configuration. Table 5 compares the torsional angles for the side chain in (I), (III), (IV), 3α,12α-dihydroxy-5β-cholan-24-oic acid (Candeloro de Sanctis, Giglio, Pavel & Quagliata, 1972) denoted (V) and cholic acid (Johnson & Schaefer, 1972) denoted (VI). Structures (III), (IV), and (VI) have the all-*trans* side-chain conformation. In structures (I) and (V), where both the carboxylic O atoms are involved in hydrogen bonding, the side chain is *gauche* about C(20)–C(22). Fig. 4 compares the stereochemistry of (I), (III), and (VI).

Table 5. *Torsional angles* (°) *for side chain in lithocholic acid* (I), *3α,6α-dihydroxy-5β-cholan-24-oic acid*(III), *3α,12α-dihydroxy-5β-cholan-24-p-bromoanilide*(IV), *3α,12α-dihydroxy-5β-cholan-24-oic acid*(V), *and cholic acid* (VI)

	(I)	(III)	(IV)	(V)	(VI)
C(13)–C(17)–C(20)–C(21)	−63	−54	−63	−59	−59
C(16)–C(17)–C(20)–C(21)	179	185	177	185	177
C(13)–C(17)–C(20)–C(22)	172	181	176	175	179
C(17)–C(20)–C(22)–C(23)	64	192	189	62	173
C(20)–C(22)–C(23)–C(24)	176	−98	173	179	175
C(22)–C(23)–C(24)–O(2)	−165	−56	164	–	167
C(22)–C(23)–C(24)–O(3)	14	124	−15	–	−15

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The Crystal and Molecular Structures of Two Polymorphic Crystalline Forms of Virazole (1-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide). A New Synthetic Broad Spectrum Antiviral Agent

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The crystal structures of two polymorphic forms of virazole, a new synthetic broad spectrum antiviral agent, have been determined. The five-membered triazole base ring of virazole makes this compound unique among the nucleoside antibiotics. Both forms crystallize in the orthorhombic system, space group $P2_12_12_1$ with $a=14{\cdot}863$, $b=7{\cdot}512$, $c=8{\cdot}788$ Å and $a=25{\cdot}034$, $b=7{\cdot}719$, $c=5{\cdot}289$ Å for crystal form V1 and crystal form V2 respectively. The structures were solved by direct methods and refined to R indices of 0·050 (V1) and 0·036 (V2) using respectively 940 and 915 intensities measured on a diffractometer. The conformations of the molecules are different in the two crystals. In V1 the glycosyl torsion, the sugar pucker (pseudorotation phase angle **P**) and the exocyclic C(4′)–C(5′) bond torsion are respectively *anti* ($\chi=10{\cdot}4°$), ${}^3T_2$ ($\mathbf{P}=11{\cdot}7°$) and *gauche*$^+$ (g^+) while in V2 they are 'high *anti*' ($\chi=119{\cdot}0°$), ${}_2T^1$ ($\mathbf{P}=335{\cdot}8$ or $-24{\cdot}2°$) and *trans* (t). The 2′-*exo* puckering observed for V2 is uncommon for β-nucleosides. The carboxamide group in V2 is engaged in hydrogen bonding to the base ring of a symmetry-related molecule whereas there is no interbase hydrogen bonding in V1. The usual hydrogen-bonding sites of the base ring in V1 are involved in hydrogen bonding, while the N(2) site of the base in V2 is not hydrogen bonded. Interestingly, in both structures one of the amino hydrogen atoms is not engaged in hydrogen bonding.

Introduction

Virazole (Fig. 1) is a new synthetic broad spectrum antiviral agent and belongs to a class of nucleoside antibiotic structures containing a five-membered triazole ring (Sidwell, Huffman, Khare, Allen, Witowski & Robins, 1972). Virazole crystallizes in two polymorphic modifications which exhibit differences in their KBr infrared spectra and melting points (Robins, 1972) suggesting differences in their hydrogen bonding and crystal packing schemes. X-ray structure analysis of the two polymorphic forms of virazole was undertaken to unequivocally establish the molecular structure and conformation and to elucidate the differences in the properties of the polymorphs in terms of differences in their packing patterns. It is also of interest to compare the structure of virazole with showdomycin (Tsukuda & Koyama, 1970) and pyrazomycin (Jones & Chaney, 1972), the two other known five-membered base nucleoside antiviral agents and antibiotics. A preliminary communication of this work has been presented elsewhere (Prusiner & Sundaralingam, 1973).

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Experimental section

Crystals of both polymorphic forms of virazole (V1 and V2) were kindly supplied by Dr Roland K. Robins of the Nucleic Acid Research Center, Irvine, California. The pertinent crystal data are given in Table 1. The cell constants were determined by a least-squares refinement of the goniostat angles 2θ, ω, and χ of 12 reflections measured in the 2θ range of 40–60° on a diffractometer.

Three-dimensional monochromatized X-ray intensity data were collected for V1 on an automatic FACS-1 Picker diffractometer using Cu radiation whereas for V2 no monochromator was used. The θ–2θ scan mode was employed with a scan rate of 2° min^{-1}. The data were corrected for Lorentz and polarization effects, but no absorption corrections