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Molecular and Crystal Structure of 5,6-Dihydro-2-thiouridine, $C_9H_{14}N_2O_5S$

By Biserka Kojić-Prodić, R. Liminga,* M. Šljukić and Živa Ružić-Toroš
'Rudjer Bošković' Institute, 41001 *Zagreb*, *Box* 1016, *Yugoslavia*

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5,6-Dihydro-2-thiouridine crystallizes in the space group $P2_1$ with $a=15{\cdot}330$, $b=7{\cdot}517$, $c=5{\cdot}070$ Å, $\beta=107{\cdot}89°$, $Z=2$. The structure was solved by direct methods and refined by the full-matrix least-squares technique to R 0·098. Because of the saturated C(5)–C(6) bond, the nucleobase is not planar. The ribose moiety has C(3′)-*endo* conformation and the nucleoside molecule exhibits the usual *anti* conformation. The thiouridine molecules are connected by hydrogen bonds between sugar–sugar and base–base residues to form a three-dimensional network. There is no base stacking.

Introduction

The presence of several sulphur-containing nucleosides in transfer-RNA's has been established and their crystal structures are thus of special interest. The structures of sulphur-containing nucleosides such as 2,4-dithiouridine monohydrate (Saenger & Suck, 1971*a*), 3′-acetyl-4-thiothymidine (Saenger & Suck, 1971*b*), 2-thiocytidine (Lin, Sundaralingam & Arora, 1971), 4-thiouridine hydrate (Saenger & Scheit, 1970), 2-thiouridine (Hawkinson, 1970), 4-thiouridine disulphide (Shefter & Kalman, 1968) have been published. A very peculiar structure is that of 4-thiouridine hydrate (Saenger & Scheit, 1970), the only pyrimidine nucleoside so far found in *syn* conformation.

The synthesis of thio analogues of 5,6-dihydrouridine forms part of a study of possible unusual constituents of t-RNA. These investigations have been undertaken at the 'Rudjer Bošković' Institute by Dr V. Škarić and his coworkers (Škarić, Gašpert & Hohnjec, 1970; Škarić & Gašpert, 1969; Škarić, Gašpert, Jerkunica & Škarić, 1965). The crystals of 5,6-dihydro-2-thiouridine for the present structure determination were kindly provided by Dr V. Škarić.

Experimental

The yellow needle-like crystals elongated along [001] are monoclinic with:

$a=15{\cdot}330\,(5)$,† $b=7{\cdot}517\,(2)$, $c=5{\cdot}070\,(2)$ Å,
$\beta=107{\cdot}89\,(1)°$,
$V=555{\cdot}6$ Å^3,
$D_m=1{\cdot}55$, $D_c=1{\cdot}56$ g cm^{-3},
$Z=2$,
Cu $K\alpha$ radiation, $\mu=26{\cdot}8$ cm^{-1}.

Table 1. *Final coordinates and thermal parameters*

The anisotropic thermal parameters refer to the expression $\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$.
Hydrogen coordinates are × 10^3; other atom coordinates are × 10^4.

	x	y	z	B (Å^2)/β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N(1)	8041 (6)	5554 (17)	3660 (18)	1·09 (14)					
C(2)	8404 (7)	4110 (21)	2594 (23)	1·57 (20)					
N(3)	9023 (7)	4516 (22)	1197 (23)	2·19 (18)					
C(4)	9453 (7)	6129 (22)	1227 (24)	1·66 (20)					
O(4)	17 (8)	6307 (19)	−22 (27)	0·0037 (4)	0·0180 (35)	0·0472 (46)	−0·0007 (10)	0·0102 (12)	0·0011 (38)
C(5)	9245 (9)	7532 (25)	2995 (27)	2·40 (24)					
C(6)	8270 (8)	7342 (26)	3077 (26)	2·17 (23)					
S	8125 (2)	2000	2852 (8)	0·0025 (1)	0·0085 (8)	0·0488 (17)	−0·0005 (3)	0·0066 (4)	−0·0010 (13)
C(1′)	7278 (7)	5158 (21)	4835 (22)	1·46 (18)					
C(2′)	6395 (7)	4814 (23)	2584 (21)	1·31 (18)					
O(2′)	5830 (5)	3708 (17)	3748 (17)	0·0023 (3)	0·0064 (19)	0·0246 (33)	−0·0009 (8)	0·0039 (9)	0·0006 (26)
C(3′)	5984 (6)	6648 (20)	2164 (18)	0·88 (16)					
O(3′)	5036 (4)	6730 (20)	781 (15)	0·0004 (2)	0·0210 (36)	0·0211 (30)	−0·0007 (8)	−0·0014 (7)	0·0059 (29)
C(4′)	6268 (7)	7422 (25)	5100 (21)	1·27 (18)					
C(5′)	6282 (8)	9352 (31)	5237 (25)	0·0033 (6)	0·0208 (62)	0·0156 (44)	0·0026 (14)	0·0050 (31)	−0·0003 (40)
O(5′)	6395 (7)	29 (19)	8044 (14)	0·0036 (5)	0·0152 (35)	0·0243 (35)	0·0012 (10)	0·0037 (11)	0·0006 (31)
O(1′)	7164 (5)	6616 (15)	6349 (14)	1·47 (13)					

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* Institute of Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala 1, Sweden.

† Numbers in parentheses here and throughout this paper are the estimated standard deviations in the least significant digits.

Table 1 (*cont.*)

	x	y	z	$B(\text{Å}^2)$
H(3)	917	358	2	3·5
H(5)1	930	875	212	3·5
H(5)2	968	752	490	3·5
H(6)1	783	777	126	3·5
H(6)2	817	820	449	3·5
H(1′)	744	411	609	3·5
H(4′)	584	698	607	3·5
H(5′)1	571	979	391	3·5
H(5′)2	678	977	454	3·5
H(2′)	649	428	88	3·5
H(3′)	630	734	104	3·5

The space group was determined from Weissenberg photographs recorded with Cu $K\alpha$ radiation. The diffraction symmetry and systematic absences indicated space groups $P2_1$ or $P2_1/m$. As the unit cell contains two asymmetric molecules, $P2_1$ is the only possibility. The subsequent refinement showed that this choice was appropriate.

The unit-cell parameters were determined from Straumanis photographs round **b** and **c**. A least-squares treatment of 13 $h0l$ and 23 $hk0$ high-angle reflexions was performed after taking into account the angular dependence of systematic aberration in the form $\Delta d/d = \cos^2\theta/\theta + \cos^2\theta/\sin\theta$ (Popović, 1974). The density was measured at 25°C pycnometrically with decalin as the medium.

Two crystals shaped into spheres were used for the collection of the intensities, with radii $r_1 = 0{\cdot}015$ cm for rotation round [010] and $r_2 = 0{\cdot}022$ cm for rotation round [001]. Equi-inclination Weissenberg photographs were taken with filtered Cu $K\alpha$ radiation and the multiple-film technique (five films). The number of independent reflexions recorded was 945. Out of these, 804 had observable intensities, which were measured with a microdensitometer. The corrections for absorption, Lorentz and polarization factors were made in the usual way.

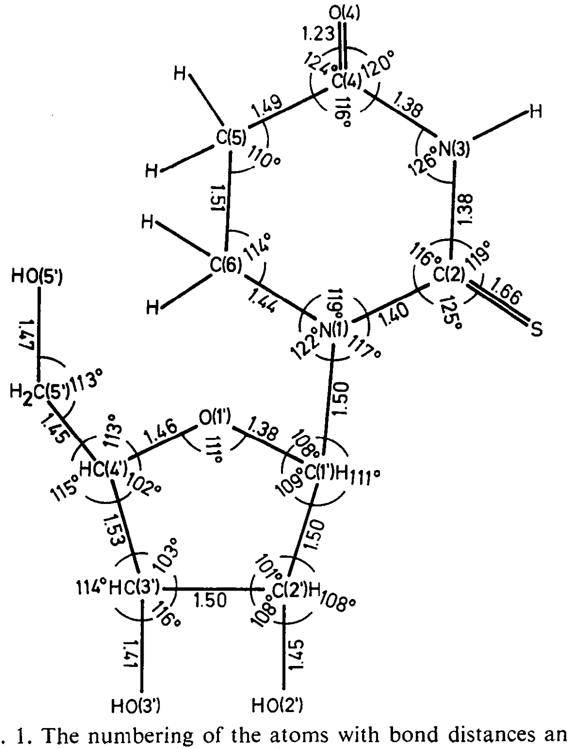

Fig. 1. The numbering of the atoms with bond distances and angles.

Structure determination and refinement

An overall temperature factor ($B = 5{\cdot}96$ Å^2) and scale factors were determined (Wilson, 1942) and used to compute normalized structure factors (Karle & Hauptman, 1956). The E statistics suggested a non-centrosymmetric structure.

The structure was solved by direct methods with the program *MULTAN* (Main, Woolfson & Germain, 1971). The solution was based on 156 reflexions with $E > 1{\cdot}4$. The E map corresponding to the solution with the best 'figure of merit' revealed the positions of 14 non-hydrogen atoms. C(5), C(6) and C(5′) were located from the resulting Fourier synthesis.

The structure was refined by a full-matrix least-squares procedure using the program *UPALS* (Lundgren, 1972). The function minimized was $\sum w(|F_o|^2 - |F_c|^2)^2$ with each reflexion assigned a weight w according to Cruickshank, with the values of constants $c_1 = 10{\cdot}00$, $c_2 = 0{\cdot}050$. The scale factors, positional and isotropic thermal parameters were refined to $R = 0{\cdot}135$. The hydrogen atom positions, except those belonging to hydroxyl groups, were calculated on stereochemical grounds. Inclusion of all atoms in the calculation of structure factors, the refinement of all non-hydrogen atomic positions and isotropic temperature factors together with anisotropic thermal parameters for the

Table 2. *Observed and calculated structure factors*

The columns are in the order h, l, $|F_o|$ and $|F_c|$. Reflexions not included in the refinement are marked with an asterisk.

non-ring atoms resulted in $R=0{\cdot}103$. Introduction of anisotropic thermal parameters for all non-hydrogen atoms lowered R to 0·098, but the temperature factor of C(5′) was not positive definite. The inter-layer scale factors were fixed to the values obtained from the isotropic refinement, and only one scale factor was refined. The number of parameters varied was 98.

The atomic scattering factors used were those for neutral C, N, O and S given by Hanson, Herman, Lea & Skillman (1964) and the spherical scattering factor for H proposed by Stewart, Davidson & Simpson (1965). An anomalous dispersion correction was included for S according to Cromer (1965).

The calculations were carried out on the IBM 370/155 computer in Uppsala and the CAE 90-40 computer in Zagreb. Final atomic coordinates and thermal parameters are given in Table 1. Observed and calculated structure factors are listed in Table 2.

Description and discussion of the structure

The numbering of the atoms and bond distances and angles are shown in Fig. 1. A stereoscopic drawing of the molecule is given in Fig. 2 and hydrogen bonds are illustrated in Fig. 3.

Interatomic distances and angles are listed in Table 3; displacements of the atoms from the least-squares planes through the nucleobase and ribose are given in Table 4. Some dihedral angles defining the conformation of the molecule are presented in Table 5. Hydrogen-bond distances are given in Table 6.

Interatomic distances and angles with estimated standard deviations based on the correlation matrix were calculated with the program *ORFFE* (Busing, Martin & Levy, 1964).

The figures were prepared with the plotting program *ORTEP* (Johnson, 1965).

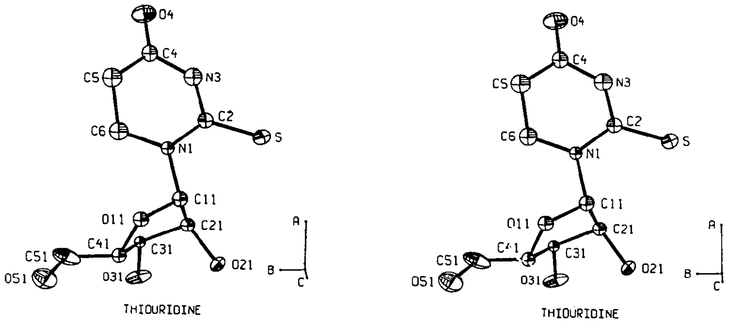

Fig. 2. Stereoscopic drawing. Thermal ellipsoids are scaled to enclose 50 % probability.

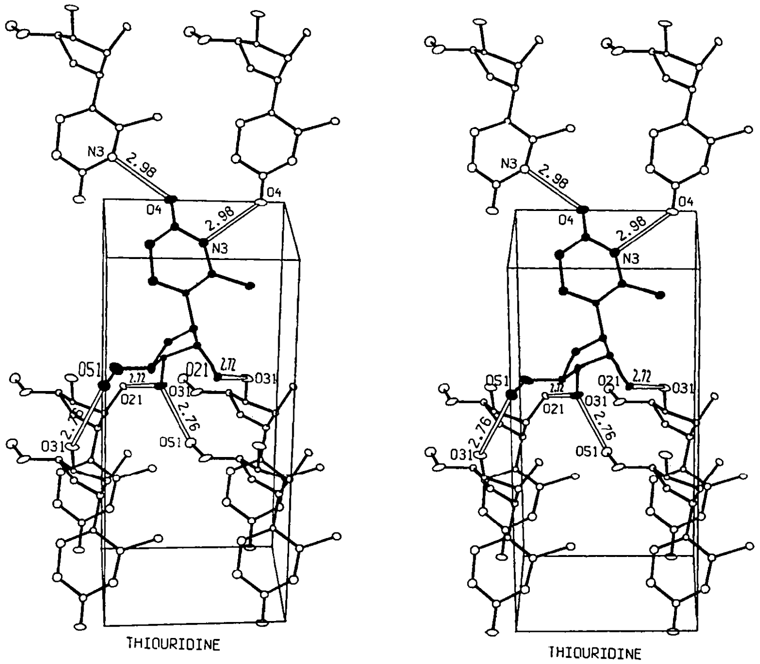

Fig. 3. Hydrogen-bond scheme.

Table 3. *Bond distances* (Å) *and angles* (°)

N(1)–C(2)	1·40 (2)
C(2)–S	1·66 (2)
C(2)–N(3)	1·38 (1)
N(3)–C(4)	1·38 (2)
C(4)–O(4)	1·23 (1)
C(4)–C(5)	1·48 (2)
C(5)–C(6)	1·51 (2)
C(6)–N(1)	1·44 (2)
N(1)–C(1′)	1·50 (1)
C(1′)–C(2′)	1·50 (2)
C(2′)–O(2′)	1·45 (1)
C(2′)–C(3′)	1·50 (2)
C(3′)–O(3′)	1·41 (1)
C(3′)–C(4′)	1·53 (1)
C(4′)–C(5′)	1·45 (2)
C(5′)–O(5′)	1·47 (2)
C(4′)–O(1′)	1·46 (1)
O(1′)–C(1′)	1·38 (2)
N(3)–H(3)	0·99
C(5)–H(5)1	1·03
C(5)–H(5)2	0·99
C(6)–H(6)1	1·01
C(6)–H(6)2	1·01
C(1′)–H(1′)	1·00
C(2′)–H(2′)	1·00
C(3′)–H(3′)	1·00
C(4′)–H(4′)	0·99
C(5′)–H(5′)1	0·99
C(5′)–H(5′)2	0·99

N(1)—C(2)–S	125 (1)
N(1)—C(2)–N(3)	116 (1)
S—C(2)–N(3)	119 (1)
C(2)—N(3)–C(4)	126 (1)
N(3)—C(4)–O(4)	120 (1)
N(3)—C(4)–C(5)	116 (1)
O(4)—C(4)–C(5)	124 (1)
C(4)—C(5)–C(6)	110 (1)
C(5)—C(6)–N(1)	114 (1)
C(6)—N(1)–C(2)	119 (1)
C(6)—N(1)–C(1′)	122 (1)
C(2)—N(1)–C(1′)	117 (1)
N(1)—C(1′)–O(1′)	108 (1)
N(1)—C(1′)–C(2′)	111 (1)
O(1′)—C(1′)–C(2′)	109 (1)
C(1′)—C(2′)–O(2′)	108 (1)
C(1′)—C(2′)–C(3′)	101 (1)
O(2′)—C(2′)–C(3′)	108 (1)
C(2′)—C(3′)–O(3′)	116 (1)
C(2′)—C(3′)–C(4′)	103 (1)
O(3′)—C(3′)–C(4′)	114 (1)
C(3′)—C(4′)–C(5′)	115 (1)
C(3′)—C(4′)–O(1′)	102 (1)
O(1′)—C(4′)–C(5′)	113 (1)
C(4′)—O(1′)–C(1′)	111 (1)
C(4′)—C(5′)–O(5′)	113 (1)
C(2)—N(3)–H(3)	117
C(4)—N(3)–H(3)	116
C(4)—C(5)–H(5)1	108
C(4)—C(5)–H(5)2	112
H(5)1–C(5)–H(5)2	108
C(6)—C(5)–H(5)1	108
C(6)—C(5)–H(5)1	108
C(6)—C(5)–H(5)2	110
C(5)—C(6)–H(6)1	109
C(5)—C(6)–H(6)2	109
H(6)1–C(6)–H(6)2	104
N(1)—C(6)–H(6)1	110
N(1)—C(6)–H(6)2	111
N(1)—C(1′)–H(1′)	110
O(1′)—C(1′)–H(1′)	109
C(2′)—C(1′)–H(1′)	110

Table 3 (*cont.*)

C(1′)—C(2′)–H(2′)	113
O(2′)—C(2′)–H(2′)	112
C(3′)—C(2′)–H(2′)	114
C(2′)—C(3′)–H(3′)	108
O(3′)—C(3′)–H(3′)	108
C(4′)—C(3′)–H(3′)	108
C(3′)—C(4′)–H(4′)	108
O(1′)—C(4′)–H(4′)	109
C(4′)—C(5′)–H(5′)1	108
C(4′)—C(5′)–H(5′)2	108
H(5′)1–C(5′)–H(5′)2	106
O(5′)—C(5′)–H(5′)1	111
O(5′)—C(5′)–H(5′)2	111

Table 4. *Least-squares planes through the heterocycle and ribose moieties*

Atoms defining the planes are marked by an asterisk.

		Displacement (Å)
Heterocycle	N(1)*	0·02 (1)
	C(2)*	−0·06 (1)
	N(3)*	0·06 (1)
	C(4)*	−0·03 (1)
	O(4)	0·04 (1)
	C(5)	−0·32 (1)
	C(6)	0·30 (1)
	S	−0·24 (0)
	C(1′)	0·08 (1)
	C(2′)	1·44 (1)
Ribose	C(1′)*	0·04 (1)
	C(2′)*	−0·02 (1)
	C(4′)*	0·02 (1)
	O(1′)*	−0·02 (1)
	C(3′)	0·56 (1)
	C(5′)	0·80 (2)
	O(2′)	−1·42 (1)
	O(3′)	0·30 (1)

Table 5. *Dihedral angles describing the conformation of the molecule*

The positive sense of the rotation is clockwise from *A* to *D* while looking down the *BC* bond. Greek letters correspond to Sundaralingam's (1969) notation. Estimated standard deviations are 1° for all listed angles.

	A	*B*	*C*	*D*	Angles (°)
χ	O(1′)	C(1′)	N(1)	C(2)	166 (1)
τ_0	C(4)	O(1′)	C(1′)	C(2′)	−6
τ_1	O(1′)	C(1′)	C(2′)	C(3′)	27
τ_2	C(1′)	C(2′)	C(3′)	C(4′)	−36
τ_3	C(2′)	C(3′)	C(4′)	O(1′)	34
τ_4	C(3′)	C(4′)	O(1′)	C(1′)	−18
ψ	O(5′)	C(5′)	C(4′)	C(3′)	170
	C(2)	N(1)	C(6)	C(5)	−36
	N(3)	C(4)	C(5)	C(6)	−32
	C(4)	C(5)	C(6)	N(1)	49
	C(2′)	C(1′)	N(1)	C(2)	−75
	C(2′)	C(1′)	N(1)	C(6)	92
	O(1′)	C(1′)	N(1)	C(6)	−27
	O(2′)	C(2′)	C(3′)	O(3′)	−49
	O(5′)	C(5′)	C(4′)	O(1′)	−73
	N(1)	C(1′)	C(2′)	O(2′)	155
	N(1)	C(1′)	C(2′)	C(3′)	−92
	N(1)	C(1′)	O(1′)	C(4′)	115
	C(5′)	C(4′)	C(3′)	O(3′)	−76
	C(5′)	C(4′)	C(3′)	C(2′)	157
	C(5′)	C(4′)	O(1′)	C(1′)	−142

Table 6. *Hydrogen bond*

Hydrogen bond	Distance (Å)	Symmetry operation
O(2′)···O(3′)	2·72 (1)	x, y, z $\bar{x}, \frac{1}{2}+y-1, \bar{z}$
O(3′)···O(5′)	2·76 (1)	$x, y+1, z$ x, y, z
N(3)–H···O(4)	2·98 (2)	x, y, z $\bar{x}, \frac{1}{2}+y-1, \bar{z}$

5,6-*Dihydro-2-thiouracil residue*

The nucleobase is puckered owing to the saturation of the C(5)–C(6) double bond. The deviations of C(5) and C(6) from the least-squares plane defined by N(1), C(2), N(3), C(4) are −0·32 and 0·30 Å, respectively (Table 4.) The sulphur atom is also displaced by 0·24 Å from this plane. In the structure of 4-thiouridine hydrate (Saenger & Scheit, 1970) a displacement by 0·177 Å of the sulphur atom from the pyrimidine plane was observed. The heterocycle exists in the diketo form; C(2)–S and C(4)–O(4) both have double-bond character. Bond distances and angles in the base are comparable with those found in 5,6-dihydrouridine (Suck, Saenger & Zechmeister, 1972).

Ribose moiety

The ribose exists in the envelope C(3′)-*endo* conformation; the C(3′) atom is displaced by 0·56 Å from the least-squares plane defined by the atoms C(1′), C(2′), C(4′) and O(1′), and is situated on the same side of this plane as C(5′) (Table 4). Bond lengths and angles (Table 3) are in agreement with the values found in compounds containing C(3′)-*endo* ribose (Sundaralingam & Jensen, 1965). The conformation about the C(4′)–C(5′) bond is defined by the dihedral angles φ_{OO}=O(5′)–C(5′)–C(4′)–O(1′) and φ_{OC}=O(5′)–C(5′)–C(4′)–C(3′) (Shefter & Trueblood, 1965). The values of these angles are $\varphi_{OO}=-73°$ and $\varphi_{OC}=170°$, *i.e.* the conformation about the C(4′)–C(5′) bond is *gauche-trans*. The variation of the energy with rotation about C(4′)–C(5′) indicates that for C(3′)-*endo* and C(2′)-*endo* sugars the *gauche–gauche*, *gauche–trans*, and *trans–gauche* orientations are equally favourable and all three have been observed in nucleosides, although the *gauche–gauche* is the most common (Wilson & Rahman, 1971). In the structure of inosine I (Munns & Tollin, 1970) containing C(3′)-*endo* pucker, a *gauche–trans* conformation with $\varphi_{OC}=169°$ was observed.

Conformation of the molecule

The orientation of the heterocycle with respect to the sugar moiety is defined by the dihedral angle round the glycosidic bond C(1′)–N(1). This angle is defined with different sets of atoms by various authors. One recent suggestion is that the dihedral angle φ_{CN}=O(1′)–C(1′)–N(1)–C(2) should be used to define this conformation (Saenger, 1973). In the present study this angle is 166°, *i.e.* in the *anti* range (110 to 290°). The sulphur atom is thus pointing away from the sugar (Fig. 2). Sundaralingam's (1969) notation of dihedral angles describing the conformation is given in Table 5.

Hydrogen bonding and molecular packing

Each molecule is involved in three independent hydrogen bonds to neighbouring molecules (Fig. 3, Table 6). The base–base interaction is realized through the N(3)–H···O(4) hydrogen bond of length 2·98 Å. There are hydroxyl groups in the ribose part which could act as donors of H to hydrogen bonds (as well as acceptors). Only two intermolecular contacts in a suitable range exist: O(3′)···O(5′) 2·76 Å and O(2′)···O(3′) 2·72 Å. There is a third intramolecular contact, O(2′)···O(3′), of length 2·78 Å, which might also be a hydrogen bond. However, the O–H···O angle is necessarily unfavourable. As long as the positions of the O–H hydrogen atoms are unknown, the exact details of the hydrogen-bond system cannot be determined. An attempt to locate the hydrogen atoms from a difference synthesis was not successful.

The crystal packing cannot be classified in any of the three types described by Motherwell, Riva di Sanseverino & Kennard (1973).

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The Crystal and Molecular Structure of a Bicyclo[3,3,1]nonane System: Structure of D,L-1,7-Dicarbomethoxy-3a,7-methano-3a*H*-decahydrocyclopentacyclooctene-2,10-dione

BY E. E. ABOLA

Department of Crystallography, University of Pittsburgh, Pittsburgh, Pa. 15260, *U.S.A.*

AND J. PLETCHER AND M. SAX

Biocrystallography Laboratory, VA Hospital, Pittsburgh, Pa. 15240, *U.S.A.*

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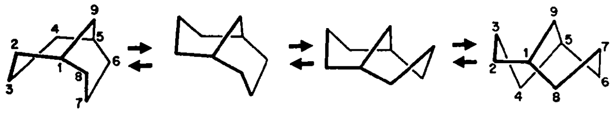
The crystal and molecular structure was determined from three-dimensional diffractometer data. The compound crystallizes in the monoclinic space group $P2_1/c$, with four molecules in a unit cell of dimensions $a = 10{\cdot}907$ (3), $b = 9{\cdot}520$ (7), $c = 15{\cdot}638$ (13) Å, $\beta = 111{\cdot}19$ (4)°. The crystal structure was solved by direct-method phasing and it was refined by the full-matrix least-squares method to a conventional R of 0·056 on 2390 independent reflections. The structure is disordered. The bicyclo[3,3,1]nonane system in the molecule assumes two conformations, the di-chair and the boat–chair forms. The occupancy factors are 0·7 and 0·3 respectively. Strain due to the close contact, 2·097 Å, between C(5) and C(9) and the *trans* fused perhydroindane system cause considerable flattening of the rings and distortions of the valency angles and bond lengths. The carbomethoxy group at C(1) and the methylene group at C(4) are in the *trans* configuration.

Introduction

The crystal structure of 1,7-dicarbomethoxy-3a,7-methano-3a*H*-decahydrocyclopentacyclooctene-2,10-dione (DCPCO) was undertaken to study the conformation of the bicyclo[3,3,1]nonane system and to determine the configurations at C(1) and at the junction of the *A* and *B* rings (see Fig. 1 for numbering scheme). The results were essential for establishing the stereochemical relationships in a one-step assemblage of 3a,7-methano-3a*H*-cyclopentacyclooctene systems (Danishefsky, Hatch, Sax, Abola & Pletcher, 1973). The crystal structure is of further interest in that it shows how the conformation of the bicyclo[3,3,1]nonane system is affected by the fusion of a cyclopentanone ring to one of its bicyclo rings.

It has been suggested that certain 9-keto derivatives [C(10) in DCPCO] of the bicyclononane system would exhibit an equilibrium distribution consisting of the boat–chair (1*b*) and di-twist-boat (1*d*) conformations, because of the removal of the flag-pole hydrogen and certain torsional interactions (Eliel, Allinger, Angyal & Morrison, 1966). Neither of these conformers was found in previous structure determinations of bicyclononane systems (Webb & Becker, 1967; Brown, Martin & Sim, 1965). Only (1*a*) was observed previously. However, two of the conformers, the di-chair (1*a*) and boat–chair (1*b*) forms, do occur in this crystal structure. The possible role of the *trans* fused perhydroindane in facilitating a distribution of conformations is considered.



(1*a*) (1*b*) (1*c*) (1*d*)

Experimental procedures

DCPCO was synthesized and given to us by Dr W.E. Hatch and Dr Danishefsky of the Chemistry Department in the University of Pittsburgh. Crystals were grown by slow evaporation from an ethanol solution.