Structural Studies of *O*-Cyclocytidine Derivatives.
III. The Crystal and Molecular Structure of 2,2′-Anhydro-1-β-D-arabinofuranosylcytosine-3′,5′-diphosphate Monohydrate

By Yuriko Yamagata, Yutaka Suzuki, Satoshi Fujii, Takaji Fujiwara and Ken-ichi Tomita

Faculty of Pharmaceutical Sciences, Osaka University, Yamadakami, Suita, Osaka 565, Japan

Abstract

The title compound, $C_9H_{13}N_3O_{10}P_2 \cdot H_2O$, crystallizes in the monoclinic system with space group $P2_1$, $Z = 2$ and unit-cell dimensions $a = 10\cdot286$ (2), $b = 6\cdot594$ (3), $c = 11\cdot177$ (3) Å and $\beta = 96\cdot27$ (3)°. The structure was solved by the heavy-atom method and refined to a final R value of 0·045. The glycosidic torsion angle χ_{CN} is 298·8° and the sugar moiety is puckered with a C(4′)-*endo* conformation. The exocyclic torsion angles ψ, φ and φ' are 48·8, 155·5 and −137·3°, respectively. Short intramolecular contacts are observed between the sugar O(5′) atom or the phosphate O(5) atom and the base atoms. No base stacking is observed.

Introduction

The title compound, 2,2′-anhydro-1-β-D-arabinofuranosylcytosine-3′,5′-diphosphate (2,2′-cyclo-3′,5′-CDP), is a derivative of 2,2′-anhydro-1-β-D-arabinofuranosylcytosine (2,2′-cyclo-C) which possesses strong antitumor activity against leukemia and various tumor cells (Hoshi, Kanzawa, Kuretani, Saneyoshi & Arai, 1971). To date, several structure determinations of the β-pyrimidine cyclonucleosides have been reported, and much information about the effect of the cyclization reaction on the molecular conformations of the base and sugar moieties has been obtained. These include 2,2′-cyclo-C (Brennan & Sundaralingam, 1973), 2,2′-anhydro-1-β-D-arabinofuranosyluracil (Suck & Saenger, 1973; Delbaere & James, 1973), 6,2′-anhydro-1-β-D-arabinofuranosyl-6-hydroxycytosine (6,2′-cyclo-C; Yamagata, Fujii, Kanai, Ogawa & Tomita, 1979), 2,2′-anhydro-1-β-D-arabinofuranosyl-5-dimethylsulfonio-6-oxocytosine chloride [5-S(CH₃)₂-2,2′-CC] and 2,2′-anhydro-1-{3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl}-5-chloro-6-oxocytosine (5-Cl-2,2′-CC; Yamagata, Koshibe, Tokuoka. Fujii, Fujiwara, Kanai & Tomita, 1979). This paper deals with the crystal and molecular structure of 2,2′-cyclo-3′,5′-CDP which is the first example of a pyrimidine

cyclonucleotide determined by X-ray diffraction, and is a good example for comparison of the molecular structure in the crystalline form with that in solution, and also for discussion of the influence of cyclization on the conformation of the 3′- or 5′-phosphate moieties.

Experimental

2,2′-cyclo-3′,5′-CDP was synthesized in a manner similar to that described by Kanai & Ichino (1971) and crystallized from aqueous solution as colorless plates. Preliminary data on the unit-cell dimensions and space group were obtained from Weissenberg and precession photographs, which were then refined by a least-squares procedure using the 2θ values of 15 high-angle reflections measured on a four-circle diffractometer. The density was measured by the flotation method in chloroform–ethylene bromide mixture. The crystallographic data are shown in Table 1.

The intensities of 1883 independent reflections within $\sin\theta/\lambda = 0\cdot65$ Å⁻¹ were measured on the Rigaku automatic four-circle diffractometer with Mo $K\alpha$ radiation. Intensity data were corrected for the usual Lorentz and polarization factors but not for absorption because of the small crystal dimensions (0·4 × 0·3 × 0·07 mm). All numerical calculations were carried out on an ACOS-800 computer of the computation center of this university with the programs of *The Universal Crystallographic Computing System* (1973). In the structure factor calculations, the atomic scattering

Table 1. *Crystal data*

$C_9H_{13}N_3O_{10}P_2 \cdot H_2O$	FW 403·18
Monoclinic	Space group $P2_1$
$a = 10\cdot286$ (2) Å	$Z = 2$
$b = 6\cdot594$ (3)	$F(000) - 416$
$c = 11\cdot177$ (3)	$V = 753\cdot5$ (4) Å³
$\beta = 96\cdot27$ (3)°	$D_m = 1\cdot778$ (2) Mg m⁻³
$\lambda(\text{Mo }K\alpha) = 0\cdot71069$ Å	$D_x = 1\cdot777$
$\mu = 0\cdot367$ mm⁻¹	

factors used were those cited in *International Tables for X-ray Crystallography* (1974).

Structure determination and refinement

The structure was solved by application of the heavy-atom method. Successive Fourier syntheses revealed the locations of all non-hydrogen atoms. Refinements were carried out by a block-diagonal least-squares method with anisotropic temperature factors. All the H atoms could be located in the difference Fourier syntheses. The final refinements including the H atoms with isotropic temperature factors reduced the R value to 0·045. Throughout the refinement each reflection was given a weight based on counting statistics.

Results and discussion

The atomic coordinates with their estimated standard deviations are given in Tables 2 and 3.* The bond lengths and angles are shown in Figs. 1 and 2.

---

* Lists of structure factors, anisotropic thermal parameters and bond lengths and angles involving H atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34200 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Final atomic coordinates for the non-hydrogen atoms* ($\times 10^4$) *with their estimated standard deviations in parentheses*

	x	y	z
P(3)	1204 (1)	−11 (2)	2190 (1)
P(5)	5532 (1)	50 (2)	7256 (1)
N(1)	1826 (3)	1137 (5)	7362 (2)
C(2)	2288 (3)	2849 (6)	6893 (3)
N(3)	3012 (3)	4209 (5)	7461 (2)
C(4)	3321 (3)	3876 (6)	8654 (3)
C(5)	2884 (3)	2086 (7)	9239 (3)
C(6)	2136 (3)	738 (6)	8573 (3)
N(4)	4047 (3)	5266 (6)	9265 (3)
O(2′)	1912 (3)	2994 (4)	5710 (2)
C(1′)	1070 (3)	−99 (7)	6446 (3)
C(2′)	1190 (3)	1183 (6)	5312 (3)
C(3′)	1983 (3)	−149 (6)	4521 (3)
C(4′)	2457 (3)	−1963 (6)	5305 (3)
O(1′)	1631 (3)	−2010 (4)	6278 (2)
O(3′)	1103 (2)	−886 (4)	3518 (2)
C(5′)	3900 (3)	−1931 (6)	5762 (3)
O(5′)	4281 (2)	25 (5)	6290 (2)
O(1)	−229 (2)	−331 (5)	1643 (2)
O(2)	2117 (3)	−1324 (5)	1565 (2)
O(3)	1555 (3)	2188 (5)	2277 (2)
O(4)	6661 (2)	−765 (5)	6580 (2)
O(5)	5721 (3)	2362 (5)	7450 (2)
O(6)	5336 (3)	−1128 (5)	8340 (2)
O(W)	812 (3)	5177 (6)	624 (2)

(a) Bond lengths and angles

Comparison of the molecular geometry with that of 1-β-D-arabinofuranosylcytosine (Ara-C; Chwang & Sundaralingam, 1973; Tougard & Lefebvre-Soubeyran, 1974) shows that the cyclization between atoms O(2′) and C(2′) produces large changes in the molecular dimensions of the base and sugar moieties. For example, the bonds N(1)—C(2) and C(2)—N(3) are both shorter by *ca* 0·06 Å than those in Ara-C, whereas the bonds C(2)—O(2′) and C(2′)—O(2′) are longer by 0·09 and 0·03 Å, respectively. Also the bond angles around the N(1), C(1′) and C(2′) atoms are consider-

Table 3. *Final atomic coordinates for the hydrogen atoms* ($\times 10^3$) *and isotropic temperature factors with their estimated standard deviations in parentheses*

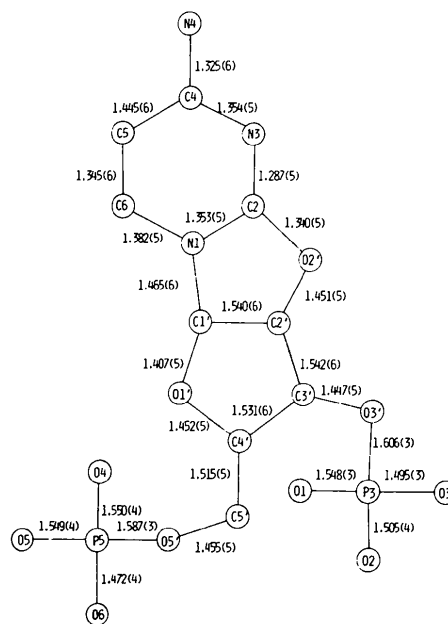|	x	y	z	B (Å^2)
H(5)	308 (4)	196 (9)	1007 (4)	1·3 (0·9)
H(6)	180 (5)	−38 (10)	889 (4)	2·6 (1·1)
H(N4)	441 (5)	624 (10)	886 (5)	2·4 (1·1)
H(N4′)	427 (5)	521 (10)	1004 (4)	2·8 (1·1)
H(1′)	14 (5)	−34 (9)	671 (4)	1·6 (1·0)
H(2′)	22 (5)	170 (10)	489 (6)	3·3 (1·3)
H(3′)	278 (4)	64 (9)	421 (4)	1·8 (1·0)
H(4′)	241 (5)	−326 (9)	476 (4)	2·0 (1·1)
H(5′)	406 (4)	−312 (8)	639 (4)	1·0 (0·9)
H(5″)	440 (4)	−200 (9)	507 (4)	1·5 (0·9)
H(O1)	−33 (5)	−7 (10)	80 (4)	3·1 (1·1)
H(O4)	732 (5)	−163 (9)	707 (4)	3·1 (1·1)
H(O5)	658 (5)	281 (10)	784 (4)	3·5 (1·3)
H(W)	90 (5)	402 (10)	120 (5)	3·1 (1·2)
H(W′)	127 (6)	682 (13)	82 (5)	5·0 (1·6)

Fig. 1. Bond lengths (Å) with estimated standard deviations in parentheses.

ably distorted, as are those found in other cyclo-cytidine derivatives (Table 4).

However, the bond lengths and angles in the phosphate group show only small variations from those found in the other non-cyclized 3'- or 5'-nucleotides.

(b) Molecular conformation

A stereoview showing the molecular conformation is given in Fig. 3. The torsion angles of the ribose ring and phosphate linkage and the deviations of individual atoms from the least-squares planes are listed in Tables 5 and 6. As a result of the migration of a proton attached to O(2) or O(3) in the 3'-phosphate group, the

cytosine base is thought to be cationic. The observed bond lengths of the base moiety suggest that the possible major canonical structures (I–III) can be written and structure (I) contributes predominantly.

(I)   (II)   (III)
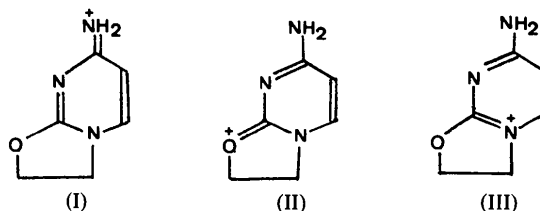
The glycosidic torsion angle χ_{CN} is 298·8° which is similar to those of other 2,2'-cyclonucleosides. The 6 + 5-membered fused-ring system which forms by cyclization between O(2') and C(2') is essentially planar (Table 6). The deviations of atoms from the least-squares plane are smaller than those in 5-S(CH$_3$)$_2$-2,2'-CC, 5-Cl-2,2'-CC (Yamagata, Koshibe, Tokuoka, Fujii, Fujiwara, Kanai & Tomita, 1979) and 6,2'-cyclo-C (Yamagata, Fujii, Kanai, Ogawa & Tomita, 1979). The dihedral angle between this fused ring and the five-membered sugar ring is 110·6°. The sugar ring is puckered in the C(4')-*endo* conformation, where the C(4') atom is displaced by 0·30 Å from the least-squares plane formed by the other four atoms (Table 6). It is interesting that in 2,2'-cyclonucleoside and nucleotide derivatives the sugar-ring conformations all exhibit the C(4')-*endo* form except for molecule (*A*) of   2,2'-anhydro-2-hydroxy-1-*β*-D-arabinofuranosyl-4-
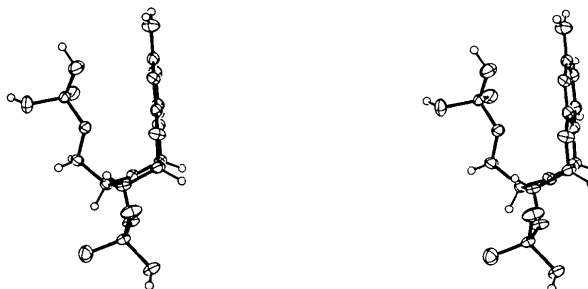

Fig. 2. Bond angles (°) with estimated standard deviations in parentheses.

Fig. 3. Stereoview of the molecular conformation.

Table 4. *Comparison of some bond lengths* (Å) *and angles* (°) *in   2,2'-cyclo-3',5'-CDP   and   related compounds*

	2,2'-cyclo-3',5'-CDP	5-S(CH$_3$)$_2$-2,2'-CC^a	5-Cl-2,2'-CC^a	Ara-C^b
N(1)—C(2)	1·353	1·339	1·345	1·410
C(2)—N(3)	1·287	1·299	1·287	1·347
C(2)—O(2')	1·340	1·327	1·329	1·247
C(2')—O(2')	1·451	1·469	1·451	1·423
N(1)—C(2)—N(3)	126·8	128·2	126·4	119·8
C(2)—N(1)—C(1')	112·1	111·6	112·8	120·4
C(6)—N(1)—C(1')	128·9	126·5	125·1	119·3
C(2)—N(3)—C(4)	115·7	114·5	115·4	119·7
N(1)—C(1')—C(2')	100·7	100·3	99·5	115·1
C(1')—C(2')—O(2')	106·5	106·2	105·9	113·7

References: (*a*) Yamagata, Koshibe, Tokuoka, Fujii, Fujiwara, Kanai & Tomita (1979). (*b*) Chwang & Sundaralingam (1973); Tougard & Lefebvre-Soubeyran (1974).

Table 5. *Torsion angles* (°)

Notation	Designation	Angle
χ	C(6)—N(1)—C(1')—O(1')	298·8 (5)
τ_0	C(4')—O(1')—C(1')—C(2')	16·9 (4)
τ_1	O(1')—C(1')—C(2')—C(3')	−4·5 (4)
τ_2	C(1')—C(2')—C(3')—C(4')	−8·5 (4)
τ_3	C(2')—C(3')—C(4')—O(1')	18·1 (4)
τ_4	C(3')—C(4')—O(1')—C(1')	−22·2 (4)
ψ	C(3')—C(4')—C(5')—O(5')	48·8 (4)
ψ'	O(3')—C(3')—C(4')—C(5')	138·0 (3)
φ	C(4')—C(5')—O(5')—P(5)	155·5 (3)
φ'	C(4')—C(3')—O(3')—P(3)	−137·3 (3)

pyridone (Hutcheon & James, 1977). The orientation of the $C(5')-O(5')$ bond is *gauche–gauche* [$C(3')-C(4')-C(5')-O(5')$ = 48·8° (ψ), $O(1')-C(4')-C(5')-O(5')$ = $-72·0°$], which produces some short contacts between the $O(5')$ or $O(5)$ atoms and the base atoms, as shown in Fig. 4.

The stabilization of this conformation might result partly from electrostatic interactions between the lone pairs of the $O(5')$ or $O(5)$ atoms and the positive charge on the base. Similar short contacts are found in 2,2'-cyclo-C (Brennan & Sundaralingam, 1973), 5-$S(CH_3)_2$-2,2'-CC and 5-Cl-2,2'-CC (Yamagata, Koshibe, Tokuoka, Fujii, Fujiwara, Kanai & Tomita, 1979). The observed conformations of the two phosphate groups are similar to those found in 3'- or 5'-nucleotides (Sundaralingam, 1973): torsion angles, φ, $C(4')-C(5')-O(5')-P(5)$, and φ', $C(4')-C(3')-O(3')-P(3)$, are 155·5 and $-137·3°$, respectively. They fall within the ranges, 149 to 230° and -91 to $-165°$, respectively, which were grouped by Sundaralingam (1973). The intramolecular distance between $P(3)$ and $P(5)$ is 6·810 Å, which is comparable

with that found in B-DNA (6·46 Å; Arnott & Hukins, 1972) but longer than those in A-RNA and A-DNA (5·65 and 5·64 Å respectively; Arnott, Hukins & Dover, 1972). This is due to the fact that the torsion angle ψ' in 2,2'-cyclo-3',5'-CDP (138°) is similar to that found in B-DNA (157°) but different from that in A-RNA or A-DNA (83°).

(c) Molecular packing

A stereoview of the molecular packing along the a axis is shown in Fig. 5. The hydrogen-bond distances and angles are listed in Table 7. It is interesting to note that several strong hydrogen bonds ($O-H\cdots O$; 2·510–2·562 Å) are observed between the two phosphate groups or the phosphate group and the water molecule, as was found in the orthorhombic form of 3'-CMP (Sundaralingam & Jensen, 1965). No base stacking is observed in this crystal.
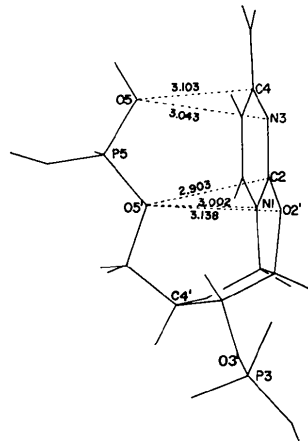
Table 6. *Deviations* (Å) *of atoms from least-squares planes through several parts of the molecule*

x, y and z refer to the orthogonal coordinate system (Å) with x along a, y along b and z along c^*. An asterisk indicates atoms included in calculating the least-squares plane.

(a) Nine-membered fused ring (base and part of sugar)

	(I)	(II)	(III)
N(1)	−0·003 (4)*	−0·024 (4)*	−0·000 (4)*
C(2)	−0·001 (4)*	−0·017 (4)*	0·011 (4)*
N(3)	0·006 (4)*	0·006 (4)*	0·060 (4)
C(4)	−0·006 (4)*	0·009 (4)*	0·088 (5)
C(5)	0·001 (5)*	0·012 (5)*	0·089 (5)
C(6)	0·003 (4)*	−0·005 (4)*	0·044 (5)
N(4)	−0·021 (5)	0·011 (4)	0·116 (5)
O(2')	0·010 (3)	−0·021 (3)*	−0·020 (3)*
C(1')	0·037 (5)	−0·005 (5)*	−0·013 (5)*
C(2')	0·096 (4)	0·048 (4)*	0·024 (5)*

Equations of the planes

(I) $0·848x − 0·491y − 0·200z + 1·171 = 0·0$
(II) $0·854x − 0·484y − 0·189z + 1·052 = 0·0$
(III) $0·863x − 0·476y − 0·170z + 0·902 = 0·0$

(b) Sugar

	(I)	(II)
C(1')	−0·068 (5)*	−0·027 (5)*
C(2')	−0·010 (5)*	0·025 (5)*
C(3')	0·099 (5)*	−0·014 (5)*
C(4')	−0·117 (5)*	−0·301 (5)
O(1')	0·105 (4)*	0·017 (4)*
C(5')	−1·461 (5)	−1·706 (5)
O(3')	1·448 (4)	1·302 (4)

Equations of the planes

(I) $-0·761x − 0·426y − 0·490z + 3·650 = 0·0$
(II) $-0·819x − 0·356y − 0·450z + 3·430 = 0·0$

Fig. 4. Short intramolecular contacts between $O(5')$ or $O(5)$ and base atoms.
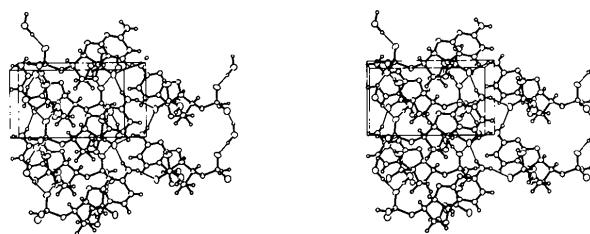
Fig. 5. Stereoview of molecular packing along the a axis. Thin lines indicate the hydrogen bonds.

Table 7. *Distances* (Å) *and angles* (°) *for the hydrogen bonds*

$D-H\cdots A$		$D\cdots A$	$H\cdots A$	$\angle D-H\cdots A$
N(4)–H(N4)$\cdots$O(6)	$(x, 1+y, z)$	2·962 (5)	2·09 (7)	166 (6)
N(4)–H(N4')$\cdots$O(6)	$(1-x, 0·5+y, 2-z)$	2·835 (5)	2·01 (7)	156 (6)
O(1)–H(O1)$\cdots$O(W)	$(-x, -0·5+y, -z)$	2·562 (5)	1·63 (7)	169 (7)
O(5)–H(O5)$\cdots$O(2)	$(1-x, 0·5+y, 1-z)$	2·522 (5)	1·54 (7)	176 (7)
O(4)–H(O4)$\cdots$O(3)	$(1-x, -0·5+y, 1-z)$	2·510 (5)	1·50 (6)	173 (6)
O(W)–H(W')$\cdots$O(3)	(x, y, z)	2·752 (5)	1·78 (7)	164 (6)
O(W)–H(W'')$\cdots$O(2)	$(x, 1+y, z)$	2·815 (5)	1·66 (9)	159 (7)

References

ARNOTT, S. & HUKINS, D. W. L. (1972). *Biochem. Biophys. Res. Commun.* **47**, 1504–1509.
ARNOTT, S., HUKINS, D. W. L. & DOVER, S. D. (1972). *Biochem. Biophys. Res. Commun.* **48**, 1392–1399.
BRENNAN, T. & SUNDARALINGAM, M. (1973). *Biochem. Biophys. Res. Commun.* **52**, 1348–1353.
CHWANG, A. K. & SUNDARALINGAM, M. (1973). *Nature (London) New Biol.* **243**, 78–79.
DELBAERE, L. T. J. & JAMES, M. N. G. (1973). *Acta Cryst.* **B29**, 2905–2912.
HOSHI, A., KANZAWA, F., KURETANI, K., SANEYOSHI, M. & ARAI, T. (1971). *Gann*, **62**, 145–146.
HUTCHEON, W. L. B. & JAMES, M. N. G. (1977). *Acta Cryst.* **B33**, 2228–2232.

International Tables for X-ray Crystallography (1974). Vol. IV, pp. 72–75. Birmingham: Kynoch Press.
KANAI, T. & ICHINO, M. (1971). *Tetrahedron Lett.* pp. 1965–1968. ·
SUCK, D. & SAENGER, W. (1973). *Acta Cryst.* **B29**, 1323–1330.
SUNDARALINGAM, M. (1973). *Jerusalem Symp. Quantum Chem. Biochem.* **5**, 417–456.
SUNDARALINGAM, M. & JENSEN, L. H. (1965). *J. Mol. Biol.* **13**, 914–929.
The Universal Crystallographic Computing System (1973). Library of Programs, Computing Center of Osaka Univ.
TOUGARD, P. & LEFEBVRE-SOUBEYRAN, O. (1974). *Acta Cryst.* **B30**, 86–89.
YAMAGATA, Y., FUJII, S., KANAI, T., OGAWA, K. & TOMITA, K. (1979). *Acta Cryst.* **B35**, 378–382.
YAMAGATA, Y., KOSHIBE, M., TOKUOKA, R., FUJII, S., FUJIWARA, T., KANAI, T. & TOMITA, K. (1979). *Acta Cryst.* **B35**, 382–389.

Crystal and Molecular Structures of Two Dithieno-[1,4]-dithiins, C8H4S4

BY H. HIEMSTRA AND C. TH. KIERS

Laboratorium voor Chemische Fysica, Rijksuniversiteit Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands

Abstract

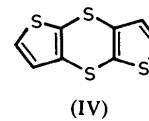The structures of two isomeric dithieno-[1,4]-dithiins, $C_8H_4S_4$, dithieno[3,4-b;3′,4′-e]-p-dithiin (I) and dithieno[2,3-b;3′,2′-e]-p-dithiin (II), have been determined. Both compounds crystallize in space group $P2_1/c$ with $Z = 4$; $a = 14\cdot093$ (2), $b = 8\cdot118$ (2), $c = 8\cdot061$ (2) Å, $\beta = 98\cdot06$ (2)° for (I), $a = 11\cdot672$ (2), $b = 6\cdot152$ (2), $c = 13\cdot607$ (3) Å, $\beta = 110\cdot63$ (2)° for (II). Refinement of (I) and (II) with respectively 2308 and 2532 independent reflections gave $R_w(|F|) = 0\cdot057$ and $0\cdot073$, $R(|F|) = 0\cdot051$ and $0\cdot063$ respectively. Both molecules are folded along the S—S axis of the [1,4]-dithiin ring. The dihedral angle is $136\cdot2°$ for (I) and $130\cdot3°$ for (II). The molecular symmetry is mm for (I) and m for (II).

Introduction

Compounds containing the [1,4]-dithiin moiety have aroused much interest during the last 25 years. X-ray diffraction studies of the parent compound (V) (Howell, Curtis & Lipscomb, 1954; Parham, Wynberg, Hasek, Howell, Curtis & Lipscomb, 1954) and of thianthrene

(VI) (Rowe & Post, 1956, 1958; Lynton & Cox, 1956) proved the non-planarity of these molecules, which had been proposed earlier on the basis of dipole measurements in solution. Since the isolation of two members of the group of dithieno-[1,4]-dithiins (I–IV) in 1969 (Voronkov & Pereferkovich, 1969; Janssen & Bos, 1969) the synthesis and chemical and physical properties of these compounds have been studied in the Department of Organic Chemistry of this University

(I)   (II)

(III)   (IV)

(V)   (VI)