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Structural Studies of O-Cyclocytidine Derivatives.

II. The Crystal and Molecular Structures of 2,2'-Anhydro-1-β-D-arabinofuranosyl-5-dimethylsulfonio-6-oxocytosine Chloride and 2,2'-Anhydro-1-{3',5'-di-O-acetyl-β-D-arabinofuranosyl}-5-chloro-6-oxocytosine and the Comparison with their Conformations in Aqueous Solution

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Abstract

The title compounds, 2,2'-anhydro-1-β-D-arabino-furanosyl-5-dimethylsulfonio-6-oxocytosine chloride [$C_{11}H_{16}N_3O_5S^+ \cdot Cl^-$, 5-S(CH$_3$)$_2$-2,2'-CC] and 2,2'-anhydro-1-{3',5'-di-O-acetyl-β-D-arabinofuranosyl}-5-chloro-6-oxocytosine ($C_{13}H_{14}ClN_3O_7$, 5-Cl-2,2'-CC) crystallize in the orthorhombic system with space group $P2_12_12_1$ and the tetragonal system with space group $I4_1$, respectively. The unit-cell dimensions are $a = 11 \cdot 156$ (3), $b = 17 \cdot 403$ (10) and $c = 7 \cdot 355$ (8) Å for 5-S(CH$_3$)$_2$-2,2'-CC and $a = b = 20 \cdot 125$ (10) and $c = 7 \cdot 566$ (8) Å for 5-Cl-2,2'-CC. Both structures were solved by the heavy-atom method and refined to R values of 0·042 for 5-S(CH$_3$)$_2$-2,2'-CC and 0·066 for 5-Cl-2,2'-CC. The molecular geometries in both compounds are very similar; the glycosidic torsion angles, χ_{CN}, are 302·7° for 5-S(CH$_3$)$_2$-2,2'-CC and 291·1° for 5-Cl-2,2'-CC, sugar conformations are C(4')-*endo*-O(1')-*exo* and C(4')-*endo*, respectively, and the orientations about the C(5')—O(5') bond are both *gauche–gauche*. The intramolecular short contacts between O(5') and the N(1), C(2) and O(2') atoms in the newly

introduced five-membered ring are observed. In connection with their NMR and CD results, it seems likely that both molecular structures found in the crystals are retained even in aqueous solution.

Introduction

5-S(CH$_3$)$_2$-2,2'-CC and 5-Cl-2,2'-CC (Fig. 1) were synthesized from AraC† (Kanai & Maruyama, 1976).

As described in the previous paper (Yamagata, Fujii, Kanai, Ogawa & Tomita, 1979), such a cyclonucleoside would be a suitable model for comparing the dihedral angles observed in the crystal structure with the corresponding angles calculated from the coupling constants of NMR by the use of the Karplus formula and also for studying the π–π* Cotton effects in the CD pattern, because of the rotational restriction around the base and the sugar moieties by cyclization.

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† Abbreviations: AraC: 1-β-D-arabinofuranosylcytosine; 2,2'-CC: 2,2'-anhydro-1-β-D-arabinofuranosylcytosine; AraU: 1-β-D-arabinofuranosyluracil; 2,2'-CU: 2,2'-anhydro-1-β-D-arabinofuranosyluracil; 2,2'-CP: 2,2'-anhydro-2-hydroxy-1-β-D-arabinofuranosyl-4-pyridone; 6,2'-CC: 6,2'-anhydro-1-β-D-arabinofuranosyl-6-hydroxycytosine; 2,2'-α-CxyloU: 2,2'-anhydro-1-α-D-xylofuranosyluracil.

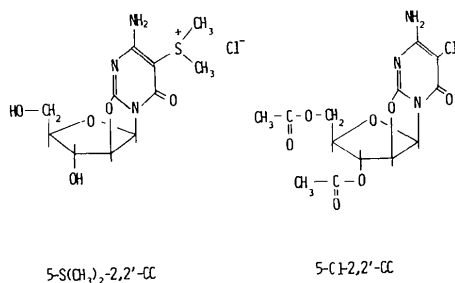* Present address: Tokyo Research Laboratories, Kohjin Co., Komiya-cho, Hachioji, Tokyo 105, Japan.

5-S(CH₃)₂-2,2'-CC   5-Cl-2,2'-CC

Fig. 1. The chemical structures of 5-S(CH₃)₂-2,2'-CC and 5-Cl-2,2'-CC.

Experimental

5-S(CH$_3$)$_2$-2,2'-CC and 5-Cl-2,2'-CC crystallized from aqueous solution as colorless prisms and needles, respectively. Preliminary Weissenberg and precession photographs showed the crystals to be orthorhombic with space group $P2_12_12_1$ for 5-S(CH$_3$)$_2$-2,2'-CC and tetragonal with space group $I4_1$ for 5-Cl-2,2'-CC. The densities of both compounds were measured by flotation method in benzene–ethylene bromide. The crystallographic data are given in Table 1.

Three-dimensional intensity data were measured on a fully automatic four-circle diffractometer (Rigaku Denki Co.) with Cu $K\alpha$ radiation. By means of the ω–2θ scan technique, the intensities of 1117 [for 5-S(CH$_3$)$_2$-2,2'-CC] and 818 (for 5-Cl-2,2'-CC) independent reflections with $\sin\theta/\lambda \leq 0.54$ Å^{-1} were obtained. In the latter case, the number of observed reflections was no more than ca 75% of the total measurable, because of the small size of the crystal (0·3 × 0·05 × 0·05 mm). Intensities were corrected for Lorentz and polarization factors, but no absorption corrections were applied. The absolute scales and overall temperature factors were determined by the usual Wilson statistics. All numerical calculations were carried out on an NEAC-2200-700 computer of the computation center of this university, with *The Universal Crystallographic Computing System* (1973) and the *ORFLS* program (Busing, Martin & Levy, 1962). In the structure factor calculation, the atomic scattering

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

Structure determination

Both structures were solved by the heavy-atom method. The successive Fourier syntheses revealed the locations of all non-hydrogen atoms. The structure refinements were carried out with anisotropic temperature factors for non-hydrogen atoms by a block-diagonal least-squares method for 5-S(CH$_3$)$_2$-2,2'-CC and by a full-matrix least-squares method for 5-Cl-2,2'-CC. 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 0·042 for 5-S(CH$_3$)$_2$-2,2'-CC and 0·066 for 5-Cl-2,2'-CC.

Table 2. *Final atomic coordinates of* 5-S(CH$_3$)$_2$-2,2'-CC ($\times 10^4$ *for non-hydrogen atoms*; $\times 10^3$ *for* H) *with their estimated standard deviations in parentheses*

	x	y	z
S	5695 (1)	8045 (1)	−700 (2)
N(1)	8552 (4)	9384 (2)	−260 (6)
C(2)	9127 (5)	8993 (3)	1044 (8)
N(3)	8742 (4)	8409 (3)	1981 (7)
C(4)	7611 (5)	8160 (3)	1504 (8)
C(5)	6980 (5)	8506 (3)	48 (9)
C(6)	7403 (5)	9178 (3)	−844 (8)
N(4)	7220 (4)	7569 (3)	2490 (7)
O(6)	6896 (4)	9544 (2)	−2040 (6)
Me(1)	6004 (6)	7871 (4)	−3037 (9)
Me(2)	4522 (5)	8749 (4)	−775 (10)
O(2')	10228 (3)	9255 (2)	1333 (6)
C(1')	9291 (5)	10027 (3)	−965 (8)
C(2')	10475 (5)	9868 (3)	13 (8)
C(3')	11349 (5)	9593 (3)	−1457 (8)
C(4')	10595 (5)	9563 (3)	−3213 (8)
O(1')	9502 (3)	9985 (2)	−2833 (5)
O(3')	12365 (4)	10079 (3)	−1645 (6)
C(5')	10310 (6)	8761 (3)	−3937 (9)
O(5')	9961 (4)	8267 (2)	−2471 (6)
Cl⁻	1374 (1)	1781 (1)	−1097 (2)
H(Me1)	526 (6)	768 (4)	−383 (9)
H(Me1')	619 (6)	829 (4)	−364 (9)
H(Me1'')	653 (6)	748 (4)	−350 (9)
H(Me2)	377 (6)	870 (4)	−132 (9)
H(Me2')	495 (6)	927 (4)	−145 (9)
H(Me2'')	437 (6)	881 (4)	56 (9)
H(1')	880 (6)	1049 (4)	−70 (10)
H(2')	1096 (6)	1027 (4)	81 (9)
H(3')	1186 (6)	904 (4)	−99 (10)
H(4')	1110 (6)	985 (4)	−434 (9)
H(5')	957 (6)	879 (4)	−489 (9)
H(5'')	1116 (6)	853 (4)	−455 (9)
H(O3')	1196 (6)	1051 (4)	−207 (10)
H(O5')	953 (6)	788 (4)	−287 (9)
H(N4)	642 (6)	736 (4)	228 (9)
H(N4')	770 (6)	739 (4)	351 (9)

Table 1. *Crystal data*

	5-S(CH₃)₂-2,2'-CC	5-Cl-2,2'-CC
Chemical formula	C₁₁H₁₆N₃O₅S⁺Cl⁻	C₁₃H₁₄ClN₃O₇
FW	337·98	359·75
Crystal system	orthorhombic	tetragonal
a (Å)	11·156 (3)	20·125 (10)
b (Å)	17·403 (10)	20·125 (10)
c (Å)	7·355 (8)	7·566 (8)
Space group	$P2_12_12_1$	$I4_1$
Z	4	8
D_m (Mg m⁻³)	1·512	1·550
D_x (Mg m⁻³)	1·570	1·559
μ(Cu $K\alpha$) (mm⁻¹)	3·62	2·63
$F(000)$	704	1488
V (Å³)	1427·96	3064·35

Results and discussion

The atomic coordinates with their estimated standard deviations are given in Table 2 for 5-S(CH$_3$)$_2$-2,2'-CC and in Table 3 for 5-Cl-2,2'-CC.*

Bond lengths and angles are shown in Fig. 2 for 5-S(CH$_3$)$_2$-2,2'-CC and Fig. 3 for 5-Cl-2,2'-CC, and also for comparison, those common to seven related pyrimidine nucleosides are listed in Table 4.

The torsion angles designating the conformation of the sugar moieties of both molecules and the 6,2'-CC molecule are listed in Table 5 and the deviations of atoms from the least-squares planes through the sugar and base atoms in both crystals are listed in Tables 6 and 7.

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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33983 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Final atomic coordinates of* 5-Cl-2,2'-CC *(×10^4 for non-hydrogen atoms; ×10^3 for H) with their estimated standard deviations in parentheses*

	x	y	z
Cl	3495 (2)	5354 (2)	5025
N(1)	4816 (6)	3998 (6)	3748 (15)
C(2)	5016 (7)	3806 (6)	5364 (20)
N(3)	4810 (6)	4049 (6)	6842 (15)
C(4)	4328 (7)	4535 (7)	6724 (21)
C(5)	4092 (7)	4758 (6)	5071 (18)
C(6)	4368 (7)	4508 (7)	3496 (20)
O(2')	5454 (4)	3311 (4)	5270 (12)
N(4)	4115 (5)	4780 (6)	8295 (14)
O(6)	4208 (5)	4683 (5)	1981 (12)
O(1')	4685 (5)	3207 (4)	1408 (13)
C(1')	5150 (6)	3612 (6)	2314 (17)
C(2')	5610 (7)	3163 (6)	3431 (17)
C(3')	5362 (7)	2437 (6)	3041 (18)
C(4')	4708 (7)	2528 (6)	2046 (20)
O(3')	5815 (4)	2140 (4)	1762 (12)
C(*A*3')	6415 (7)	1919 (7)	2466 (27)
O(*A*3')	6570 (5)	1995 (5)	3946 (16)
Me(3')	6802 (8)	1544 (9)	1026 (24)
C(5')	4105 (6)	2342 (7)	3108 (19)
O(5')	4129 (4)	2666 (4)	4823 (14)
C(*A*5')	3724 (9)	2467 (8)	6099 (27)
O(*A*5')	3398 (8)	1999 (8)	5790 (24)
Me(5')	3726 (9)	2856 (9)	7754 (26)
H(N4)	428 (5)	465 (5)	927 (15)
H(N4')	391 (5)	531 (5)	854 (17)
H(1')	533 (5)	389 (5)	128 (17)
H(2')	615 (5)	330 (5)	344 (16)
H(3')	538 (5)	212 (5)	418 (16)
H(4')	472 (5)	220 (5)	93 (15)
H(5')	423 (5)	183 (5)	298 (15)
H(5'')	379 (5)	247 (5)	244 (17)
H(Me3)	708 (5)	197 (5)	49 (15)
H(Me3')	713 (5)	127 (5)	142 (16)
H(Me3'')	651 (5)	153 (5)	−21 (16)
H(Me5)	357 (5)	265 (5)	892 (16)
H(Me5')	357 (5)	333 (5)	705 (16)
H(Me5'')	418 (5)	308 (5)	825 (16)

Table 4. *Comparison of some bond lengths and angles of pyrimidine cyclonucleosides and pyrimidine arabino-nucleosides*

(*a*) Bond lengths (Å)

	N(1)–C(2)	C(2)–N(3)	N(3)–C(4)	C(4)–C(5)
5-S(CH$_3$)$_2$-2,2'-CC	1·339	1·299	1·382	1·416
5-Cl-2,2'-CC	1·345	1·287	1·372	1·403
6,2'-CC[a]	1·382	1·342	1·332	1·411
AraC[b]	1·410	1·347	1·330	1·438
2,2'-CU[c]	1·335	1·298	1·396	1·445
2,2'-α-CxyloU[d]	1·342	1·293	1·386	1·445
AraU[e]	1·368	1·376	1·393	1·428

	C(5)–C(6)	C(6)–N(1)	N(1)–C(1')	
5-S(CH$_3$)$_2$-2,2'-CC	1·421	1·399	1·483	
5-Cl-2,2'-CC	1·407	1·388	1·490	
6,2'-CC[a]	1·351	1·351	1·436	
AraC[b]	1·340	1·360	1·471	
2,2'-CU[c]	1·342	1·370	1·472	
2,2'-α-CxyloU[d]	1·344	1·382	1·465	
AraU[e]	1·344	1·382	1·471	

	C(2')–O(2')	C(2)|C(6)]–O(2')
5-S(CH$_3$)$_2$-2,2'-CC	1·469	1·327
5-Cl-2,2'-CC	1·451	1·329
6,2'-CC[a]	1·456	1·339
AraC[b]	1·423	
2,2'-CU[c]	1·461	1·342
2,2'-α-CxyloU[d]	1·466	1·328
AraU[e]	1·412	

(*b*) Bond angles (°)

	N(1)–C(2)–N(3)	C(2)–N(3)–C(4)	C(5)–C(6)–N(1)
5-S(CH$_3$)$_2$-2,2'-CC	128·2	114·5	111·9
5-Cl-2,2'-CC	126·4	115·4	113·4
6,2'-CC[a]	118·3	119·0	121·9
AraC[b]	119·3	119·7	120·2
2,2'-CU[c]	127·3	115·7	118·3
2,2'-α-CxyloU[d]	127·1	116·7	118·0
AraU[e]	115·1	127·2	122·1

	N(1)–C(2)–O(2')	C(2)–N(1)–C(1')	C(6)–N(1)–C(1')
5-S(CH$_3$)$_2$-2,2'-CC	112·5	111·6	126·5
5-Cl-2,2'-CC	110·8	112·8	125·1
6,2'-CC[a]	118·0	126·2	111·9
AraC[b]	117·8	120·4	119·3
2,2'-CU[c]	111·8	112·3	128·1
2,2'-α-CxyloU[d]	111·8	112·4	128·5
AraU[e]	123·8	117·7	121·1

	N(1)–C(1')–C(2')	C(1')–C(2')–O(2')
5-S(CH$_3$)$_2$-2,2'-CC	100·3	106·2
5-Cl-2,2'-CC	99·5	105·9
6,2'-CC[a]	101·9	104·4
AraC[b]	115·0	113·7
2,2'-CU[c]	100·6	106·0
2,2'-α-CxyloU[d]	100·6	105·6
AraU[e]	114·3	112·1

References: (*a*) Yamagata, Fujii, Kanai, Ogawa & Tomita (1979). (*b*) Chwang & Sundaralingam (1973); Tougard & Lefebvre-Soubeyran (1974). (*c*) Suck & Saenger (1973); Delbaere & James (1973). (*d*) Birnbaum, Giziewicz, Huber & Shugar (1976). (*e*) Tollin, Wilson & Young (1973).

Table 5. *Torsion angles* (°)

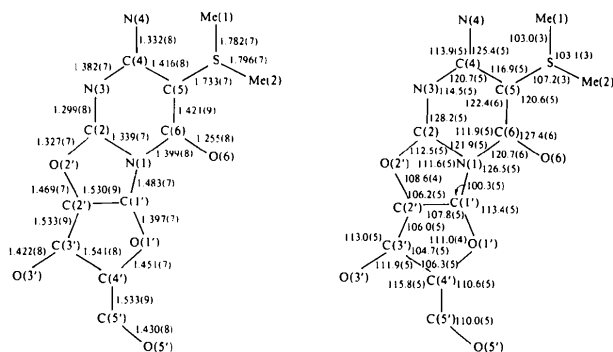| Notation	Designation	5-S(CH$_3$)$_2$-2,2'-CC	5-Cl-2,2'-CC	6,2'-CC*
χ	O(1')–C(1')–N(1)–C(6)	302·7	291·1	111·4
τ_0	C(4')–O(1')–C(1')–C(2')	19·5	10·0	−31·4
τ_1	O(1')–C(1')–C(2')–C(3')	−9·5	1·3	6·2
τ_2	C(1')–C(2')–C(3')–C(4')	−3·1	−11·1	19·7
τ_3	C(2')–C(3')–C(4')–O(1')	14·2	17·3	−38·9
τ_4	C(3')–C(4')–O(1')–C(1')	−21·4	−17·7	44·3
ψ_{OO}	O(1')–C(4')–C(5')–O(5')	−77·4	−72·7	−59·4
ψ_{OC}	C(3')–C(4')–C(5')–O(5')	43·5	50·2	56·8

* Yamagata, Fujii, Kanai, Ogawa & Tomita (1979).

Fig. 2. Bond lengths (Å) and angles (°) in 5-S(CH₃)₂-2,2'-CC with standard deviations estimated from least squares in parentheses.

C(2') results in significant alteration of the geometries of the base moiety, as compared with cytosine or cytidine derivatives. For example, the bonds N(1)—C(2) and C(2)—N(3) are shorter than those of AraC by ca 0·07 and 0·05 Å, respectively, whereas

Table 6. Deviations (Å) of atoms from least-squares planes in 5-S(CH₃)₂-2,2'-CC

X, Y and Z refer to the orthogonal coordinate system (Å) with X along a, Y along b and Z along c.

(a) Base

	(I)	(II)	(III)
N(1)	−0·007*	0·037*	−0·043*
C(2)	0·021*	0·008*	−0·034*
N(3)	−0·006*	0·039	−0·033*
C(4)	−0·025*	0·157	0·003*
C(5)	0·044*	0·293	0·095*
C(6)	−0·027*	0·155	−0·007*
N(4)	−0·071	0·168	−0·016
O(6)	−0·051	0·180	−0·015
S	0·314	0·731	0·434
Me(1)	1·806	2·235	1·926
Me(2)	−0·934	−0·434	−0·786
O(2')	0·106	−0·038*	−0·002*
C(1')	0·004	−0·053*	−0·076*
C(2')	0·231	0·047*	0·102*

Equations of the planes

(I) $0·413X − 0·608Y + 0·678Z + 5·856 = 0·0$
(II) $0·321X − 0·640Y + 0·698Z + 7·290 = 0·0$
(III) $0·376X − 0·624Y + 0·685Z + 6·428 = 0·0$

(b) Sugar

	(I)	(II)
C(1')	0·084*	0·000*
C(2')	−0·013*	0·000*
C(3')	−0·054*	0·000*
C(4')	0·104*	0·082
O(1')	−0·119*	−0·218
C(5')	1·437	1·407
O(3')	−1·248	−1·145

Equations of the planes

(I) $−0·343X − 0·929Y − 0·139Z + 19·906 = 0·0$
(II) $−0·285X − 0·945Y − 0·160Z + 19·559 = 0·0$

* Atoms included in calculating the least-squares plane.

Table 7. Deviations (Å) of atoms from least-squares planes in 5-Cl-2,2'-CC

X, Y and Z refer to the orthogonal coordinate system (Å) with X along a, Y along b and Z along c.

(a) Base

	(I)	(II)	(III)
N(1)	0·019*	−0·005*	0·001*
C(2)	0·005*	−0·011*	−0·011*
C(3)	−0·014*	−0·014	−0·018*
N(4)	−0·003*	0·009	0·005*
C(5)	0·025*	0·030	0·032*
C(6)	−0·032*	−0·045	−0·039*
Cl	0·068	0·088	0·091
N(4)	−0·022	0·007	−0·001
O(6)	−0·058	−0·078	−0·065
O(2')	0·051	0·022*	0·022
C(1')	0·059	0·016*	0·025*
C(2')	0·024	−0·023*	−0·017*

Equations of the planes

(I) $−0·724X − 0·689Y + 0·009Z + 12·557 = 0·0$
(II) $−0·730X − 0·683Y + 0·019Z + 12·512 = 0·0$
(III) $−0·730X − 0·683Y + 0·015Z + 12·530 = 0·0$

(b) Sugar

	(I)	(II)
C(1')	0·006*	−0·008*
C(2')	0·022*	0·007*
C(3')	−0·086*	−0·004*
C(4')	0·131*	0·262
O(1')	−0·067*	0·005*
C(5')	1·453	1·626
O(3')	−1·467	−1·367

Equations of the planes

(I) $−0·601X + 0·116Y + 0·791Z + 4·016 = 0·0$
(II) $−0·634X + 0·064Y + 0·770Z + 4·751 = 0·0$
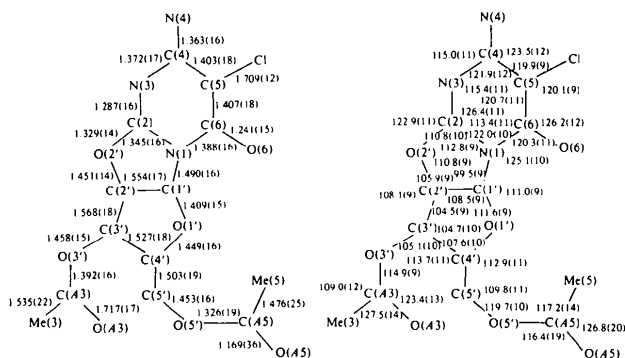
* Atoms included in calculating the least-squares plane.

Fig. 3. Bond lengths (Å) and angles (°) in 5-Cl-2,2'-CC with standard deviations estimated from least squares in parentheses.

(a) Bond lengths and angles

Most corresponding bond lengths and angles in 5-S(CH₃)₂-2,2'-CC are comparable to those found in 5-Cl-2,2'-CC. The cyclization between atoms O(2') and

the N(3)—C(4) bonds are longer by *ca* 0·04 Å. Moreover the C(5)—C(6) bonds in both crystals are shorter than that of AraC, because of the double-bond character of C(6)—O(6). It is of interest that considerable changes in the geometry of the sugar moiety and the newly formed five-membered ring are found here, as well as in the cases of 6,2′-CC and 2,2′-CU (Table 4). The C(2)—O(2′) bonds are shorter than the normal C—O single bond (1·426 Å), whereas the C(2′)—O(2′) bonds are somewhat longer. Such specific features found in aromatic and aliphatic C—O single-bond distances of the five-membered ring may result from the overlapping of the non-bonded electrons of the O atom to the π electrons in the conjugated aromatic ring system. Also the cyclization gives rise to considerable distortions (*ca* 10°) in the angles around N(1), C(1′) and C(2′) (Table 4).

(*b*) Molecular conformation

The overall molecular conformations in both crystals are shown in Figs. 4 and 5.

The glycosidic torsion angles are 302·7° for 5-S(CH₃)₂-2,2′-CC and 291·1° for 5-Cl-2,2′-CC, which agree well with those obtained for 2,2′-CC (290°; Brennan & Sundaralingam, 1973) and 2,2′-CU (294·5, 290·0°; Suck & Saenger, 1973; Delbaere & James, 1973) but differ by *ca* 180° from that found in 6,2′-CC (111·4°; Yamagata, Fujii, Kanai, Ogawa & Tomita, 1979). The nine-membered fused-ring system produced by the cyclization between C(2) and O(2′) is nearly planar. The puckering of the sugar rings is C(4′)-*endo*-O(1′)-*exo* for 5-S(CH₃)₂-2,2′-CC and C(4′)-*endo* for 5-Cl-2,2′-CC (Tables 6 and 7), which is also obvious from the phase angles of pseudorotation (262 and 237°; Altona & Sundaralingam, 1972). These confor-
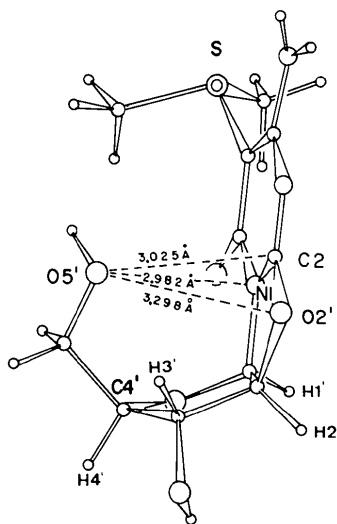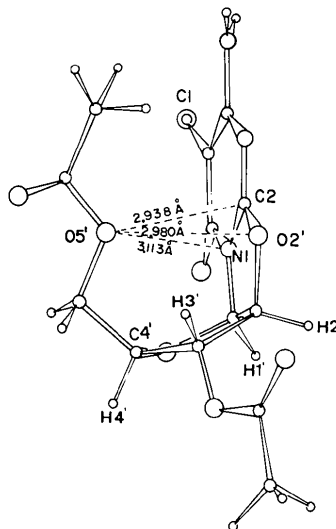

Fig. 5. The molecular conformation of 5-Cl-2,2′-CC and short intramolecular contacts between O(5′) and the base.

mations differ from that in 6,2′-CC [C(4′)-*exo*; Yamagata, Fujii, Kanai, Ogawa & Tomita, 1979]. The orientation of the C(5′)—O(5′) bond is *gauche–gauche*, which gives rise to some short intramolecular contacts between O(5′) and the base atoms as shown in Figs. 4 and 5. Similar short contacts were found in 2,2′-CC (Brennan & Sundaralingam, 1973), in which the conformation of the sugar ring is also C(4′)-*endo* and the orientation of C(5′)—O(5′) bond is *gauche–gauche*. On the other hand, 6,2′-CC (Yamagata, Fujii, Kanai, Ogawa & Tomita, 1979), 2,2′-CU (Suck & Saenger, 1973; Delbaere & James, 1973) and 2,2′-CP (Hutchoen & James, 1977) have no short contacts, as a result of the different sugar puckering or the different C(5′)—O(5′) orientation.

(*c*) Molecular packing

5-S(CH₃)₂-2,2′-CC: the molecular packing in the unit cell viewed down the *c* axis is shown in Fig. 6, in which dashed lines represent the hydrogen bonds.

The Cl ion is hydrogen-bonded to either N(4), O(5′) or O(3′), and the hydrogen-bonding scheme involving the cytosine base and Cl ion is distinct from those found in AraC.HCl (Sherfinski & Marsh, 1973), 1-methylcytosine.HCl (Trus & Marsh, 1972) and 2′-deoxycytidine.HCl (Subramanian & Hunt, 1970). In the present case, base stacking is not observed.

5-Cl-2,2′-CC: the packing of molecules viewed down the *c* axis is depicted in Fig. 7. The nine-membered fused-ring plane is nearly perpendicular to the (110) plane and the bases are infinitely connected along the *c* axis by the NH···O hydrogen bond between N(4) of the base and O(6) of the adjacent base (Fig. 8). It is interesting to note the mode of base stacking, with a distance of 3·29 Å between the adjacent molecules
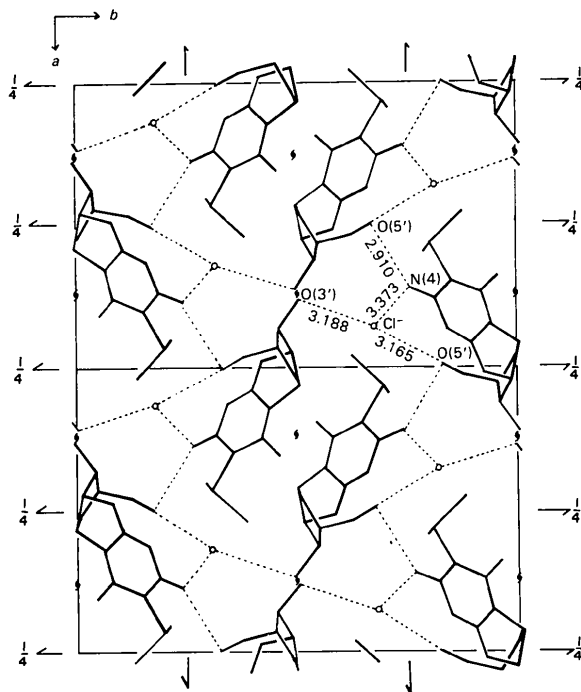

Fig. 4. The molecular conformation of 5-S(CH₃)₂-2,2′-CC and short intramolecular contacts between O(5′) and the base.

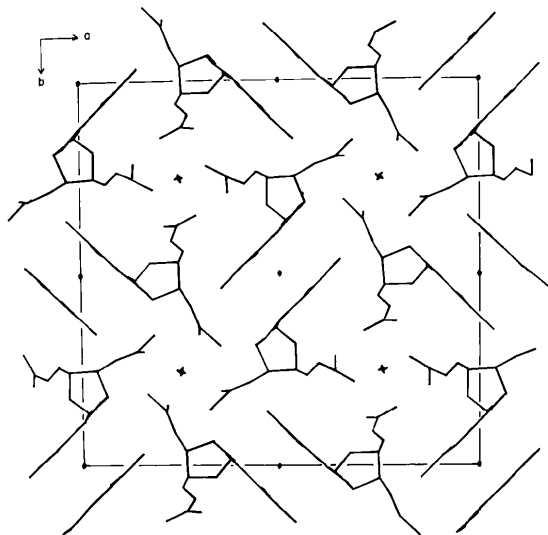Fig. 6. The molecular packing of 5-S(CH₃)₂-2,2'-CC viewed along the c axis.

Fig. 7. The molecular packing of 5-Cl-2,2'-CC viewed along the c axis.

related by the twofold symmetry operation (Fig. 7). This stacking mode is different from those found in either the halogenated derivatives or pyrimidine derivatives (Bugg, Thomas, Sundaralingam & Rao, 1971). For example, in most crystal structures of the halogenated derivatives, the observed stacking is such that the halogen substituent is in close contact with the aromatic ring portion of the adjacent base, but the
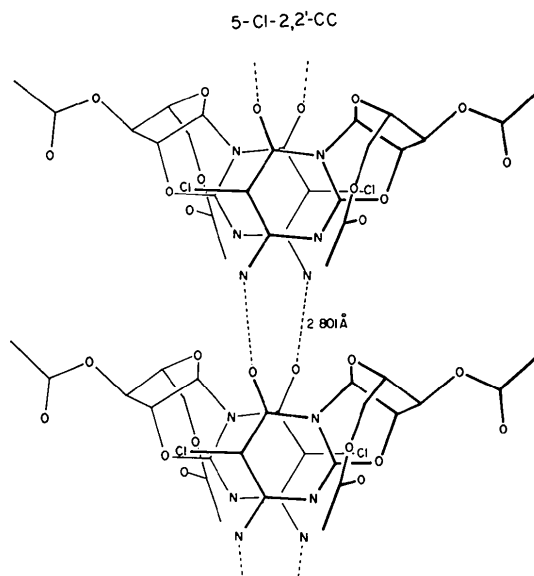
5-Cl-2,2'-CC

Fig. 8. The base stacking and hydrogen-bonding modes viewed perpendicular to the nine-membered-ring plane.

pyrimidine rings are only partially overlapped with each other. In the case of 5-Cl-2,2'-CC, however, extensive overlap between pyrimidine rings is found and the Cl atom is in close contact with the newly formed five-membered ring: this stacking might be partly due to a permanent dipole–dipole interaction between the halogenated bases.

(d) Comparison with the conformation in solution

NMR study: in Fig. 9 the observed proton–proton coupling constants are plotted against the dihedral angles obtained from X-ray diffraction studies of several cyclonucleosides. The calculated curve obtained from the modified Karplus formula (Altona & Sundaralingam, 1973) is shown in Fig. 9 by a solid line.

The agreement of the observed $J[H(2')H(3')]$ and $J[H(3')H(4')]$ values with the calculated ones, except for 6,2'-CC, seems to indicate that these molecules maintain the C(4')-endo conformation even in solution. However, the discrepancy between the observed and calculated $J[H(1')H(2')]$ coupling constants in all cases and the deviation of the observed $J[H(2')H(3')]$ and $J[H(3')H(4')]$ values of 6,2'-CC from the calculated curve indicate that the modified Karplus formula is not fully adequate in the case of five-membered sugar ring systems fused to other five-membered rings as in 6,2'- or 2,2'-cyclonucleosides. A more suitable formula should be considered, provided the rigid molecular conformation of the solid state is preserved in solution.

CD study: many experimental (Rogers & Ulbricht, 1970) and theoretical (Teng, Itzkowitz & Tinoco, 1971; Inskeep, Miles & Eyring, 1970) studies on the relationship between optical activity and conformation
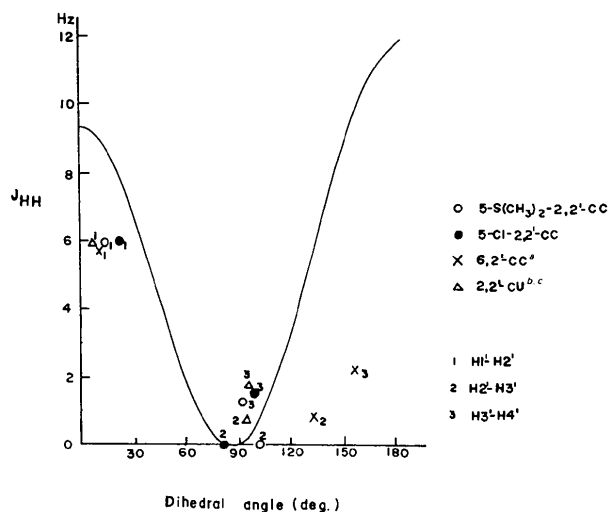
Fig. 9. The proton–proton coupling constant plotted against the dihedral angles obtained for four crystals. The solid line is the calculated J_{HH}–φ curve using the formula established for non-cyclonucleosides by Altona & Sundaralingam (1972). (*a*) Yamagata, Fujii, Kanai, Ogawa & Tomita (1979). (*b*) Suck & Saenger (1973); Delbaere & James (1973). (*c*) Cross & Schleich (1973).

Fig. 10. The CD spectra of three cyclonucleosides.

of mononucleosides have shown that the rotational strengths are highly dependent on the glycoside torsion angle which defines the orientation of the sugar relative to the base plane. Therefore, the CD method is a very powerful tool for conformational studies of cyclonucleosides having fixed glycosidic torsion angles. In these studies 5-S(CH$_3$)$_2$-2,2'-CC, 5-Cl-2,2'-CC and 6,2'-CC all have negative Cotton effects in the longer wavelength region (Fig. 10), of which 6,2'-CC has a different glycosidic torsion angle from that of the other two 2,2'-cyclonucleosides.

However, the relative orientations of the sugar ring to the vector of the transition moment calculated with the program *P-P-P DOUBLE CI* (Ohbo, Kashiwagi, Kunii, Ohta & Hirota, 1970) are all similar. Furthermore, the rotational strengths of these compounds are all negative as estimated with the atomic parameters found in the crystals according to the method of Inskeep, Miles & Eyring (1970) although these magnitudes do not agree well with the experimental results. These facts strongly suggest that these compounds all have rigid conformations in solution as well as in crystalline form, and therefore they have all negative Cotton effects in the longer wavelength region.

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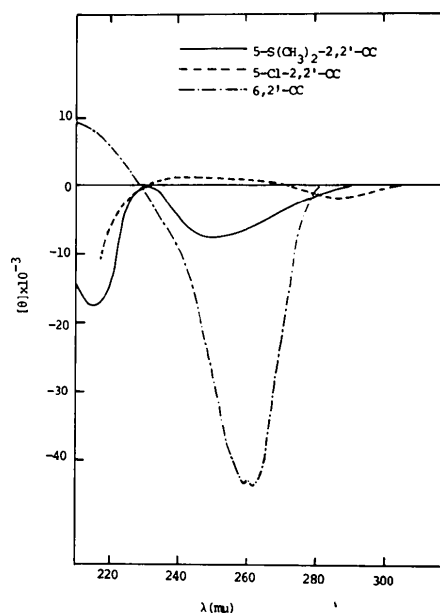
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The Crystal and Molecular Structure of 3,3'-(1-Naphthylmethylene)bis(4-hydroxycoumarin) (α-Naphthyldicoumarol) in Two Crystal Modifications

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Abstract

The crystal structure of 3,3'-(1-naphthylmethylene)-bis(4-hydroxycoumarin)–acetone, $C_{29}H_{18}O_6 . C_3H_6O$, has been determined by direct methods from three-dimensional diffractometer data collected with Cu $K\alpha$ radiation. The unit-cell parameters are $a = 12.776$ (7), $b = 11.323$ (6), $c = 10.149$ (5) Å, $\alpha = 97.70$ (5), $\beta = 109.41$ (4), $\gamma = 105.97$ (6)° and $Z = 2$ in the triclinic, and $a = 17.615$ (3), $b = 16.434$ (3), $c = 9.001$ (3) Å, $Z = 4$ in the orthorhombic crystals. Full-matrix least-squares refinement of the structural parameters gave unweighted linear R values of 0.041 (3463 reflexions) and 0.038 (1505 reflexions) for the triclinic and orthorhombic modifications respectively. The triclinic crystal structure consists of hydrogen-bonded α-naphthyl-dicoumarol dimers and space-filling acetone molecules held together by van der Waals forces. The orthorhombic crystal structure is built up from hydrogen-bonded α-naphthyldicoumarol–acetone complexes. The molecular geometries are slightly different in these two modifications.

Introduction

The present investigation is part of a research program for structural studies of some anticoagulants (for example, different coumarin and indandione derivatives). α-Naphthyldicoumarol belongs to a group of coumarin derivatives with an anticlotting effect. This substance shows a fairly high activity and a mode of action of the dicoumarol type (Guminska & Eckstein, 1961).

Crystals of α-naphthyldicoumarol, grown from acetone solution, show two different crystal forms, with triclinic and orthorhombic symmetry respectively. There is one molecule of acetone per asymmetric unit in both cases. The X-ray analysis of these two crystal modifications was undertaken in order to elucidate the possible conformational differences.

Experimental

The title compound was synthesized at the Department of Technology of Drugs in Kraków (Eckstein, Kocwa & Pazdro, 1958). Suitable single crystals were obtained by recrystallization from acetone solutions. The crystals were examined first by oscillation and De Jong–Bouman photographic techniques. The unit-cell parameters were refined by least-squares fitting to powder photograph data, taken in a Guinier–Hägg focusing camera at 298 K with Cu $K\alpha$ radiation and KCl ($a = 6.2930$ Å) as internal standard.

X-ray diffraction intensities were measured with an automatic four-circle diffractometer and graphite-monochromatized Cu $K\alpha$ radiation. The approximate dimensions of the selected single crystals were 0.18 × 0.25 × 0.20 mm for the triclinic form and 0.16 × 0.08 × 0.58 mm for the orthorhombic. 4618 and 2367 independent reflexions with $0 \leq 65°$ were measured and corrected for Lorentz and polarization effects for the triclinic and orthorhombic structures respectively. The rather low absorption effects ($\mu = 0.73–0.74$ mm^{-1}) were neglected.