

## The Crystal Structures of ( $\pm$ )-*cis*- and ( $-$ )-(1*S*,3*S*)-*trans*-3-Acetoxy-1-methylthiane Perchlorates

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The crystal structures of the acetylcholine analogues ( $\pm$ )-*cis*- and ( $-$ )-*trans*-3-acetoxy-1-methylthiane perchlorates have been determined from diffractometer collected X-ray data and refined to *R*-values of 0.049 and 0.053, respectively. The absolute configuration of the ( $-$ )-*trans* isomer was found to be (1*S*,3*S*). The geometry of the rings, which adopt chair conformations, has been further studied by empirical force field calculations.

*cis*- and *trans*-4-Acetoxy- and 3-acetoxy-1-methylthiane were synthesized as semirigid acetylcholine analogues by Lambrecht, who also showed that the compounds are muscarinic agonists of varying strength.<sup>1</sup> It was further shown<sup>2</sup> that the (+)-isomer of the *trans*-3-acetoxy compound was 1–2 orders of magnitude more potent than the ( $-$ )-isomer.

The crystal structures of the iodides of *cis*- and *trans*-4-acetoxy-1-methylthiane have previously been published.<sup>3</sup> This paper describes the crystal structures of the perchlorates of ( $\pm$ )-*cis*- and ( $-$ )-*trans*-3-acetoxy-1-methylthiane. These crystal structure determinations have been carried out with the purpose of further elucidating the geometry of substituted thiane rings and of establishing the absolute configuration of the ( $-$ )-*trans* compound.

The geometry and the conformational flexibility of the two compounds have also been studied by empirical force field calculations using the MM2 programme of Allinger,<sup>4</sup> and the results are compared with those obtained from the crystal structure determinations and from NMR-experiments.<sup>5</sup>

### EXPERIMENTAL

( $\pm$ )-*cis*- and ( $-$ )-*trans*-3-acetoxy-1-methylthiane perchlorates, in the following named RACCIS and MINTRA, were synthesized by Dr. G. Lambrecht. Colourless single crystals were obtained by diffusion of dimethoxymethane into aqueous ethanolic solutions of the compounds. Both compounds crystallize in the monoclinic crystal system, RACCIS as prisms and MINTRA as flat plates. A list of the crystal data and the experimental conditions is given in Table 1.

*Structure determination and refinement.* The crystal structures were solved by the heavy atom method and the trial structures were refined by full-matrix least-squares techniques to the final *R*-values of 0.049 and 0.053 for RACCIS and MINTRA, respectively. Programmes of the X-ray system were used.<sup>6</sup> The hydrogen atoms bonded to C11 in MINTRA could not be located in a difference electron density map and were not included in any calculations. All other hydrogen atoms were included in the refinements in calculated positions (C–H = 1.0 Å) as a fixed contribution. The isotropic temperature factors ( $B = 4.0$ – $8.0$ ) chosen for the hydrogen atoms reflect the thermal parameters of the atoms to which they are bonded. The final cycles of refinement included one scale factor and positional and anisotropic thermal parameters for all non-hydrogen atoms. The quantity minimized was  $\sum w(|F_o| - |F_c|)^2$  where weights were initially taken as unity, but in the final refinements changed to  $w = 1$ , when  $F_o \leq A$  and  $w = (A/F_o)^2$  when  $F_o > A$ ,  $A = 7.0$  for MINTRA. For RACCIS  $w = 1/\sigma(I)^2$  was used. The scattering factors used for hydrogen were those of Stewart, Davidson and Simpson<sup>7</sup> and for all other atoms those listed in International Tables for X-Ray Crystallography.<sup>8</sup> All atoms were treated as uncharged.

Table 1. Crystal data and experimental conditions. No absorption corrections have been applied.

	RACCIS	MINTRA
Stoichiometry	C <sub>8</sub> H <sub>15</sub> O <sub>2</sub> S <sub>2</sub> ClO <sub>4</sub>	C <sub>8</sub> H <sub>15</sub> O <sub>2</sub> S <sub>2</sub> ClO <sub>4</sub>
Formula weight	274.7	274.7
Z	4	2
F(000)	576	288
Space group	P2 <sub>1</sub> /n	P2 <sub>1</sub>
a (Å) <sup>a</sup>	10.132(4)	12.530(5)
b (Å)	10.129(14)	7.585(2)
c (Å)	13.072(4)	6.826(2)
β (°)	112.39(4)	102.64(2)
Cell volume (Å <sup>3</sup> )	1240.0	633.0
D <sub>x</sub> (g cm <sup>-3</sup> )	1.471	1.441
D <sub>m</sub> (floatation) (g cm <sup>-3</sup> )	1.473	1.435
μ(MoKα) (cm <sup>-1</sup> )	4.9	4.8
M.p. (°C) <sup>b</sup>	104.0	106.0
Diffractometer	CAD-3	CAD-3
Crystal size (mm)	0.4 × 0.4 × 0.5	0.14 × 0.28 × 0.40
Radiation (MoKα; λ nm)	0.71069	0.71069
Scan	ω	ω
Range (°)	3.5 ≤ θ ≤ 25.0	3.5 ≤ θ ≤ 25.0
Number of independent reflections	2585	1380
Number of observed reflections [F <sub>o</sub> ≥ 2.0σ(I)]	1507	1170

<sup>a</sup>The cell dimensions are based on diffractometer measured θ-angles. <sup>b</sup>Leitz hot stage microscope.

The absolute configuration of MINTRA was determined using a second crystal and CuKα-radiation. The intensities of a number of reflections having θ < 15° were recorded at +θ and -θ, and all possible symmetry-related reflections were measured to assure a correct result in spite of the rather unsatisfactory quality of the crystals. Some results of these measurements are given in Table 2. An attempt to collect a full data set using Cu-radiation failed as the crystals were damaged by this radiation. The final lists of structure factors are available from the author on request.

Table 2. Relative intensities of Bijvoet-sets<sup>14</sup> of reflections.

Measured	Calculated for configuration (1S,3S) Ratio I(hk̄l)/I(hkl)
011̄ < 011̄	0.96
111̄ < 111̄	0.86
021 > 021	1.18
220 < 220	0.73
211 ~ 211	0.96

## RESULTS AND DISCUSSION

The dimensions calculated from the final parameters (Table 3) are given in Tables 4 and 5, in which also geometrical results of empirical force field calculations (see below) are listed. The rings adopt chair conformations (Figs. 1a and 1b). The ring geometry is as previously observed highly dependent on the orientation of the methyl group attached to sulfur.<sup>3,9</sup> The close contacts between the axial S-methyl group and the axial 3-acetoxy group of RACCIS cause a deformation of the chair resulting in deviations of ±0.03 Å of C2, C3, C5 and C6 from the best plane through the four atoms. In the structure of MINTRA, only the acetoxy group is in the axial position, and C2, C3, C5 and C6 are found in the best plane through the atoms (calculated deviations ±.002 Å).

The atoms of the acetoxy groups are in both structures found to have large thermal parameters. The same trend was observed in the structures of the iodides of the 4-acetoxy compounds.<sup>3</sup> The phenomenon is thus not caused only by the excessive vibrations of the perchlorate ions in the two

Table 3. Final positional and thermal parameters. The estimated standard deviations are given in parentheses. Thermal parameters are  $\times 10^2$ . The temperature factor is defined by:  $\exp[-2\pi^2(U_{11}h^2a^{*2} + \dots + 2U_{12}hka^*b^* + \dots)]$ .

Atom $x/a$	$y/b$	$z/c$	$U_{11}$	$U_{22}$	$U_{33}$	$U_{12}$	$U_{13}$	$U_{23}$	
(–)- <i>trans</i> -3-Acetoxy-1-methyl-thiane perchlorate, MINTRA									
S	.2005(1)	.0(–)	.5180(2)	5.3(1)	5.6(1)	4.9(1)	–0.0(1)	2.0(1)	–0.0(1)
C2	.1996(7)	–.191(1)	.678(1)	5.5(5)	4.9(5)	6.0(5)	–1.1(5)	2.7(4)	–0.2(5)
C3	.3044(7)	–.194(1)	.835(1)	5.0(4)	5.6(5)	5.6(5)	0.1(4)	2.0(4)	0.5(5)
C4	.3179(6)	–.036(1)	.972(1)	7.5(4)	6.0(7)	5.0(4)	0.4(4)	1.5(4)	0.0(4)
C5	.3160(8)	.142(1)	.864(2)	7.5(6)	5.8(6)	6.1(6)	–0.9(5)	2.5(5)	–1.9(5)
C6	.2110(8)	.170(1)	.706(2)	7.7(6)	4.0(4)	6.9(6)	0.7(5)	2.7(5)	–0.1(5)
C7	.0620(6)	.015(2)	.383(1)	6.4(4)	8.1(6)	7.8(5)	–0.4(7)	0.6(4)	0.6(8)
O8	.3947(4)	–.193(1)	.731(1)	5.7(3)	4.3(3)	7.4(3)	0.3(3)	2.9(3)	0.6(3)
C9	.4303(6)	–.347(1)	.681(1)	5.9(4)	4.1(4)	7.3(5)	1.0(4)	1.3(4)	0.8(4)
O10	.3980(4)	–.485(1)	.724(1)	11.1(4)	4.5(3)	13.6(5)	1.2(5)	7.1(4)	1.8(5)
C11	.5155(7)	–.319(1)	.555(1)	8.4(5)	7.5(6)	9.1(7)	2.1(5)	6.0(5)	1.9(5)
C1	.8519(2)	.0007(6)	.8323(3)	9.6(1)	7.2(1)	5.6(1)	0.7(2)	3.5(1)	0.2(2)
O1	.8575(5)	–.015(2)	1.035(1)	11.2(4)	15.6(7)	6.3(3)	1.4(8)	2.2(3)	3.3(7)
O2	.793(1)	.157(2)	.773(2)	37.9(18)	11.1(8)	15.8(10)	10.7(11)	17.5(11)	5.8(8)
O3	.788(1)	–.136(2)	.738(2)	17.5(10)	22.1(14)	13.4(9)	–4.8(9)	0.3(8)	–10.3(10)
O4	.9466(7)	.004(3)	.774(2)	17.9(7)	20.6(9)	30.2(12)	1.0(14)	18.9(8)	2.9(17)
(±)- <i>cis</i> -3-Acetoxy-1-methyl-thiane perchlorate, RACCIS									
S	.4455(1)	.4188(1)	.6261(1)	5.11(6)	5.25(5)	3.88(5)	0.06(4)	1.01(4)	–0.93(4)
C2	.5553(4)	.3069(3)	.7324(3)	5.0(2)	3.9(2)	5.5(2)	0.1(1)	0.6(2)	–0.8(2)
C3	.5619(4)	.3326(3)	.8486(3)	5.7(2)	3.7(2)	4.9(2)	–0.1(2)	–0.2(2)	0.4(1)
C4	.4181(5)	.3476(4)	.8564(3)	7.7(3)	7.8(3)	4.5(2)	–1.6(2)	1.9(2)	–0.3(2)
C5	.3259(5)	.4572(4)	.7836(4)	4.9(2)	8.4(2)	5.4(2)	0.5(2)	1.6(2)	–0.7(2)
C6	.2903(4)	.4333(4)	.6609(3)	4.0(2)	7.7(2)	5.1(2)	0.3(2)	0.6(2)	–0.4(2)
C7	.5302(5)	.5782(3)	.6611(3)	6.9(3)	4.7(2)	4.7(2)	–0.1(2)	1.3(2)	0.1(2)
O8	.6413(3)	.4546(2)	.8880(2)	5.6(2)	4.0(1)	5.0(2)	0.1(1)	–0.9(1)	0.2(1)
C9	.7657(4)	.4490(3)	.9734(3)	4.6(2)	5.0(2)	3.6(2)	0.2(1)	0.2(2)	0.6(1)
O10	.8098(4)	.3515(3)	1.0236(3)	8.5(2)	6.5(2)	10.8(3)	–1.0(2)	–3.9(2)	4.0(2)
C11	.8370(5)	.5809(4)	.9948(4)	5.5(2)	5.9(2)	5.5(2)	–0.4(2)	0.2(2)	0.2(2)
C1	.8954(1)	.4104(1)	.6493(1)	4.48(6)	5.19(5)	5.45(6)	–0.16(4)	0.61(4)	0.11(4)
O1	.7515(4)	.4001(3)	.5706(3)	6.4(2)	9.7(2)	6.1(2)	–0.0(2)	–0.7(2)	0.4(2)
O2	.8873(5)	.4133(7)	.7544(4)	8.5(3)	33.4(8)	5.4(2)	1.3(4)	1.1(2)	–2.8(3)
O3	.9759(4)	.2994(3)	.6424(4)	8.3(2)	5.9(2)	16.3(4)	1.5(2)	4.9(3)	1.2(2)
O4	.9611(5)	.5240(3)	.6305(5)	9.7(3)	4.7(2)	23.4(6)	–0.9(2)	5.8(3)	0.5(2)

present structures. The thermal vibrations are visualized in Figs. 2a and 2b, which depict the packing in the two crystals.

The title compounds were designed as semirigid analogues of acetylcholine, and therefore it was of interest to examine their conformational flexibility. This has been performed using the empirical force field programme MM2.<sup>4</sup> All parameters needed were included in the programme with the exception of one, the torsional parameter O–C–C–S<sup>+</sup>, for which the values  $V_1=0.0$ ,  $V_2=-0.5$  and  $V_3=0.5$  were chosen. It can be seen from Tables 4 and 5 that

the calculated geometries are in fair agreement with the results obtained from the crystal structure determinations and the deformation of the chair caused by axial substituents is simulated satisfactorily. The calculated orientation of the acetoxy group is approximately the same for MINTRA and for RACCIS. In the crystals of MINTRA the acetoxy group is found in an orientation close to the calculated one, and a similar orientation was found in the crystals of the iodide of *trans*-4-acetoxy-1-methylthiane. In the crystals of RACCIS a different orientation of the acetoxy group is found.

Table 4. Bond lengths and angles involving non-hydrogen atoms only. The estimated standard deviations are given in parentheses. Results of crystal structure determinations (XRAY) and of force field calculations (MM2).

	RACCIS XRAY	MINTRA XRAY	RACCIS MM2	MINTRA MM2
S-C2	1.809(3)	1.82(1)	1.80	1.81
S-C6	1.802(5)	1.80(1)	1.80	1.81
S-C7	1.804(4)	1.78(1)	1.80	1.80
C2-C3	1.518(6)	1.50(1)	1.54	1.54
C3-C4	1.506(7)	1.51(1)	1.54	1.54
C4-C5	1.530(6)	1.54(1)	1.54	1.54
C5-C6	1.524(6)	1.52(1)	1.53	1.53
C3-O8	1.458(4)	1.46(1)	1.42	1.42
O8-C9	1.329(4)	1.32(1)	1.36	1.36
C9-O10	1.176(5)	1.18(1)	1.21	1.21
C9-C11	1.493(5)	1.53(1)	1.52	1.52
Cl-O1	1.433(3)	1.37(1)		
Cl-O2	1.408(5)	1.41(1)		
Cl-O3	1.412(4)	1.39(1)		
Cl-O4	1.397(4)	1.33(1)		
C2-S-C6	101.4(6)	98.6(5)	101.1	97.3
C2-S-C7	105.8(2)	103.2(5)	105.4	100.5
C6-S-C7	103.8(2)	103.5(5)	103.3	100.5
S-C2-C3	116.2(3)	108.6(7)	117.5	110.6
C2-C3-C4	114.2(3)	113.2(8)	112.2	111.7
C3-C4-C5	114.1(4)	114.4(7)	112.9	113.6
C4-C5-C6	112.6(4)	112.3(8)	112.3	112.0
C5-C6-S	113.5(3)	108.9(7)	114.9	109.5
C2-C3-O8	107.8(3)	107.6(7)	112.0	111.8
C4-C3-O8	108.0(3)	107.9(7)	109.2	108.8
C3-O8-C9	118.7(3)	117.6(7)	118.0	117.7
O8-C9-O10	122.8(3)	124.3(8)	125.2	125.2
O8-C9-C11	110.8(3)	109.6(7)	110.1	110.1
O10-C9-C11	126.4(3)	126.1(8)	124.7	124.7
O1-Cl-O2	106.3(3)	105.5(8)		
O1-Cl-O3	110.5(2)	107.5(8)		
O1-Cl-O4	110.9(2)	116.8(5)		
O2-Cl-O3	109.2(3)	106.4(8)		
O2-Cl-O4	111.3(4)	110.6(11)		
O3-Cl-O4	108.6(3)	109.6(9)		

The energy needed to effect the observed conformational changes is, however, calculated to be small (<1 kcal/mol) and may readily be delivered by the packing forces.

Results of NMR-experiments<sup>5</sup> suggest that equilibria between conformers with axial and conformers with equatorial acetoxy groups exist in solutions of both of the title compounds. Force field calculations indicate, in full agreement with

this, that the energy differences between the conformers mentioned are small (1–2 kcal/mol, *i.e.* hardly significant) for both RACCIS and MINTRA. Similar calculations have been performed for *cis*- and *trans*-4-acetoxy-1-methylthiane<sup>10,11</sup> using the programmes MM1<sup>12</sup> and MM2 and also here a satisfactory agreement was found between calculated and experimental values. It therefore seems reasonable to conclude that empirical force field

Table 5. Selected torsion and interplanar angles ( $^{\circ}$ ).

	RACCIS	MINTRA	RACCIS MM2	MINTRA MM2
C6-S-C2-C3	-42.9(3)	-60.4(8)	-42.4	-60.4
C2-S-C6-C5	46.6(3)	60.2(8)	44.6	61.0
S-C2-C3-C4	50.6(4)	62.6(9)	52.1	62.0
S-C6-C5-C4	-58.6(4)	-61.6(10)	-58.1	-64.2
C2-C3-C4-C5	-57.2(4)	-58.8(11)	-59.5	-57.7
C6-C5-C4-C3	61.9(5)	57.8(11)	63.4	59.3
S-C2-C3-O8	-69.4(3)	-56.5(9)	-71.2	-60.1
C2-C3-O8-C9	-115.0(4)	-88.6(9)	-76.6	-75.1
C4-C3-O8-C9	121.1(4)	148.9(7)	158.4	161.1
Plane 1-Plane 2	140	124	142	125
Plane 2-Plane 3	127	128	125	128

Plane 1: C2,S,C6; Plane 2: C2,C3,C5,C6; Plane 3: C3,C4,C5.

calculations for this type of compound are able to simulate the geometry and to give a fair estimate of the flexibility of the molecules.

For the acetylcholine analogues discussed in this paper it can be concluded, that they are rather flexible and really only semi-rigid.

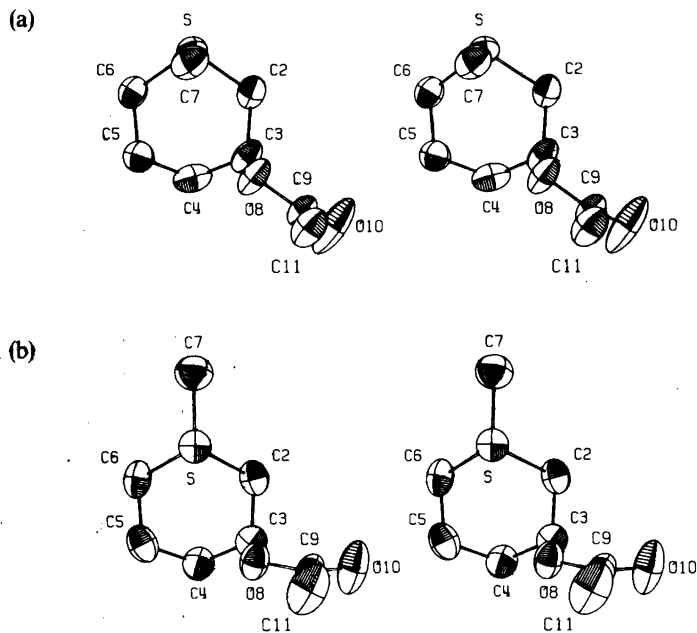


Fig. 1. (a) *cis*- and (b) (1*S*,3*S*)-*trans*-3-Acetoxy-1-methylthiane. Non-hydrogen atoms are represented by their vibration ellipsoids drawn at the 50% probability level. The examined (and depicted) *trans* isomer is the one with minor effect on muscarinic receptors. The drawings were produced by ORTEP.<sup>13</sup>

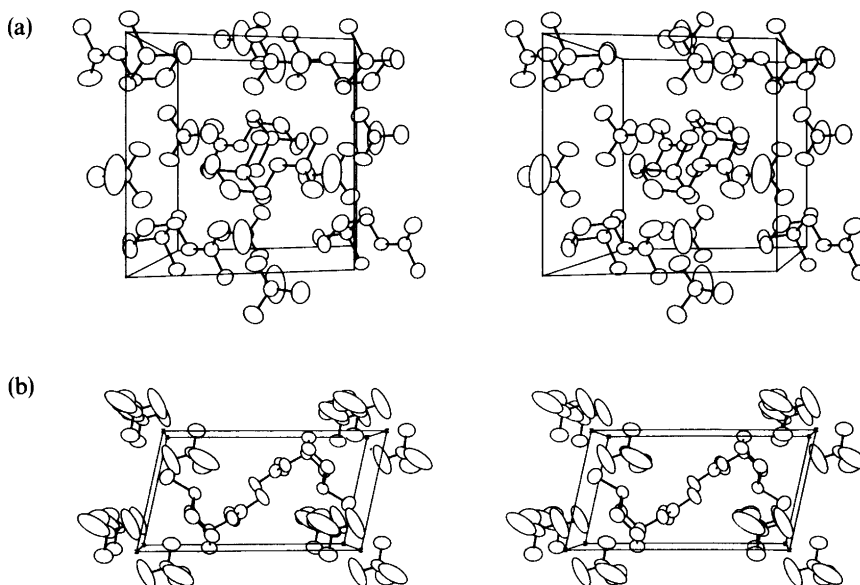


Fig. 2. Stereo view of the packing of (a) RACCIS ( $x \rightarrow, y \uparrow$ ) and (b) MINTRA ( $x \rightarrow, z \downarrow$ ).

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