

The Crystal Structures of *cis*- and *trans*-4-Acetoxy-1-methylthiacyclohexane Iodides

BIRTHE JENSEN

Royal Danish School of Pharmacy, Department of Chemistry BC, DK-2100 Copenhagen Ø, Denmark

The crystal structures of the acetylcholine analogues *cis*- and *trans*-4-acetoxy-1-methylthiacyclohexane iodides have been determined from diffractometer-collected three-dimensional X-ray data and refined by full-matrix least-squares methods to *R* values of 0.046 and 0.040, respectively. The rings adopt chair conformations substantially flattened by axial substituents.

cis- and *trans*-4-Acetoxy-1-methylthiacyclohexane (in the following named CIS and TRANS) have been shown to be cholinergic agonists and to be substrates for acetylcholinesterase.¹

It is not possible to find a direct atom-to-atom correspondence between acetylcholine and the title compounds, and it was considered of interest to examine their crystal structures as part of an investigation of structure activity relationships of a series of cyclic acetylcholine analogues.²

EXPERIMENTAL

CIS and TRANS were synthesized by Dr. G. Lambrecht¹ and colourless single crystals were obtained by diffusion of dimethoxymethane into aqueous ethanolic solutions of the compounds. A list of the crystal data and the experimental conditions is given in Table 1.

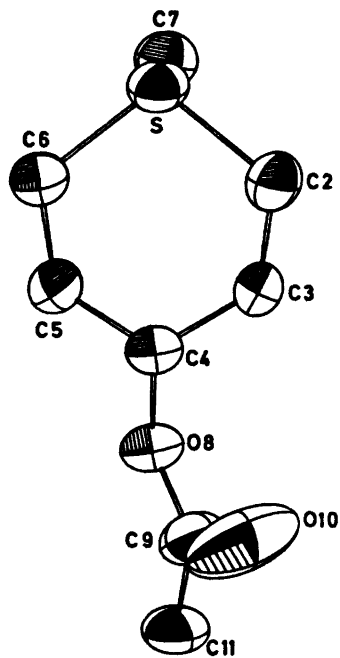
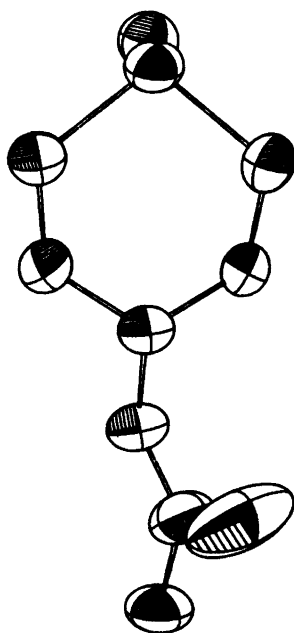
Structure determination and refinement. The crystal structures were solved by the heavy atom method, and the trial structures were refined by full-matrix least-squares techniques to the final *R* values of 0.046 and 0.040 for CIS and TRANS, respectively. Programs of the X-RAY system³ were used. The hydrogen atoms of TRANS were located in a difference electron density map and included in the refinements in calculated positions (C—H = 1.0 Å, *B* = 4.0) as a fixed contribution. The positions of the hydrogen atoms of CIS were not indi-

cated in the difference electron density map, probably due to systematic errors in the data set caused by instrumental difficulties, and they have not been included in any calculations. The final cycles of refinement included positional and anisotropic thermal parameters for all non-hydrogen atoms together with one scale factor for TRANS and four scale factors for CIS. 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 $F_o > A$, $A = 40.0$ for TRANS and $A = 35.0$ for CIS. The scattering factors used for hydrogen were those of Stewart, Davidson and Simpson⁴ and for all other atoms those listed in International Tables for X-Ray Crystallography.⁵ All atoms but I⁻ were treated as uncharged. The final lists of structure factors are available from the author on request.

RESULTS AND DISCUSSION

The dimensions calculated from the final parameters (Table 2) are given in Tables 3 and 4. The six-membered rings adopt chair conformations (*cf.* Figs. 1a and b). In the examined crystal structures both substituents of TRANS are axial while the acetoxy group of CIS is equatorial. It has been shown by ¹H NMR studies^{2,6} that conformers with an axial and conformers with an equatorial acetoxy group coexist in solutions of salts of CIS as well as of TRANS, and theoretical calculations² have indicated that the energy differences between the conformers are very small. The axial groups seem (Table 4) to cause considerable flattening of the rings, while the parts of the ring adjacent to the equatorial 4-acetoxy-group of CIS are puckered. The plane through C4—O8—C9 is not bisecting the angle C3—C4—C5

a



b

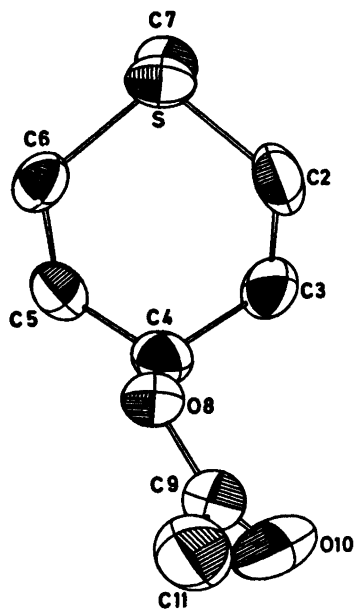
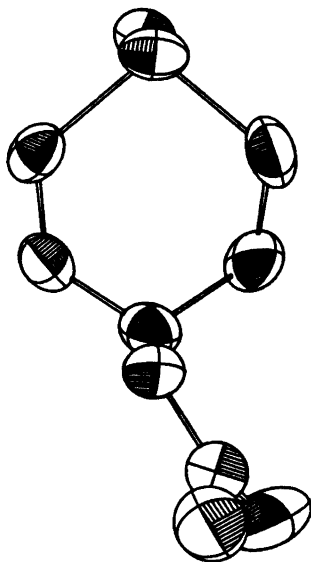


Fig. 1. (a) *cis*- and (b) *trans*-4-Acetoxy-1-methylthiacyclohexane. Stereoscopic view of the ions showing the atomic numbering and vibration ellipsoids at the 50 % probability level. The drawings were produced by ORTEP.¹¹

Table 1. Crystal data and experimental conditions.

	CIS	TRANS
Stoichiometry	C ₈ H ₁₆ O ₂ SI	C ₈ H ₁₆ O ₂ SI
Formula weight	299.15	299.15
Z	4	4
F(000)	580	580
Space group	P2 ₁ /c	P2 ₁ /c
a (Å) ^a	6.860(2)	6.219(1)
b (Å)	13.12(1)	25.519(3)
c (Å)	13.216 (4)	7.369(1)
β (°)	99.85(3)	100.00(1)
Cell volume (Å ³)	1171.7	1151.7
D _x (g cm ⁻³)	1.695	1.725
D _m (floatation) (g cm ⁻³)	1.71	1.73(1)
μ(MoKα) (cm ⁻¹)	29.2	29.6
M.p. (°C) ^b	138–39	149–50
M.p. (°C) ^c	159	163
Diffractometer	CAD-3	CAD-4
Crystal size (mm)	0.24 × 0.36 × 0.5	0.11 × 0.18 × 0.37
Radiation	Graphite monochromated MoKα λ=0.71069	
Scan	ω	
Range (°)	4.0 ≤ θ ≤ 25.0	θ ≤ 27.0
Number of independent reflections	2133	2691
Number of observed reflections (F _o ≥ 2σ(I))	1650	1598

No absorption corrections have been applied. ^a The cell dimensions are based on diffractometer measured θ-angles. ^b Oil bath. ^c Leitz hot stage microscope. Rearrangements were observed, but the shape of the crystals was unchanged.

Table 2. Final positional and thermal parameters. The estimated standard deviations are given in parentheses. Thermal parameters are × 10³. The temperature factor is defined by: exp[-2π²(U₁₁h²a^{*2} + ... + 2U₁₂hka^{*}b^{*} + ...)].

Atom	x/A	y/B	z/C	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
<i>cis</i> -S-Methyl-4-acetoxythiacyclohexane iodide									
I-	.34071(7)	.14565(4)	.15957(4)	4.70(3)	6.19(3)	5.08(5)	.56(2)	.48(3)	.12(2)
S	1.2761(3)	.0839(2)	.8558(1)	3.84(9)	7.2(1)	4.6(1)	-.27(9)	.30(8)	-.01(9)
C2	1.253(1)	.0541(7)	.7197(5)	5.5(5)	9.2(6)	4.0(4)	1.1(4)	1.4(3)	-.2(4)
C3	1.036(1)	.0377(6)	.6668(5)	5.6(4)	7.1(5)	4.2(4)	1.5(4)	.3(3)	-1.4(3)
C4	.913(1)	.1336(6)	.6761(5)	4.5(4)	5.6(4)	4.3(4)	.4(3)	-.2(3)	-.1(3)
C5	.882(1)	.1489(6)	.7870(6)	4.9(4)	6.5(5)	4.7(4)	.4(4)	.3(3)	-1.0(3)
C6	1.081(1)	.1782(6)	.8541(6)	4.6(4)	6.5(5)	5.2(4)	.4(4)	-.2(3)	-1.0(3)
C7	1.187(1)	-.0285(7)	.9116(6)	5.7(5)	7.7(5)	5.3(4)	.1(4)	1.5(4)	1.2(4)
O8	.717(1)	.1183(4)	.6176(4)	5.1(3)	6.3(3)	4.4(3)	-.2(2)	-.5(2)	.4(2)
C9	.685(2)	.1502(6)	.5205(6)	8.0(6)	6.7(5)	4.2(4)	.4(5)	-.2(4)	.5(4)
O10	.816(1)	.1797(8)	.4796(5)	11.0(7)	20.6(9)	5.7(4)	-4.5(7)	.2(4)	3.9(5)
C11	.473(1)	.1396(7)	.4706(7)	6.9(6)	8.0(6)	6.1(5)	1.5(5)	-2.4(4)	-0.8(4)

Table 2. Continued.

trans-S-Methyl-4-acetoxythiacyclohexane iodide

I-	.11886(7)	.57456(2)	.22308(7)	3.72(2)	5.64(3)	4.33(3)	-0.17(3)	0.32(2)	-0.05(3)
S	.6148(3)	.5606(1)	.8703(3)	4.8(1)	4.8(1)	4.3(1)	0.86(8)	-0.54(8)	-0.97(8)
C2	.528(2)	.6255(4)	.917(1)	6.9(5)	6.7(6)	5.9(5)	0.8(4)	3.8(4)	1.2(4)
C3	.447(1)	.6580(4)	.751(2)	5.2(4)	5.1(5)	9.8(7)	-1.2(4)	3.3(5)	-0.8(5)
C4	.607(1)	.6644(3)	.619(1)	5.0(4)	5.7(5)	5.7(5)	-0.9(4)	1.4(4)	-2.0(4)
C5	.685(1)	.6132(3)	.556(1)	5.5(4)	5.6(5)	4.3(4)	0.9(4)	1.7(4)	0.2(4)
C6	.789(1)	.5769(3)	.706(1)	3.5(3)	3.8(4)	6.9(5)	-0.3(3)	1.0(3)	0.1(4)
C7	.378(1)	.5309(3)	.736(1)	4.1(4)	5.5(5)	5.1(5)	0.8(4)	0.3(4)	-0.5(4)
O8	.801(1)	.6920(2)	.712(1)	5.9(3)	4.0(3)	6.3(4)	0.3(2)	2.2(3)	-0.5(3)
C9	.790(2)	.7444(4)	.718(1)	9.3(7)	4.9(5)	7.3(6)	-0.4(5)	4.2(6)	-0.5(5)
O10	.634(1)	.7686(3)	.658(1)	12.3(7)	4.9(4)	14.5(8)	-1.8(4)	4.2(6)	-2.3(5)
C11	1.006(2)	.7675(4)	.810(2)	11.0(8)	6.1(6)	8.8(8)	2.0(6)	4.6(7)	1.5(6)

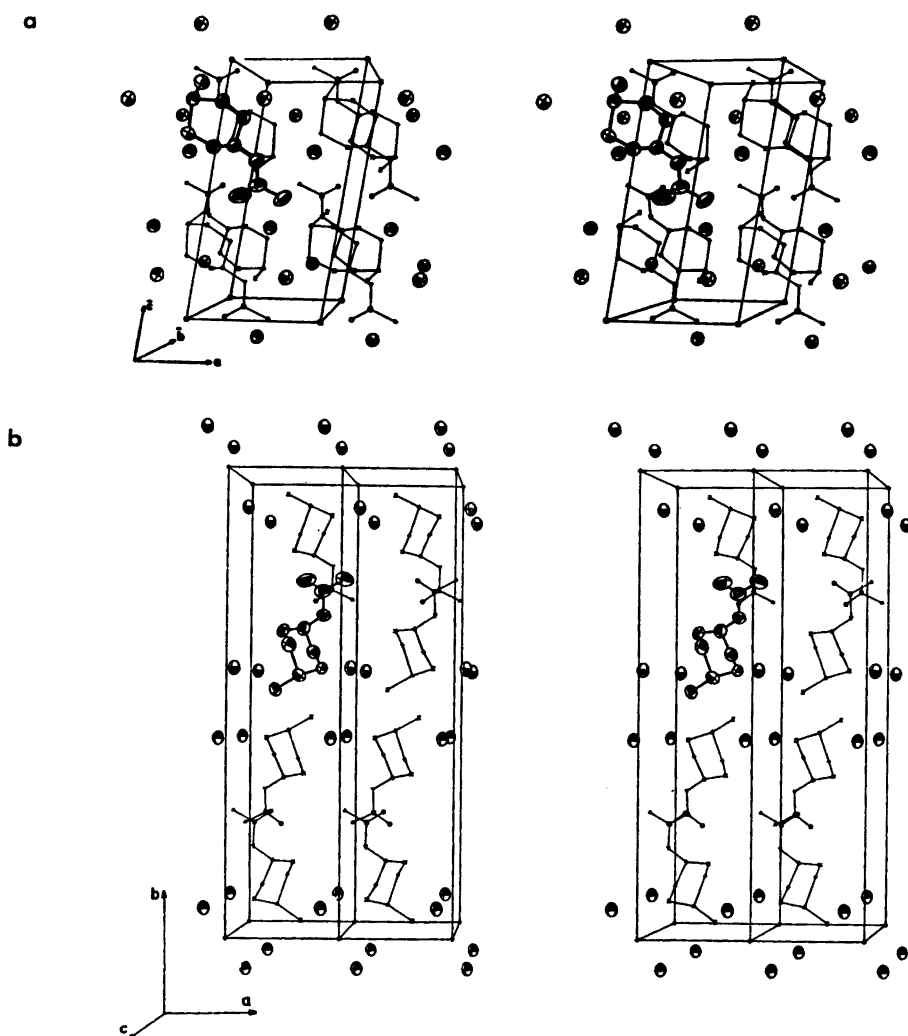


Fig. 2. Stereo views of the packing of (a) CIS and (b) TRANS.

Table 3. Bond lengths and angles involving non-hydrogen atoms only. The estimated standard deviations are given in parentheses.

	CIS	TRANS
S—C2	1.82(1)	1.79(1)
S—C6	1.82(1)	1.81(1)
S—C7	1.80(1)	1.79(1)
C2—C3	1.55(1)	1.49(1)
C3—C4	1.53(1)	1.52(1)
C4—C5	1.53(1)	1.49(1)
C5—C6	1.54(1)	1.50(1)
C4—O8	1.45(1)	1.46(1)
O8—C9	1.33(1)	1.34(1)
C9—O10	1.19(1)	1.17(1)
C9—C11	1.49(1)	1.52(1)
C2—S—C6	101.3(4)	98.8(4)
C2—S—C7	104.6(4)	104.7(4)
C6—S—C7	105.1(4)	105.0(4)
S—C2—C3	112.8(5)	115.0(7)
C2—C3—C4	110.6(6)	114.9(7)
C3—C4—C5	110.7(6)	112.9(7)
C4—C5—C6	109.4(7)	115.6(7)
C5—C6—S	114.4(6)	113.7(5)
C3—C4—O8	108.6(6)	109.1(7)
C5—C4—O8	105.2(6)	106.5(6)
C4—O8—C9	117.4(7)	117.0(7)
O8—C9—O10	121.5(9)	123.9(9)
O8—C9—C11	112.8(8)	110.8(8)
O10—C9—C11	125.6(8)	125.3(9)

in any of the two structures. The torsion angles C3—C4—O8—C9 and C5—C4—O8—C9 are for CIS $\pm 93(1)$ and $\mp 149(1)^\circ$, respectively, and for TRANS $\mp 83(1)$ and $\pm 155(1)^\circ$, respectively. The torsions about the bond C4—O8 observed in the crystals were also by theoretical calculations for the isolated ions² found to correspond to low energy conformations. In both structures the carbonyl oxygen atom is approaching C3, and in both cases the angle C3—C4—O8 is bigger than the angle C5—C4—O8.

The packing arrangements in both of the crystal structures are visualized in Figs. 2a and b and seem to be dominated by many weak electrostatic interactions between the iodide ions and sulfur atoms or carbon atoms bonded to the sulfur atoms. The packing arrangements in these and related crystal structures^{2,6} indicate in agreement with results of theoretical calculations^{3,9} that part of the positive charge of the sulfur atom is delocalized to the adjacent methyl- and methylene-groups. Similar charge delocalization has been found in the quaternary ammonium group, where hardly any positive charge seems to remain on the nitrogen atom.^{2,10}

The acetoxy-groups are not found to be involved in any close contacts, and atoms of this moiety are in both crystal structures oscillat-

Table 4. Selected torsion and interplanar angles of CIS and TRANS together with corresponding values for related compounds: (I), *S*-methylthiacyclohexane(methyl equatorial);⁷ (II), *cis-S*-methyl-4-*t*-butylthiacyclohexane(methyl axial, *t*-butyl equatorial);⁸ (III), *trans-S*-methyl-4-*t*-butylthiacyclohexane (both substituents equatorial).⁸ The values are for each compound given for one enantiomer only.

Torsion angles	CIS	TRANS	(I)	(II)	(III)
C6—S—C2—C3	45(1)	49(1)	58	46	64
C2—S—C6—C5	-46(1)	-49(1)	-58	-46	-64
S—C2—C3—C4	-60(1)	-56(1)	-64	-58	-68
S—C6—C5—C4	59(1)	57(1)	64	59	69
C2—C3—C4—C5	70(1)	55(1)	64	62	62
C6—C5—C4—C3	-69(1)	-56(1)	-64	-63	-64
S·C4—O8—C9	155(1)	-144(1)			
C3—C4—O8—C9	93(1)	-83(1)			
C5—C4—O8—C9	-149(1)	155(1)			
Interplanar angles					
Plane 1—Plane 2	139(1)	136(1)	126	140	121
Plane 2—Plane 3	118(1)	131(1)	124	126	124
Plane 1: C2, S, C6.		Plane 2: C2, C3, C5, C6.		Plane 3: C3, C4, C5.	

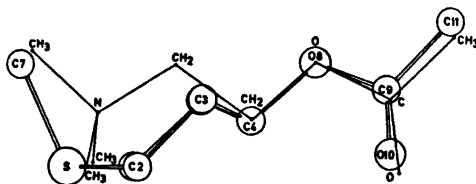


Fig. 3. CIS in the conformation found in the present crystal structure together with acetylcholine in its fully extended conformation. Most of the non-hydrogen atoms of acetylcholine are in the plane of the paper, and so are C7, S, C4 and O8 of CIS. C4—O8 and the corresponding bond in acetylcholine have been chosen as the common bond. Rotation of the ester group about this bond in choline esters is known to demand only very little energy.

ing violently, as indicated by the high values of some of the thermal parameters.

The muscarinic activity of CIS is as high as that of acetylcholine while that of TRANS is two orders of magnitude lower.^{1,2} The fit between groups of CIS as found in the examined crystal structure and corresponding groups of acetylcholine in the unobserved extended conformation (Fig. 3) is remarkably good, but the question whether this observation is of any relevance concerning the biological activities of CIS and of acetylcholine remains to be answered.

Acknowledgements. The author gratefully acknowledges the permission to use the CAD-4 diffractometer of the Technical University of Denmark and thanks Professor Rolf Norrestam for his assistance.

REFERENCES

1. Lambrecht, G. *Experientia* 32 (1976) 365.
2. Höltje, H.-D., Jensen, B. and Lambrecht, G. *Eur. J. Med. Chem. Chim. Ther.* In press.
3. Stewart, J. M., Kruger, G. J., Ammon, H. L., Dickinson, C. and Hall, S. R. *The X-Ray System, Version of 1972*, Technical Report TR-192, Computer Science Center, University of Maryland, College Park 1972.
4. Stewart, R. F., Davidson, E. R. and Simpson, W. T. *J. Chem. Phys.* 42 (1965) 3175.
5. *International Tables for X-Ray Crystallography*, Kynoch Press, Birmingham 1974, Vol. IV.
6. Lambrecht, G. *Arch. Pharm. (Weinheim)* 311 (1978) 636.
7. Gerdil, R. *Helv. Chim. Acta* 57 (1974) 489.

8. Eliel, E. L., Willer, R. L., Mc Phail, A. T. and Onan, K. D. *J. Am. Chem. Soc.* 96 (1974) 3021.
9. Yamabe, T., Aoyagi, T., Nagata, S., Sakai, H. and Fukui, K. *Chem. Phys. Lett.* 28 (1974) 182.
10. Langlet, J., Claverie, P., Pullman, B., Piazzola, D. and Daudry, J. P. *Theor. Chim. Acta* 46 (1977) 105.
11. Johnson, C. K. *ORTEP II*. Report ORNL-3794, revised 1971. Oak Ridge National Laboratory, Oak Ridge 1971.

Received January 19, 1979.