

DITHIOACETAL; AS A CHIROPTICAL FUNCTIONAL GROUP TO DETERMINE ABSOLUTE AND RELATIVE CONFIGURATIONS BY CD AND ^1H NMR SPECTRA¹

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Abstract—Ethylene dithioacetal (EDT) was first used as a chiroptical group to determine both absolute and relative configurations of asymmetric centers in α - and β -positions in relation to EDT by the signs of the Cotton effect in CD and by an aromatic solvent-induced shift of ^1H NMR, respectively, in a series of EDTs of 4,10-dimethyldecal-3-ones compared with those of steroid ketones.

The preceding paper in this series was concerned with the inversion of the methyl group adjacent to ketone (ketonic methyl) by virtue of the 1,3-peri repulsion of the hydroxyl group formed by opening γ -lactone, and with the determination of the absolute configuration of the methyl group by chemical interconversion using ethylene dithioacetal (EDT) as a protective group to prevent epimerization of the ketonic methyl in a series of 4,10-dimethyldecal-3-ones. The inversion method should be a useful tool to prepare axial methyl, which is usually difficult to synthesize and can be fixed by dithioacetal in this method. We attempted to expand the function of dithioacetal from merely a protective group to a chiroptical group to determine both relative and absolute configurations at asymmetric centers in α - and β -positions in relation to EDT.

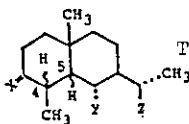


Table 1. Absolute and relative configurations at C-4 and C-5 in ethylene acetal and dithioacetal derivatives of 4,10-dimethyldecal-3-ones

Compounds	C ₄	C ₅	X	Y	Z	mp (°C)	Compounds	C ₄	C ₅	X	Y	Z	mp (°C)
(1a) α -THS	S (BH)	S (aH)	=O	-O-CO-		153-154	(5a) α -THS-EDT	S (BH)	S (aH)	x _s ^S	-O-CO-		191-192
(1b) β -THS	R (aH)	S (aH)	=O	-O-CO-		147	(5b) β -THS-EDT	R (aH)	S (aH)	x _s ^S	-O-CO-		172-173
(1c) γ -THS	R (aH)	R (BH)	=O	-O-CO-		100-101	(5c) γ -THS-EDT	R (aH)	R (BH)	x _s ^S	-O-CO-		118-120
(2a) α -THS-EAC	S (BH)	S (aH)	x _s ^O	-O-CO-		167-168.5	(5d) δ -THS-EDT	S (BH)	R (BH)	x _s ^O	-O-CO-		155-156
(2b) β -THS-EAC	R (aH)	S (aH)	x _s ^O	-O-CO-		180	(6a) α -THS-EDT-DIOL	S (BH)	S (aH)	x _s ^O	OH	CH ₂ OH	184-186
(2c) γ -THS-EAC	R (aH)	R (BH)	x _s ^O	-O-CO-		162-163	(6b) β -THS-EDT-DIOL	R (aH)	S (aH)	x _s ^O	OH	CH ₂ OH	127-128
(3a) α -THS-DIOL	S (BH)	S (aH)	=O	OH	CH ₂ OH	117-118	(6c) γ -THS-EDT-DIOL	R (aH)	R (BH)	x _s ^O	OH	CH ₂ OH	190-192
(3a-DIAC)	S (BH)	S (aH)	=O	OAc	CH ₂ OH	oil	(6d) δ -THS-EDT-DIOL	S (BH)	R (BH)	x _s ^O	OH	CH ₂ OH	182-183
(3a-NB)	S (BH)	S (aH)	=O	OH	CH ₂ ONB	oil							
(3d) δ -THS-DIOL	S (BH)	R (BH)	=O	OH	CH ₂ OH	111-112							
(4a) α -THS-EAC-DIOL	S (BH)	S (aH)	x _s ^O	OH	CH ₂ OH	149-151							
(4c) γ -THS-EAC-DIOL	R (aH)	R (BH)	x _s ^O	OH	CH ₂ OH	182-183							

Abbreviation: THS; tetrahydro-1- α -santonin, EAC; ethylene acetal, DIOL, 6,12-diol, EDT; ethylene dithioacetal, DIAC; 6,12-diacetate and NB; 12-*p*-nitrobenzoate.

The CD spectrum and the aromatic solvent-induced shift of ^1H NMR (ASIS NMR), known as the "octant rule"³ and the "carbonyl plane rule",⁴ respectively, have been applied to the ketonic methyl to determine the configuration in steroids. In this study, these two physical methods have been extended from ketone to dithioacetal by using a series of tetrahydro- α -santonins (THS) as typical and systematic compounds having few asymmetric carbon centers.

A pair of 3-ethylene acetal (EDC) derivatives (2a and 2b) from α - and β -THS (1a and 1b) were first prepared in the usual manner using benzene as a solvent with p-TsOH as thermodynamically controlled products which were separated by the column chromatography on silica gel. Another pair of EDTs (5a and 5b) were prepared from 1a and 1b as described in the preceding paper.² The ASIS for these 4,10-dimethyl-decal-3-one derivatives described in Table 1 including acetals and dithioacetals are shown in Table 2. The eq- and ax-methyls adjacent to acetal and dithioacetal were found to show down- and up-field shifts, respectively, without exception in the ASIS using CDCl_3 and C_6H_6 , the same tendency as in the pair of ketones (1a and 1b) and also in the steroid series;⁴ eq-methyl showed down-field shifts by ca. 0.26 ppm in ASIS, [1a (-0.27), 1c (-0.11), 2a (-0.26), 2c (-0.27), 4c (-0.26), 5a (-0.26), 5c (-0.25), 6a (-0.27) and 6c (-0.28)] and ax-methyl showed, in contrast, up-field or small down-field shifts by ca. 0.1 ppm [1b (+0.17), 2b (-0.09), 3d (-0.04), 5b (-0.02), 6b (-0.13) and 6d (0.0)].

These solvent shifts should be very useful for determining the relative configuration of methyl groups adjacent to acetal and dithioacetal which can be removed by reduction with Raney nickel to retain the configuration (ax-methyl, for example). While the configurations at C-6, C-7, C-10 and C-11 in β - α -santonin are retained in the corresponding tetrahydro compounds, two more asymmetric centers at C-4 and C-5 in tetrahydro- β - α -santonins will now be discussed. Their absolute configurations are closely related to the relative configuration which would be determined by ASIS, as described above, in the case of the chair form conformation in the A ring.

Table 2. ASIS ($\Delta\delta^{\text{CDCl}_3-\text{C}_6\text{H}_6}$) of methyl peak at C-4 in ^1H NMR of 4,10-dimethyldecal-3-ones and its derivatives

Config. of C ₄ -Me		ppm (Solvents) (from TMS)			$\Delta\delta(\text{ppm})$	Config. of C ₄ -Me		ppm (Solvents) (from TMS)			$\Delta\delta(\text{ppm})$
		CDCl_3	$\text{CDCl}_3-\text{C}_6\text{H}_6$	C_6H_6				CDCl_3	$\text{CDCl}_3-\text{C}_6\text{H}_6$	C_6H_6	
(1a)	eq	1.20(6.6)	1.26(6.6)	1.41(6.0)	-0.21	(4a)	eq	1.10(7.2)	1.19(6.0)	1.39(6.6)	-0.29
(1b)	ax	1.25(7.2)	1.10(7.8)	1.08(7.2)	+0.17	(4c)	eq	1.07(7.2)	1.13(6.0)	1.33(6.0)	-0.26
(1c)	eq	1.15(5.4)	1.12(6.0)	1.26(6.6)	-0.11						
						(5a)	eq	1.34(6.6)	1.42(6.6)	1.60(6.0)	-0.26
(2a)	eq	1.04(6.0)	1.10(6.0)	1.30(6.0)	-0.26	(5b)	ax	1.19(7.8)	1.15(7.2)	1.19(7.8)	+0.00
(2b)	ax	1.01(6.6)	1.01(7.2)	1.10(7.2)	-0.09	(5c)	eq	1.21(6.6)	1.27(6.0)	1.46(6.0)	-0.25
(2c)	eq	0.93(6.0)	1.00(6.0)	1.20(5.4)	-0.27	(5d)	ax	1.31(7.0)	1.28(7.0)	1.26(7.0)	+0.05
(3a)	—	1.70(7.8)	1.50(6.6)	1.47(6.9)	+0.23	(6a)	eq	1.42(6.6)	1.49(7.0)	1.69(7.0)	-0.27
(3a-BIAC)	—	1.12(6.6)	1.08(6.6)	1.14(7.2)	-0.02	(6b)	ax	1.14(7.0)	1.16(7.0)	1.27(7.0)	-0.13
(3a-NB)	—	1.34(7.0)	1.30(7.0)	1.39(7.0)	-0.05	(6c)	eq	1.36(7.0)	1.38(6.0)	1.64(7.0)	-0.28
(3d)	—	1.06(6.6)	1.03(6.0)	1.10(6.0)	-0.04	(6d)	ax	1.34(7.0)	1.29(6.0)	1.34(7.0)	+0.00

On the other hand, it has long been argued whether d-orbital participation of divalent sulfur in thioacetal can or can not contribute to the UV primary band near 245 nm, which should be responsible for its CD absorption.

We now wish to present the interesting finding that the signs of the cotton effect in the THS-EDT series at 237 and 252 are closely related to the absolute configurations at C-4 and C-5, respectively. This empirical rule, described below, indicated that the processes of electronic excitation are not the same in acetal and dithioacetal. The rule also may suggest that the assignment of the CD sign to the absolute configurations, mentioned above, should be a clue to find out the contribution from d-orbitals of divalent sulfur in the thioacetal. Although acetals (**2a** and **2b**) showed no significant CD absorption except the peak responsible for γ -lactone near 210 nm, dithioacetals (**5a** and **5b**) had a strong peak near 245 nm or two peaks at 234.5 and 256 nm. Another pair of dithioacetals (**6a** and **6b**) without γ -lactone had distinctive CD bands in the range from 220 to 260 nm as shown Fig. 1. CD data for EDTs of trans- and cis-4,10-dimethyldecal-3-ones are shown in Table 3 in connection with the absolute configurations at C-4 and C-5 in each compound.

Table 3. Correlation between the sign of CD and absolute configuration for 4,10-dimethyldecal-3-ones in dioxane

	Absolute config. C ₄ C ₅		λ_{\max}	$[\theta]_{\max}$	$[\theta]_{237 \text{ nm}}$	$[\theta]_{252 \text{ nm}}$
(5a)	S	S	224.5	+2,054	-2,920	-2,800
			245	-5,426		
(5b)	R	S	234	+4,029	+3,500	-1,380
			256	-1,854		
(5c)	R	R	245.5	+8,327	+6,320	+6,130
(5d)	S	R	239	-3,818	-2,450	
			258	+2,945		+1,730
(6a)	S	S	245	-21,120	-18,220	-18,900
(6b)	R	S	234.5	+3,113	+2,920	
			256	-3,736		-2,740
(6c)	R	R	245.5	+11,196	+7,480	+9,070
(6d)	S	R	238	-4,010	-4,020	
			258	+1,948		• 995
(7b)	R	S	224	+7,595	+3,230	
			254.5	-3,574		-3,300
(7b-Me)	R	S	224	+7,000	+4,410	
			254.5	-3,574		-2,830
(6a-NB)	S	S	245	-19,622	-15,340	-16,280

7b, γ -tetrahydrosantoninic acid
ethylene dithioacetal,
7b-Me, methyl ester of **7b**

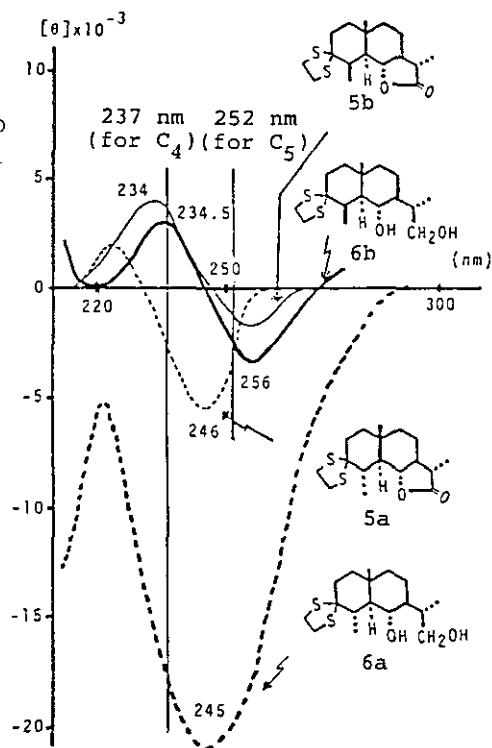


Fig. 1. CD absorption curves of dithioacetals with γ -lactone (**5a** and **5b**) and without γ -lactone (**6a** and **6b**)

It is obvious that the signs of CD absorption of dithioacetal at 237 and 252 nm were related to the absolute configurations at C-4 and C-5. Because, first, the EDT of racemic 4,10-dimethyldecal-3-one itself showed no CD absorption in the region 220-260 nm. Second, the rectus configuration (R) was related to the plus sign (+) and the sinister (S) to the minus sign (-) in the CD curves. For example, the (+)-sign data [amplitude (θ) at 237 nm] for [**5b** (+3,500), **5c** (+6,320), **6b**

(+7,480), **7b** (+3,230) and the methyl ester of **7b** (+4,410)] corresponded well to the R configuration at C-4 adjacent to EDT without exception.

The (-)-sign data for [**5a** (-2,920), **5d** (-2,450), **6a** (-18,220), **6d** (-4,020) and the p-nitrobenzoate of **6a** (-15,340)] also correlated with the S configuration at C-4. Furthermore, the R configuration at the C-5 -position detached from EDT corresponded well to the (+)-sign in the data for **5c**, **5d**, **6c** and **6d**, and the S configuration at C-5 was related to the (-)-sign in data for **5a**, **5b**, **6a**, **6b**, **7b**, the methyl ester of **7b** and p-nitrobenzoate of **6a** without exception at 252 nm in CD (Table 3). The strong peak near 245 nm was considered to be an additive peak in the compounds having the same absolute configurations at both C-4 and C-5 (Fig.1). The forgoing empirical rule in the Cotton effect of the CD spectrum for THS-EDT derivatives is a new finding in the chiroptical studies including the determination of the absolute configuration in the detached β -position. This rule also can be used for stereochemical problems of natural products in both structure elucidation and synthetic work. For example, when CD data in EDT derivatives of steroid ketones are classified along this empirical rule, most of the (+ or -)-signs in the derivatives of cholestenones and androstanones^{5,6} are correlated well with the absolute configuration (R and S) of asymmetric carbon adjacent to α - and detached β -positions relative to the EDT in the A and D rings of the steroids. The theoretical assignment of this electronic excitation for CD and UV by using the ligand field theory and the molecular orbital calculations (CNDO-2) including d-orbital participation of divalent sulfur atoms will be published in the following paper.

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The acknowledgements given in the preceding paper apply to this paper.
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