1,3-*PERI*-REPULSION; A NEW SYNTHETIC CONTROL FACTOR FOR METHYL EPIMERS BY OPENING OR CLOSING γ-LACTONE AND ITS FIXATION BY DITHIOACETAL[1]

Tetsuichi Shibata,* Tamiko Ohkura, Nobuko Shimizu, and Seiichi Inayama
Pharmaceutical Institute, School of Medicine, Keio University
35 Shinanomachi, Shinjuku-ku, Tokyo 160, Japan

Abstract—The inversion of methyl adjacent to ketone from equatorial to axial was achieved by virture of 1,3-*peri*-repulsion of the hydroxyl group formed by opening γ-lacone in a series of tetrahydro-ℓ-α-santonin and their derivatives, and was confirmed chemically by fixation of the adjacent ketone by ethylene dithioacetal without epimerization of the methyl group.

Although the 1,3-diaxial effect has been well documented,[2] the peri effect, one of the 1,3-interactions between peri substituents in a bicyclic system, has seldom been discussed.[2] On the other hand, the stereochemistry of γ-tetrahydro-ℓ-α-santonic acid (γ-THSA) was studied by Cocker and McMurry,[3] and Barton and coworkers,[4] as well as Yanagita[5] and Ogura,[6] but the configurations of the 4-methyl and 7-(1-carboxyethyl) groups in γ-THSA in solution are still uncertain owing to the conformational change. Dukes and Lythgoe[7] reported without their comment that the ratio of the methyl epimers (α/β) in 3-methyl-4-ketocyclohexane-1,2-dicarboxylic acid was changed from high (3/2) to low (1/3) during thioacetalization procecess of the carbonyl. For clarifying the above ambiguity, dithioacetal[8] should be useful tools as functional groups not only to fix the configuration at C-4 owing to the high reactivity of the sulfhydryl group with carbonyl, but also to compare the 1,3-peri effect with the diaxial effect in the series of both trans- and cis-decal-3-ones, such as (5S)- and (5R)-tetrahydro-ℓ-α-santonins (THS), respectively. There have been few reports concerning the synthetic application of the 1,3-peri effect in an alicyclic system.

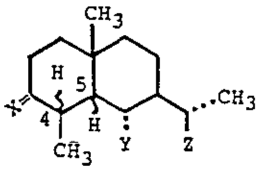
This paper is concerned with the thermodynamic and exclusive epimerization of equatorial methyl to axial one adjacent to the carbonyl group (ketonic methyl) in a series of 6-hydroxy-4-methyldecal-3-ones, such as tetrahydro-ℓ-α-santonins (THS) and their derivatives. And this epimerization can be attributed to the peri effect of the hydroxyl group formed by opening γ-lactone with alkali, followed by kinetic fixation of the ketonic methyl by ethylene dithioacetalization at below -10°C without epimerization.

The structures of the compounds in this series were identified mainly by the mixed melting point method with authentic samples for known compounds. And new compounds were determined by elemental analyses, IR and NMR spectral data, after quantitative fixation of axial methyls at C-4 by dithioacetalization, followed by reductive desulfurization with Raney nickel or by oxidation with chromic acid to give γ-lact-

one, as shown in Scheme 1.

For preserving the asymmetric carbon adjacent to the carbonyl, dithioacetalization of the carbonyl at C-3, followed by desulfulization was used. (4R,5S)-THS (**1b**)[9] with axial methyl at C-4 was chosen as a model compound in order to find the optimum conditions for its ethylene dithioacetal (EDT) derivative (**4b**; mp 172-173° C:84%).[10] The reaction was performed at below -10°C to prevent epimerization of the C-4 methyl.

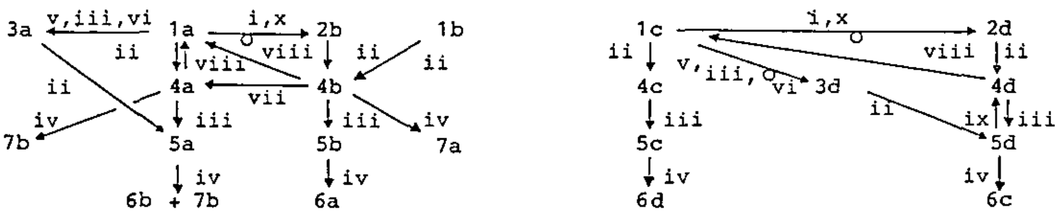
Table 1. Absolute configurations at C-4 and C-5 in 4,10-dimethyl-decal-3-one derivatives with or without γ-lactone



Compds	Substituents X	Y	Z	Absolute configs at C_4 and C_5 (sub-groups)
1	=O	-O-CO-		
2	=O	-OH	-COOMe	a: 4S 5S
3	=O	-OH	$-CH_2OH$	b: 4R 5S
4	{S S}	-O-CO-		c: 4R 5R
5	{S S}	-OH	$-CH_2OH$	d: 4S 5R
6	$=H_2$	-OH	$-CH_2OH$	
7	$=H_2$	-OCO-		

While the conversion of **1b** into **4b** by boron trifluoride etherate ($BF_3.OEt_2$) and ethanedithiol ($(CH_2SH)_2$) in dry diethyl ether[11] proceeded without epimerization of the axial methyl at C-4, the axial methyl in **4b** was epimerized in the addition of acetic acid to equatorial to give **4a** (mp 191-192°C) in a yield of 92%, which was also prepared from **1a** in the same manner with acetic acid (yield: 95.2%).

trans A/B series (sinister at C-5) **cis A/B series** (rectus at C-5)



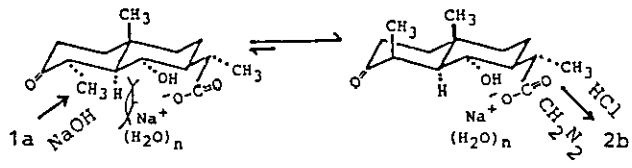
[4S,5S] [4R,5S] [4R,5R] [4S,5R]

Reagents: i) OH^-(NaOH) ii) $(CH_2SH)_2/BF_3.OEt_2$ iii) $LiAlH_4$ iv) Ni(W-1)/dioxane v) $(CH_2OH)_2$/p-TsOH/C_6H_6 vi) $H^+(H_2SO_4)$ vii) $(CH_2SH)_2/BF_3.OEt_2$/AcOH viii) $HgCl_2-CdCO_3$ ix) CrO_3-Py x) $CH_2N_2/MeOH/H_2O$

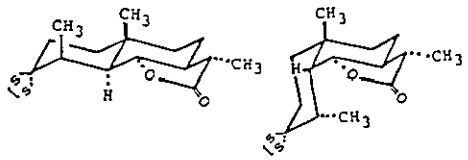
Scheme 1. Correlation of absolute configurations of 4-methyl in the series of (5S)- and (5R)-4,10-dimethyldecal-3-one derivatives

Also, **1a** was obtained from both **4a** and **4b** in good yield by treatment with mercuric chloride and cadmium carbonate. **4a** and **4b** were desulfurized with Raney nickel (W-1) to give (4R,5S)-3-desoxy-THS (**7b**; mp 151-152°C:97.1%)[12] and (4S,5S)-desoxy-THS (**7a**; 155-156°C: 97%),[6] respectively, whose structures were identified with the authentic

samples.[10] Since the rate of dithioacetalization of carbonyl at C-3 is faster than that of epimerization of the 4-ax-methyl in **1b** under the above conditions (at below -10°C and without addition of acetic acid), this thioacetalization conditions should provide a new tool to solve the problem of the structure of γ-THSA.[3-6]
The hypothesis that the 1,3-peri repulsion between the hydroxyl group at C-6 and the methyl at C-4 is effected by the 2-substituted propionic acid or hydroxypropyl groups at C-7, was confirmed as follows. Two series of 7-substituted 6-hydroxy-4-methyldecal-3-one ethylene dithioacetals were prepared from THSs by opening their γ-lactone ring. Treatment of (4S,5S)-THS (**1a**)[13] with sodium hydroxide solution gave a hitherto unknown hydroxy acid as colorless crystals, which reacted with diazomethane in methanol containing a trace of water to yield the methyl ester (mp 106-106.5° C). The ester was stirred with $(CH_2SH)_2$ and $BF_3.Et_2$ at below -10°C to yield an EDT as colorless leaflets (mp 172-173°C: quantitative), which was not **4a** but **4b** derived from **1b** as mentioned bove. Therefore, the starting ester was confirmed not to be **2a** but **2b** owing to the epimerizing 4-methyl as shown in Scheme 1 and Scheme 2 including a plausible reaction course.
On the other hand, (4R,5R)-THS (**1c**) possessing cis A/B ring fusion (5R-series) was derived to the methyl ester of γ-THSA, which was then treated under the same conditions as described above to give EDT derivatives (i.e. hydrolysis of **1c** with alkali, methylation and dithioacetalization). The resulting EDT was not identical with **4c** (4R,5R-configuration) but identical with **4d** (4S,5R-configuration), the epimer of **4b** (4R,5S-configuration) (Scheme 3). Thus, the methyl ester of γ-THSA correlated with the dithioacetal (**4d**) can be represented with **2d** (Table 1).



Scheme 2. A Plausible steric course from eq- to ax-methyl at C-4 caused by steric peri repulsion to hydroxy group at C-6



Scheme 3. The stereostrctures of **4b** and **4d**

Furthermore, **2d** and **4d** are the first compounds in the 4th series of 4S,5R-THS, which have so far not been isolated. The hydroxypropyl group at C-7 in the A/B trans series did not effect the hydroxy group at C-6 which is usually responsible for 1,3-peri repulsion. Thus, 6,12-diol (**3a**),[6a,14] derived from **1a** in the trans A/B series by reductive cleavage of the γ-lactone with $LiAlH_4$, was transformed to its EDT. This EDT was identical with **5a** but not with **5b** derived from **1b** via **4b** as shown in Scheme 1. Therefore, there is no inversion at C-4 in the course of the transformation of **1a** to **3a** with hydroxypropyl group, despite of the hydroxyl group existing at C-6, in trans A/B series.

A 6,12-diol in the cis series, regarded to be **3c** but of unknown configuration at C-4 was derived from **1c** with $LiAlH_4$, followed by treatment with $(CH_2SH)_2$ and $BF_3.OEt_2$ to give its EDT. As this was identical with **5d** but not with **5c** derived, the 6,12-diol was found to be **3d**, as shown Scheme 1. In order to correlate these conversions with those of known compounds, the EDT derivative of 6,12-diol, **5d**, was oxidized with chromic acid to derive a γ-lactone (**4d**). The dithioacetal group of **4d** was removed by mercuric chloride to give **1c**.

These results led us to the following conclusion: 1) The 4-methyls are fixed by the EDT group at the 3-ketones without epimerization. 2) The methyls at C-4 in the trans A/B, (5S)-series, were sterically more effected by 1,3-peri repulsion of hydroxyl groups at C-6 rather than 1,3-diaxial effect of methyl at C-10, when C-7 substituent was 1-carboxyethyl group. 3) The peri repulsion was superior to the diaxial effect in the cis A/B, (5R)-series, regardless of the substituent at C-7. 4) Furtherore, the 1,3-peri repulsion is also controlled by the reversible reaction between γ-lacotne and hydroxy acid by using alkli or acid. (This may suggest to be a means of controlling system in biological synthesis).

A further consideration would be necessary for the conformational change in the cis series of 4-methyldecal-3-ones, because the steroid-nonsteroid equilibrium may occur together with the configurational change. This conformational problem will be reported in the following paper of this series.

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