BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 2588—2591 (1970)

Stereochemical Studies of Monoterpene Compounds. VIII.[1] The Stereochemistry of Dihydro-β-campholenolactone and 1,2-Campholide[2]

Toshifumi HIRATA, Takayuki SUGA[3] and Tamon MATSUURA

Department of Chemistry, Faculty of Science, Hiroshima University, Hiroshima

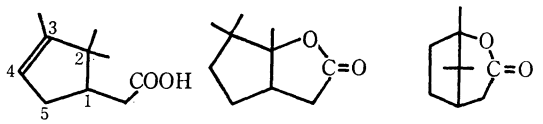
(Received February 25, 1970)

The stereochemistry of (+)-dihydro-β-campholenolactone (II) and (−)-1,2-campholide (III) was clarified to be IIa and IVc, respectively, by a combination of nuclear magnetic resonance, optical rotatory dispersion and circular dichroism measurements.

The reaction of α-campholenic acid (I) with sulfuric acid has been reported[4] to produce only dihydro-β-campholenolactone (II). However, no report has been given on that with organic acid. The stereochemistry of lactone II has been only presumed[5] by considering the reaction of pinonic acid with sulfuric acid. While the peracetic acid oxidation of camphor[5] has been reported to produce 1,2-campholide (III), its stereochemistry has not been reported yet. Our recent study of the stereochemistry and rearrangement of 2-hydroxypinocamphone necessitated our working on the reaction of α-campholenic acid (I) with anhydrous oxalic acid, and the stereochemistry of (+)-dihydro-β-campholenolactone (II) and (−)-1,2-campholide (III) produced.[6-8] The present paper deals with the stereochemistry of these lactones.

Results and Discussion

A mixture of (+)-α-campholenic acid (I) and anhydrous oxalic acid suspended in acetone was refluxed for 6 hr. The reaction gave not only



I II III

1) Paper VII of this series: T. Shishibori, T. Suga, S. Watanabe and T. Matsuura, This Bulletin, **42**, 3284 (1969).

2) Presented at the 20th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1967.

3) To whom all inquiries should be addressed.

4) R. R. Sauers, *J. Amer. Chem. Soc.*, **81**, 925 (1959).

5) M. Harispe and D. Mea, *Bull. Soc. Chim. Fr.*, **1962**, 1340.

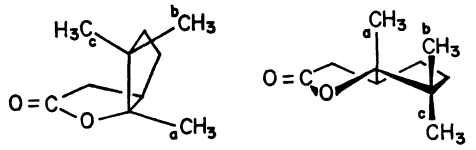
6) T. Suga, K. Mori and T. Matsuura, *J. Org. Chem.*, **30**, 669 (1965).

7) T. Suga, T. Shishibori, T. Hirata and T. Matsuura, This Bulletin, **41**, 1180 (1968).

8) R. G. Carlson, J. K. Pierce, T. Suga, T. Hirata, T. Shishibori and T. Matsuura, *Tetrahedron Lett.*, **1968**, 5941.

(+)-dihydro-β-campholenolactone (II) but also (−)-1,2-campholide (III) in 74% and 25% yield, respectively, in contrast to the reaction with mineral acid.[4] Lactones II and III were identified by a combination of infrared and nuclear magnetic resonance spectra measurements and the conversion to 1-(2-hydroxyethyl)-2,3,3-trimethyl-2-cyclopentanol and 1-(2-hydroxyethyl)-2,2,3-trimethyl-3-cyclopentanol respectively.

The Stereochemistry of (+)-Dihydro-β-campholenolactone (II). The spatial arrangement of the lactone ring of II was decided by the solvent effect of NMR spectra with benzene and pyridine. A reference plane was imagined through the carbonyl carbon atom at right angles to the carbon-oxygen bond of the carbonyl group as an aid in predicting the benzene-induced shift of methyl groups (*cf.* Fig. 1).[9] For the *cis*-form, a large upfield



cis-form *trans*-form

Fig. 1. *cis* and *trans*-Forms of dihydro-β-campholenolactone (II).

shift by the solvent is predicted to occur equally on the a- and b-methyl signals (*cf.* Fig. 1), and a smaller upfield shift for the c-methyl group. For the a-methyl group of the *trans*-form, a large upfield shift is predicted and a small one for the b- and c-methyl groups. The a-, b- and c-methyl resonances underwent an upfield shift by 0.43, 0.39 and 0.10 ppm, respectively, by changing a solvent from deuteriochloroform to benzene.

In order to predict the pyridine-induced shift, the reference plane was drawn through the α-position to the carbonyl group[10] (*cf.* Fig. 1). For the a- and b-methyl groups of the *cis*-form, a large upfield shift is expected, and a down field shift for the c-methyl group. The a-, b- and c-methyl signals of γ-lactone II exhibited shifts by +0.17, +0.27 and −0.08 ppm, respectively. It was thus found that the spatial arrangement of the lactone ring is *cis*. The stereochemistry of γ-lactone II is therefore assigned as either IIa or its optical antipode (IIb).

The octant and the sector projection diagrams of each conformer are shown in Fig. 2. According to the lactone sector rule,[11] the sign of the Cotton effect is predictable to be positive for IIa and negative for IIb. The ORD and CD curves of (+)-γ-lactone II exhibited the positive Cotton effect as shown in Fig. 3. The stereochemistry of (+)-dihydro-β-campholenolactone (II) was consequently found to be IIa.

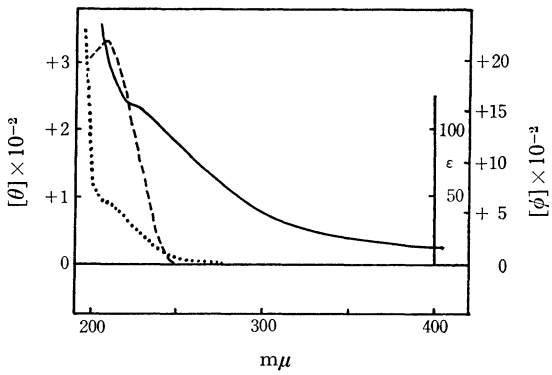


Fig. 3. Optical rotatory dispersion (the full line) and circular dichroism curves (the broken line) and ultraviolet spectrum (the dotted line) of (+)-dihydro-β-campholenolactone (II) in methanol.

The Stereochemistry of (−)-1,2-Campholide (III). Examination of the stereochemical structure of III by a molecular model[12] indicated that it was impossible for the lactone to take the *trans*-form. The stereochemistry of III is consequently

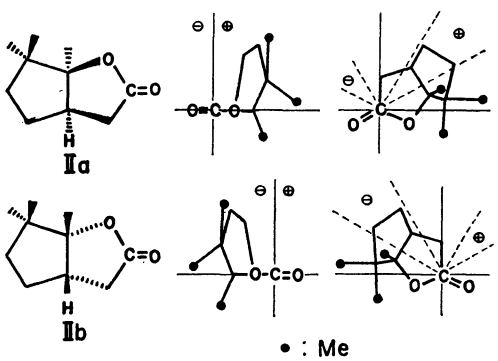
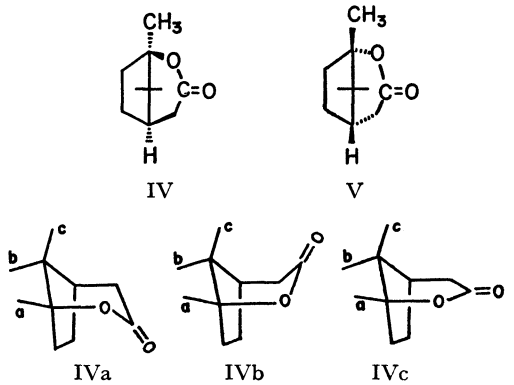


Fig. 2. Octant and sector projections of stereoisomers IIa and IIb.



9) J. D. Connolly, *Chem. & Ind.* (London), **1965**, 2066.
10) D. H. Williams, *Tetrahedron Lett.*, **1965**, 2305.
11) J. P. Jennings, W. Klyne and P. M. Scopes, *J. Chem. Soc.*, **1965**, 7211.
12) Examined by "HGS Molecular Structure Model," Maruzen Co., Tokyo.

assigned as either IV or its optical antipode (V). Conformers IVa, IVb and IVc are considered the possible preferred conformation for IV. Three conformers are also possible for V. A large upfield shift of the NMR spectrum by the solvent effect of benzene is expected equally for the a- and c-methyl groups of conformer IVa, and a smaller one for the b-methyl signal. The a- and b-methyl signals of conformer IVb may exhibit a large upfield shift, and the c-methyl signal a very small one. Three methyl signals of conformer IVc will show larger upfield shifts in the order of the b-, a- and c-methyl groups. The a-, b- and c-methyl signals of campholide III were observed to shift upfield by 0.37, 0.31 and 0.52 ppm, respectively.

Pyridine may induce the large upfield shift on a-, b- and c-methyl signals of IVa. On the other hand, a- and b-methyl groups of IVb may be shifted to a large upfield, and the c-methyl group to a down field shift. The a- and b-methyl signals of IVc may exhibit a large upfield shift, and the c-methyl signal a small one. The experimental data were +0.29, +0.13 and +0.08 ppm for a-, b- and c-methyl groups, respectively. The preferred conformation of III was thus found to be either IVc or its optical antipode (Vc).

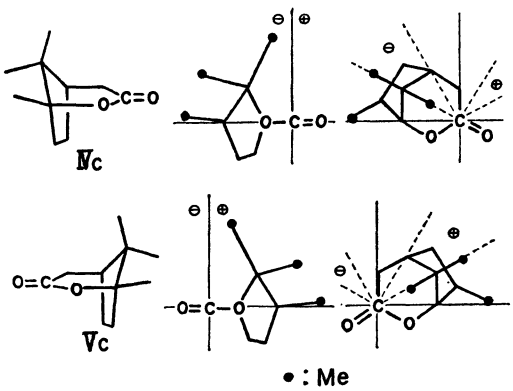


Fig. 4. Octant and sector projections of stereoisomers IVc and Vc.

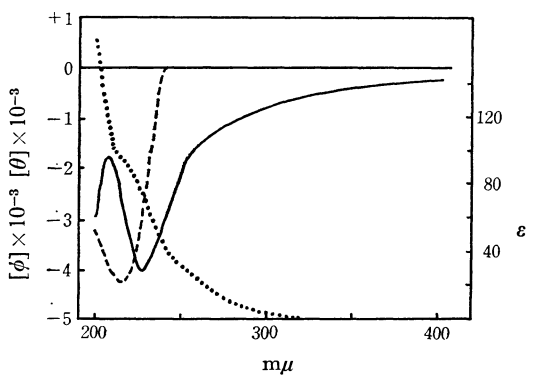


Fig. 5. Optical rotatory dispersion (the full line) and circular dichroism curves (the broken line) and ultraviolet spectrum (the dotted line) of (−)-1,2-campholide (III) in methanol.

The octant and the sector projection diagrams for IVc and Vc are shown in Fig. 4. According to the lactone sector rule,[11] a negative Cotton effect was predicted for IVc, and a positive one for Vc. The ORD and CD curves of (−)-1,2-campholide (III) showed a negative Cotton effect (Fig. 5). The stereochemical structure of III was thus concluded to be IVc.

The mechanism of the lactonization of α-campholenic acid (I) by anhydrous oxalic acid will be discussed in the near future.

Experimental

The NMR spectra were recorded with a Varian Associates A-60 spectrometer using tetramethylsilane as an internal standard. The ORD curves were obtained at 25°C with a Japan Spectroscopic Co. Ltd. automatically recording spectropolarimeter, Model ORD/UV-5, using the normally programmed slit width, and a cell 1 mm long. A monochromator and a cell compartment of the spectropolarimeter were kept in an atmosphere of dry nitrogen. The CD curves were also obtained by the same spectropolarimeter equipped with a circular dichroism attachment. Microanalyses were performed at the Microanalytical Center in the Faculty of Pharmacy of Kyoto University.

(+)-α-Campholenic Acid (I). A mixture of 25 g of (+)-10-camphorsulfonic acid, mp 192°C, $[\alpha]_D^{20}$ +37.5° (*c* 10.2, ethanol) and 25 g of potassium hydroxide was fused for 30 min in an iron crucible with stirring. After cooling, the mixture was dissolved in 200 m*l* of water. After the reaction mixture was washed with ether, then with dichloromethane, the mixture was acidified with 6N-hydrochloric acid solution and then extracted with ether. The usual treatment of the ether extract afforded 9.5 g of crude acid. The crude acid was rectified by distillation under reduced pressure to yield 6.6 g of pure (+)-α-campholenic acid (I): bp 138°C/8 mmHg (lit,[5] bp 95.5—97.5°C/0.54—0.65 mmHg), n_D^{25} 1.4675 (lit,[5] n_D^{25} 1.4695), d_4^{25} 0.9922, $[\alpha]_D^{25}$ +7.21° (*c* 10.1, ethanol).

(+)-Dihydro-β-campholenolactone (II) and (−)-1,2-Campholide (III). A mixture of 35 g of (+)-α-campholenic acid (I) and 140 g of anhydrous oxalic acid suspended in 112 m*l* of acetone was heated under reflux for 6 hr with stirring. After removal of acetone under reduced pressure, the reaction miture dissolved in water was extracted with ether to obtain 21.8 g of a reaction product. The product was subjected to column chromatography on silica gel with a mixture of ethyl acetate and *n*-hexane to separate into two kinds of lactone. The initial eluate gave 15.6 g of (+)-β-lactone II and the second eluate 5.9 g of (−)-δ-lactone III. The lactones were identified by a combination of physicochemical measurements and chemical treatment as follows.

(+)-Dihydro-β-campholenolactone (II) (15.6 g) was obtained from the initial eluate and showed following properties: mp 30—31°C (lit,[5] mp 32°C); $[\alpha]_D^{25}$ +49.9° (*c* 10.0, ethanol); $\nu_{C=O}$ 1774 cm^{-1} (lit,[4] 1786 cm^{-1}); $\lambda_{shoulder}^{MeOH}$ 210 mμ (ε 44.6); ORD (*c* 2.64, methanol),

$[\phi]_{400}$ +272, $[\phi]_{225}$ +1550, $[\phi]_{210}$ +2000; CD (*c* 2.64, methanol), $[\theta]_{250}$ 0, $[\theta]_{210}$ +328, $[\theta]_{200}$ +300.

Found: C, 71.45; H, 9.70%. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%.

The methyl proton signals of the NMR spectra appeared at δ 0.90 (a-CH_3), 1.29 (b-CH_3) and 1.08 ppm (c-CH_3) in 10% deuteriochloroform solution and δ 0.53 (a-CH_3), 0.90 (b-CH_3) and 0.98 ppm (c-CH_3) in 10% benzene solution and δ 0.73 (a-CH_3), 1.02 (b-CH_3) and 1.16 ppm (c-CH_3) in 10% pyridine solution.

The reduction of 0.30 g of γ-lactone II with 0.3 g of lithium aluminum hydride in 50 m*l* of dry ether gave 0.24 g of 1-(2-hydroxyethyl)-2,3,3-trimethyl-2-cyclopentanol: mp and mixed mp 147—148°C (lit,[5] mp 147°C); $[\alpha]_D^{25}$ +38.9° (*c* 1.49, ethanol) (lit,[5] $[\alpha]_D^{25}$ +15±2° (*c* 2, alcohol); $\nu_{OH(free)}^{CCl_4}$ 3626 cm^{-1}, $\nu_{OH(bonded)}^{CCl_4}$ 3462 cm^{-1}.

Found: C, 69.86; H, 11.93%. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70%.

(−)-1,2-Campholide (III) (5.9 g) was obtained from the second eluate and showed the following properties: mp 162—163°C (lit,[4] 168.5—171.5°C); $[\alpha]_D^{25}$ −43.0° (*c* 3.0, ethanol) (lit,[4] $[\alpha]_D^{25}$ −37°); $\nu_{C=O}$ 1729 cm^{-1} (lit,[4] 1745 cm^{-1}); $\lambda_{shoulder}^{MeOH}$ 215 mμ (ε 95.4); ORD (*c* 1.62, methanol), $[\phi]_{400}$ −250, $[\phi]_{227}$ −4010, $[\phi]_{208}$ −1770, $[\phi]_{200}$ −2970; CD (*c* 1.62, methanol), $[\theta]_{242}$ 0, $[\theta]_{215}$ −4270, $[\theta]_{200}$ −3200.

Found: C, 71.41; H, 9.73%. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%.

The methyl proton signals of the NMR spectra appeared at δ 1.07 (a-CH_3), 1.29 (b-CH_3) and 1.00 ppm (c-CH_3) in 5% deuteriochloroform solution and δ 0.70 (a-CH_3), 0.98 (b-CH_3) and 0.48 ppm (c-CH_3) in 5% benzene solution and δ 0.78 (a-CH_3), 1.16 (b-CH_3) and 0.91 ppm (c-CH_3) in 5% pyridine solution.

Reduction of 0.20 g of lactone III with 0.20 g of lithium aluminum hydride in 100 m*l* of dry ether afforded 0.09 g of 1-(2-hydroxyethyl)-2,2,3-trimethyl-3-cyclopentanol: mp and mixed mp 93—94°C (lit,[4] 91—93°C); $[\alpha]_D^{25}$ +72.4° (*c* 1.85, ethanol); $\nu_{OH(free)}^{CCl_4}$ 3624 cm^{-1}.

Found: C, 70.00; H, 11.76%. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70%.

The authors wish to express their thanks to Dr. Marcelle Harispe of College of Paris for a gift of 1-(2-hydroxyethyl)-2,3,3-trimethyl-2-cyclopentanol, to Dr. J. D. Connolly of the Glasgow University for a gift of 1-(2-hydroxyethyl)-2,2,3-trimethyl-3-cyclopentanol, and Dr. Shô Itô of Tohoku University for measuring the NMR spectra.