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The Absolute Configuration of Isopropylidenecamphor Oxide

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The conversion of (+)-isopropylidenecamphor derived from (+)-camphor into (1R:2S:4S)-isopropylideneborneol and (1R:2R:4S)-isopropylideneisoborneol was described. In light of this configurational correlation, it was concluded that (+)-isopropylidenecamphor oxide derived from isopropylideneborneol has (1R:3R:4S)-, and (−)-isopropylidenecamphor oxide derived from isopropylideneisoborneol, (1R:3S:4S)-configurations.

Djerassi and coworkers[1] have shown that the reversed octant rule is applicable to the Cotton effect at n-π^* transition of transoid cyclopropyl- and epoxy-ketones. To date, however, the optical rotatory dispersion curves of cisoid epoxy-ketones have been reported only with scanty examples and it has not yet been known whether or not the reversed octant rule is applicable to cisoid epoxy-ketones. With a view to formulating the relationship between the Cotton effect and the absolute configuration of cisoid epoxy-ketones, the author has recently reported the assignment of absolute configuration of *trans*- and *cis*-pulegone oxides,[2] *trans*- and *cis*-pinocarvone oxides[3] and discussed the ORD data obtained with these epoxides.

We wish, to describe the determination of absolute configurations of *trans*- and *cis*-isopropylidenecamphor oxides and to report the ORD and CD spectra thereof.

(+)-α-Bromocamphor (**2**), obtained by the bromination of (+)-camphor in the presence of anhydrous aluminum chloride, was grignardized and condensed with acetone in tetrahydrofuran to give a mixture of (+)-camphor (**1**), (+)-α-bromocamphor (**2**), 3-α-hydroxyisopropylcamphor (**3**) and (+)-isopropylidenecamphor (**4**) in the ratio of 44 : 16 : 16 : 24 as determined by VPC analysis. (+)-Isopropylidenecamphor (**4**) was obtained pure from the mixture and was then oxidized with 30% hydrogen peroxide in methanolic 30% sodium hydroxide solution to afford a mixture of *trans*- and *cis*-isopropylidenecamphor oxides. Separation of the mixed isomers was achieved by preparative VPC which afforded chemically pure (+)-**5** (oily) and (−)-**6** (mp 42°C) in an isomer ratio of 33:67.

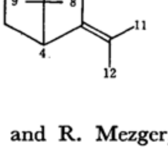
(+)-Isopropylidenecamphor (**4**) was reduced with lithium aluminum hydride to yield the corresponding alcohol mixture consisting of the crystalline **7** (mp 88°C) in 9 parts and the liquid diastereomeric alcohol **8** in 91 parts.

Beckmann[4] reported that the lithium aluminum hydride reduction of camphor gave isoborneol (exo alcohol) which resulted from the attack of the hydride reagent to the less hindered side of camphor, *i. e.* opposite the geminal dimethyl group. Accordingly, judging from the product ratio found for the present reduction, it may be deduced that the major product **8** is (1R:2R:4S)-isopropylideneisoborneol and the minor diastereomer **7** is (1R:2S:4S)-isopropylideneborneol.

This assignment is supported also by the NMR analysis[5] of these diastereomeric alcohols **7** and **8**. The Δ value, 17.4 Hz, found for chemical shift of C-8 methyl group in **8** reasonably supported the *cis*-configuration of hydroxyl group relative to the methyl group. (See Table 1)

TABLE 1. CHEMICAL SHIFT (τ) OF METHYL GROUP

	7 (endo)			8 (exo)		
	H-8	H-9	H-10	H-8	H-9	H-10
$CDCl_3$ soln	9.12	9.23	9.00	9.02	9.17	9.05
Pyridine soln	9.10	9.15	8.97	8.73	9.12	8.90
Δ Value (c/sec)	1.2	4.8	1.8	17.4	3.0	9.0



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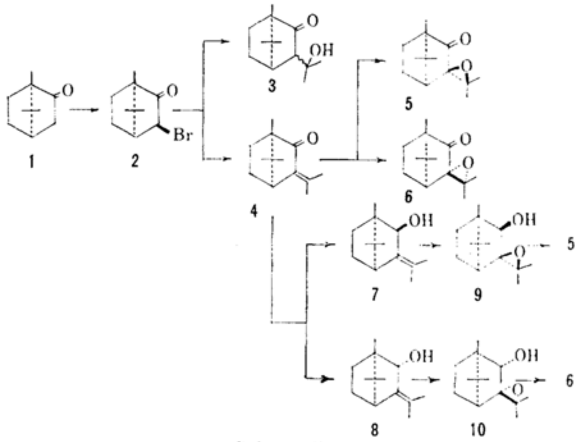
[1] C. Djerassi, W. Klyne, T. Norin, G. Ohloff and E. Klein, *Tetrahedron*, **21**, 163 (1965).

[2] J. Katsuhara, *J. Org. Chem.*, **32**, 797 (1967).

[3] J. Katsuhara, This Bulletin, **41**, 2700 (1968).

[4] C. Beckmann and R. Mezger, *Chem. Ber.*, **89**, 2738 (1956).

[5] K. Tori and K. Aono, *Annual Report of Shionogi Research Laboratory*, **14**, 136 (1964).

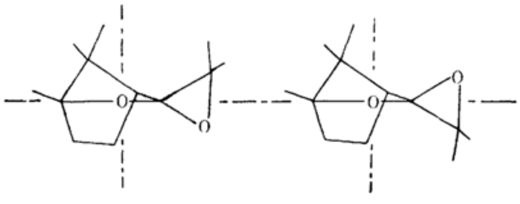


Scheme I.

Epoxidation with perbenzoic acid of **7** and **8** in chloroform afforded the β-epoxide (**9**)[6] of the (1R:2R:3R:4S)-configuration and the α-epoxide (**10**) having the (1R:2S:3S:4S)-configuration, respectively. These diastereomeric epoxides **9** and **10** were then oxidized with chromic acid in acetone, when (+)-*cis*-(1R:3R:4S)-isopropylidenecamphor oxide (**5**) was obtained from **9** and (−)-*trans*-(1R:3S:4S)-isopropylidenecamphor oxide (**6**) from **10**, the absolute configurations naturally having followed from the respective parent compounds. Compounds **5** and **6**, which were derived *via* an alternative route of transformation from the same parent ketone (**4**), were identified by means of IR- and VPC-comparison with (+)-*cis*-**5** and (−)-*trans*-**6** (See Scheme 1.).

Based on the ORD-studies of various bicyclo[2.2.1]heptanone systems, Klyne[7] suggested that the octant rule is applicable to bicycloheptanone systems and accounted for the contribution of substituents to the overall ORD of the systems. For example, the ORD contributions of C-8 ,C-9 and C-10 in camphor was estimated as $a=+96$, by comparing the molar amplitude (+71) found for camphor[8] with that (−25) for camphenilone.

When this empirical generalization is applied to the systems **5** and **6**, whose octant projection diagrams are shown in Scheme II, the contribution of oxirane ring to the overall ORD of the respective diastereomeric isopropylidenecamphor oxides may be calculated in the same way: the β-oxirane group in **5** has a positive contribution (in ORD), $a=72-71=+1$ whereas the α-oxirane in **6** has a negative one, $a=41-71=-30$.



cis-**5** *trans*-**6**

Scheme II.

The magnitude of the amplitude contribution by the substituents in the ORD curve of the present cisoid epoxy-ketone is too small to draw any definite conclusion on the validity of the reversed octant rule being applied to transoid epoxy-ketones in general.

Experimental[9]

Bromination of Camphor (1). Bromine (121 g) was added dropwise with stirring during 2 hr into a mixture of camphor (mp 178°C, $[\alpha]^{25}_{D}$ +44.18° (*c* 0.94, ethanol): 100 g, 0.66 mol) and anhydrous aluminum trichloride in 200 m*l* of dried carbon tetrachloride and the reaction mixture was stirred for further 6 hr at 60°C. After removal of solvent *in vacuo*, the crude product was washed with chilled *n*-hexane to give (+)-α-bromocamphor (**2**), mp 77°C, $[\alpha]^{20}_{D}$ $+136.0\pm0.4°$ (*c* 0.89, ethanol), UV λ^{MeOH}_{max} mμ (ε), 306 (97): CD mμ ([θ]) in methanol, 350 (0), 315 (+5645), 265 (0), 220 (−1392), 212 (0), 205 (+5721), 34% yield.

Preparation of Isopropylidenecamphor (4). α-Bromocamphor (**2**) (35 g, 0.15 mol) in 280 m*l* of tetra-

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[6] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, **1957**, 1958.

[7] W. Klyne, *Tetrahedron*, **13**, 29 (1961).

[8] G. Jacob, G. Ourisson and A. Rassat, *Bull. Soc. Chim. France*, **1959**, 1374.

[9] Infrared spectra were recorded on a Shimadzu Model 27-G spectrophotometer. Optical rotatory dispersion and circular dichroism measurements were made on a Nippon Bunko Spectropolarimeter Model ORD/UV-5. Optical rotation measurements were recorded on a Perkin-Elmer Model 141 with a 10 cm-cell. Gas-liquid partition chromatography analyses were carried out using a Shimadzu 2-C gas chromatograph. A 3 mm×2.25 m column of 20% Hyporose-80 on Celite-545 served for VPC analyses. Nuclear magnetic resonance spectra were recorded with a Varian A-60 spectrometer.

hydrofuran was added to 3.5 g (0.14 g atom) of magnesium in 20 m*l* of THF under a nitrogen atmosphere during 1 hr. After 3 hr stirring, acetone (41 m*l*, 0.64 mol) was added to the reaction mixture and was reacted for 4 hr. The reaction mixture was poured onto ice-water and the organic layer was extracted with ether after ammonium chloride solution was added. Ethereal extracts were combined, washed and dried. Removal of solvent under reduced pressure yielded a crude product (27.9 g, 99%), which was analyzed by VPC. The product consisted of 44% **1**, 16% **2**, 16% 3-α-hydroxyisopropylcamphor (**3**),[10] mp 88°C, Found: C, 74.58; H, 10.61%. Calcd for $C_{13}H_{22}O_2$: C, 74.22; H, 10.56%, and 24% (+)-isopropylidenecamphor (**4**), liquid, $[\alpha]_D^{22}$ $+201.1\pm6.6°$ (*c* 0.36, methanol), UV λ_{max}^{MeOH} mμ (ε), 248 (9110), 332 (70): CD mμ ([θ]) in methanol, 377 (0), 335 (+980), 305 (+1076), 250 (+21573), 210 (0).

Preparation of Mixture of Isopropylidenecamphor Oxides. A mixture of (+)-**4** (5 g, 0.038 mol) in methanol (50 m*l*) and 50 m*l* of 30% hydrogen peroxide in 50 m*l* of water was kept at 60°C, and to this was added dropwise a 30% aqueous solution (50 m*l*) of sodium hydroxide over a 30 min period. Stirring was continued for 7 hr, the temperature being maintained at 60°C. The reaction mixture was poured into 100 m*l* portion of ether, and the organic layer was separated and worked up as usual to give a crude product (4.5 g). The VPC analysis indicated that the crude product contained 33% of **5** and 67% of **6**.

Isolation and Properties of Pure Isopropylidenecamphor Oxides (5) and (6). Isolation of each diastereomer from the mixture was effected by preparative VPC. Further purification of the fraction on a silica gel column gave pure **5**: the IR-spectrum exhibited the following peaks ν_{max} 1760, 1380, 910 cm⁻¹: $[\alpha]_D^{23}$ $+176.3\pm2.4°$ (*c* 0.9, methanol): ORD mμ ([ϕ]) in methanol, 400 (+1300), 333 (+5312), 295 (−1887), 228 (+7316), 210 (−7712): CD mμ ([θ]) in methanol, 350 (0), 316 (+5536), 255 (+184), 215 (+12263), 208 (+9073): UV λ_{max}^{MeOH} mμ (ε), 310 (50), Found: C, 74.37; H, 9.71%. Calcd for $C_{13}H_{20}O_2$: C, 74.94; H, 9.70%, and **6**: the IR-spectrum main bands ν_{max} 1750, 1380, 1015, 960, 930, 920, 830, 770 cm⁻¹; $[\alpha]_D^{23}$ $-21.7\pm0.7°$ (*c* 0.9, methanol): ORD mμ ([ϕ]) in methanol, 400 (+343), 334 (+1532), 298 (−2475), 294 (−2541), 276 (−2312), 226 (−7728), 206 (+8608): CD mμ ([θ]) in methanol, 347 (0), 318.5 (+2477), 265 (0), 213 (−9554), 207 (−6176): UV λ_{max}^{MeOH} mμ (ε), 310 (49), mp 42°C, Found: C, 74.70; H, 9.70%. Calcd for $C_{13}H_{20}O_2$: C, 74.94; H, 9.70%.

Lithium Aluminum Hydride Reduction of Isopropylidenecamphor (4). Isopropylidenecamphor (5 g, 0.038 mol) dissolved in absolute ether (30 m*l*) was added dropwise with stirring to a chilled (−10°C) slurry of lithium aluminum hydride (3 g, 0.079 mol) in ether. Upon completion of addition, the reaction mixture was stirred at 0°C for an additional hr and then at 15—20°C for 10 hr, and finally, refluxed for 2 hr. Excess hydride was then decomposed by addition of moistened ether under effective cooling. The organic layer was separated, filtered and dried. Removal of ether gave a mixture of **7** and **8** (yield 4.5 g, 89%). The alcohols **7** and **8** were obtained pure by means of silica gel chromatography: **7**, 9 parts, mp 88°C, Found: C, 80.27; H, 11.39%. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41%, and its NMR spectrum indicated in $CDCl_3$ three three-hydrogen singlets (τ 9.23, 9.12, 9.00) for methyl at C-9, C-8, C-10, a three-hydrogen doublet (τ 8.36, *J*=1.5 Hz) for methyl at C-12, a three-hydrogen singlet (τ 8.25) for methyl at C-11, one-hydrogen doublet (τ 7.69, *J*=4.0 Hz) at C-4, and one-hydrogen singlet (τ 5.77) for the hydrogen on the carbon bearing the hydroxyl group; in pyridine three three-hydrogen singlets (τ 9.15, 9.10, 8.97) for methyl at C-9, C-8, C-10, a three-hydrogen doublet (τ 8.30, *J*=1.5 Hz) for methyl at C-12, a three-hydrogen singlet (τ 8.05) for methyl at C-11, one-hydrogen doublet (τ 7.60, *J*=4.0 Hz) at C-4, and one-hydrogen singlet (τ 5.55) for the hydrogen on the carbon bearing the hydroxyl group; **8**, 91 parts, liquid, $[\alpha]_D^{20}$ $+127.7\pm0.8°$ (*c* 0.4 ethanol), and its NMR spectrum indicated in $CDCl_3$ three three-hydrogen singlets (τ 9.17 9.05, 9.02) for methyl at C-9, C-10, C-8, a three-hydrogen doublet (τ 8.32, *J*=1.0 Hz) for methyl at C-12, a three-hydrogen singlet (τ 8.18) for methyl at C-11, one-hydrogen doublet (τ 7.59, *J*=4.0 Hz) at C-4, and one-hydrogen singlet (τ 6.12) for the hydrogen on the carbon bearing the hydroxyl group; in pyridine three three-hydrogen singlets (τ 9.12, 8.90, 8.73) for methyl at C-9, C-10, C-8, a three-hydrogen doublet (τ 8.27, *J*=1.0 Hz) for methyl at C-12, a three-hydrogen singlet (τ 8.03) for methyl at C-11, one-hydrogen doublet (τ 7.53, *J*=4.0 Hz) at C-4, and one-hydrogen singlet (τ 5.87) for the hydrogen on the carbon bearing the hydroxyl group.

Preparation of *cis*- (5) and *trans*-Isopropylidenecamphor Oxide (6). To an ice-cold solution of perbenzoic acid in chloroform was added 0.26 g of **7** in 5 m*l* of chloroform. The reaction mixture was kept at 0°C for 16 hr. The reaction mixture was then washed with 5% sodium carbonate solution and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure gave an oily residue, which upon purification on an alumina column, afforded the epoxide **9** (0.13 g). A solution of **9** (100 mg) in acetone (1 m*l*) was added to a solution of chromic acid (55 mg) in water (1 m*l*) containing sulfuric acid (0.2 m*l*) with stirring at 0°C for 1 hr. Water (5 m*l*) was added and the reaction mixture was extracted with ether. The combined ether extract was washed with a 3% sodium hydrogencarbonate solution, water, and then dried over anhydrous sodium sulfate. Removal of solvent yielded a crude product (82 mg), which was then purified by silica gel column chromatography to give pure **5**. In exactly the same manner as described above, epoxidation of **8** (0.64 g) with perbenzoic acid furnished an oily epoxide (**10**) (0.42 g), which in turn, was further oxidized with chromic anhydride to give **6** (0.31 g).

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[10] S. M. Malmgren, *Ber.*, **35**, 3910 (1902).