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The Absolute Configuration of Pinocarvone Oxide

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The conversion of (−)-pinocarvone oxide derived from (+)-pinocarvone into (−)-(1R : 2S : 3R : 5R)-*cis*-2-hydroxypinocampheol and the conversion of (+)-pinocarvone oxide in (+)-(1R : 2R : 3R : 5R)-*trans*-2-hydroxyneoisopinocampheol and (−)-(1R : 2R : 3R : 5R)-*cis*-2-hydroxyisopinocampheol are described. With the knowledge of the absolute configurations of these glycols, it was concluded that (−)-pinocarvone oxide and (+)-pinocarvone oxide have the (1R : 2S : 5R)- and (1R : 2R : 5R)-configurations, respectively.

Although Djerassi and coworkers[1] have determined the ORD curve of a mixture of diastereomeric pinocarvone oxides, the separation of the diastereomeric pinocarvone oxides and then ORD curves have not yet been described. It seemed of interest to undertake the isolation of these epoxides and to examine the ORD and CD curves of these compounds, in order to determine the applicability of the Octant Rule to oxirane systems. We wish, at this time, to report the assignment of the absolute configuration of the pinocarvone oxides by means of unequivocal chemical transformations into diols of established configuration.

(+)-*trans*-Pinocarveol (I) was oxidized with chromic acid anhydride pyridine-complex to (+)-(1S : 5R)-pinocarvone (II) which, on the Treibs epoxidation, afforded a mixture of trans-, (III) and *cis*-pinocarvone oxide (IV) in an isomer ratio of 35.5 : 64.5 as indicated by vpc analysis. The mixed isomers were separated by means of preparative vpc followed by silica gel column chromatography, and chemically pure (−)- and (+)-pinocarvone oxides were obtained.

The diastereomeric pinocarvone oxide III gave, upon the lithium aluminum hydride reduction, (−)-2-hydroxypinocampheol (V), whose IR spectrum indicated the presence of *cis*-glycol by the absorption bands of free (3628 cm^{-1}) and bonded hydroxyl (3572 cm^{-1}; $\Delta\nu$ 56 cm^{-1}).

The (+)-diastereomer (IV) was reduced with lithium aluminum hydride to give (+)-*trans*-2-hydroxyneoisopinocampheol (VIII) and (−)-*cis*-2-hydroxyisopinocampheol (IX).

(+)-2-Hydroxypinocamphone (X) derived from (−)-α-pinene, was reduced with lithium aluminum hydride to give the diol (XI). The identity of the diol (VIII) melting at 158° with the diol XI of the same melting point was established by direct comparison of the melting points and the IR spectra. The IR spectrum of the diol XI exhibited an absorption band at 3628 cm^{-1} corresponding to a free hydroxyl group and one 3612 cm^{-1} ($\Delta\nu$ 16 cm^{-1}) of the neighboring two hydroxyl groups. The NMR spectra of XI and of monoacetate of XI also substantiated the structure.

As for the geometry of 2-hydroxypinocamphone, Schmidt[2] concluded that (−)-2-hydroxypinocamphone derived from (+)-α-pinene should be assigned the *cis*-configuration (relative to the carbon-7 bridge carrying geminal dimethyl and 10-methyl group). Accordingly, the (1R : 2R : 3R : 5R)-configuration VIII may be assigned to (+)-2-hydroxyneoisopinocampheol (XI).

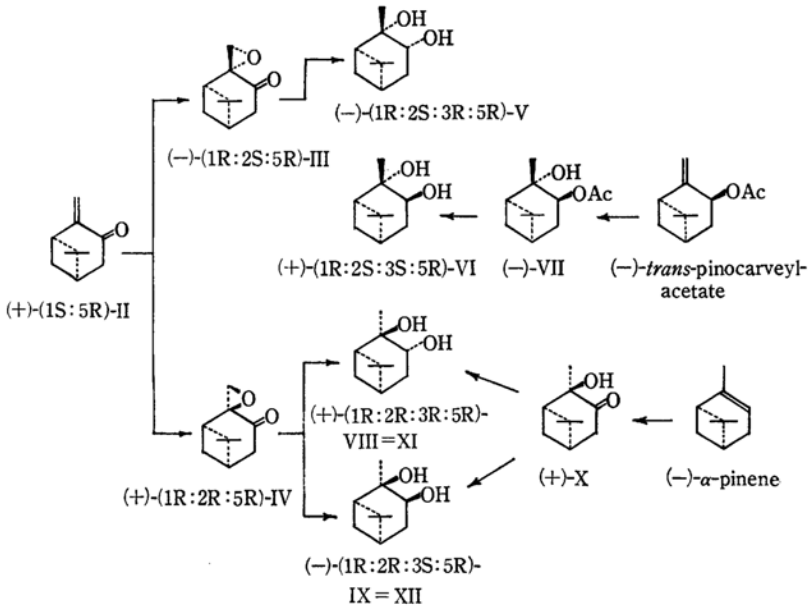
The Meerwein-Ponndorf-Verley reduction of (+)-X gave a diol XII, whose IR spectrum exhibited absorption bands at 3620 cm^{-1} (free hydroxyl) and at 3552 cm^{-1} ($\Delta\nu$ 68 cm^{-1}; bonded hydroxyl), suggesting the *cis*-arrangement of the two hydroxyl groups. It was shown by tlc comparison that the diol XII was identical with the diol IX, and consequently the (1R : 2R : 3S : 5R)-*cis*-structure may be assigned to (−)-*cis*-2-hydroxyisopinocampheol (IX).

For the purpose of comparison, another diastereomeric diol VI was prepared through (−)-pinocarveyl acetate from (+)-*trans*-pinocarveol (I) as follows: Hydroxymercuration[3] of (−)-*trans*-pinocarveyl acetate yielded the corresponding hydroxy acetate VII which on alkaline hydrolysis gave the diol VI. IR spectrum of VI indicated the presence of *trans*-diol by the absorption bands of free (3625 cm^{-1}) and bonded hydroxyl (3610 cm^{-1}; $\Delta\nu$ 15 cm^{-1}). With the knowledge of absolute configuration of the starting (+)-*trans*-pinocarveol, the (1R : 2S : 3S : 5R)-configuration can be assigned for (+)-*trans*-2-hydroxyneopinocampheol (VI).

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

2) H. Schmidt, *Chem. Ber.*, **93**, 2485 (1960).

3) H. C. Brown and W. J. Hammar, *J. Am. Chem. Soc.*, **89**, 1524 (1967).



Scheme 1

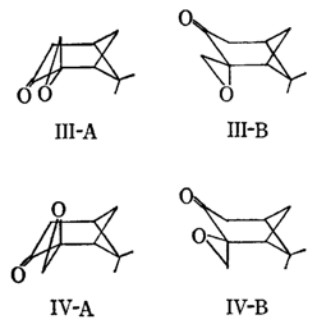
The comparison of IR spectra, R_f values and physical properties proved that neither VI, VIII nor IX was identical with the diastereomeric *cis*-diol V. Since VI, VIII and IX are excluded, it may be concluded that the diol V, the product resulting from the lithium aluminum hydride reduction of (−)-epoxide III, must have the sole remaining configuration, *i. e.*, (1R : 2S : 3R : 5R).

It naturally follows that the parent (−)-pinocarvone oxide (III) from which the levorotatory diol V was derived, should have the *trans*-(1R : 2S : 5R)-configuration.

In the consequence, (+)-pinocarvone oxide (IV), the parent compound of both VIII and IX, is assigned to the *cis*-(1R : 2R : 5R)-configuration. (See Scheme 1).

The ORD and CD curves of the isomeric pinocarvone oxides whose absolute configuration is now clarified seem to permit one to speculate with some certainty on the preferred conformation of these epoxides. The red shift at 323 mμ ($\Delta\nu$=20 mμ) in the CD curve of (−)-III strongly suggests the axial disposition[4] would be expected to assume the III-B conformation rather than the other possibility, III-A, as implicit in Scheme 2. In contrast, however, the isomeric (+)-epoxide IV may reasonably be expected to exist largely in the IV-A conformation with the oxirane oxygen disposed in an axial position as cogently supported by the red shift ($\Delta\nu$=20 mμ) in the observed positive Cotton curve.

If one accepts conformation III-B for (−)-III and conformation IV-A for (+)-IV, one finds,



Scheme 2

with the knowledge of the absolute configurations and the experimentally determined Cotton effects, that the "reversed" Octant Rule is applicable to these oxirane systems, in agreement with the previous deduction.[1]

Experimental[5]

Preparation of Pinocarvone (II). Chromic acid anhydride (65 g) was carefully added to 1 *l* of dried pyridine at 0°. The resulting mixture was added to

4) C. Djerassi, O. Halpern, V. Halpern, O. Schindler and Ch. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958).

5) 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 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.

30.0 g of I,[6] $[\alpha]_D^{22}$ +51.8°±1.0 (*c* 0.94, methanol), optical purity 71%, *trans*-pinocarveyl *p*-nitrobenzoate mp 91°C, in 50 m*l* of pyridine and was kept at room temperature for 18 hr. Water was then added to the mixture and was extracted with benzene - ether (1 : 1) solution. The combined benzene - ether extract was washed with 2 N hydrogen chloride solution, 3% hydrogen sodium carbonate solution and water, and dried over anhydrous sodium sulfate. After removal of solvent *in vacuo*, the crude product (26.0 g, 88% yield) was distilled to yield II[7]; bp 84—86°C/8 mmHg, (14.5 g). The IR spectrum exhibited the following characteristic absorptions (cm^{-1}): 1700s, 1680m, 1620s, 1390m, 1380m, 930s, 920s; λ_{max} 234 mμ (ε 6030) (in ethanol); $[\alpha]_D^{22}$ +48.0°±1.0 (*c* 0.84, methanol), optical purity 70%.

Preparation of Pinocarvone Oxide Mixture. A mixture of 10.0 g of pinocarvone in 65 m*l* of methanol and 22 m*l* of 30% hydrogen peroxide was cooled to −15°C, and a solution of 1.25 g of sodium hydroxide in 6 m*l* of water was added dropwise with stirring over a 15 min period. Stirring was continued for 4 hr, the temperature being maintained at 20—25°C. The reaction mixture was poured into 100 m*l* portions of ethyl ether. After the combined ether extract was washed and dried, the solvent was removed under reduced pressure and the residue was analyzed by vpc. The crude product, 8.0 g (yield 75%), consisted of 35.5%, III and 64.5%, IV.

Isolation and Properties of Pure Pinocarvone Oxides III and IV. Isolation of the pure diastereomer was effected by preparative vpc, of the fraction of distillation through a 30 cm concentric column, boiling at 98°C/5 mmHg. Further purification of the fraction on silica gel column chromatography gave III: the IR spectrum showed the following peaks (cm^{-1}): 1720s, 1390m, 1370m, 1275m, 1250m, 940w, 890m, 870m, 840m, 785m; $[\alpha]_D^{29}$ −22°±5 (*c* 0.10, dioxane); ORD mμ ([ϕ] in dioxane): 400 (−154), 340 (−789), 328sh(−369), 316sh(+478), 307(+921), 303 (+856), 300(+895), 265(−1000), 228(−3268): CD mμ ([θ] in dioxane): 333 (−668), 322.5 (−985), 313 (−788), 302 (−255); IV, IR spectra main bands (cm^{-1}): 1725s, 1385m, 1370m, 1275m, 1260m, 940m, 900m, 885m, 840m, 820m, 800m, $[\alpha]_D^{29}$ +74°±7 (*c* 0.27, dioxane): ORD mμ ([ϕ] in dioxane): 400 (+493), 340 (+2051), 332.5 (+1417), 327 (+1807), 318.5 (+390), 314 (+629), 306 (−383), 302.5 (−171), 297 (−500), 291.5 (−276), 290 (−293), 224 (+6829), 210 (−850); CD mμ ([θ] in dioxane): 336 (+967), 323 (+1781), 311 (+1628), 302 (+1018), 292 (+545), 275 (+143), 252 (+50).

Lithium Aluminum Hydride Reduction of (−)-Pinocarvone Oxide (III). The oxide III (37.0 mg) dissolved in 3 m*l* of absolute ether was added dropwise with stirring to a chilled (−10°C) slurry of 100 mg of lithium aluminum hydride in 3 m*l* of absolute ether. Upon completion of addition, the solution was stirred at 0°C for an additional hour, stirring was continued at room temperature (15—20°C) for 10 hr and finally, the reaction mixture was refluxed on water bath and cooled. Excess hydride was decomposed by addition of the ether saturated with water under cooling, and the organic layer was separated, filtered and dried. Removal of the solvent gave the diol V, $[\alpha]_D^{22}$ −17.6±1.4 (*c* 0.40, methanol), and its NMR spectrum indicated a three hydrogens singlet (τ 8.94) for methyl, a six hydrogens singlet (τ 8.78) for the geminal dimethyl, and one hydrogen AB quartet (τ_A 6.22; τ_B 6.06, J=7 Hz) for the hydrogen on the carbon bearing the hydroxyl group.

Lithium Aluminum Hydride Reduction of (+)-Pinocarvone Oxide (IV). The oxide IV (60.4 mg) was reduced with lithium aluminum hydride (100 mg) in 5 m*l* of absolute ether, in the same way as mentioned above, to give a mixture of VIII and IV, yield 54.6 mg (yield 88%). Diols VIII and IX were separated by means of silica gel column chromatography: VIII, mp 158°C, $[\alpha]_D^{22}$ −42.5°±1.0 (*c* 0.57, methanol) and oily crude (−)-IX.

Preparation of Hydroxypinocamphone (X).[2] To a solution of 28 g of (−)-α-pinene ($[\alpha]_D^{29}$ −26.8° ±1.0, *c* 0.67, methanol, optical purity 52%) in 250 m*l* of 90% acetone was added 56 g of potassium permanganate with stirring at 0—5°C for 8 hr. The manganese dioxide was filtered off, and the acetone was removed under reduced pressure to afford a crude product 20 g (58%) of (+)-X.

Reduction of Hydroxypinocamphone (X). Lithium aluminum hydride reduction of 513 mg of X in the same way as mentioned above gave 508 mg (98%) of XI, mp 158°, $[\alpha]_D^{22}$ −39.1° ±3.0 (*c* 0.21, methanol).

Found: C, 70.68; H, 10.67%. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66%.

The NMR spectrum of the monoacetate of XI indicated a three hydrogens singlet (τ 9.04) for methyl, a six hydrogens doublet (τ 8.75) for geminal dimethyl, a three hydrogens singlet (τ 7.87) for acetoxy and one hydrogen AB quartet (τ_A 5.02: τ_B 4.84, J=7 Hz) for the hydrogen on the carbon bearing the acetoxy group.

The Meerwein-Ponndorf-Verley reduction of 3.0 g of X was carried out with 10 g of aluminum isopropylate in 20 m*l* of absolute isopropanol in the usual manner.[2] There were obtained 2.9 g of the diol XII (95%).

Preparation of (+)-*trans*-2-Hydroxyneopinocampheol (VI). A mixture of 2.0 g of (+)-I and 0.4 g of anhydrous sodium acetate in 2 m*l* of acetic anhydride was heated at 140°C for 1 hr and the reaction mixture was poured into water. The reaction mixture was extracted with ether and the solvent was removed under reduced pressure to give 1.6 g (63%) of *trans*-pinocarveyl acetate, $[\alpha]_D^{22}$ −7.5°±0.7 (*c* 0.69, methanol). A mixture of 1.6 g of mercuric acetate in 10 m*l* of aqueous-tetrahydrofuran (1 : 1 by volume) was added dropwise to 0.5 g of *trans*-pinocarveyl acetate with stirring for 4 hr and then kept at room temperature for 16 hr. Then 5 m*l* of 3 M sodium hydroxide was added, followed by 6 m*l* of 0.5 M sodium borohydride in 3.0 M sodium hydroxide. The water layer was saturated with sodium chloride. The upper layer of tetrahydrofuran was separated. It contained 0.45 g (81%) of VII $[\alpha]_D^{22}$ −15.9°±0.9 (*c* 0.62, methanol).

The acetate VII (0.4 g) was refluxed in 10 m*l* of methanol with 0.2 g of potassium hydrioxide on a water bath (95°C) for 1 hr. The reaction mixture was poured

6) (+)-*trans*-Pinocarveol (I), derived from (−)-α-pinene, by means of photo-oxidation method using Rose Bengal as a photosensitizer in methanol, was supplied by Takasago Kogyo Co., Ltd. Research Laboratory.

7) J. L. Simonsen, "The Terpenes," Vol. II, The University Press, Cambridge (1957), p. 221.

into water and was extracted with ether. The solvent was removed under reduced pressure. The crude product was recrystallized from ether to yield VI (0.3 g, 95%), mp 144°C, $[\alpha]_D^{22}$ +42°±13 (*c* 0.05, methanol).

Found: C, 70.42; H, 10.97%. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66%.

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