precipitate which was collected by filtration, washed with water, dried, and recrystallized from isopropyl alcohol to afford 40 mg (37%) of needles, mp 72°, followed by resolidification to needle clusters and final melting at 130–140°. The infrared spectrum was identical with that of the product prepared from pseudodiosgenin 27-iodide (**13**): 5.92 (sh) (enol ether), 5.7 (m), 5.9, 13.8, and 14.0 μ (phthalimide).[4]

3β-Hydroxy-27-methoxy-5,20(22)-furostadiene (Pseudodiosgenin 27-Methyl Ether) (14).—A solution of 228 mg (0.0004 mole) of **1** and 2.5 g of potassium hydroxide in 10 ml of methanol was heated under reflux during 1 hr. The mixture was diluted with water to give a precipitate which was collected by filtration and dissolved in ether. The ethereal solution was washed with water, dried, and concentrated. Crystallization of the residue from methanol gave 150 mg (88%) of needles, mp 117–122°. Recrystallization from acetone afforded glistening plates, mp 128–129°, [α] −34°, infrared spectrum: 5.92 (m) (enol ether) and 9.05 μ (OCH_3).

Anal. Calcd for $C_{28}H_{44}O_3$ (428.63): C, 78.45; H, 10.35. Found: C, 78.49; H, 10.44.

3β-Hydroxy-25α-5,20(22),25(27)-furostatriene (16).—A mixture of 105 mg (0.0002 mole) of pseudodiosgenin 27-iodide (**13**),[4,5,8] 112 mg (0.002 mole) of potassium hydroxide, and 5 ml of methanol was heated under reflux during 50 hr. The solution was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal phase was dried and chromatographed over 2.4 g of aluminum oxide. The ether eluate was crystallized from a mixture of dichloromethane and methanol to give 78 mg (94%) of needles, mp 129–136°. Recrystallization from acetone gave long, asbestos-like needles, mp 132–136°, [α] −36°. Although both the 3β-ol and its 3β-acetate appear to crystallize with a mole of tenaceously held water, rendering analyses ambiguous, the infrared spectra give unquestionable evidence for the presence of terminal methylene unsaturation: 2.8, 3.1 (hydroxyl), 5.92 (m) (enol ether), 6.1 (w) (C=C), and 11.25 μ (=CH_2).

Anal. Calcd for $C_{27}H_{40}O_2 \cdot H_2O$ (414.61): C, 78.21; H, 10.21. Found (average of three determinations): C, 78.42; H, 9.84.

Treatment of pseudodiosgenin 27-iodide (**13**) with 25% methanolic potassium hydroxide during 1 hr at reflux temperature gave 82% of the same product.

Acetylation with acetic anhydride in pyridine during 20 hr at 25°, followed by crystallization of the product from a mixture of dichloromethane and methanol gave long needles: mp 126–131°; [α] −45°; infrared spectrum: 5.8, 8.05 (acetate): 5.92 (m) (enol ether), 6.05 (w) (C=C), and 11.25 μ (=CH_2).

Anal. Calcd for $C_{29}H_{42}O_3 \cdot H_2O$ (456.64): C, 76.27; H, 9.71. Found: C, 76.56; H, 9.43.

Clarke–Eschweiler Methylation of 5β-Tomatidine.—A mixture of 86 mg (0.0002 mole) of 5β-tomatidine (mp 207–217°),[4] 0.2 ml of 37% aqueous formaldehyde, and 2 ml of formic acid was heated under reflux during 10 hr. The solution was concentrated to give a residue which was dissolved in 15 ml of 80% aqueous ethanol, made basic with 330 mg of potassium hydroxide and heated under reflux during 1 hr. The mixture was concentrated to give a remainder which was diluted with water and extracted with ether. The ethereal phase was washed with water, dried, and concentrated. A solution of the concentrate in 2 ml of pyridine was acetylated with 0.5 ml of acetic anhydride during 20 hr. The mixture was diluted with aqueous potassium chloride to give a precipitate which was collected, washed with water, and dried. The precipitate was fully soluble in 10% aqueous acetic acid, denoting complete conversion to a tertiary amine. Crystallization from methanol gave 9 mg of kernels: mp 220–255°; infrared spectrum: 5.75, 8.05 (acetate), 9.2, 9.4, 9.75, 10.05, 10.1, 10.2, 10.45, 10.7, 10.8, 11.3, and 11.7 μ. Although this spectrum appears consistent with an N-methylazaoxaspirane formulation, it differs, particularly in the 10–14-μ region, from the spectrum of the N-methyl-5β-tomatidine 3β-acetate (mp 215–217°)[4] prepared by acid-catalyzed cyclization of 3β-hydroxy 27-methylamino-5β,25β-20(22)-furostene synthesized from pseudosarsasapogenin.

Registry No.—**2**, 7648-74-0; **2** N-acetyl derivative, 7648-75-1; **9**, 7604-92-4; **9** methiodide, 7604-93-5; **8**, 7604-94-6; **8** acetate, 7604-95-7; **6**, 126-17-0; **11**, 7604-96-8; **15**, 512-04-9; **12**, 7604-97-9; **13**, 7604-98-0; **14**, 7604-99-1; **16**, 7605-00-7; **16** acetate, 7605-01-8.

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Absolute Configuration of Pulegone Oxide and Piperitenone Dioxide

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The conversion of (−)-pulegone oxide to (−)-(1*R*:3*S*:4*R*)-*trans*-4-hydroxyneomenthol and (+)-(1*R*:3*R*:4*R*)-*cis*-4-hydroxymenthol and of (+)-pulegone oxide to (−)-(1*R*:3*R*:4*S*)-*trans*-4-hydroxyneoisomenthol is described. (−)-Piperitenone dioxide, derived from (+)-piperitenone oxide, has been converted to (+)-(1*S*:3*S*:4*S*)-*cis*-1-*cis*-4-dihydroxyisomenthol. From the absolute configurations of these alcohols, it follows that (−)-pulegone oxide and (+)-pulegone oxide are *trans* and *cis* isomers, respectively, and that (−)-piperitenone dioxide has the *cis*-(1*S*:2*S*:4*S*) configuration.

Reusch and Johnson[1] recently discussed the configuration of the diastereomeric pulegone oxides and concluded that, on the basis of infrared, ultraviolet, nmr, and ORD data, (−)-pulegone oxide, derived from (+)-pulegone, should be assigned the *cis* configuration (**3**) and (+)-pulegone oxide should be given the *trans* structure (**2**).

Djerassi, *et al.*,[2] on the other hand, suggested that this assignment should be reversed in the light of an extensive ORD investigation.

We wish, at this time, to report the determination of the absolute configuration of the pulegone oxides by an unequivocal chemical transformation into known diols of well-defined configuration.[3] (+)-(1*R*)-Pulegone (**1**) was oxidized with 30% hydrogen peroxide in 30% sodium hydroxide solution to a mixture of *cis*- and *trans*-pulegone oxides (mp 43°). Fractional distillation followed by zone-melting purification of the mixture afforded (−)-pulegone oxide (**2**, mp 54°) and (+)-pulegone oxide (**3**, mp 59°).

(1) W. Reusch and C. K. Johnson, *J. Org. Chem.*, **28**, 2557 (1963).

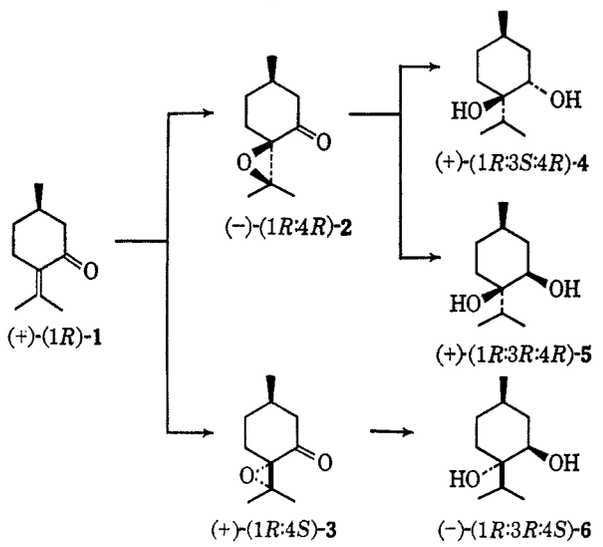
(2) C. Djerassi, W. Klyne, T. Norin, G. Ohloff, and E. Klein, *Tetrahedron*, **21**, 163 (1965).

(3) This was briefly described in a preliminary short communication: J. Katsuhara, *Bull. Chem. Soc. Japan*, **39**, 1825 (1966).

The (−)-diastereomer (2) was then reduced with lithium aluminum hydride in ether to (+)-*trans*-4-hydroxyneomenthol (**4**, 83% yield, mp 72°), and (+)-*cis*-4-hydroxymenthol (**5**, 17% yield, mp 76°). Diols **4** and **5** were identified by comparison with authentic (+)-(1*R*:3*S*:4*R*)-*trans*-4-hydroxyneomenthol[4] and (+)-(1*R*:3*R*:4*R*)-*cis*-4-hydroxymenthol,[5] respectively.

The diastereomeric (+)-pulegone oxide (**3**) was reduced with lithium aluminum hydride to (−)-*trans*-4-hydroxyneoisomenthol (**6**, mp 76°) in almost quantitative yield, which was identified by comparison with authentic (−)-(1*R*:3*R*:4*S*)-*trans*-4-hydroxyneoisomenthol.[5] (See Scheme I.)

SCHEME I

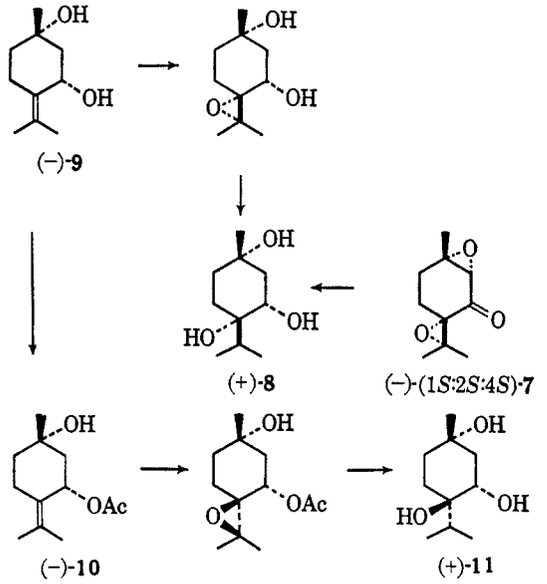


These results support the configurations of the pulegone oxides assigned by Djerassi. The observed negative and positive Cotton effects of **2** and **3**, respectively, also suggest that it is reasonable to apply the "reversed" octant rule[2] to spiro[5.2] systems.

Shimizu[6] has described the preparation of piperitenone dioxide (mp 78°) by perbenzoic acid oxidation of (+)-piperitenone oxide. We have obtained the same piperitenone dioxide (**7**, mp 78°), by oxidation of piperitenone oxide with 30% hydrogen peroxide in 30% sodium hydroxide solution. The dioxide **7** was then reduced with lithium aluminum hydride in ether to (+)-*cis*-1-*cis*-4-dihydroxyisomenthol (**8**, mp 185°). Compound **8** was identified by comparison with authentic (+)-(1*S*:3*S*:4*S*)-*cis*-1-*cis*-4-dihydroxyisomenthol which was derived from (−)-1α-3α-dihydroxy-4,8-menthene[7] (**9**) in the following manner. Compound **9** was epoxidized with *m*-chloroperbenzoic acid in chloroform to the noncrystalline α epoxide[8] of **9** which was then reduced with lithium aluminum hydride in ether to (+)-*cis*-1-*cis*-4-dihydroxyisomenthol (mp 185°).

Treatment of **9** with acetic anhydride in pyridine at room temperature furnished (−)-1α-hydroxy-3α-acetoxy-4,8-menthene (**10**, mp 114°) which was converted with *m*-chloroperbenzoic acid in chloroform to the noncrystalline β epoxide of **10**. The latter was reduced with lithium aluminum hydride in ether to (+)-*cis*-1-*trans*-4-dihydroxyneomenthol (**11**, mp 140–141°). (See Scheme II).

SCHEME II



The results of the present study demonstrate that the absolute configuration of (−)-piperitenone dioxide is *cis*-(1*S*:2*S*:4*S*) (**7**).

Optical rotatory dispersion curves of the epoxides obtained in the present study are summarized in Table I.

As can be seen from the data, no additivity of amplitude of the Cotton curves has been observed.

TABLE I
ORD CURVES OF EPOXIDES IN MEOH

Compd	1st λ, mμ	1st [α] × 10⁻², deg	2nd λ, mμ	2nd [α] × 10⁻², deg	a
(+)-Piperitenone oxide[a]	366	−4.0	278	+309.0	−313.0
(−)-Piperitone oxide[a]	330	−70.4	286	+79.2	−149.6
(−)-*trans*-Pulegone oxide[b]	324	+14.25	285	−20.9	+35.15
(−)-*cis*-Pulegone oxide[b]	327	−19.8	293	+13.2	−32.0
(−)-*cis*-Piperitenone dioxide	329	−46.0	282	+75.3	−121.3
(−)-(1*S*:2*S*:4*S*)-4,8-Dihydroxypiperitenone oxide[c]	325	−104.8	284	+101.4	−206.2

[a] S. Shimizu, J. Katsuhara, and Y. Inouye, *Bull. Agr. Chem. Soc. Japan*, **30**, 89 (1966). [b] Reference 1. [c] Reference 6.

Experimental Section[9]

Preparation of Pulegone Oxide Mixtures.—A mixture of 49 g of pulegone in 250 ml of methanol and 125 ml of 30% hydrogen

(4) T. Suga, T. Shishibori, and T. Matsuura, *Bull. Chem. Soc. Japan*, **37**, 310 (1964).
(5) W. Tagaki and T. Mitsui, *J. Org. Chem.*, **25**, 1476 (1960).
(6) S. Shimizu, *Bull. Agr. Chem. Soc. Japan*, **21**, 107 (1957).
(7) J. Katsuhara, K. Ishibashi, K. Hashimoto, and M. Kobayashi, *Kogyo Kagaku Zasshi*, **69**, 1170 (1966).
(8) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1957 (1958).

(9) Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer. Optical rotatory dispersion measurements were made on a Yanagimoto Spectropolarimeter Type III. Gas–liquid partition chromatography analyses were carried out using Shimazu 1-B and 2-C gas chromatographs. A 3 mm × 1.5 m column of 20% polyethylene glycol-6000 on Celite-545 served for vpc analyses.

peroxide was cooled to 5°, and a solution of 37.5 g of potassium hydroxide in 125 ml 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°. The reaction mixture was poured into 500 ml of brine and extracted with three 500-ml 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, which consisted of 64.5% **2** and 35.5% **3**, gave 48.5 g (89%) of a mixture of diastereomeric pulegone oxides.

Isolation and Properties of 2 and 3.—Isolation of the pure diastereomer was effected by distillation through a 80-cm spinning-band column. The fraction boiling at 94–97° (5 mm) was purified using a zone-melting method. Recrystallization from petroleum ether (bp 40–60°) furnished **2**: mp 54–55°, $[\alpha]^{20}D$ −18.8° (*c* 2.4, ethanol). The fraction boiling at 99–102° (5 mm) was purified using a zone-melting method. Recrystallization from petroleum ether gave **3**: mp 59°, $[\alpha]^{20}D$ +46.6° (*c* 0.3, methanol).

Lithium Aluminum Hydride Reduction of 2 and 3.—Diol **2** (17 g) dissolved in 100 ml of absolute ether was added dropwise to a chilled (−10°) slurry of 14 g of lithium aluminum hydride in 10 ml of absolute ether with stirring, under anhydrous conditions. Upon completion of addition the solution was stirred at 0° for 1 additional hr, stirring was continued at room temperature (15–20°) for 10 hr, and, finally, the reaction mixture was refluxed on the water bath and cooled. Excess hydride was decomposed by addition of 200 ml of ether saturated with water under cooling, the organic layer was separated, filtered, and dried, and the solvent was removed. This resulted in a mixture of **4** (83%) and **5** (17%), yield 16.7 g. Diols **4** and **5** were separated by means of gas–liquid partition chromatography: **4**, mp 72°, $[\alpha]^{23}D$ +22.6° (*c* 1.1, chloroform); **5**, mp 76°, $[\alpha]^{23}D$ +10.4° (*c* 0.2, chloroform).

The lithium aluminum hydride reduction of 3.9 g of **3** was carried out in the same manner to yield **6**: 2.5 g (81.5%), mp 76°, $[\alpha]^{20}D$ −22.0° (*c* 1.0, methanol); the 3,5-dinitrobenzoate had mp 142°.

Preparation of Piperitenone Dioxide.—A mixture of 1.77 g of (+)-piperitenone oxide, 12 ml of isopropyl alcohol, and 5 ml of 30% hydrogen peroxide was chilled to 5°. A solution of sodium hydroxide (0.6 g in 6 ml 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°, and the reaction mixture was then poured into 20 ml of brine and extracted with ether. The ether extract was washed and dried and the solvent was removed under reduced pressure. The crude product was recrystallized from petroleum ether to yield 822 mg (42.4%): mp 78°, $[\alpha]^{20}D$ −45.5° (*c* 2.0 chloroform).

Lithium Aluminum Hydride Reduction of 7.—Lithium aluminum hydride reduction of 287 mg of **7** carried out in the usual manner gave triol **8**: yield 262 mg (88%), mp 185°, $[\alpha]^{20}D$ +57.2° (*c* 0.5, methanol).

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.83; H, 10.64. Found: C, 63.89; H, 10.81.

Preparation of *cis*-1-*cis*-4-Dihydroxyisomenthol.—To an ice-cold solution of 190 mg of *m*-chloroperbenzoic acid in 4 ml of chloroform was added of 117 mg of **9** in 4 ml of chloroform. The reaction mixture was kept at 0° for 10 min, and stirring was continued at 25° for 1 hr. The solution was washed with 5% sodium carbonate and dried over sodium sulfate. Removal of solvent under diminished pressure gave an oily epoxide (yield 125 mg, 98%). This was reduced with lithium aluminum hydride reduction in the usual manner to yield *cis*-1-*cis*-4-dihydroxyisomenthol: 113 mg (90%), mp 185° (ethyl ether), $[\alpha]^{26}D$ +21.5° (*c* 0.04, methanol).

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.83; H, 10.64. Found: C, 63.01; H, 10.48.

Acetylation of 9.—Diol **9** (129 mg) was dissolved in 0.65 ml of pyridine at 0° and mixed with 0.39 ml of acetic anhydride under effective stirring. Stirring was continued at 0° for 30 min, and at room temperature for 10 hr. Finally, the excess of acetic anhydride in the reaction solution was decomposed by the addition of 2 ml of water at 30°. The product was extracted with three 20-ml portions of chloroform. The combined chloroform extracts were washed and dried, the solvent was removed under reduced pressure, and the crude crystalline residue was recrystallized from ether to give 1α-hydroxy-3α-acetoxy-4,8-menthene (**10**): yield 90 mg (56%), mp 114°, $[\alpha]^{26}D$ −3.8° (*c* 0.24, methanol).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 69.84; H, 10.69.

Preparation of *cis*-1-*trans*-4-Dihydroxyneomenthol (11).—Oxidation of 70 mg of **10** with *m*-chloroperbenzoic acid furnished an oily epoxide (71.4 mg, 95%). This was reduced with 62 mg of lithium aluminum hydride in the usual manner to yield 27 mg of **11** (53%): mp 140–141°, $[\alpha]^{24}D$ +2.4° (*c* 0.12, methanol).

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.83; H, 10.64. Found: C, 62.65; H, 10.79.

Registry No.—**10**, 7599-87-3; **11**, 7599-88-4; (+)-piperitenone oxide, 7647-93-0; (−)-piperitenone oxide, 7599-89-5; **2**, 7599-90-8; **3**, 7599-91-9; **7**, 7599-92-0; (−)-(1*S*:2*S*:4*S*)-4,8-dihydroxypiperitenone oxide, 7599-93-1; **4**, 6070-07-1; **5**, 7599-95-3; **6**, 7647-94-1; **8**, 7599-96-4.

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